

**5.08 MOMETASONE FUROATE with INDACATEROL,
Capsule containing powder for oral inhalation
mometasone furoate 80 micrograms with indacaterol
150 micrograms (as acetate) (for use in Breezhaler),
30 capsules,
Capsule containing powder for oral inhalation
mometasone furoate 160 micrograms with
indacaterol 150 micrograms (as acetate) (for use in
Breezhaler), 30 capsules,
Capsule containing powder for oral inhalation
mometasone furoate 320 micrograms with
indacaterol 150 micrograms (as acetate) (for use in
Breezhaler), 30 capsules,
Aectura[®] Breezhaler[®],
Novartis Pharmaceuticals Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The submission requested an Authority Required (STREAMLINED) listing of Aectura[®] Breezhaler[®], the fixed dose combination (FDC) of mometasone furoate (MF), an inhaled corticosteroid (ICS) with indacaterol (IND), a long-acting beta2 agonist (LABA) for the maintenance treatment of asthma. The submission requested the listing of three strengths of capsules containing powder for oral inhalation with increasing doses of MF (MF/IND 80/150 mcg, MF/IND 160/150 mcg and MF/IND 320/150 mcg). Patients must load a capsule into the single dose dry powder inhaler (DPI) device prior to each use.
- 1.2 If recommended, MF/IND will be one of five ICS/LABA FDC drug combinations available on the PBS for asthma, and will be the first ICS/LABA FDC formulation listed for asthma requiring patients to load dry powder capsules into the inhaler device. Currently, all ICS/LABA FDCs available on the PBS for asthma are delivered via multidose DPI and/or metered dose inhaler (MDI).
- 1.3 The basis of the requested listing was a cost-minimisation analysis to three corresponding formulations of fluticasone propionate (FP)/salmeterol (SAL) FDC

Public Summary Document – July 2020 PBAC Meeting

delivered via a DPI (Seretide® Accuhaler®). A cost-minimisation analysis versus other relevant comparator products was conducted during the evaluation.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with asthma for whom the use of ICS/LABA is appropriate. Patients must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.
Intervention	Aectura® Breezhaler®, a once-daily DPI (capsules) containing MF and IND. Available in three strengths: 80/150 mcg per actuation ('low'), 160/150 mcg per actuation ('medium'), 320/150 mcg per actuation ('high').
Comparator	For the clinical comparison, the submission nominated the following comparators: (i) Primary comparator: FP/SAL (Seretide® Accuhaler®) (ii) Supplementary comparator: MF (Asmanex® Twisthaler® DPI not PBS listed) as a proxy for FP (Flixotide® Accuhaler® DPI PBS listed). Clinical evidence presented informs the following comparisons: MF/IND 80/150 mcg daily versus MF 200 mcg daily and FP 250 mcg twice daily (via indirect comparison); MF/IND 160/150 mcg daily versus MF 400 mcg daily and FP/SAL 500/50 mcg twice daily (post-hoc analysis); MF/IND 320/150 mcg daily versus MF 400 mcg twice daily and FP/SAL 500/50 mcg twice daily.
Outcomes	Trough FEV1; AQLQ; FVC; FEV ₂₅₋₇₅ ; ACQ-7; exacerbations; rescue medication use; PEF; symptoms; health status
Clinical claim	MF/IND once daily is equivalent to FP/SAL twice daily at the corresponding doses (low, medium, high), respectively

Abbreviations: ACQ-7=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; DPI=dry powder inhaler; FEF₂₅₋₇₅=forced expiratory flow; FEV1=forced expiratory volume in one second; FP=fluticasone propionate; FVC=forced vital capacity; ICS inhaled corticosteroid; IND=indacaterol; LABA=long acting beta2-adrenergic agonist; MF=mometasone furoate; PEF=peak expiratory flow; SAL=salmeterol; D=daily; BD=twice daily;

Source: Table 1.1, p25 of the submission.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of the evaluation, the TGA Clinical Evaluation Report (Round 1) was available. At the time of the ESC advice the TGA Clinical Evaluation Report (Round 2) was available.

2.2 The proposed TGA indication for MF/IND is:

“as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta2-agonist and inhaled corticosteroid is appropriate: patients not adequately controlled with inhaled corticosteroids and ‘as needed’ short-acting beta2-agonists, or patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled corticosteroids.”

2.3 The pre-PBAC response stated that in June 2020, the sponsor was informed that the TGA intended to move the submission past the June Advisory Committee on Medicines meeting and straight to a file note and product information negotiations. The TGA delegate file note (dated 15/6/2020) was provided with the pre-PBAC response and the sponsor stated the TGA decision letter was expected in July 2020.

- 2.4 In addition, the pre-PBAC response stated the TGA recommended the dosage to be reported as:
- MF/IND 80/150 mcg (low dose); delivered dose (dose that leaves the mouthpiece of the inhaler) 62.5 mcg MF, 125 mcg IND.
 - MF/IND 160/150 mcg (medium dose); delivered dose 127.5 mcg MF, 125 mcg IND.
 - MF/IND 320/150 microgram (high dose); delivered dose 260 mcg MF, 125 mcg IND.

Previous PBAC consideration

- 2.5 This is the first PBAC submission for MF/IND. MF and IND are not currently available on the PBS for asthma, either individually or in combination products. The PBAC however, recommended MF delivered via DPI (Asmanex[®] Twisthaler[®]) for asthma in June 2002 (and July 2011) but the product was never listed. The PBAC considered:
- MF 400 mcg once daily (or 200 mcg twice daily) was equi-effective to FP 250 mcg twice daily.
 - MF 400 mcg twice daily was equi-effective to FP 500 mcg twice daily.
- 2.6 The PBAC Guidelines (v5) state it is preferable that the individual components of FDCs are also listed on the PBS, however this is less relevant for ICS/LABA FDCs given the restriction does not require patients to be stabilised on the components prior to use. In March 2014, the PBAC considered “in view of significant clinical experience with LABA/ICS FDCs in asthma and the availability of advice on switching from existing products... its concern regarding the availability of the FDC in the absence of the components were addressed” (Paragraph 6.23, fluticasone furoate with vilanterol, Public Summary Document (PSD) March 2014 PBAC meeting).
- 2.7 The Sponsor is also requesting PBS listing of a triple ICS/LABA/long-acting muscarinic antagonist (LAMA) FDC inhaler for asthma at the July 2020 meeting. Enerzair[®] dry powder capsules for inhalation contains the same components as Ateectura[®] (MF and IND) plus glycopyrronium, delivered via the same Breezhaler[®] device.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 The proposed listing is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – July 2020 PBAC Meeting

