An addendum to this minute has been included at the end of the document.

5.07 MOMETASONE FUROATE WITH INDACATEROL and GLYCOPYRRONIUM, Capsule containing powder for oral inhalation mometasone furoate 80 micrograms with indacaterol 150 micrograms (as acetate) with glycopyrronium 50 micrograms (as bromide) (for use in Breezhaler®), Capsule containing powder for oral inhalation mometasone furoate 160 micrograms with indacaterol 150 micrograms (as acetate) with glycopyrronium 50 micrograms (as bromide) (for use in Breezhaler®), Enerzair® Breezhaler®, Novartis Pharmaceuticals Australia Pty Limited.

1 Purpose of submission

1.1 The submission requested an Authority Required (Streamlined) listing of Enerzair® Breezhaler®, fixed dose combination (FDC) of mometasone furoate (MF), an inhaled corticosteroid QA(ICS) with indacaterol acetate (IND), a long-acting beta2 agonist (LABA) and glycopyrronium (GLY), a long acting muscarinic antagonist (LAMA) for maintenance therapy of severe asthma.

1.2 The proposed listing is for two strengths of capsules containing powder for oral inhalation with different doses of MF: medium dose MF/IND/GLY 80/150/50 and high dose MF/IND/GLY 160/150/50. Patients must load a capsule into the Breezhaler® device, a single dose dry powder inhaler (DPI), prior to each use. In the PBAC Public Summary Document (PSD), 'medium' dose ICS refers to 800 mcg of budesonide per day or equivalent and 'high' dose ICS refers to 1600 mcg of budesonide per day or equivalent, in line with Australian and international guidelines.

1.3 If recommended, Enerzair® Breezhaler® (MF/IND/GLY) will be the first triple therapy ICS/LABA/LAMA FDC available on the PBS for treatment of severe asthma, and one of the first inhalers listed for asthma that requires capsules to be loaded by the patient prior to use. None of the individual components of MF/IND/GLY are listed on the PBS for asthma, but none are new drugs to the PBAC. Triple therapy is PBS listed for severe asthma, but patients must use multiple inhalers, e.g. ICS/LABA FDC + tiotropium (TIO).

1.4 The basis of the requested listing was a cost-minimisation analysis to high dose fluticasone propionate with salmeterol (FP/SAL) FDC Seretide® Accuhaler® plus tiotropium (TIO) Spiriva® Respimat®, which included a 'small' price advantage for MF/IND/GLY. The evaluation also presents a cost-minimisation analysis versus other relevant combinations of products (e.g. ICS/LABA FDC plus LAMA).

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

Component	Description
Population	Asthma patients who are currently uncontrolled on ICS/LABA treatments
Intervention	Enerzair® Breezhaler®, a once-daily dry powder inhaler (capsules) containing mometasone (MF), indacaterol (IND) and glycopyrronium (GLY), available in two strengths:150/50/80 mcg per actuation ("medium") or 150/50/160 mcg per actuation ("high").
Comparator	The submission stated that medium and high dose MF/IND/GLY FDC will substitute for high dose ICS/LABA FDCs (DPI formulations only) plus LAMA on the PBS, including: (i) FP/SAL 500/50 mcg one actuation twice daily (Seretide® Accuhaler®) plus TIO 2.5 mcg two inhalations once daily (Spiriva® Respimat®). Clinical evidence presented informs the following comparisons: - MF/IND/GLY 80/150/50 mcg one actuation once daily versus FP/SAL 500/50 mcg one actuation twice daily + TIO 2.5 mcg two actuations once daily - MF/IND/GLY 160/150/50 mcg one actuation once daily versus FP/SAL 500/50 mcg one actuation twice daily + TIO 2.5 mcg two actuations once daily
Outcomes	AQLQ; FEV1; FVC; FEF_{25-75}; ACQ-7; exacerbations; rescue medication use; PEF; symptoms; health status
Clinical claim	MF/IND/GLY is non-inferior to salmeterol/fluticasone plus tiotropium in the treatment of patients with asthma who remain uncontrolled on LABA/ICS

Abbreviations: ACQ-7=Asthma Control Questionnaire; AQLQ=Asthma Quality of Life Questionnaire; DPI=dry powder inhaler; FDC=fixed dose combination; FEF_{25-75}=forced expiratory flow; FEV1=forced expiratory volume in one second; FP=fluticasone propionate; FVC=forced vital capacity; GLY=glycopyrronium; ICS=inhaled corticosteroid; IND=indacaterol; LABA=long-acting beta2-adrenergic agonist; LAMA=long-acting muscarinic receptor antagonist; MF=mometasone furoate; PEF=peak expiratory flow; SAL=salmeterol; TIO=tiotropium;
Source: Table 1.1, p20 of the submission.

2 Background

Registration status

2.1 TGA status at time of PBAC consideration: Not registered.

2.2 The submission was made under the TGA/PBAC Parallel Process. At the time of the evaluation, the TGA Clinical Evaluation Report (CER) (round 1) was available. The TGA CER (round 2) was received on 2 June 2020.

2.3 The proposed TGA indication for MF/IND/GLY is:

'as a once-daily maintenance treatment of asthma, and to reduce asthma exacerbations, in adults not adequately controlled with a maintenance combination of a long-acting beta2-agonist and an inhaled corticosteroid.'

2.4 The pivotal clinical evidence in the TGA CER round 1 was the Iridium trial (Clinical Study Report I, 26 week results only), comparing medium and high dose MF/IND/GLY to medium and high dose MF/IND. When the TGA dossier was submitted, results at 52 weeks (Iridium Clinical Study Report II) and results of the Argon trial, comparing medium and high dose MF/INF/GLY to high dose FP/SAL+TIO, were unavailable.

2.5 Based on 26-week results in Iridium, the TGA evaluator concluded that 'the evidence to support the additional benefit of GLY on top of MF/IND … in patients whose asthma was poorly controlled with medium and high dose LABA/ICS was not adequate with only modest improvements in trough FEV1 and no significant reduction in asthma exacerbations'. Given this, the TGA evaluator recommended approval for marketing authorisation cannot be granted but the final decision could be taken after review of i) 52 week efficacy results in Iridium, and ii) results from the Argon trial. The ESC noted that these data were provided in the TGA CER (round 2).

2.6 The Pre-Sub-Committee Response (PSCR) stated that the MF/IND/GLY application had progressed through the registration process and a positive round 2 evaluation was issued by the TGA. The ESC noted that after reviewing the additional data provided in the TGA CER (round 2), the TGA evaluator (pp 100-101) recommended MF/IND/GLY be approved for the indication proposed in paragraph 2.3.

2.7 The pre-PBAC response included a TGA delegate file note (dated 18 June 2020). The pre-PBAC response indicated that the conditions of TGA registration would include changes to labelling and product information (PI), such that the delivered dose would be displayed rather than the metered dose, as follows:

Current labelled dose (MF/IND/GLY mcg)	Updated labelled dose (MF/IND/GLY mcg)
80/150/50	68/114/46
160/150/50	136/114/46

2.8 The PBAC noted the TGA delegate file note stated the submitted data indicated a positive benefit-risk profile for the high dose MF/IND/GLY for the proposed indication, but did not support the proposed use of the medium dose MF/IND/GLY. The TGA advised that the application would be considered at the August 2020 Advisory Committee on Medicines (ACM) meeting.

