5.9 INDACATEROL + GLYCOPYRRONIUM, indacaterol 110 microgram + glycopyrronium 50 microgram inhalation: powder for, Ultibro Breezhaler 110/50®, Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

1.1 The submission sought a section 85 Restricted Benefit listing for indacaterol/glycopyrronium fixed dose combination (FDC) for treatment of chronic obstructive pulmonary disease (COPD) in patients currently on long-acting beta 2 agonist (LABA) or long-acting muscarinic antagonist (LAMA) monotherapy and requiring further relief from symptoms.

2 Requested listing

2.1 Restricted benefit
Once-daily maintenance dual bronchodilator treatment to relieve symptoms in patients with COPD currently on LABA or LAMA monotherapy and who require additional relief from symptoms.

2.2 Listing was requested on a cost-minimisation basis with the component product prices at equivalent dosing.

2.3 The PBAC noted the different dose of indacaterol in the combination product (110 micrograms) compared to the single ingredient product (150 micrograms). The submission claimed that this was due to the increased deposition of particles when indacaterol is added to a LAMA in the combination product. The PBAC agreed with the ESC that both doses are likely to be on the plateau of the dose-response curve (for bronchodilator response). The PBAC considered that the bronchodilator effect of both the 110 and 150 microgram doses was likely to be similar in most patients.

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report, TGA Delegate's Summary and ACPM outcome (February 2014) were available.

3.2 The product was TGA registered on 21 March 2014, as a once-daily maintenance bronchodilator therapy to relieve symptoms in patients with chronic obstructive pulmonary disease.

3.3 Indacaterol/glycopyrronium FDC capsules for inhalation had not previously been considered by the PBAC.

4 Clinical place for the proposed therapy

4.1 According to the Australian guidelines for COPD (COPD-X), LABAs and LAMAs are recommended in the treatment algorithm for patients with moderate, severe and very severe COPD, and some patients with mild COPD who may be experiencing high levels of breathlessness. Where patients are beginning to experience further

exacerbations then a bronchodilator with an inhaled corticosteroid (ICS) is currently recommended.

4.2 The submission proposed that 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.

4.3 The PBAC noted the advice received from the Thoracic Society of Australia and New Zealand (TSANZ) in relation to the use of fixed dose combination LABA/LAMA products in the treatment of COPD. The TSANZ recommended that:

1. Fixed dose LABA/LAMA products will provide improvement in terms of symptomatic breathlessness. However, there is no evidence that they would be superior to the individual agents used concurrently;
2. There is scant data at present to suggest that they are superior to LAMA agents used alone to prevent future events (such as exacerbations and hospitalisations). Further long-term data are still awaited;
3. Given the current practice to prescribe ICS/LABA when stepping up therapy in persistently symptomatic patients from regular LAMA, these agents are likely to provide an effective, convenient and potentially safer alternative. Their availability would promote the current evidence based recommendation of step wise care and reduce the overuse of ICS in this group.

4.4 The PBAC noted that the treatment algorithm for COPD is changing. The PBAC considered it was appropriate to delay the introduction of ICS/LABA combination therapy in less severe disease, given the potential safety risks associated with ICS use. The PBAC considered that use of the combination of a LAMA and a LABA (as single agents given concurrently or as a fixed dose combination) was preferred to the earlier introduction of an ICS/LABA combination. Such use would be consistent with the Australian COPD-X guidelines, where introduction of an ICS is recommended for patients with very severe disease (FEV_1 % predicted <50% predicted and the patient has had two or more exacerbations in the previous 12 months[1]).

5 Comparator

5.1 The submission nominated four comparators:

1. Indacaterol 150 µg and glycopyrronium 50 µg given concurrently;
2. Currently available LABA plus LAMA (indacaterol + tiotropium);
3. LABA/inhaled corticosteroids (ICS) plus tiotropium;
4. Indacaterol 150 µg and glycopyrronium 50 µg (mono-components).