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Dispensed price for Max. Qty	Proprietary and Manufacturer	Name
MOMETASONE FUROATE + INDACATEROL Indacaterol 150 microgram + mometasone furoate 80 microgram powder for inhalation, 30 capsules	NEW	1	1	5	\$41.95	Ateectura Breezhaler 150/80	Novartis
Indacaterol 150 microgram + mometasone furoate 160 microgram powder for inhalation, 30 capsules	NEW	1	1	5	\$48.64	Ateectura Breezhaler 150/160	
Indacaterol 150 microgram + mometasone furoate 320 microgram powder for inhalation, 30 capsules	NEW	1	1	5	\$61.78	Ateectura Breezhaler 150/320	

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (NEW CODE)
Episodicity: Daily
Severity: Patients uncontrolled on ICS
Condition: Asthma
Indication: Asthma
Clinical criteria: Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.
Treatment criteria: This product is not indicated for the initiation of treatment in asthma.
AND
Treatment criteria: The patient must not be on a concomitant single agent long-acting beta-2-agonist (LABA)
AND
Population criteria: Patient must be aged 12 years or over.
Administrative Advice This product is not indicated for the initiation of treatment in asthma.
Administrative Advice This drug product is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD).
Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.

3.2 The Sponsor requested an Authority Required (STREAMLINED) listing for three formulations: 'low' dose MF/IND (80/150), 'medium' dose MF/IND (160/150), and 'high' dose MF/IND (320/150). The requested DPMQs were based on a cost-

minimisation analysis to corresponding low, medium and high doses of FP/SAL DPI at the nominated equi-effective dose. No special pricing arrangement was proposed.

- 3.3 The requested DPMQs are higher than some alternative ICS/LABA FDCs at similar/equi-effective doses (see Economic analysis). The submission did not provide any justification to support a higher price compared to alternative therapies. Under Section 101(3B) of the National Health Act (1953), the PBAC cannot recommend listing a therapy at a price that is substantially more costly than an alternative therapy unless it is satisfied that the therapy provides, for some patients, a significant improvement in efficacy or reduction in toxicity.
- 3.4 The wording of the requested restriction was based on the current restriction of FP/SAL DPI and is generally consistent with other ICS/LABA FDCs listed for maintenance treatment of asthma. A key difference across the products is the population criteria, which restricts treatment to patients aged ≥ 12 years or over for MF/IND compared to ≥ 4 years for FP/SAL DPI.

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

4 Population and disease

- 4.1 Asthma is a chronic inflammatory disease of the airways that is defined clinically as the presence of airflow limitation and respiratory symptoms (e.g. wheeze, shortness of breath, cough, and chest tightness) that vary over time. The primary goal of asthma pharmacotherapy is to reduce underlying inflammation and promote bronchodilation.
- 4.2 Asthma severity is determined by the type and amount of treatment needed to maintain adequate symptom control, with more serious disease requiring a greater intensity of treatment. Pharmacological management involves a stepwise approach. In the current Australian guidelines (Australian Asthma Handbook, 2019), patients who experience exacerbations or uncontrolled asthma despite ICS treatment would initiate low dose ICS/LABA, progressing to medium or high dose ICS/LABA if asthma is uncontrolled. In addition to regular maintenance treatment to prevent symptoms, patients use short-acting beta2 agonist (SABA) for relief of symptoms or use budesonide/formoterol as both maintenance and reliever therapy.
- 4.3 The submission proposed that MF/IND would add to existing low, medium and high dose ICS/LABA FDCs available on the PBS for asthma. The recommended dose is the inhalation of the contents of one capsule of MF/IND 80/150 once daily for patients who need a combination of a LABA and a low dose ICS or MF/IND 160/150 for a medium dose ICS or MF/IND (320/150) for a high dose ICS. The maximum recommended dose is MF/IND (320/150) once daily. Given MF is currently not available on the PBS, patients commencing treatment with MF/IND will need to either 'step up' from an alternative ICS or switch from another ICS/LABA FDC available on the PBS. This is similar to patients currently treated with fluticasone furoate (FF)/vilanterol (VI) FDC (Breo[®] Ellipta[®]), where FF is not available in a separate inhaler.

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

5 Comparator

- 5.1 The submission appropriately acknowledged that MF/IND would substitute for other available ICS/LABA FDCs at comparable doses, but argued that the most likely replacements would be within DPI formulations since there is little switching between DPI and MDI formulations on the PBS. Given Atectura® Breezhaler® (MF/IND) will be the first ICS/LABA FDC on the PBS for asthma that requires patients to load capsules into an inhaler device, it is unclear which substitutions are most likely.
- 5.2 All ICS/LABA FDCs including MDI and DPI formulations at comparable doses are potential comparators because they could be replaced in practice. In past decisions, the PBAC has accepted DPI and MDI formulations as relevant comparators for each other (Page 2, budesonide with eformoterol fumarate FDC, PSD July 2013 PBAC meeting). The pre-PBAC response argued that the most appropriate comparator would be of a similar delivery system, in this case a DPI, to minimise any variability of a different delivery system on patient outcomes. The PBAC reaffirmed that DPI and MDI formulations are relevant comparators for each other in this context.
- 5.3 For the clinical comparison to the three doses (low, medium and high) of MF/IND, the submission appropriately nominated comparable doses of the following comparators:
- i. FP/SAL DPI where
 - Low dose = FP/SAL 100/50 mcg one actuation twice daily
 - Medium dose = FP/SAL 250/50 mcg one actuation twice daily
 - High dose = FP/SAL 500/50 mcg one actuation twice daily
 - ii. MF alone delivered via the Twisthaler® (which is assumed as a proxy for the FP alone), where
 - Low dose = MF 200 mcg one actuation once daily
 - Medium dose = MF 400 mcg one actuation once daily
 - High dose = MF 400 mcg one actuation twice daily
- 5.4 A different Sponsor is requesting listing of Fostair®, which is an ICS/LABA FDC delivered via MDI containing beclometasone dipropionate with formoterol fumarate at the July 2020 PBAC meeting. Hence, Fostair® may be a potential near market 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 and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The comment from Asthma Australia described a range of benefits of treatment with MF/IND including the once daily dosing regimen.