Previous PBAC consideration

2.9 This is the first PBAC submission for MF/IND/GLY. None of the components are currently available on the PBS for asthma, either individually or in combination products. The PBAC however, recommended MF delivered via a multidose 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) is equi-effective to FP 250 mcg twice daily.
- MF 400 mcg twice daily is equi-effective to FP 500 mcg twice daily.

2.10 The PBAC Guidelines (v5) state it is preferable that the individual components of FDCs are listed on the PBS, however this is less relevant for FDC inhalers for asthma given restrictions do not require patients to be stabilised on the components prior to use. In the context of ICS/LABA FDCs, in March 2014 the PBAC considered 'in view of significant clinical experience … and the availability of advice on switching from existing products… concerns regarding the availability of the FDC in the absence of the

components were addressed' (paragraph 6.23, fluticasone furoate (FF) with vilanterol (VI) FDC, PSD March 2014 PBAC meeting).

2.11 In a separate submission to the July 2020 PBAC meeting, the sponsor requested PBS listing for Atectura® Breezhaler® dry powder capsules for inhalation containing MF/IND at the July 2020 meeting for asthma, which contain the same ICS and LABA components as Enerzair® Breezhaler® dry powder capsules delivered using the same device. In that submission, the sponsor requested low, medium and high dose MF/IND based on cost-minimisation to corresponding low, medium and high dose FP/SAL.

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

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
INDACATEROL + GLYCOPYRRONIUM + MOMETASONE indacaterol ~~150~~ 114 microgram + glycopyrronium ~~50~~ 46 microgram + mometasone furoate ~~80~~ 68 microgram, powder for inhalation, 30 capsules	NEW	1	30	5	$97.50	Enerzair Breezhaler 114/46/68 ~~150/50/80~~
indacaterol ~~150~~ 114 microgram + glycopyrronium ~~50~~ 46 microgram + mometasone furoate ~~160~~ 136 microgram, powder for inhalation, 30 capsules	NEW	1	30	5	$97.50	Enerzair Breezhaler 114/68/136 ~~150/50/160~~

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners ☒*Nurse practitioners*
Restriction type / Method: ☒ Authority Required – Streamlined *(new code)*
Episodicity: ~~Daily~~ *[blank]*
Severity: Severe
Condition: asthma
Indication: Severe asthma
Clinical criteria:
Patient must have experienced at least one severe exacerbation, which has required documented use of systemic corticosteroids, in the previous 12 months while receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented
Population criteria:
Patient must be aged 18 years or over
Prescribing Instructions: Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long acting beta-2 agonist.
Administrative Advice: *Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at ~~www.humanservices.gov.au or~~ www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).*
Administrative Advice: *This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD)*
Administrative Advice: *This product is not indicated for the initiation of treatment in asthma*
Administrative Advice: *The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy*
Administrative Advice: *A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.*
Administrative Advice: *A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.*
Administrative Advice: *An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.*

3.2 The pre-PBAC response stated the TGA requires the label and PI to show the delivered dose rather than the metered dose and that the Australian Medicines Terminology (AMT) assigned to this new drug product will be revised. In the requested listing shown above, the drug doses have been revised for this PSD in accordance with the TGA labelling, and the anticipated AMT revision.

3.3 The sponsor requested a flat pricing structure for both doses of MF/IND/GLY including a 'small' price advantage compared to high dose FP/SAL DPI plus TIO at the nominated equi-effective doses. The requested flat pricing structure was based the clinical claim that both medium and high dose MF/IND/GLY are non-inferior to high dose FP/SAL plus TIO. No special pricing arrangement was proposed.

3.4 The sponsor requested an Authority Required (Streamlined) listing for two formulations: medium dose MF/IND/GLY (80/150/50) and high dose MF/IND/GLY (160/150/50). This is consistent with the Streamline Authority Required listings for ICS/LABA FDC products used for the treatment of asthma. As the first triple therapy FDC for asthma, a more restrictive Authority Required listing or limits on prescriber type may be justified to minimise inappropriate use particularly in patients with less severe asthma otherwise managed on ICS or ICS/LABA. The PSCR argued that an Authority Required (Streamlined) listing was appropriate and is consistent with other FDC products such as the triple therapy fluticasone furoate with vilanterol and umeclidinium (FF/VI/UMEC) (Trelegy® Ellipta®) for chronic obstructive pulmonary disease (COPD). The PBAC considered a more restrictive Authority Required listing (immediate assessment via telephone/online application) would be appropriate to minimise the risk of inappropriate use in patients with less severe asthma. In addition, the PBAC considered that confirmation that a patient is aged 18 years and over as part of the assessment of eligibility for PBS subsidised therapy may assist in minimising any potential confusion regarding MF/IND/GLY age restrictions (see paragraph 6.44).

3.5 The requested restriction for MF/IND/GLY is consistent with the restriction of TIO for treatment of severe asthma in adults (in combination with ICS/LABA). Under the requested listing, symptomatic patients optimised on medium dose ICS (i.e. 800 mcg budesonide per day or equivalent) are eligible for treatment with triple therapy ICS/LABA/LAMA.

3.6 For consistency across FDC asthma products, the PBAC considered it would be appropriate for the listing to include the following administrative advice (and associated explanatory notes):

- This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD);
- This product is not indicated for the initiation of treatment in asthma;
- The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.

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 for mild to moderate asthma and a targeted approach for severe asthma. In the current Australian guidelines (Australian Asthma Handbook, 2019), patients who

experience exacerbations or uncontrolled asthma despite medium and high dose ICS/LABA can trial triple ICS/LABA/LAMA treatment. In the Australian and international guidelines, medium dose ICS includes 800 mcg of budesonide per day or equivalent (at the upper dosage limit), and high dose ICS refers to more than 800 mcg of budesonide per day or equivalent.

4.3 The submission proposed that MF/IND/GLY would be an alternative treatment option to add-on LAMA (i.e. TIO) in 'add-on specialised treatment' (Step 5) for patients with uncontrolled asthma taking moderate (i.e. medium) or high dose ICS/LABA. Australian guidelines state that if an adult with confirmed severe asthma continues to experience frequent symptoms or flare-ups despite optimisation of inhaler technique and adherence, and treatment of comorbidities, a trial of add-on treatment with tiotropium or montelukast can be considered in primary care before referring for specialist assessment for monoclonal antibody therapy. If there is no improvement in asthma symptoms after an adequate trial, then the add-on treatment is ceased.

4.4 Currently, none of the individual components of MF/IND/GLY are available on the PBS for asthma, therefore patients would need to step up or switch from alternative drug combinations. This is similar to patients treated with other FDCs on the PBS, where the components are not available. However, if Atectura® Breezhaler® (MF/IND) became available on the PBS, then patients taking medium or high dose MF/IND could step up to triple therapy using medium or high dose MF/IND/GLY.

4.5 Table 2 summarises comparable doses of MF/IND across different formulations. The Breezhaler® device permits lower doses of MF and IND compared to the Twisthaler®. In addition, MF 80 mcg and 160 mcg in the Enerzair® Breezhaler® is comparable to MF 160 mcg and 320 mcg in the Atectura® Breezhaler® respectively (due to a physico-chemical interaction affecting MF fine particle mass).[1] The pre-PBAC response noted changes to the labelling and PI, such that the delivered dose would be displayed rather than the metered dose for MF/IND and MF/IND/GLY (see paragraph 2.7).