5.2 The PBAC considered the nominated comparators were generally appropriate. Given the changing treatment algorithm as noted in paragraph 4.4 the PBAC therefore considered that the comparisons with LAMA/LABA presented in the submission were the most relevant.

6 PBAC consideration of the evidence

6.1 The PBAC noted and welcomed the input received from the TSANZ in relation to the clinical place of fixed-dose combination LABA/LAMA products in the treatment of COPD.

[1] http://www.copdx.org.au/images/stories/pdf/alf%20stepwise%20management%20of%20copd%20a4%202014%20proof.pdf

6.2 The sponsor requested a hearing for this item. The PBAC noted the views of the thoracic physician in relation to the management of COPD and the role of combination bronchodilator therapy.

6.3 The clinician advised that dual bronchodilator therapy may appropriately reduce use of ICS therapy in some patients with COPD, noting that there is a risk of pneumonia in COPD patients using ICS. Dual bronchodilator therapy was described as being associated with symptom relief, reduced exacerbations and improvements in quality of life.

6.4 The clinician described epidemiological projections for COPD with increasing incidence due to the impact of ageing and history of exposure to tobacco smoke, air pollution and industrial pollutants.

6.5 In response to the Committee's request to comment on the issue of the effect of LAMA or LABA treatment alone on FEV_1 being greater than the effect of combination therapy, the clinician advised that a ceiling effect on FEV_1 was biologically plausible.

Clinical trials

6.6 The submission presented evidence for the indacaterol/glycopyrronium FDC compared to:

1. LAMA (glycopyrronium)
2. LABA (indacaterol)
3. LAMA + LABA (glycopyrronium + indacaterol, given concurrently);
4. LABA + LAMA (indacaterol + tiotropium); and
5. LABA/ICS + LAMA (tiotropium)

6.7 For the comparison versus indacaterol + glycopyrronium given concurrently, the submission presented one head-to-head, 4-week multi-centre randomised controlled trial (BEACON). Details are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
BEACON	A study to compare the efficacy and safety of once daily QVA149 vs. the once daily concurrent administration of QAB149 plus NVA237 in patients with moderate to severe chronic obstructive pulmonary disease.	*2012*
	Dahl et al. Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study.	*International J. of COPD.* (2013). 8: 501-508

Source: Table 15, pp42-44 of the submission.

6.8 The comparison of fixed dose indacaterol/glycopyrronium versus indacaterol plus tiotropium was based on an indirect comparison with tiotropium as the common arm. The SHINE and SPARK trials compared indacaterol/glycopyrronium with tiotropium. The INTRUST1 and INTRUST 2 trials compared indacaterol + tiotropium with tiotropium. Details are presented in the table below.

Trials (and associated reports) presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Fixed dose combination indacaterol/glycopyrronium		
SHINE	26-week treatment, multi-center, randomized, double-blind, parallel-group, placebo and active controlled (open label) study to assess the efficacy, safety and tolerability of QVA149 (110/50µg q.d.) in patients with moderate to severe chronic obstructive pulmonary disease (COPD). Bateman et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study.	*Eur Respir J* (2013), epub ahead of print.
SPARK	64-week treatment, multi-center, randomised, double-blind, parallel-group, active controlled study to evaluate the effect of QVA149 (110/50µg q.d.) vs NVA237 (50µg q.d.) and open-label tiotropium (18µg q.d.) on COPD exacerbations in patients with severe to very severe chronic obstructive pulmonary disease (COPD). Wedzicha et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study.	*The Lancet. (*2013) Published online http://dx.doi.org/10/1016/S2213-2600(13)70052-3
Indacaterol + tiotropium		
INTRUST1	Randomized, double-blind, controlled, parallel group, 12-week treatment study to compare the efficacy and safety of the combination of indacaterol 150 µg once daily with open label tiotropium 18 µg once daily versus open label tiotropium 18 µg once daily in patients with moderate-to severe chronic obstructive pulmonary disease	Thorax 2012. 67: 781-788. (Paper combines data from both Trials)
INTRUST2	A randomized, double-blind, controlled, parallel group, 12-week treatment study to compare the efficacy and safety of the combination of indacaterol 150 µg once daily with open label tiotropium 18 µg once daily versus open label tiotropium 18 µg once daily in patients with moderate-to severe chronic obstructive pulmonary disease. Mahler DA et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison.	