Clinical trials

6.3 The submission is based on three head-to-head randomised clinical trials comparing MF/IND to MF and/or FP/SAL DPI (Palladium, Iridium, Quartz), and one head-to-head clinical trial comparing MF to FP (O'Connor et al 2001) which is used for an indirect treatment comparison.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PALLADIUM (2301)	A multi-center, randomized, 52 week treatment, double-blind, triple dummy, parallel-group design to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma. Additional trial registrations: EUCTR2015-002899-25-EE and NCT025717777.	2019
IRIDIUM (2302)	A multi-center, randomized, 52-week, double-blind, parallel-group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma. Additional trial registrations: EUCTR2015-002529-21-DE and NCT02554786.	2018
QUARTZ (2303)	A multi-center, randomized, 12-week treatment, double-blind study to assess the efficacy and safety of QMF149 (150/80 µg) compared with mometasone furoate (MF) Twisthaler® (200 µg) in adult and adolescent patients with asthma. Additional trial registrations: NCT02892344, CTRI/2017/07/00900; JPRN-JapicCTI-173559; EUCTR2016-00472-22-SK. Koommann O et al. Efficacy and safety of inhaled once-daily low-dose indacaterol acetate/mometasone furoate in patients with inadequately controlled asthma: Phase III randomised QUARTZ study findings.	2018 Respiratory Medicine 2020; 161
O'Connor et al 2001	O'Connor B et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator	Ann Allergy Asthma Immunol 2001; 86:397-404

Source: Table 2.7 and Table 2.8, pp43-44 of the submission.

6.4 Table 3 summarises the key features of the included trials.

Public Summary Document – July 2020 PBAC Meeting

Table 3: Key features of the included evidence

Trial	N	Design/duration	Bias	Treatment arms	Population	Key efficacy outcomes
Palladium	2216	MC, R, DB, 3D, parallel, 2w run-in + 52w tx (+30d follow-up)	Low	MF/IND DPI (160/150 and 320/150 mcg D) MF DPI (400mcg D and 400mcg BD) FP/SAL DPI (500/50 mcg BD)	Aged 12-75y, Asthma, FEV1 ≥50% and <85%	1°: trough FEV1 (26w) 2°: ACQ-7 (26w) Other: spirometry [#] , PRO ^a , salbutamol use, exacerbations
Iridium ^b	1853 ^c 3092	MC, R, DB, 2D parallel, 2w run-in + 52w tx (+30d follow-up)	Low	MF/IND DPI (160/150 and 320/150 mcg D) FP/SAL (500/50 mcg BD)	Aged 18-75y, Asthma, FEV1 <80%	1°: trough FEV1 (26w) 2°: ACQ-7 (26w) Other: spirometry [#] , PRO ^a , salbutamol use, exacerbations
Quartz	802	MC, R, DB, 2D, parallel, 3w run-in + 12w tx (+30d follow-up)	Low	MF/IND DPI (80/150 mcg D) MF DPI (200mcg D)	Aged 12-75y, Asthma, FEV1 ≥60% and <90%	1°: trough FEV1 (12w) 2°: ACQ-7 (12w) Other: spirometry [#] , AQLQ, asthma symptoms, salbutamol use, exacerbations
O'Connor et al 2001	732	MC, R ^d , DSB, 1-2w run-in + 12w tx	Low	MF DPI (100, 200 and 400 mcg BD) FP DPI (250mcg BD)	Aged ≥12y, Moderate persistent asthma, FEV1 ≥60% and <90%	1°: FEV1 (last treatment visit) [^] 2°: PEF, FEF _{25-75%} , FVC, asthma symptoms, salbutamol use, nocturnal waking

Abbreviations: ACQ=asthma control questionnaire; AQLQ=asthma quality of life questionnaire; DB=double blind; DSB=dose blind; FEV25-75%=forced expiratory flow between 25% and 75%; FP=fluticasone propionate; FVC=forced vital capacity; GLY=glycopyrronium bromide; IND=indacaterol; MC=multicentre; MF=mometasone furoate; OL=open label; PEF=peak expiratory flow rate; PRO=patient reported outcome; R=randomised; SAL=salmeterol; 2D=double dummy; 3D=triple dummy; BD=twice daily; D=once daily; d=day; tx=treatment; w=week; y=year;

[^] Change from baseline to endpoint (last evaluable treatment visit). Treatment visits occurred after 1, 2, 4, 8, and 12 weeks of treatment.

[#] spirometry assessment included: FEV1, PEF, FVC, FEF_{25-75%}, trough FEV1 (other visits)

^a PRO (health status): ACQ-7, AQLQ-S, Work Productivity and Activity Impairment Questionnaire (WPAI-Asthma), EQ-5D-5L

^b The trial was designed to compare efficacy of MF/IND/GLY 80/150/50 and 160/150/50 vs MF/IND 160/150, 320/150 and FP/SAL 500/50

^c Total randomised to MF/IND and FP/SAL.

^d Double blind for MF dosages, but evaluator blind for FP dosage (MF vs FP) because Diskhaler placebo devices were not available.

Source: Section 2.4.1, pp49-52 of the submission.

6.5 All trials were multicentre (none in Australia), double- or dose-blind, randomised trials. The three MF/IND trials investigated the incremental benefit of MF/IND versus MF (Palladium and Quartz) or MF/IND/glycopyrronium versus MF/IND (Iridium), whereas O'Connor et al 2001 was a dose ranging study for MF. Two of the MF/IND FDC trials (Palladium and Iridium) also included a treatment comparison to high dose FP/SAL DPI (500/50) twice daily, as a secondary objective.

- The primary objective of Palladium was to demonstrate superiority of (i) medium dose MF/IND (160/150) once daily to medium dose MF (400 delivered via the Twisthaler[®]) once daily, and (ii) high dose MF/IND (320/150) once daily to high dose MF (800 delivered via the Twisthaler[®]) once daily. The secondary objective was to test non-inferiority (and then superiority) between high dose MF/IND (320/150) once daily to high dose FP/SAL DPI (500/50) twice daily.