[1] Therapeutic Goods Administration (TGA), 2019. Clinical Evaluation Report. Submission PM-2019-02514-1-5 Clinical Evaluation Report for indacaterol acetate/ glycopyrronium bromide/mometasone furoate (ENERZAIR).

Table 2: Comparable doses (mcg) of MF and IND across different formulations

	MF/IND via Twisthaler®	Atectura® Breezhaler® (MF/IND)	Enerzair® Breezhaler® (MF/IND/GLY)
Medium dose MF	400/500 once daily	160/150 once daily	80/150/50 once daily
High dose MF	400/500 twice daily	320/150 once daily	160/150/50 once daily

Abbreviations: GLY=glycopyrronium; IND=indacaterol; MF=mometasone furoate;
Source: constructed during the evaluation from the TGA Clinical Evaluation Report, Section 2.4.1 Formulation development.

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

5 Comparator

5.1 The submission stated that medium and high dose MF/IND/GLY would substitute for the 'loose' combination of high dose ICS/LABA FDC + LAMA available on the PBS. For the clinical comparison, the submission nominated FP/SAL DPI 500/50 mcg one actuation twice daily plus TIO 2.5 mcg two actuations once daily as the main comparator.

5.2 During the evaluation, it was considered the nominated comparison between medium dose MF/IND/GLY versus high dose ICS/LABA + LAMA was not adequately justified and may not be clinically appropriate. In practice, medium dose MF/IND/GLY may substitute for medium dose ICS/LABA FDC + LAMA given:

- Symptomatic patients taking optimised medium dose ICS/LABA (i.e. 800 mcg of budesonide per day or equivalent) are eligible for triple therapy on the PBS. Patients are likely to step up from optimised medium dose ICS/LABA to medium dose ICS/LABA/LAMA without concurrently changing the dose of ICS.

5.3 A comparison between medium dose MF/IND/GLY versus medium dose ICS/LABA + LAMA was also consistent with the submission for Atectura® Breezhaler® (MF/IND). In that submission, the sponsor requested listing of medium dose MF/IND assuming non-inferiority to medium dose FP/SAL. Given medium dose MF/IND/GLY provides a step up for medium dose MF/IND at comparable doses of MF, then it follows that medium dose MF/IND/GLY also provides a step up for medium dose FP/SAL at comparable doses of ICS.

5.4 The submission argued that MF/IND/GLY dry powder capsules would most likely replace ICS/LABA DPIs (+LAMA) rather than ICS/LABA metered dose inhalers (MDIs) given little switching between DPIs and MDIs on the PBS. ICS/LABA MDIs are relevant comparators given they can be replaced in practice. Furthermore, it is likely that patients taking the loose combination of an ICS/LABA MDI + LAMA may prefer to switch to MF/IND/GLY given a single inhaler is more convenient and has lower out-of-pocket costs (i.e. one co-payment rather than two co-payments). 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).

5.5 The submission also identified Trelegy® Ellipta®, the triple therapy FDC of FF/VI/UMEC as a near-market comparator, noting that it was recently approved for asthma in Europe and that the sponsor expects TGA registration and a PBAC submission is

forthcoming. One strength of Trelegy® Ellipta® (FF/VI/UMEC 100/25/62.5) is PBS listed for COPD.

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

6 Consideration of the evidence

Consumer comments

6.1 The PBAC noted and welcomed the input from Asthma Australia via the Consumer Comments facility on the PBS website. Asthma Australia described a range of benefits of treatment with MF/IND/GLY and supported the addition of a fixed dose triple-combination product to the PBS as an alternative option for patients with difficult-to-treat asthma, poor control of symptoms and poor lung function.

Sponsor hearing

6.2 There was no hearing for this item.

Clinical trials

6.3 The submission was based on one head-to-head randomised trial comparing medium and high dose MF/IND/GLY to high dose FP/SAL plus TIO (Argon), and one head-to-head randomised trial comparing medium and high dose MF/IND/GLY to medium and high dose MF/IND respectively (Iridium) as supportive evidence.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MF/IND/GLY (80/150/50 and 160/150/50) vs FP/SAL plus TIO		
ARGON (2306)	A multicentre, partially blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone plus tiotropium in patients with uncontrolled asthma. Additional trial registrations: EUCTR2017-000136-34-HU and EUCTR2017-000136-34-ES and NCT03158311	2019
MF/IND/GLY (80/150/50 and 160/150/50) vs MF/IND (160/150 and 320/150)		
IRIDIUM (2302)	A multicentre, 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

Abbreviations: FP=fluticasone propionate; GLY=glycopyrronium; IND=indacaterol; MF=mometasone furoate; SAL=salmeterol; TIO=tiotropium; QVM149=MF/IND/GLY; QMF149=MF/IND
Source: Table 2.3, p39 of the submission and Attachment 13 Iridium.

6.4 The submission also presented limited available efficacy data from the Captain trial (NCT02924688) comparing FF/VI/UMEC one actuation once daily versus FF/VI one actuation once daily for patients with uncontrolled asthma. Captain was a multi-centre randomised, double-blind, 52 week, 6-arm parallel group trial evaluating FF/VI/UMEC (100/25/31.25, 100/25/62.5, 200/25/31.25 and 200/25/62.5 mcg) versus FF/VI (100/25 and 200/25 mcg). Patients enrolled were aged 18-75 years with symptomatic asthma despite taking medium to high dose ICS/LABA (>250 mcg FP or equivalent). There was limited published information to appraise the potential risk of bias.

6.5 For completeness, the evaluation also presented comparable data from Kerstjens et al 2012[2], which was the main trial supporting the PBS listing of TIO in triple therapy for severe asthma. The publication included data from two randomised, double-blind, 48-week, placebo-controlled twin trials, conducted concurrently (Trial 1 and Trial 2) of TIO as add-on therapy to maintenance asthma treatment consisting of medium to high dose ICS (≥800mcg budesonide or equivalent) and LABA. Patients enrolled were aged 18-75 years with symptomatic asthma despite taking medium to high dose ICS (≥800 mcg budesonide or equivalent) and LABA. The risk of bias for the trials was considered low (paragraph 6.7, tiotropium bromide PSD, July 2015 PBAC meeting).