Source: Table 15, pp42-45 of the submission
COPD = chronic obstructive pulmonary disorder; q.d. = quaque die (once daily).

6.9 The comparison of fixed dose indacaterol/glycopyrronium versus LABA/ICS plus tiotropium was based on an indirect comparison comprising:
Two trials for the proposed treatment:
- SHINE: fixed dose combination and tiotropium;
- SPARK: fixed dose combination and tiotropium;

And six published studies for the main comparator (LABA/ICS + tiotropium compared to tiotropium 18µg). Details are in the table below.
- Aaron et al. (2007);
- Cazzola et al. (2007);
- Hanania et al. (2012);
- Hoshino et al. (2011);
- Jung et al. (2012);
- Welte et al. (2009).

Trials (and associated reports) presented in the submission

LABA/ICS + tiotropium	
Aaron 2007	Aaron SD et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: A randomized trial. Annals of Internal Medicine 2007; 146(8):545-555.
Cazzola 2007	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 and Therapeutics 2007; 20(5):556-561.
Hanania 2012	Hanania NA et al. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. Respiratory Medicine 2012; 106(1):91-101.
Hoshino 2011	Hoshino M et al. Effects of adding salmeterol/fluticasone propionate to tiotropium on airway dimensions in patients with chronic obstructive pulmonary disease. Respirology 2011; 16(1):95-101.
Jung 2012	Jung KS et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: A randomized controlled study. Respiratory Medicine 2012; 106(3):382-389.
Welte 2009	Welte T et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 2009; 180(8):741-750.

Source: Table 15, pp42-45 of the submission
COPD = chronic obstructive pulmonary disorder; LABA/ICS = long acting β2-agonist/inhaled corticosteroid.

Comparative effectiveness

6.10 Trough FEV_1 at 28 days was the primary outcome measure in the BEACON trial, and at 26 weeks in the SHINE trial. Trough FEV_1 was a secondary outcome at 12 weeks in SHINE, and in the SPARK and INTRUST 1 and 2 studies.

6.11 The PBAC noted that it had previously accepted trough FEV_1 as a surrogate measure of effect in COPD. However, the PBAC considered that additional clinical outcomes such as frequency of exacerbations and hospitalisations would be informative as more direct, patient relevant measures of effect.

6.12 A summary of results for trough FEV_1 is presented in the table below.

Results of trough FEV_1 (Litres) at different time points against each nominated comparator

Trial ID	Fixed dose combination Mean difference (95% CI)	Comparator (for indirect) Mean difference (95% CI)	Indirect estimate of effect
1. Comparison Ind/Gly vs. indacaterol + glycopyrronium, 4 weeks			
BEACON [a] PP	-0.01 (-0.05; 0.04)		–
2. Comparison Ind/Gly vs. indacaterol + tiotropium, 12 weeks			
	Ind/Gly vs tio	**Ind + Tio vs tio**	
Meta-analysis [b]	**0.09 (0.07; 0.11)** I^2 =18%	**0.08 (0.06; 0.10)** I^2 =0%	0.01 (-0.02; 0.04)
3. Comparison Ind/Gly vs. LABA/ICS + tiotropium, 12 weeks			
	Ind/Gly vs Tio	**LABA/ICS + Tio vs. Tio**	
Meta-analysis [c]	**0.09 (0.07; 0.11)** I^2 = 18%	**0.04 (0.01; 0.06)** I^2 = 0%	**0.05 (0.02; 0.08)**
4a. Comparison Ind/Gly vs. indacaterol, 12 weeks			
SHINE [d] FAS	**0.07 (0.05; 0.10)**		–
4b. Comparison Ind/Gly vs. glycopyrronium			
SHINE [d] FAS, 12 weeks	**0.09 (0.06; 0.11)**		–
SPARK			
Week 12	**0.07 (0.05; 0.09)**		–
Week 26	**0.07 (0.05; 0.10)**		–