- The primary objective of Iridium was to demonstrate superiority of medium and high doses of MF/IND/glycopyrronium once daily to corresponding medium and high doses of MF/IND once daily. A secondary objective was to test superiority of the medium and high doses of MF/IND/glycopyrronium once daily to high dose FP/SAL DPI (500/50) twice daily.
- 6.6 Overall, patients enrolled in Palladium, Quartz and O'Connor et al 2001 had mild to moderate asthma, whereas patients enrolled in Iridium had moderate to severe asthma, which is in line with the trials' primary objectives. However, there were a number of differences across the trials that may have influenced the results.
- 6.7 Differences in asthma treatments at screening and symptoms at baseline may mean that some patients 'stepped down', 'stepped across' or 'stepped up' one or more lines of treatment depending on the assigned treatment arms in the trials. Differences in prior asthma treatment may indicate that patients in the 'common comparator' arm of the indirect comparison between Quartz and O'Connor may not be comparable in terms of asthma symptom control.
- 6.8 The three MF/IND trials all included a run-in phase with either low dose FP (100) twice daily (Quartz and Palladium) or medium dose FP/SAL (250/50) twice daily (Iridium), and enrolled patients meeting the eligibility criteria at the end of the run-in period. Despite 'stepping up' to higher doses of FP in the treatment phases of Palladium and Iridium, it is possible that patients with inadequate symptom control while taking FP may achieve better symptom control by switching to an alternative ICS. If so, then this may potentially bias comparison between MF/IND and FP/SAL in favour of MF/IND.
- 6.9 For comparison to MF alone, the clinical trials provided head-to-head evidence for all of the nominated comparisons:
- i. Low dose MF/IND versus low dose MF.
 - ii. Medium dose MF/IND versus medium dose MF.
 - iii. High dose MF/IND versus high dose MF.
- 6.10 For comparison to FP/SAL DPI, the clinical trials only provided head-to-head evidence for one of the nominated comparisons:
- i. High dose MF/IND versus high dose FP/SAL DPI.
- 6.11 In the absence of direct pre-specified evidence comparing medium dose MF/IND versus medium dose FP/SAL DPI, the Sponsor conducted a series of direct post-hoc comparisons in Palladium and Iridium comparing medium dose MF/IND and high dose FP/SAL DPI. As discussed, Palladium and Quartz were not designed to test for non-inferiority between the medium and high dose formulations and therefore the results should be interpreted with caution.
- 6.12 In the absence of direct evidence comparing low dose MF/IND versus low dose FP/SAL DPI, the Sponsor conducted an indirect comparison between low dose MF/IND and

medium dose FP alone (250 twice daily), assuming MF as a common reference arm. The rationale for the indirect comparison was poorly justified and the submission did not present any evidence that subsequently linked MF/IND to the nominated comparator FP/SAL DPI. Inappropriately, the indirect comparison used MF 200 once daily as the common reference arm in one trial (Quartz) but MF 200 twice daily as the common reference arm in the other trial (O'Connor et al 2001).

- 6.13 The clinically relevant outcomes in asthma are differences in lung function tests, rescue medication use, symptom free days, percentage of patients with asthma exacerbations and quality of life. In past decisions, the PBAC has relied on lung function tests to determine non-inferiority between ICS/LABA FDCs, including change in morning peak expiratory flow (PEF), and less commonly change in pre-dose or trough FEV1.
- 6.14 The clinical claim in the submission was based on trough FEV1 at the end of the treatment period (and/or change from baseline), which was the primary endpoint across the trials. The definition of the trials trough FEV1 was measured as the mean FEV1 at 23h 15min and 23h 45min post-evening dose, at Week 12 (Quartz) or Week 26 (Palladium and Iridium). O'Connor et al 2001 reported change in FEV1 from baseline to the last evaluable treatment visit (up to Week 12). It was unclear whether the outcome measured in O'Connor et al 2001 was trough FEV1 or was adequately comparable to the FEV1 outcome measured in Quartz for the indirect comparison.
- 6.15 For comparison to FP/SAL DPI, the submission nominated a non-inferiority margin for the difference in trough FEV1 of -90 mL (or - 0.09 L), based on the pre-specified non-inferiority margin in Palladium. The threshold is lower than the non-inferiority margin of -0.15 to -0.2 L that was previously accepted by the PBAC and the minimal clinically important difference (MCID) in the Australian guidelines¹.

Comparative effectiveness

- 6.16 Table 4 summarises the results of the direct and indirect comparisons for the change in trough FEV1 from baseline and morning PEF.

¹ National Asthma Council Australia, 2019. The Australian Asthma Handbook. astmahandbook.org.au [accessed 1 April 2020].

Public Summary Document – July 2020 PBAC Meeting

Table 4: Least squares mean change (SE) from baseline in FEV1 (L) and morning PEF (L/min)

FEV1 (L)	FP	MF	Mean diff. (95% CI)		
			FP vs MF		
Medium dose FP 250 BD vs MF vs MF 100 BD (O'Connor 2001 endpoint) ^a vs MF 200 BD (O'Connor 2001 endpoint)	0.16 (0.04) 0.16 (0.04)	0.07 (0.04) 0.16 (0.04) ^b	0.09 (-0.02, 0.20) 0.00 (-0.11, 0.11) ^b		
Trough FEV1 (L)	MF/IND	FP/SAL	MF	MF/IND v FP/SAL	MF/IND v MF or FP
Low dose MF/IND 80/150 D vs MF 200 D (Quartz Wk 12) ITC: Quartz Wk 12, O'Connor 2001 endpoint	0.23 (0.013)	-	0.051(0.013)		0.18 (0.15,0.22)
vs FP 250 BD via MF 100 BD	-	-	-		0.09 (-0.03, 0.21) ^c
vs FP 250 BD via MF 200 BD	-	-	-		0.18 (0.06, 0.30)^b
Medium dose MF/IND 160/150 D vs MF 400 D (Palladium Wk 26) vs FP/SAL 500/50 BD (Palladium Wk 26) vs FP/SAL 500/50 BD (Iridium Wk 26)	0.29 (0.016) 0.29 (0.016) 0.22 (0.013)	- 0.25 (0.016) 0.20 (0.013)	0.075(0.016)	0.04(-0.00,0.09) 0.02(-0.01,0.06)	0.21 (0.17, 0.26)
High dose MF/IND 320/150 D vs MF 400 BD (Palladium Wk 26) vs FP/SAL 500/50 BD Palladium (Wk 26) vs FP/SAL: 500/50 BD (Iridium Wk 26)	0.28 (0.016) 0.28 (0.016) 0.26 (0.013)	- 0.25 (0.016) 0.20 (0.013)	0.15 (0.016)	0.04(-0.01,0.08) 0.05 (0.02,0.09)	0.13 (0.09, 0.18)
Pre-dose morning PEF (L/min)	MF/IND	FP/SAL	MF	MF/IND v FP/SAL	MF/IND v MF or FP
Low dose MF/IND 80/150 D vs MF 200 D (Quartz Wk 12)	31.0 (2.0)		3.8 (2.0)		27.2 (22.1, 32.4)
Medium dose MF/IND 160/150 D vs MF 400 D (Palladium Wk 52) vs FP/SAL 500/50 BD (Palladium Wk 52) vs FP/SAL 500/50 BD (Iridium Wk 52)	36.9 (2.2) 36.9 (2.2) 25.6 (2.1)	- 28.3 (2.2) 12.7 (2.1)	6.7 (2.2)	8.6 (2.4, 14.8) 12.9 (7.2, 18.6)	30.2 (24.2, 36.3)
High dose MF/IND 320/150 D vs MF 400 BD (Palladium Wk 52) vs FP/SAL 500/50 BD (Palladium Wk 52) vs FP/SAL 500/50 BD (Iridium Wk 52)	42.1 (2.2) 42.1 (2.2) 28.8 (2.1)	- 28.3 (2.2) 12.7 (2.1)	13.4 (2.2)	13.8 (7.7, 19.8) 16.1 (10.4, 21.8)	28.7 (22.7, 34.8)