6.6 Table 4 summarises the key features of the Argon and Iridium trials. Both trials were multicentre but neither included Australian sites.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Bias	Treatment arms	Population	Key efficacy outcomes
MF/IND/GLY (80/150/50 and 160/150/50) vs FP/SAL 500/50 + TIO 5						
Argon	1426	MC, R, OL[a], parallel, 2w run-in + 24w tx (+7d follow-up)	High	MF/IND/GLY DPI (80/150/50 and 160/150/50 µg D) FP/SAL (500/50 µg BD) + TIO (2.5 µg 2 D)	Aged ≥18y, Asthma, FEV1 <85%	1º: AQLQ (24w) 2º: trough FEV1 and ACQ-7 (24w) Other: spirometry#, PRO[b], salbutamol, exacerbations
MF/IND/GLY (80/150/50 and 160/150/50) vs MF/IND (160/150 and 320/150) and FP/SAL 500/50						
Iridium	3092	MC, R, DB, 2D parallel, 2w run-in + 52w tx (+30d follow-up)	Low	MF/IND DPI (160/150 and 320/150 µg D) FP/SAL (500/50 µg BD)	Aged 18-75y, Asthma, FEV1 <80%	1º: trough FEV1 (26w) 2º: ACQ-7 (26w) Other: spirometry#, PRO[c], salbutamol, exacerbations

Abbreviations: ACQ=asthma control questionnaire; AQLQ=asthma quality of life questionnaire; DB=double blind; FEV_{25-75}=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; TIO=tiotropium; BD=twice daily; D=once daily; d=day; tx=treatment; w=week; y=year;

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

[a] Partial blind/open-label study. Investigators and patients had knowledge of treatment allocation between MF/IND/GLY and/or comparator; however, MF/IND/GLY dosage strength allocation was masked. The global sponsor team responsible for data review and analysis was blinded to all treatment allocation.

[b] PRO (health status): ACQ-7, AQLQ, SGRQ

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

Source: Section 2.4.1, p44 of the submission.

6.7 Argon was a three-arm open-label non-inferiority trial, comparing medium dose and high dose MF/IND/GLY to high dose FP/SAL plus TIO in terms of Asthma Quality of Life Questionnaire (AQLQ) at 24 weeks. The dose of MF/IND/GLY was blinded to patients and investigators, but treatment allocation to FP/SAL plus TIO was not blinded.

6.8 Iridium was a five-arm double-blind superiority trial. The primary objective was to demonstrate superiority of medium dose MF/IND/GLY to medium dose MF/IND and high dose MF/IND/GLY to high dose MF/IND in terms of trough FEV1 at 26 weeks. Comparison to high dose FP/SAL was a secondary objective. Placebo doses were used to maintain blinding between treatment arms.

[2] Kerstjens HAM, et al. Tiotropium in asthma poorly controlled with standard combination therapy. NEJM 2012; 367:1198-1207.

6.9 Overall, the risk of bias in Iridium (for the primary comparisons of MF/IND/GLY vs MF/IND) was considered low; however, the risk of bias in Argon was considered high and potentially favours MF/IND/GLY over FP/SAL plus TIO:

- Patients and investigators were not blinded to the treatment allocation in the FP/SAL+TIO arm, and the primary outcome is a patient reported questionnaire.
- The trial enrolled symptomatic patients after a run-in period with FP/SAL, therefore there may be a selection bias working against FP/SAL plus TIO during the treatment phase. It is possible that switching background ICS/LABA may reduce symptoms.
- The trial permitted patients with symptom control in the FP/SAL plus TIO arm to 'step-down' treatment including ceasing TIO but this option was not possible in the MF/IND/GLY arms, which potentially favours MF/IND/GLY. The ESC noted that very few patients discontinued TIO (Table 12-1 Argon trial Clinical Study Report, p98).

6.10 The clinically relevant outcomes for asthma are differences in lung function tests, rescue medication use, symptom free days / control (e.g. Asthma Control Questionnaire, ACQ), asthma exacerbations and quality of life (e.g. AQLQ). 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 trough forced expiratory volume in one second (FEV1). The PBAC recommended TIO for triple therapy ICS/LABA+LAMA in severe asthma based on acceptable cost-effectiveness versus dual therapy ICS/LABA, supported by a clinically relevant improvement in FEV1 in the trial data and where ACQ-7 and exacerbations informed the health states in the model (paragraph 6.9, tiotropium bromide PSD March 2016 PBAC meeting).

6.11 The submission based the clinical claim on the primary outcome in Argon, the change from baseline in AQLQ at the end of 24 weeks of treatment. The submission nominated a non-inferiority margin of 0.25 reduction in AQLQ score in line the pre-specified margin in Argon. Iridium measured the change in the standardised AQLQ (AQLQ-S) over 52 weeks as a secondary outcome.

6.12 The submission also presented results for a large number of other outcomes, including the change from baseline at Week 24 or 26 in trough FEV1 (the primary outcome in Iridium), PEF (an exploratory outcome in Argon) and ACQ-7 and identified the following minimal clinically important difference (MCID) for these key outcomes:

- Trough FEV1, 0.23 L or 10% change from baseline. The PBAC has considered that an increase in FEV1 of 0.10 L was likely to be clinically meaningful for severe asthma (paragraph 7.5, tiotropium bromide PSD July 2015 PBAC meeting), which is lower than the MCID (or non-inferiority margin) of between 0.15 to 0.20 L accepted by the PBAC for less severe asthma (page 4, fluticasone propionate with eformoterol fumarate FDC, PSD July 2013 PBAC meeting; and paragraph 6.4, fluticasone furoate with vilanterol FDC, PSD March 2014 PBAC meeting).

- PEF, 5.39% (corresponding to 18.8 L / min) to 12% change from baseline. Australian guidelines[3] refer to a 10% variation in PEF as being clinically important, which is also consistent with previous PBAC considerations for ICS/LABA FDCs. Baseline mean morning PEF in Argon was approximately 300 L / min across all patients, therefore a 10% improvement corresponds to an increase of 30 L / min.
- ACQ-7, change from baseline of ≥ 0.5. ACQ-7 is the 7-item version of the ACQ (5 items on symptom and activity limitations, 1 on rescue drug use, and 1 on FEV% predicted)

Comparative effectiveness

6.13 Table 5 summarises results from the relevant comparisons reported in Argon and Iridium for the change from baseline in AQLQ, trough FEV1, mean morning PEF and ACQ-7.

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

Table 5: Mean change (SE) from baseline in AQLQ total score, trough FEV1 (L), PEF (L/min) and ACQ-7 in MF/IND/GLY trials, Argon and Iridium

	MF/IND/GLY	FP/SAL+TIO	MF/IND	Mean diff. (95% CI)	
				MF/IND/GLY vs FP/SAL+TIO	MF/IND/GLY vs MF/IND
AQLQ total score^					
Medium dose MF/IND/GLY 80/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	0.76 (0.05)	0.80 (0.05)		-0.04 (-0.14,0.06)	
MF/IND 160/150 D; Iridium Wk26	0.67 (0.03)		0.71 (0.03)		-0.04 (-0.14,0.06)
High dose MF/IND/GLY 160/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	0.87 (0.05)	0.80 (0.05)		0.07 (-0.03,0.17)	
MF/IND 320/150 D; Iridium Wk26	0.73 (0.03)		0.77 (0.03)		0.03 (-0.13,0.06)
Trough FEV1 (L)#					
Medium dose MF/IND/GLY 80/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	0.25 (0.02)	0.24 (0.02)		0.01 (-0.04,0.06)	
MF/IND 160/150 D; Iridium Wk26	0.30 (0.01)		0.22 (0.01)		**0.08 (0.04, 0.11)**
High dose MF/IND/GLY 160/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	0.33 (0.02)	0.24 (0.02)		**0.096 (0.05,0.15)**	
MF/IND 320/150 D; Iridium Wk26	0.32 (0.01)		0.26 (0.01)		**0.07 (0.03, 0.10)**
Mean morning PEF (L/min)					
Medium dose MF/IND/GLY 80/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	30.0 (2.18)	24.1 (2.18)		**5.9 (0.33, 11.5)**	
MF/IND 160/150 D; Iridium Wk52	41.2 (2.05)		25.6 (2.06)		**15.6 (10.2, 20.9)**
High dose MF/IND/GLY 160/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	35.8 (2.17)	24.1 (2.18)		**11.8 (6.1, 17.4)**	
MF/IND 320/150 D; Iridium Wk52	47.5 (2.03)		28.8 (2.05)		**18.7 (13.4, 24.1)**
ACQ-7					
Medium dose MF/IND/GLY 80/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	-1.08 (0.05)	-1.05 (0.05)		-0.03 (-0.13,0.06)	
MF/IND 160/150 D; Iridium Wk26	-0.97 (0.03)		-0.90(0.03)		-0.07 (-0.15,0.01)
High dose MF/IND/GLY 160/150/50 D vs FP/SAL 500/50 BD +TIO 5 D; Argon Wk24	-1.17 (0.05)	-1.05 (0.05)		**-0.12(-0.22,-0.03)**	
MF/IND 320/150 D; Iridium Wk26	-0.98 (0.03)		-0.99(0.03)		0.01 (-0.07,0.09)