FEV_1 = Forced expiratory volume in one second; PP = per protocol; FAS = full analysis set; Ind/Gly = fixed dose combination indacaterol/glycopyrronium; CI = confidence interval; LABA/ICS = long acting β2-agonist/inhaled corticosteroid; Tio - tiotropium.

[a] Trough FEV_1 at week 4.

[b] Trough FEV_1 at week 12; Meta-analysis includes SHINE and SPARK for the proposed treatment and INTRUST 1 & 2 for the main comparator.

[c] Trough FEV_1 at week 12; Meta-analysis includes SHINE and SPARK for the proposed treatment and Cazzola, Hoshino and Welte for the main comparator.

[d] Trough FEV_1 at week 26.

Source: Table 3, p3-4 of the commentary.

6.13 The PBAC noted that there was no statistically significant difference in trough FEV_1 at four weeks in the BEACON trial. However, the PBAC noted that the duration of the trial was short, and may be inadequate to provide a reliable estimate of the long-term treatment effect.

6.14 From the SHINE and SPARK trials, the PBAC noted that the incremental gain in FEV_1 of adding glycopyrronium to indacaterol was 70 mL (95% CI: 50-100 mL), and the incremental gain in FEV_1 of adding indacaterol to glycopyrronium was 90 mL (95% CI: 60-100 mL) at 26 weeks. While these results were statistically significant for indacaterol/glycopyrronium compared to either of its components as monotherapy, the difference did not exceed the accepted minimal clinically important difference (MCID) of 100-140 mL.

6.15 The PBAC noted that the results of the meta-analyses presented in the submission showed incremental gains in FEV_1 of less than 100 mL.

6.16 The PBAC noted the advice of the clinician during the hearing that there was biological plausibility to a ceiling effect of combination therapy on FEV_1. The PBAC therefore considered that it might be reasonable to accept that the same MCID should not apply to add-on therapy, and the effect of add-on therapy in terms of frequency of exacerbations may be a more patient relevant measure of effect.

Comparative harms

6.17 A summary of harms for the comparisons presented in the submission is presented in the table below.

Harm summary (adverse events only)

Outcome	N	OR (95%CI)	Event rate/100 patients		Increment
			Ind/Gly	Comparator	
1. Comparison Ind/Gly vs. indacaterol + glycopyrronium					
AE	193	1.02 (0.14; 7.34)	25.6	25.2	0.3
2. Comparison Ind/Gly vs. indacaterol + tiotropium					
Ind/Gly vs tio	2420	0.93 (0.75; 1.16)	78.1	79.0	-0.9
Tio vs. Ind+Tio	2273	1.16 (0.98; 1.37)	40.7 [a]	44.2	-3.5
Indirect		0.80 (0.61; 1.06)			
3. Comparison Ind/Gly vs. LABA/ICS + tiotropium					
Ind/Gly vs. tio	2418	0.94 (0.76; 1.17)	78.2	79.0	-0.8
Tio vs. LABA/ICS + Tio	1057	1.11 (0.85; 1.45)	34.0 [a]	36.5	-2.5
Indirect		0.85 (0.60; 1.19)			
4. Comparison Ind/Gly vs. mono components					
SHINE					
AE vs. Indacaterol	950	0.78 (0.14; 7.34)	55.1	61.1	-6.1
AE vs. Glycopyrronium	947	0.77 (0.14; 4.33)	55.1	61.3	-6.2
SPARK					
AE vs. Glycopyrronium	1469	0.88 (0.14; 5.55)	93.0	93.8	-0.8

Ind/Gly = fixed dose combination indacaterol/glycopyrronium; CI = confidence interval; LABA/ICS = long acting β2-agonist/inhaled corticosteroid; OR = Odds ratio; AE = adverse event; Tio = tiotropium.
[a] Tiotropium arm.
Source: Table 4 p4 of the commentary

6.18 The PBAC noted that there were no statistically significant differences in adverse events between the fixed combination product and the comparators.