Abbreviations: FAS=full analysis set; FEV1=forced expiratory volume in one second; FP=fluticasone propionate; IND=indacaterol; ITC=indirect treatment comparison; MF=mometasone furoate; PEF=peak expiratory flow; SA=sensitivity analysis; SAL=salmeterol; BD=twice daily; D=once daily; wk=week;

^a The primary outcome reported in O'Connor et al 2001 is change from baseline in FEV1 at endpoint (last evaluable visit), which could be Wk 2, 4, 6, 8, 10 or 12. A sensitivity analysis was conducted during the evaluation in which data for mean change (SE) from baseline in FEV1 at Wk 12 was read from Figure 1 in O'Connor et al 2001.

^a The submission presented mean difference between MF 200 bd (medium dose) and FP 250 bd (medium dose) from O'Connor et al 2001 for its indirect comparison, however the common comparator between O'Connor et al 2001 and QUARTZ was MF 100 bd (low dose), hence mean difference between MF 100 bd and FP 250 bd was calculated during the evaluation.

^b corrected during the evaluation. O'Connor et al 2001 reported mean change (SE) from baseline at endpoint in FEV1 for MF 200 bd as 0.16 (0.04). The submission incorrectly used 0.16 (0.05).

^c Indirect comparison was derived during the evaluation for the common comparator (MF 100 bd).

Source: Table 2.35, pp86-87, Table 2.56, pp108-109, Table 2.83, p133, Tables 2.104-105, pp149-152 of the submission, Attachment 3 of the submission.

6.17 MF/IND versus MF

The three doses of MF/IND (80/150 once daily, 160/150 once daily and 320/150 once daily) demonstrated a statistically significantly larger improvement in trough FEV1 compared to the corresponding doses of MF (200 once daily, 400 once daily, and 400 twice daily).

A number of secondary outcomes also demonstrated a statistically significant difference in favour of MF/IND, including change in pre-dose morning PEF.

6.18 High dose MF/IND versus high dose FP/SAL

In Palladium, the treatment difference between MF/IND (320/150) once daily and FP/SAL DPI (500/50) twice daily met the test for non-inferiority given the lower 95%CI of the primary endpoint (-0.01 L) was greater than -0.09 L.

A post-hoc analysis in the Iridium trial found MF/IND (320/150) once daily had a statistically significantly larger improvement in trough FEV1 compared to FP/SAL DPI 500/50 twice daily.

A comparison of secondary outcomes (pre-specified and post-hoc) across both Palladium and Iridium generally favoured MF/IND (320/150) compared to FP/SAL DPI (500/50), including change in pre-dose morning PEF. The small statistically significant difference in PEF was unlikely to be clinically relevant. There was some variation in the magnitude of the treatment effect for secondary outcomes across the Palladium and Iridium trials, which was likely due to differences in the patient characteristics and trial design.

6.19 Medium dose MF/IND versus high dose FP/SAL

Post-hoc analysis of Palladium and Iridium showed there was no statistically significant difference between medium dose MF/IND (160/150) once daily and high dose FP/SAL (500/50) DPI twice daily in regards to mean change in trough FEV1. There was however, a significantly larger improvement with MF/IND (160/150) for pre-dose morning PEF and a number of other secondary outcomes. The small statistically significant difference in PEF was unlikely to be clinically relevant.

As discussed above, none of the trials were designed to compare the medium and high dose FDCs and therefore the results should be interpreted with caution. The results of these trials also showed there was a similar improvement in trough FEV1 (and other secondary outcomes) for the medium and high dose MF/IND.

6.20 Low dose MF/IND versus medium dose FP alone

Based on the indirect comparison presented, there was a significantly larger improvement in trough FEV1 for MF/IND (80/150) once daily compared to FP (250) twice daily.

The result requires consideration given there are some differences across the trials in terms of population and outcome, and the submission did not assume the same common reference arm from each trial. A sensitivity analysis assuming a total daily dose of MF (200) as the common reference showed a smaller difference favouring MF/IND (80/150) over FP (250) that did not reach statistical significance.

Comparative harms

- 6.21 The submission presented safety outcomes reported in Quartz, Palladium and Iridium by treatment arm. Like efficacy outcomes, the trials did not provide a comparison between low or medium dose MF/IND with low or medium dose FP/SAL for safety outcomes.
- 6.22 Overall, there were no significant safety issues identified for MF/IND, however across the trials there were variations, with a higher proportion of patients with ≥ 1 adverse events (AEs) in Palladium (68%) and Iridium (76%), which were reported to 52 weeks compared to Quartz (35%) and O'Connor et al (26%) at 12 weeks.
- 6.23 The majority of AEs were mild to moderate in severity. The most frequently reported serious AEs related to infections and respiratory disorders. One death was reported for the MF arm in Palladium and four deaths for the high dose MF/IND group in Iridium, however none related to the trial treatments.

Benefits/harms

- 6.24 There were no expected clinically meaningful differences between MF/IND and FP/SAL in efficacy and safety when used for the treatment of asthma in patients who experience exacerbations or uncontrolled asthma while receiving treatment with oral corticosteroids or optimal doses of ICS.

Clinical claim

- 6.25 Based on the evidence presented, the submission described MF/IND as at least non-inferior/equivalent in terms of effectiveness and safety compared with equivalent doses of FP/SAL DPI in patients with asthma, and proposed the following:
- MF/IND 80/150 one actuation once daily is equivalent to FP/SAL DPI 100/50 one actuation twice daily.
 - MF/IND 160/150 one actuation once daily is equivalent to FP/SAL DPI 250/50 one actuation twice daily.
 - MF/IND 320/150 one actuation once daily is equivalent to FP/SAL DPI 500/50 one actuation twice daily.
- 6.26 The clinical trial evidence presented in the submission supported the claim of non-inferior effectiveness for the high dose MF/IND (320/150), but the claim requires consideration for the other doses.