Bold text indicates statistical significance at p<0.05

Abbreviations: AQLQ=asthma quality of life questionnaire; FEV1=forced expiratory volume in one second; FP=fluticasone propionate; GLY=glycopyrronium; IND=indacaterol; MF=mometasone furoate; PEF=peak expiratory flow; SAL=salmeterol; TIO=tiotropium; wk=week; D=once daily; BD=twice daily;

^ LS mean treatment difference of the change from baseline in AQLQ at Week 24 (adjusted one-sided p-value) is the primary outcome in Argon. The two-sided test of the between-treatment comparison (as presented in the table) is a secondary outcome

Change from baseline in trough FEV1 is the primary outcome in Iridium

Source: Tables 2.21, 2.22 and 2.25, pp69-74, Table 2.28, p77 and Table 2.35, p82 of the submission and Attachments 11 and 14 of the submission

6.14 Table 6 compares the incremental benefit of triple therapy ICS/LABA/LABA with dual therapy ICS/LABA in terms of FEV1 and ACQ-7 reported in Iridium (MF/IND/GLY vs MF/IND), Captain (FF/VI/UMEC vs FF/VI) and Kerstjens et al 2012 (ICS/LABA+TIO vs ICS/LABA).

Table 6: Mean change from baseline in trough FEV1 (L) and ACQ-7, in trials comparing ICS/LABA/LAMA vs ICS/LABA

	ICS/LABA/ LAMA	ICS/LABA	Mean diff. (95%CI)
Trough FEV1 (L)			
Med/high# dose ICS/LABA/LAMA vs med/high# dose ICS/LABA			
ICS/LABA# + TIO 5 D vs ICS/LABA#; Kerstjens 2012 Wk24, Trial 1[a]	0.14 (0.02)	0.06 (0.03)	**0.09 (0.03,0.15)**
ICS/LABA# + TIO 5 D vs ICS/LABA#; Kerstjens 2012 Wk24, Trial 2[a]	0.16 (0.02)	0.04 (0.02)	**0.11 (0.05,0.17)**
Medium dose ICS/LABA/LAMA vs medium dose ICS/LABA			
MF/IND/GLY 80/150/50 D vs MF/IND 160/150 D; Iridium Wk26	0.30 (0.01)	0.22 (0.01)	**0.08 (0.04,0.11)**
FF/VI/UMEC 100/25/31.25 D vs FF/VI 100/25 D; Captain Wk24	0.12 (0.02)	0.02 (0.02)	**0.10 (0.05,0.14)**
FF/VI/UMEC 100/25/62.5 D vs FF/VI 100/25 D; Captain Wk24	0.13 (0.02)	0.02 (0.02)	**0.11 (0.07,0.15)**
High dose ICS/LABA/LAMA			
MF/IND/GLY 160/150/50 D vs MF/IND 320/150 D; Iridium Wk26	0.32 (0.01)	0.26 (0.01)	**0.07 (0.03,0.10)**
FF/VI/UMEC 200/25/31.25 D vs FF/VI 200/25 D; Captain Wk24	0.16 (0.02)	0.08 (0.02)	**0.08 (0.04,0.13)**
FF/VI/UMEC 200/25/62.5 D vs FF/VI 200/25 D; Captain Wk24	0.17 (0.02)	0.08 (0.02)	**0.09 (0.05,0.14)**
ACQ-7			
Med/high# dose ICS/LABA/LAMA vs med/high# dose ICS/LABA			
ICS/LABA# + TIO 5 D vs ICS/LABA#; Kerstjens 2012 Wk24, Trial 1[a]	NR	NR	-0.13 (p>0.05)
ICS/LABA# + TIO 5 D vs ICS/LABA#; Kerstjens 2012 Wk24, Trial 2[a]	NR	NR	**-0.20 (p<0.05)**
FF/VI/UMEC^ 31.25 D vs FF/VI^; Captain Wk24	-0.73 (0.02)	-0.68 (0.02)	-0.06 (-0.12,0.01)
FF/VI/UMEC^ 62.5 D vs FF/VI^; Captain Wk24	-0.77 (0.02)	-0.68 (0.02)	**-0.09 (-0.16,-0.02)**
Medium dose ICS/LABA/LAMA vs medium dose ICS/LABA			
MF/IND/GLY 80/150/50 D vs MF/IND 160/150 D; Iridium Wk26	-0.97 (0.03)	-0.90 (0.03)	-0.07 (-0.15,0.01)
High dose ICS/LABA/LAMA			
MF/IND/GLY 160/150/50 D vs MF/IND 320/150 D; Iridium Wk26	-0.98 (0.03)	-0.99 (0.03)	0.01 (-0.07,0.09)

Bold text indicates statistical significance at p<0.05,

Abbreviations: FEV1=forced expiratory volume in one second; FF=fluticasone furoate; FP=fluticasone propionate; GLY=glycopyrronium; ICS=inhaled corticosteroid; IND=indacaterol; LABA=long-acting beta-agonist; LAMA=long-acting muscarinic receptor antagonist; MF=mometasone furoate; SAL=salmeterol; TIO=tiotropium; UMEC=umeclidinium; VI=vilanterol; wk=week; D=once daily; BD=twice daily;

TIO or matching placebo as add-on therapy to individual pre-trial maintenance asthma therapy consisting 800 to 1600 mcg budesonide equipotent dose ICS and LABA.

^ FF/VI 100/25 D or FF/VI 200/25 D

[a] Compiled during the evaluation

Source: Table 2.28, p77 of the submission, Attachments 11 and 14 of the submission, Kerstjens et al 2012, and Table 4, tiotropium bromide PSD July 2015 PBAC meeting.

6.15 Medium and high dose MF/IND/GLY versus high dose FP/SAL+TIO

In Argon, non-inferiority between high dose and medium dose MF/IND/GLY versus high dose FP/SAL plus TIO was accepted, given the one-sided 97.5%CIs (-0.03 and -0.14) for AQLQ total score were above the pre-specified non-inferiority margin (-0.25). The trial also found statistically significant differences across a number of secondary/exploratory outcomes, mainly in favour of high dose MF/IND/GLY, including trough FEV1, mean morning PEF, ACQ-7 and others (various lung function parameters, AQLQ responders, ACQ-5, SGRQ score, rate of moderate exacerbations, and percentage days with no symptoms).