6.19 The PBAC noted that a safety issue not measured in the trials was the potential for patients to be prescribed a higher than recommended dose of LABA and/or LAMA. A predicted versus actual utilisation review of indacaterol conducted by the Drug Utilisation Sub Committee (DUSC) highlighted the potential for confusion and incorrect dosing of FDC products. The DUSC analysis showed that 20.8% of patients who initiated indacaterol between December 2011 and November 2012 were also taking, and continued to take, an ICS/LABA concomitantly (i.e. these patients added indacaterol to an ICS/LABA); there is no clinical evidence to support the safety or efficacy of using two LABAs. The PBAC agreed with the ESC that the introduction of a LABA/LAMA FDC could further increase the risk of incorrect or double-dosing of products for COPD. The PBAC also considered there is a risk that patients with concomitant asthma may be co-prescribed indacaterol/glycopyrronium and an ICS/LABA FDC. The use of inappropriately high doses of LABA (or LAMA) would lead to an unknown but likely increased risk of harm.

Clinical claim

6.20 The submission claimed that indacaterol/glycopyrronium FDC is superior in terms of comparative effectiveness and equivalent in terms of safety over either of the components given as monotherapy. The PBAC considered this claim was reasonable. The PBAC noted that the incremental gain in FEV_1 was below the MCID of 100 mL specified in the submission but accepted that it was reasonable to accept that the incremental gain associated with add-on therapy would not be as great as the incremental gain associated with monotherapy compared with placebo.

6.21 The submission claimed that indacaterol/glycopyrronium FDC is non-inferior in terms of comparative effectiveness and equivalent in terms of safety compared to the component products given concurrently. The PBAC considered that while the results of the BEACON study showed no significant difference in FEV_1, at four weeks, the duration of the trial was too short to reliably demonstrate long-term non-inferiority, particularly in terms of other clinically relevant endpoints such as frequency of exacerbations and hospitalisations.

6.22 The submission claimed that indacaterol/glycopyrronium FDC is non-inferior in terms of comparative effectiveness and equivalent in terms of safety over (i) indacaterol + tiotropium, and (ii) LABA/ICS + tiotropium. While noting that these claims were based on indirect comparisons, the PBAC considered the claims to be reasonable.

Economic analysis

6.23 The submission presented a cost-minimisation analysis based on the non-inferiority claims. A summary of the cost-minimisation is presented in the table below.

Summary of cost minimisation

Molecule	Ex-man	[redacted]	Price per µg	Requested price
Indacaterol 150 µg	[redacted]	[redacted]	[redacted]	[redacted]
Glycopyrronium 50 µg	[redacted]	[redacted]	[redacted]	[redacted]
Ex-manufacturer				[redacted]
Price to pharmacist				[redacted]
DPMQ				[redacted]

Source: Table 158 & Table 159, p279 of the submission;
Ex-man = ex –manufacturer price; DPMQ = dispensed price for maximum quantity

[redacted]

6.24 The PBAC noted from the SHINE study that the incremental gain in FEV_1 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)). Therefore, the PBAC considered that the submission's proposal to price the FDC based on the sum of the prices of the individual components, while consistent with the PBAC Guidelines for combination products, could not be justified given that the price would be approximately twice the cost of monotherapy in the absence of evidence to demonstrate an incremental benefit of this magnitude. In this situation, the PBAC considered it would be more appropriate for the price of indacaterol/glycopyrronium FDC to be based on the value of the incremental gain in clinically relevant efficacy endpoints.