For the medium dose, the post-hoc analyses showed similar efficacy between the medium dose MF/IND (160/150) once daily and high dose FP/SAL DPI (500/50) twice daily. The trials were not designed to compare those formulations and therefore the submission “accepted” equivalence between medium dose MF/IND (160/150) and medium dose FP/SAL DPI (250/50). The PBAC considered this may be a reasonable conclusion based on the evidence available.

For the low dose, the submission did not present any evidence linking low dose MF/IND (80/150) once daily to low dose FP/SAL DPI (100/50) twice daily. An indirect comparison conducted during the evaluation using the same common reference arm, suggested low dose MF/IND (80/150) had improved or similar efficacy to ‘medium’ dose FP (250) twice daily. The clinical claim is therefore dependent on accepting that low dose FP/SAL (100/50) is superior or at least not inferior to FP (250), which may be a reasonable conclusion². The PBAC agreed with the evaluation that this may be a reasonable conclusion based on the evidence available.

- 6.27 The PBAC considered that the claim of MF/IND being at least non-inferior/equivalent in terms of comparative effectiveness with equivalent doses of FP/SAL DPI was reasonable.
- 6.28 The PBAC considered that the claim of MF/IND being at least non-inferior/equivalent in terms of comparative safety was reasonable.

Economic analysis

- 6.29 The submission presented a cost-minimisation analysis based on AEMP (per day) between the three formulations of MF/IND and the corresponding formulations of FP/SAL DPI. The analysis assumed no additional costs or cost-offsets.
- 6.30 The submission proposed the following equi-effective doses based on the trial evidence presented:
- MF/IND 80/150 one actuation once daily = FP/SAL 100/50 DPI one actuation twice daily
 - MF/IND 160/150 one actuation once daily = FP/SAL 250/50 DPI one actuation twice daily
 - MF/IND 320/150 one actuation once daily = FP/SAL 500/50 DPI one actuation twice daily
- 6.31 The submission did not explicitly nominate equi-effective doses for the other ICS/LABA FDC comparators, but assumed that the MF/IND will substitute 1:1 for other DPI products in the financial estimates at the dose relativities shown in Table 5. Based on the Therapeutic Relativities, the following dose relativities to MDI products would also apply.

² Condemni et al. 1999. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. *Annals of Allergy, Asthma & Immunology* 82(4): 383-389.

Public Summary Document – July 2020 PBAC Meeting

Table 5: Available ICS/LABA FDCs on the PBS, at comparable doses to Ateectura® Breezhaler® DPI capsules

	Comparable DPI formulations & doses	Comparable MDI formulations & doses
MF/IND 80/150, D	FP/SAL 100/50 (Seretide Accuhaler®), BD BUD/FOR 100/6 (Symbicort® Turbuhaler®), 2 BD	FP/SAL 50/25 (Seretide®), 2 BD BUD/FOR 50/3 (Symbicort Rapihaler®), 4 BD FP/FOR 50/5 (Flutiform®), 2 BD
MF/IND 160/150, D	FP/SAL 250/50 (Seretide Accuhaler®), BD BUD/FOR 200/6 (Symbicort® Turbuhaler®), 2 BD FF/VI 100/25 (Breo Ellipta®), D	FP/SAL 125/25 (Seretide®), 2 BD BUD/FOR 100/3 (Symbicort Rapihaler®), 4 BD FP/FOR 125/5 (Flutiform®), 2 BD
MF/IND 360/150, D	FP/SAL 500/50 (Seretide Accuhaler®), BD BUD/FOR 400/12 (Symbicort® Turbuhaler®), 2 BD FF/VI 200/25 (Breo Ellipta®), D	FP/SAL 250/50 (Seretide®), 2 BD BUD/FOR 200/6 (Symbicort Rapihaler®), 4 BD FP/FOR 250/10 (Flutiform®), 2 BD

Abbreviations: BUD=budesonide; DPI=dry powder inhaler; FOR=formoterol; FF=fluticasone furoate; FP=fluticasone propionate; ICS inhaled corticosteroid; IND=indacaterol; LABA=long acting beta2-adrenergic agonist; MDI=metered dose inhaler; MF=mometasone furoate; SAL=salmeterol; VI=vilanterol; D=once daily; BD=twice daily;

Source: Table 1.4, p34 of the submission, Therapeutic Relativity Sheets and available PSDs

6.32 At the requested price, the three formulations of MF/IND are cost equivalent to the corresponding formulations of FP/SAL DPI, and each provides 30 days of treatment.

6.33 A cost-minimisation analysis conducted during the evaluation versus other ICS/LABA FDCs at comparable doses (see Table 5) indicated the following comparators are less costly:

- For low dose MF/IND (80/150): fluticasone propionate with formoterol (FP/FOR) 50/5, DPMQ = \$37.30.
- For medium dose MF/IND (160/150): budesonide with formoterol (BUD/FOR) 200/6 DPI, DPMQ = \$44.79; and FP/FOR 125/5, DPMQ = \$45.16.
- For high dose MF/IND (320/150): FP/FOR 250/10, DPMQ = \$60.07.

Drug cost/patient/year

6.34 The annual cost of MF/IND per patient is \$510.74 for low dose formulation, \$592.19 for medium dose formulation and \$752.17 for the high dose formulation. These calculations assume 12.18 scripts per year at the requested DPMQs.

Estimated PBS usage & financial implications

6.35 This submission was not considered by DUSC. The estimated financial impact of the proposed listing assumed a market share approach with other ICS/LABA FDC products delivered via DPI formulations.

6.36 Table 6 summarises the key inputs used in the financial estimates.

Table 6: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Annual market growth of ICS/LABA DPI	Average decline 3-5% per year; Source: PBS statistics 2015 to 2019. Average script numbers from the past 5 years (2016 to 2019)	Annual market growth of FF/VI DPI may be an underestimate. PBS items serviced for asthma and dual restriction asthma and COPD from 2016 to