The conclusion of non-inferiority between both doses of MF/IND/GLY and high dose FP/SAL plus TIO based on AQLQ requires consideration (see Clinical claim). In addition, the small but statistically significant differences reported in Argon in favour of MF/IND/GLY across some outcomes were unlikely to be clinically important. For example, an increase in FEV1 of 96 mL with high dose MF/IND/GLY is less than the MCID of 100 mL accepted by the PBAC in severe asthma and the differences in other

outcomes (mean morning PEF, ACQ-7) are below the MCIDs identified in the submission. The ESC considered that, while unlikely to be clinically important differences, the results for medium dose MF/IND/GLY versus high dose FP/SAL plus TIO favoured medium dose MF/IND/GLY for the objective secondary outcomes of lung function (e.g. FEV1 and PEF).

6.16 Medium and high dose MF/IND/GLY versus medium and high dose MF/IND

In Iridium, results showed medium and high dose MF/IND/GLY had a significantly larger improvement in FEV1 and mean morning PEF compared to medium and high dose MF/IND, respectively. There was no significant difference for the change in AQLQ or ACQ-7 across the treatment comparisons.

The incremental benefit in terms of FEV1 for triple therapy MF/IND/GLY versus dual therapy MF/IND (at corresponding doses of ICS) was below the MCID of 100 mL and was described as 'modest' by the TGA evaluator. The benefit was also numerically smaller than the benefit demonstrated for add-on TIO in Kerstjens et al 2012 and triple therapy FF/VI/UMEC versus dual therapy FF/VI in Captain. The results for ACQ-7 suggested there was no clear benefit for MF/IND/GLY versus MF/IND (across both doses), which was inconsistent with the other trials. The ESC noted that Virchow et al 2019[4] reported a mean difference in trough FEV1 of 0.073L (95% CI 0.03, 0.12) for beclometasone dipropionate with formoterol fumarate and glycopyrronium (BEC/FOR/GLY) versus BEC/FOR in adults with uncontrolled asthma. The ESC considered that the lung function improvements for MF/IND/GLY were comparable with those demonstrated in other studies evaluating the benefit of LAMA in addition to LABA/ICS in similar patient populations.

The submission did not present results for the proportion of trough FEV1 responders (patients with change from baseline ≥ 100 mL), which may be of more relevance than the mean change in trough FEV1 across all patients. In severe asthma, add-on LAMA is one of a number of potential alternatives and therefore non-responders are likely to trial alternative therapies. The PSCR provided information on the proportion of patients who achieved improvement of ≥100mL in trough FEV1 at Week 26 and 52 from Iridium (Table 7). The PSCR noted that at Week 26 high dose MF/IND/GLY had higher proportion of responders compared with high dose MF/IND and FP/SAL. The PSCR also noted medium dose MF/IND/GLY had higher proportion of responders than both doses of MF/IND and FP/SAL. The PSCR stated there was no significant difference in the proportion of responders between the two doses of MF/IND/GLY. In addition, the PSCR noted the results were similar at Week 52, except there was no significant difference between medium dose MF/IND/GLY and high dose MF/IND. The ESC considered the results also indicate that the incremental benefit of triple therapy

[4] Virchow JC et al. Single inhaler extra fine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel group, randomised, controlled phase 3 trials. Lancet 2019;394:1737-49.

MF/IND/GLY versus dual therapy MF/IND in terms of proportion of responders at Week 26 was similar for medium and high dose ICS.

Table 7: Proportion of patients with improvement of ≥100mL in trough FEV1 at Week 26 and 52 from Iridium

	ICS/LABA/LAMA	ICS/LABA	Odds Ratio (95%CI)
Improvement of ≥100mL in trough FEV1			
Medium dose ICS/LABA/LAMA vs ICS/LABA; Iridium Wk 26 MF/IND/GLY 80/150/50 D vs MF/IND 160/150 D; MF/IND/GLY 80/150/50 D vs MF/IND 320/150 D; MF/IND/GLY 80/150/50 D vs FP/SAL 500/50 BD; Medium dose ICS/LABA/LAMA vs ICS/LABA; Iridium Wk 52 MF/IND/GLY 80/150/50 D vs MF/IND 160/150 D; MF/IND/GLY 80/150/50 D vs MF/IND 320/150 D; MF/IND/GLY 80/150/50 D vs FP/SAL 500/50 BD;	[redacted]	[redacted]	[redacted]
High dose ICS/LABA/LAMA vs ICS/LABA; Iridium Wk 26 MF/IND/GLY 160/150/50 D vs MF/IND 320/150 D; MF/IND/GLY 160/150/50 D vs FP/SAL 500/50 BD; High dose ICS/LABA/LAMA vs ICS/LABA; Iridium Wk 52 MF/IND/GLY 160/150/50 D vs MF/IND 320/150 D; MF/IND/GLY 160/150/50 D vs FP/SAL 500/50 BD;	[redacted]	[redacted]	[redacted]

Bold text indicates statistical significance at p<0.05

Abbreviations: FEV1=forced expiratory volume in one second; FP=fluticasone propionate; GLY=glycopyrronium; ICS=inhaled corticosteroid; IND=indacaterol; LABA=long-acting beta-agonist; MF=mometasone furoate; SAL=salmeterol; wk=week; D=once daily; BD=twice daily;

Source: Table 1, p4 of the PSCR

Comparative harms

6.17 The submission presented safety outcomes to the end of the treatment phases of Argon and Iridium. The incidence of AEs was similar between treatment arms. The proportion of patients with at least 1 AE was lower in Argon compared to Iridium due to the shorter safety follow-up of 24 weeks versus 52 weeks, respectively.

6.18 Overall, there were no significant safety issues identified for MF/IND/GLY. The proportion of patients reporting any AEs was comparable between MF/IND/GLY treatment arms (53%) and FP/SAL plus TIO (52%) in Argon, and between MF/IND/GLY (75%) and MF/IND treatment arms (74%) in Iridium. The most frequently reported serious AEs were related to infections and infestations and respiratory disorders. One death was reported for FP/SAL plus TIO treatment group in Argon, however the death was not deemed as related to the trial treatments.

Benefits/harms

6.19 There were no clinically meaningful differences between MF/IND/GLY and FP/SAL plus TIO, at corresponding doses of ICS, in efficacy and safety when used for the treatment of severe asthma.