6.25 As the incremental gain in FEV_1 of indacaterol/glycopyrronium FDC was not able to be translated into more clinically relevant measures of effect (e.g., frequency of exacerbations, hospitalisations), the PBAC considered it was unable to determine and value the incremental benefit associated with use the FDC compared with use of

components given concurrently. Therefore, the Committee was unable to determine an appropriate price for the FDC.

Estimated PBS usage & financial implications

6.26 The submission used a market share approach to estimate the utilisation and financial implications associated with PBS-listing of the indacaterol/glycopyrronium FDC. A summary of the submission's estimates is presented in the table below.

	Y1	Y2	Y3	Y4	Y5
Estimated extent of use					
Ind/Gly prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated net cost to PBS					
Total cost (DPMQ)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Co-payments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to R/PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated changes in use and cost of other drugs					
Total tiotropium packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total indacaterol packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fluticasone/ salmeterol packs replaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budesonide/ eformoterol packs replaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts replaced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost offset	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net Cost R/PBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: DUSC Advice p3

6.27 The PBAC agreed with the DUSC that the total substitutable market was underestimated in the submission. The PBAC agreed that it was possible that patients may switch from ICS/LABA to LAMA/LAMA regardless of the treatment algorithm, due to the availability of new LAMA/LABA combination products. The PBAC noted that the most recent GOLD guidelines[2] reiterate the risks associated with long-term use of inhaled corticosteroids (pneumonia and increased fracture risk) and emphasise that these medicines should not be prescribed outside their indications. The PBAC agreed with the DUSC that it was possible that such advice might delay movement of COPD patients to treatment with ICS/LABA and expand use of LAMA/LABA. The PBAC agreed that excluding switching from ICS/LABA to LAMA/LABA had underestimated the total substitutable market.

6.28 The PBAC shared the DUSC's concerns in relation to the trade names and proliferation of inhalers being confusing for prescribers and patients. The PBAC agreed that a quality use of medicines (QUM) issue exists where this potential confusion may lead to use of multiple LAMAs or LABAs and associated clinical consequences.

[2] From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from: http://www.goldcopd.org/.

6.29 The PBAC also noted newly emerging data that shows there may be a role for LAMAs in asthma, when used in conjunction with and ICS +/- LABA, although this has not yet been fully determined[3].

7 PBAC Outcome

7.1 The PBAC rejected the submission requesting PBS-listing for indacaterol/glycopyrronium FDC for the treatment of COPD. The PBAC considered that the cost-minimisation approach used, where the price of the FDC was cost-minimised to the sum of the prices of the component products (dose adjusted) was not justified by the evidence presented in the submission.

7.2 The PBAC considered the nominated comparators were generally appropriate. The PBAC noted that the position of ICS/LABA in the treatment algorithm for COPD is changing, and ICS/LABA is currently recommended in patients with very severe disease. The PBAC therefore considered that the comparisons with LAMA/LABA presented in the submission were the most relevant.

7.3 The PBAC considered the submission's claim that the FDC is superior in terms of comparative effectiveness and equivalent in terms of safety over either of the components given as monotherapy was reasonable. The PBAC noted that the incremental gain in FEV_1 for this comparison was below the MCID of 100 mL specified in the submission. However, the Committee considered that it was reasonable to accept that the incremental gain associated with add-on therapy would not be as great as the incremental gain associated with monotherapy compared with placebo.

7.4 The PBAC considered that while the results of the BEACON study showed no significant difference in FEV_1 between indacaterol/glycopyrronium FDC compared to the component products given concurrently, at four weeks, the duration of the trial was too short to reliably demonstrate long-term non-inferiority, particularly in terms of other patient relevant endpoints such as effect on frequency of exacerbations and quality of life measures.