Public Summary Document – July 2020 PBAC Meeting

Parameter	Value applied and source	Comment	
		2019 indicate FF/VI scripts was increasing (15% in 2017, 19.7% in 2018, and 21.6% in 2019).	
Substitution rates for ICS/LABA DPI	FP/SAL DPI and BUD/FOR DPI: 12-20% (Yr 1 to Yr 6) FF/VI DPI: 6-10% (Yr 1 to Yr 6) Source: assumed higher rate of substitution for FP/SAL and BUD/FOR as older products and less switching from FF/VI given its more recent PBS listing in 2017.	Could not be verified. However, doubling the substitution rate increases the net savings to the PBS/RPBS by 76% (corrected for 1:1 substitution).	
% asthma use in dual restriction (asthma and COPD)	2015 - 2017: 36-38% 2018 - 2019 (projected): 42-44% Source: PBS 10% sample data ^a	Could not be verified. However, assuming 100% asthma use in dual restriction PBS items (i.e. more expensive items including FP/SAL 500/50, BUD/FOR 400/12 and FF/VI 100/25 are substituted for MF/IND) increases the net savings to the PBS by 142%.	
MF/IND DPI dose form substitution	Assumed 1:1 replacement	Despite the lack of clinical evidence in the submission, the proposed dose equivalence between MF/IND and other substituted ICS/LABA DPI FDCs (aside from FP/SAL) was generally reasonable based on Therapeutic Relativities. Despite the assumed 1:1 substitution, the submission inconsistently estimated the number of substituted MF/IND scripts from a proportional 'split' of the projected ICS/LABA market, which underestimated the impact of listing MF/IND.	
	MF/IND		ICS/LABA
	80/150		FP/SAL 100/50 BUD/FOR 100/6
	160/150		FP/SAL 250/50 BUD/FOR 200/6 FF/VI 100/25
	320/150	FP/SAL 500/50 BUD/FOR 400/12 FF/VI 200/25	
DPMQ MF/IND DPI	Requested price: 80/150 = \$41.95; 160/150 = \$48.64; 320/150 = \$61.78	Reasonable	
DPMQ ICS/LABA DPI	FP/SAL: 100/50 = \$41.95; 250/50 = \$48.64; 500/50 = \$61.78 BUD/FOR: 100/6 = \$48.06; 200/6 = \$44.79; 400/12 = \$64.06 FF/VI: 100/25 = \$56.51; 200/25 = \$72.01 Source: PBS items 8430Q, 8431R, 8432T, 8796Y, 8750M, 11301T, 8625Y, 11273H, 11129R, 11124L	Reasonable	
Patient copayment	PBS: \$20.02; RPBS: \$4.80 Source: Weighted average across general and concessional PBS/RPBS services	Reasonable	
MBS costs	\$0	Reasonable	

Abbreviations: BUD=budesonide; DPI=dry powder inhalation; FOR=formoterol; FDC=fixed dose combination; FF=fluticasone furoate; FP=fluticasone propionate; ICS=inhaled corticosteroid; LABA=long acting beta2-agonst; IND=indacaterol; MF=mometasone furoate; VI=vilanterol; SAL=salmeterol; Yr=year;

^a Weighted average calculated from known usage in Asthma-only restriction and Total market. Used to adjust Medicare statistics data to exclude COPD usage from the defined market. Details of calculation are provided in Attachment 9; PBS summary worksheet.

^b 100% total usage from dual restriction (asthma and COPD).

Source: Sections 4.1 to 4.2, pp158-165 of the submission and Attachment 9 Utilisation and cost model.xlsm

6.37 The financial estimates presented in the submission included a calculation error associated with the substitution of the nominated comparators. The submission correctly estimated the reduction in ICS/LABA scripts based on the assumed uptake rate (or % ICS/LABA FDCs displaced) for MF/IND, but incorrectly estimated the increase in the number of MF/IND scripts by multiplying the annual total scripts displaced by the proportional 'split' of the projected annual script numbers.

Public Summary Document – July 2020 PBAC Meeting

6.38 Overall, this error did not favour MF/IND because the submission overestimated the net cost of MF/IND to the PBS. Table 7 provides the uncorrected results presented in the submission and corrected results assuming the stated 1:1 substitution rate to comparator ICS/LABA FDCs.

Table 7: Estimated use and financial implications to the PBS/RPBS of MF/IND

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of substituted scripts						
Total scripts displaced from existing ICS/LABA FDC						
Low dose ICS/LABA FDCs						
Medium dose ICS/LABA FDCs						
High dose ICS/LABA FDCs						
ICS/LABA net PBS/RPBS cost	-\$	-\$	-\$	-\$	-\$	-\$
Estimated number of MF/IND scripts#						
Total scripts replaced and substituted by MF/IND						
MF/IND 80/150						
MF/IND 160/150						
MF/IND 320/150						
MF/IND PBS/RPBS cost	\$	\$	\$	\$	\$	\$
MF/IND patient co-payment	\$	\$	\$	\$	\$	\$
MF/IND net PBS/RPBS cost	\$	\$	\$	\$	\$	\$
Estimated number of MF/IND scripts (corrected for 1:1 substitution)^						
Total scripts replaced and substituted by MF/IND						
MF/IND 80/150						
MF/IND 160/150						
MF/IND 320/150						
MF/IND PBS/RPBS cost	\$	\$	\$	\$	\$	\$
MF/IND patient co-payment	\$	\$	\$	\$	\$	\$
MF/IND net PBS/RPBS cost	\$	\$	\$	\$	\$	\$
Estimated financial implication to government						
PBS/RPBS cost	\$	\$	\$	\$	\$	\$
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost to health budget	\$	\$	\$	\$	\$	\$
Estimated financial implication to government (corrected for 1:1 substitution)						
PBS/RPBS cost	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to health budget	-\$	-\$	-\$	-\$	-\$	-\$

Abbreviations: BUD=budesonide; DPI=dry powder inhalation; FOR=formoterol; FDC=fixed dose combination; FF=fluticasone furoate; FP=fluticasone propionate; ICS=inhaled corticosteroid; LABA=long acting beta2-agonst; IND=indacaterol; MF=mometasone furoate; VI=vilanterol; SAL=salmeterol; Yr=year;

The submission estimated the number of MF/IND scripts from the proportional 'split' of the projected annual ICS/LABA DPI market that will be substituted. Further, the submission erroneously applied the (Yr-1) proportions i.e. Yr6 had used Yr5 proportions (3a. Script-new tab -> cells L113 to Q120 should reference 2d. Scripts-market tab -> cells S245 to X252 in), which was corrected during the evaluation. The error became obsolete when the financial estimates were corrected for the submission's assumed 1:1 substitution of MF/IND scripts.

^ Corrected for the assumed 1:1 substitution between the equivalent dose inhalers, i.e., low/median/high dose of ICS/LABA DPI displaced is equivalent to the number of scripts for MF/IND replaced.

Source: Tables 4.15 to 4.18, pp168-171 of the submission and Attachment 9; PBS summary worksheet.

6.39 At the requested price, the submission estimated the net cost to the PBS/RPBS for the proposed listing of MF/IND was less than \$10 million (uncorrected) over the first 6

years. After correcting for the assumed 1:1 substitution rate with comparator DPI formulations, the net cost was -less than \$10 million (cost saving) over the first 6 years. At the requested price, MF/IND will mostly substitute for costlier ICS/LABA DPI formulations.