Clinical claim

6.20 Based primarily on the Argon trial, the submission described medium and high dose MF/IND/GLY as non-inferior in terms of effectiveness and safety compared with high dose FP/SAL plus TIO in patients with severe asthma:

- MF/IND/GLY 80/150/50 one actuation once daily is non-inferior to FP/SAL DPI 500/50 one actuation twice daily plus TIO 2.5 two actuations once daily;
- MF/IND/GLY 160/150/50 one actuation once daily is non-inferior to FP/SAL DPI 500/50 one actuation twice daily plus TIO 2.5 two actuations once daily;

6.21 During the evaluation, the clinical trial evidence presented in the submission was considered to support the claim of non-inferior safety. The claim of non-inferior effectiveness however, particularly for the medium dose MF/IND/GLY versus high dose FP/SAL plus TIO, required consideration:

- The Argon trial, on which the clinical claim is based, was a partial open label trial with a high risk of bias that may potentially favour MF/IND/GLY compared to FP/SAL plus TIO.
- In practice, patients step up to triple therapy by adding a LAMA to the optimised ICS/LABA dose without concurrently adjusting the dose of ICS, but Argon does not provide evidence between different medium dose ICS/LABA/LAMA treatments for patients optimised on medium dose ICS/LABA (i.e. there is no medium dose FP/SAL plus TIO arm).
- The Argon trial showed that both doses of MF/IND/GLY met the non-inferiority margin for AQLQ versus high dose FP/SAL plus TIO; however, it was unclear whether the AQLQ is adequately sensitive to detect small differences between the treatments in severe asthma and therefore support the conclusion of non-inferiority between the treatment alternatives. For example, in the Iridium trial, there was no difference in AQLQ for patients treated with triple therapy ICS/LABA/LAMA versus dual therapy ICS/LABA. The American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations[5] describes AQLQ as providing complementary rather than direct information about asthma control or severity. The PSCR argued that AQLQ is appropriate as a primary endpoint as it is a well-established instrument with good responsiveness[6] and has been shown to correlate with measures of asthma control[7,8]. The ESC considered AQLQ outcomes of the Argon trial to be subjective and at a high risk of bias due to the partial open label nature of the trial.

6.22 Alternatively, it may be preferable to rely on Iridium (and other supportive trials) for decision-making purposes. Based on that evidence, it may be more reasonable to

[5] Reddel HK, et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Am J Resp Critical Care Med 2009;180:59-99.
[6] Juniper EF, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. Euro Resp J 1999;14;1038-1043.
[7] Juniper EF, et al. Development and validation of a questionnaire to measure asthma control. European Resp J 1999;14;902-907.
[8] Vollmer WM, et al. Association of asthma control with health care utilization and quality of life. Am J Resp Critical Care Med 1999;160;1647-1652.

describe medium and high dose MF/IND/GLY as potentially being similar to medium and high dose ICS/LABA + LAMA respectively, given:

- Results from Iridium and Kerstjens et al 2012, both double-blind trials, show that the incremental benefit in terms of trough FEV1 of adding GLY to medium and high dose MF/IND was similar to but numerically smaller than the benefit of adding TIO to medium and high dose ICS/LABA (with the caveat that the point estimates were below the MCID); and
- The sponsor requested PBS listing of medium and high dose MF/IND in a separate submission to the PBAC, based on a cost-minimisation analysis to medium and high dose FP/SAL respectively

6.23 The PBAC considered the clinical claim that medium and high dose MF/IND/GLY are non-inferior in effectiveness to high dose FP/SAL plus TIO to be uncertain for medium dose MF/IND/GLY and reasonable for high dose MF/IND/GLY.

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

Economic analysis

6.25 The submission presented a cost-minimisation analysis based on AEMP (per day) between medium and high dose MF/IND/GLY and high dose FP/SAL plus TIO. The analysis assumed no additional costs or cost-offsets.

6.26 The submission proposed the following equi-effective doses based on trial evidence presented:

- MF/IND/GLY 80/150/50 one actuation once daily = MF/IND/GLY 160/150/50 one actuation once daily = FP/SAL 500/50 one actuation twice daily + TIO 2.5 two actuations once daily.

6.27 During the evaluation it was considered that the clinical evidence presented in the submission did not adequately support the nominated equi-effective dose between medium dose MF/IND/GLY and high dose FP/SAL plus TIO, and it may be more reasonable to describe medium dose MF/IND/GLY as being similar or equivalent to medium dose ICS/LABA + LAMA products (see Clinical claim).

6.28 In practice, medium dose MF/IND/GLY will likely substitute for medium dose ICS/LABA + LAMA (800 mcg budesonide per day or equivalent), and high dose MF/IND/GLY would likely substitute for high dose ICS/LABA + LAMA. The submission explored this scenario as a sensitivity in the financial estimates, based on the dose relativities shown in Table 8. Corresponding dose relativities to MDI products were based on the Therapeutic Relativities.

Table 8: Equi-potent ICS/LABA FDCs available on the PBS that provides 30 days of treatment

	"Medium" dose ICS/LABA FDCs, providing 800 mcg budesonide equi-potent per day for 30 days	"High" dose ICS/LABA FDCs, providing 1600 mcg budesonide equi-potent per day for 30 days
DPI	FP/SAL 250/50 BD (Seretide® Accuhaler®, 60) BUD/FOR 200/6 2 BD (Symbicort® Turbuhaler®, 120) FF/VI 100/25 D (Breo® Ellipta®, 30)	FP/SAL 500/50 BD (Seretide® Accuhaler®, 60) BUD/FOR 400/12 2 BD (Symbicort® Turbuhaler®, 120) FF/VI 200/25 D (Breo® Ellipta®, 30)
DPI caps	MF/IND 160/150 D (Atectura® Breezhaler®, 30)*	MF/IND 320/150 D (Atectura® Breezhaler®, 30)*
MDI	FP/SAL 125/25 2 BD (Seretide®, 120) BUD/FOR 100/3 4 BD (Symbicort® Rapihaler®, 240) FP/FOR 125/5 2 BD (Flutiform®, 120) BEC/FOR 100/6 2 BD (Fostair®, 120)*	FP/SAL 250/50 2 BD (Seretide®, 120) BUD/FOR 200/6 4 BD (Symbicort® Rapihaler®, 240) FP/FOR 250/10 2 BD (Flutiform®, 120) -

Abbreviations: BEC=beclometasone; BUD=budesonide; DPI=dry powder inhaler; FOR=formoterol; FF=fluticasone furoate; FP=fluticasone propionate; IND=indacaterol; MDI=metered dose inhaler; MF=mometasone furoate; SAL=salmeterol; VI=vilanterol; D=once daily; BD=twice daily;

* PBS listing of Fostair® FDC containing BEC/FOR and Atectura® Breezhaler® containing MF/IND will be considered by the PBAC at the July 2020 meeting.

Source: compiled during the evaluation from the GINA guidelines, the Therapeutic Relativity Sheets and pbs.gov.au

6.29 The PBAC considered two submissions for new ICS/LABA FDCs at the July 2020 meeting, including Atectura® Breezhaler® dry powder capsules for inhalation containing MF/IND and Fostair® MDI containing extra-fine BEC/FOR. Hence, both of these products may be potential near market comparators for the ICS/LABA components of MF/IND/GLY (shown in Table 8).

6.30 The cost-minimisation analysis presented in the submission showed that the requested price for medium and high dose MF/IND/GLY (DPMQ = $[redacted]) was more than the cost equivalent price for high dose FP/SAL DPI plus TIO (DPMQ = $92.77) at current prices, but less than the cost equivalent price in February 2020 (DPMQ = $103.10)[9]. The sponsor argued a small price advantage was justified given evidence from the Argon trial showed high dose MF/IND/GLY was statistically better than high dose FP/SAL plus TIO for a number of secondary outcomes.