7.5 As COPD is a chronic disease, the PBAC considered that longer-term data, demonstrating incremental clinical and patient relevant benefits of the FDC compared to the component products given concomitantly would be required to justify the price requested in the submission.

7.6 The proposed DPMQ for the indacaterol/glycopyrronium FDC was $122.81, based on the sum of the prices of the individual components, [redacted]

7.7 The PBAC noted from the SHINE study that the incremental gain in FEV_1 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)). Therefore, the PBAC considered that the submission's proposal to price the FDC based on the sum of the prices of the individual components, while consistent with

[3] Lipworth B. Emerging role of long acting muscarinic antagonists for asthma. Br J Clin Pharmacol 2014; 77(1):55–62.

the PBAC Guidelines for combination products, could not be justified given that the price would be approximately twice the cost of monotherapy, in the absence of evidence to demonstrate an incremental benefit of this magnitude. In this situation, the PBAC considered it would be more appropriate for the price of indacaterol/glycopyrronium FDC to be based on the value of the incremental gain in clinically relevant efficacy endpoints.

7.8 As the incremental gain in FEV_1 of indacaterol/glycopyrronium FDC was not able to be translated into more clinically relevant measures of effect (e.g., frequency of exacerbations, hospitalisations), the PBAC considered it was unable to determine and value the incremental benefit associated with use the FDC compared with use of components given concurrently. Therefore, the Committee was unable to determine an appropriate price for the FDC.

7.9 The PBAC did not accept the estimates of utilisation presented in the submission. The PBAC agreed with the DUSC that the total substitutable market was underestimated. The PBAC agreed that it was possible that patients may switch from ICS/LABA to LAMA/LAMA regardless of the treatment algorithm, due to the availability of new LAMA/LABA combination products. The PBAC considered that as a consequence of advice in the most recent GOLD guidelines in relation to risks associated with long-term use of inhaled corticosteroids (pneumonia and increased fracture risk) that it was possible that there would be delayed movement of COPD patients to treatment with ICS/LABA, which would result in expanded use of LAMA/LABA. The PBAC considered that the advice received from the TSANZ supported this view.

7.10 The PBAC considered that should indacaterol/glycopyrronium FDC be recommended for PBS listing in the future, a risk-sharing arrangement would be required to manage the risk associated with higher than estimated usage and cost.

7.11 The PBAC again raised concerns in relation to the trade names and proliferation of inhalers for treatment of COPD being confusing for prescribers and patients. The PBAC agreed that a quality use of medicines (QUM) issue exists where this potential confusion may lead to use of multiple LAMAs or LABAs and associated clinical consequences. The PBAC referred the matter of QUM of COPD treatments to NPS MedicineWise and requested they produce information and education for prescribers in relation to this.

7.12 The PBAC noted and welcomed the input received from the TSANZ in relation to the to the clinical place of fixed-dose combination LABA/LAMA products in the treatment of COPD.

7.13 The PBAC noted that the individual components indacaterol and glycopyrronium are currently available individually on the PBS for treatment of COPD. However, the PBAC accepted that a single inhaler may be perceived as more convenient than multiple inhalers for some patients. Further, the PBAC accepted that a single co-payment may be preferred by patients.

7.14 The PBAC noted that the submission meets the criteria for an Independent Review.

Outcome:
Rejected

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.

Sponsor's Comment

The sponsor believes the comment regarding the submission asking for an incremental benefit over the component products given concurrently is misleading (Paragraphs 6.26, 7.8). The submission did not ask for an incremental or increased price over the components given concurrently. It asked for the same price as the components given concurrently. The Sponsor believes that the submission covers the best possible summary of evidence in accordance with the PBAC's fixed dose combination guidelines and that Ultibro 110/50 provides a cost saving alternative for concurrent LABA plus LAMA bronchodilator therapy. Novartis is committed to working with the PBAC to ensure the timely availability of Ultibro Breezhaler 110/50 to COPD patients.