- 6.40 The financial estimates do not take account of the following uncertainties:
- The estimates do not include potential substitution with MDI products.
 - The requested price for MF/IND is higher than corresponding doses of some other ICS/LABA FDCs.
 - The results are sensitive to the assumed decline and growth of different comparator ICS/LABA FDCs. Assuming no change in the market reduces the estimated cost offsets by substituting less for the most expensive alternatives that were predicted to grow (e.g. Breo[®] Ellipta[®](FF/VI)).
- 6.41 The PBAC noted that the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis. The PBAC considered that on this basis, the concerns raised in paragraph 6.40 were adequately addressed.

Quality Use of Medicines

- 6.42 The submission stated that the Sponsor has no quality use of medicine activities planned for MF/IND. The Breezhaler[®] device is not new to Australian prescribers, and is available for COPD treatments (Onbrez[®] containing IND, and Ultibro[®] FDC containing IND/glycopyrronium).
- 6.43 In 2015, DUSC considered that given there are “already many different inhalers available which require different inhaler techniques... adding to the number of inhalers available can cause confusion and increases the likelihood of poor inhaler technique” (Tiotropium DUSC ADV July 2015 PBAC meeting). If listed, Ateectura[®] Breezhaler[®] will be the first ICS/LABA FDC listed for asthma that requires capsules to be loaded by the patient prior to use, which may add to this confusion for patients. The pre-PBAC response stated that the National Asthma Council is aware of the upcoming asthma indication and an instruction video on use of the device is available on their webpage.

Financial Management – Risk Sharing Arrangements

- 6.44 The Sponsor stated that the proposed listing was not expected to require additional risk sharing arrangements. The listing of MF/IND is proposed on a cost-minimisation basis in a market with drugs which currently do not have ‘list and effective’ prices or expenditure caps, and the Commonwealth is not expected to be exposed to any greater risk or expenditure than from currently listed drugs if MF/IND is listed.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of the fixed dose combination (FDC) of mometasone furoate (MF) with indacaterol (IND) for the maintenance treatment of asthma. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of MF/IND would be acceptable if it were cost-minimised against the least costly inhaled corticosteroid (ICS) with long-acting beta2 agonist (LABA) FDC product for each MF/IND strength.
- 7.2 The PBAC noted the input from Asthma Australia supporting MF/IND listing for maintenance treatment of asthma.
- 7.3 The PBAC noted the nomination of fluticasone propionate (FP)/salmeterol (SAL) FDC dry powder inhaler (DPI) as the primary comparator and the submissions argument that the most likely replacements for MF/IND would be within DPI formulations. The PBAC reaffirmed its previous recommendation that all ICS/LABA FDCs including metered dose inhaler (MDI) and DPI formulations at comparable doses are relevant comparators (see paragraph 5.2).
- 7.4 The PBAC noted the data presented from three head-to-head randomised clinical trials comparing MF/IND to MF and/or FP/SAL DPI (Palladium, Iridium, Quartz), and one head-to-head clinical trial comparing MF to FP (O'Connor et al 2001). The PBAC considered that the data presented adequately supported the claim of MF/IND being at least non-inferior/equivalent in terms of comparative effectiveness and safety when compared to equivalent doses of FP/SAL DPI.
- 7.5 The PBAC noted that the submission presented a cost-minimisation analysis between the three formulations of MF/IND and the corresponding formulations of FP/SAL DPI. The PBAC accepted the following equi-effective doses as the basis for the analysis:
- MF/IND 80/150 one actuation once daily = FP/SAL 100/50 DPI one actuation twice daily
 - MF/IND 160/150 one actuation once daily = FP/SAL 250/50 DPI one actuation twice daily
 - MF/IND 320/150 one actuation once daily = FP/SAL 500/50 DPI one actuation twice daily.

However, the PBAC considered that the cost-minimisation analysis should be against the least costly ICS/LABA FDC product for each MF/IND strength at the comparable doses outlined in Table 5.

- 7.6 The PBAC noted the concerns raised regarding the financial estimates not including potential substitution with MDI products and the requested price for MF/IND (see paragraph 6.40) and considered these were addressed by the Committee's recommendation that listing should be on a cost-minimisation basis against the least costly ICS/LABA FDC as outlined in the paragraph 7.5.

Public Summary Document – July 2020 PBAC Meeting

- 7.7 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* MF/IND should be treated as interchangeable on an individual basis with other ICS/LABA FDC products on the PBS including FP/SAL, BUD/FOR, FP/FOR and FF/VIL.
- 7.8 The PBAC advised that MF/IND is suitable for prescribing by nurse practitioners.
- 7.9 The PBAC recommended that the Early Supply Rule should not apply.
- 7.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because MF/IND is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over FP/SAL, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Add new medicinal product as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Proprietary Name and Manufacturer	
MOMETASONE FUROATE + INDACATEROL						
Indacaterol 150 microgram + mometasone furoate 80 microgram powder for inhalation, 30 capsules	NEW	1	1	5	Aectura Breezhaler 150/80	Novartis
Indacaterol 150 microgram + mometasone furoate 160 microgram powder for inhalation, 30 capsules	NEW	1	1	5	Aectura Breezhaler 150/160	
Indacaterol 150 microgram + mometasone furoate 320 microgram powder for inhalation, 30 capsules	NEW	1	1	5	Aectura Breezhaler 150/320	

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners
Restriction Type/ Method: <input checked="" type="checkbox"/> Authority Required – Streamlined (NEW CODE)
Episodicity: [blank]
Severity: [blank]
Condition: Asthma
Indication: Asthma
Clinical criteria:
Patient must have previously had frequent episodes of asthma while receiving treatment with oral corticosteroids or optimal doses of inhaled corticosteroids.
AND
Population criteria:
Patient must be aged 12 years or over.

Public Summary Document – July 2020 PBAC Meeting

Administrative Advice This product is not indicated for the initiation of treatment in asthma.
Administrative Advice This product is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD).
Administrative Advice: The patient must not be on a concomitant single agent long-acting-beta-2-agonist (LABA).
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
Administrative Advice: Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

During the TGA evaluation the recommendation was that the MF/IND doses be changed from metered dose to delivered dose levels and the PSD does not reflect this change. As such, it is important to note that the doses referenced in the PI and the packaging will reflect the following changes: MF/IND 80/150 mcg is now 567/125, MF/IND 160/150 mcg is now 127.5/125 and MF/IND 320/150 is now 260/125. Additionally while the PSD indicates an error in the estimates, discussions with the Department after PBAC consideration confirmed there were no errors as reported in paragraphs 6.37 and 6.38.