6.31 During the evaluation the requested price advantage was considered not justified given the submission did not provide any evidence that MF/IND/GLY provides any patient relevant improvement in compliance, efficacy or safety over the nominated comparator. The ESC considered that the comparisons presented in Argon likely favoured MF/IND/GLY and the magnitude of the effects reported were unlikely to be clinically important. In addition, the ESC considered that any potential difference for one strength cannot reasonably support a price advantage for both strengths. The ESC agreed with the evaluation that the requested price premium over high dose FP/SAL plus TIO was not adequately justified.

6.32 The PBAC guidelines (v5) state that the pricing of a combination product would normally be no greater than the sum of its individual components. In recommending the triple ICS/LABA/LAMA FDC Trelegy® Ellipta® (FF/VI/UMEC) for COPD, the PBAC considered that the 'the ceiling price of Trelegy (or any other fixed combination of

[9] The price of Spiriva® Respimat® (TIO) 2.5 mcg inhaler in severe asthma was reduced in February 2020 due to listing of a generic formulation for COPD, Braltus® Zonda® (TIO) 13 mcg dry powder capsules.

triple therapy of LAMA/LABA/ICS) should be no greater than the lowest priced combination of any listed components of the triple therapy' (paragraphs 7.6 to 7.8, fluticasone furoate with umeclidinium and vilanterol FDC, PSD December 2017 PBAC meeting).

6.33 Based on cost equivalent prices for all combinations of loose medium and high dose ICS/LABA FDCs plus LAMA available on the PBS, that provide 800 mcg and 1600 mcg budesonide per day or equivalent for 30 days of treatment respectively (see Table 8 above):

- The least costly combination of any listed high dose ICS/LABA + LAMA products on the PBS results in a cost-equivalent DPMQ of $91.06 (FP/FOR 250/10 plus TIO 2.5), which is [redacted]% less than the requested DPMQ of $[redacted].
- The least costly combination of any listed medium dose ICS/LABA + LAMA products on the PBS results in a cost-equivalent DPMQ of $76.14 (FP/FOR 125/5 plus TIO 2.5), which is [redacted]% less than the requested DPMQ of $[redacted].

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.

6.34 The pre-PBAC response proposed a revised DPMQ of $[redacted] (AEMP $[redacted]).

Drug cost/patient/year

6.35 The annual cost of MF/IND/GLY per patient was $[redacted] for either medium or high dose formulations. These calculations assumed 12.18 scripts per year at the requested DPMQs ($[redacted]).

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC. The estimated financial impact of the proposed listing assumed a market share approach with high dose ICS/LABA FDC (DPI products only) + LAMA products available on the PBS for asthma. Substitution with medium dose ICS/LABA FDCs + LAMA was presented as a sensitivity analysis.

6.37 Table 9 summarises the key inputs used in the financial estimates.

Table 9: Key inputs for financial estimates

<table>
<tr><th>Parameter</th><th>Value applied and source</th><th>Comment</th></tr>
<tr><td>Triple therapy market (scripts)</td><td>2019:
- 351,413 scripts of ICS/LABA
- 351,413 scripts of LAMA
Source: PBS statistics for tiotropium (item 11043F) Jan 2019 to Dec 2019, as a proxy for ICS/LABA and LAMA scripts.</td><td>Reasonable. Item 11043F is restricted to triple therapy in combination with ICS/LABA.</td></tr>
<tr><td>Annual growth of triple therapy market (scripts)</td><td>2020: 10%
Yr 1 (2021): 8%
Yrs 2 to 6 (2022 to 2026): 5%
Source: Assumption based on PBS statistics for tiotropium (item 11043F). Growth of 99.8% in 2018 and 12.9% in 2019.</td><td>Reasonable. Growth of triple therapy is likely to slow over time but remain positive.</td></tr>
<tr><td>Substitution rate for ICS/LABA FDC + LAMA</td><td>Each MF/IND/GLY script would substitute: 1 ICS/LABA FDC script, and 1 LAMA script, with proportional substitution based on the projected market share of the individual products.

Assumed dose relativities
<table>
<tr><th></th><th>Dose</th><th>Sub rate</th><th>Base case</th></tr>
<tr><td colspan="4">LAMA</td></tr>
<tr><td>TIO 2.5</td><td>2 D</td><td>1 : 1</td><td>Yes</td></tr>
<tr><td colspan="4">High dose ICS / LABA FDC (BUD 1600 mcg / day or equivalent)</td></tr>
<tr><td>FP/SAL 500/50</td><td>BD</td><td>1 : 1</td><td>Yes</td></tr>
<tr><td>BUD/FOR 400/12</td><td>2 BD</td><td>1 : 1:</td><td>Yes</td></tr>
<tr><td>FF/VI 200/25</td><td>D</td><td>1 : 1</td><td>Yes</td></tr>
<tr><td colspan="4">Medium dose ICS / LABA FDC (BUD 800 mcg / day or equivalent)</td></tr>
<tr><td>FP/SAL 250/50</td><td>BD</td><td>1 : 1</td><td>No</td></tr>
<tr><td>BUD/FOR 200/12</td><td>2 BD</td><td>1 : 1</td><td>No</td></tr>
<tr><td>FF/VI 100/25</td><td>D</td><td>1 : 1</td><td>No</td></tr>
</table></td><td>The assumed dose relativities were consistent with the Therapeutic Relativity Sheets and clinical guidelines. However, the assumption that medium and high dose MF/IND/GLY would only substitute for high dose ICS/LABA + LAMA in the base case was poorly justified. A sensitivity analysis with substitution from medium dose ICS/LABA + LAMA showed that the model was highly sensitive to this assumption.</td></tr>
<tr><td>Uptake rate (medium and high dose combined)</td><td>Yr 1: 23% increasing to Yr 6: 60%
Source: Yrs 1 to 2 based on the estimated uptake of Trelegy Ellipta® (PBS item 11379X) in COPD, as a proportion of LAMA/LABA FDCs. Yrs 3 to 6 based on an assumption</td><td>Not reasonable. The methodology used was not precise given there is no requirement that LAMA/LABA FDCs must be used in combination with ICS for COPD (and therefore cannot proxy for triple therapy scripts). Patients treated with ICS/LABA may also be using triple therapy, which were not included in the denominator. Overall, the uptake rates based on this methodology (Yr 1 and Yr 2) could be over- or under-estimates of triple therapy FDC in the triple therapy market. On face-value, the estimates seemed low given reduced out-of-pocket costs to patients but the submission argued that some clinicians may not prescribe a triple FDC using three components not currently PBS-listed for asthma.</td></tr>
<tr><td>Compliance rate</td><td>100%
Source: assumption</td><td>Compliance is likely less than 100%, and may improve with the proposed listing but assuming no difference in compliance is reasonable given the submission did not present any evidence of improved compliance with MF/IND/GLY over loose ICS/LABA + LAMA.</td></tr>
</table>

Abbreviations: BUD=budesonide; FOR=formoterol, FDC=fixed dose combination; FF=fluticasone furoate; FP=fluticasone propionate; ICS=inhaled corticosteroid; GLY=glycopyrronium; IND=indacaterol; LABA=long-acting beta2-agonist; LAMA=long-acting muscarinic receptor antagonist; MF=mometasone furoate; SAL=salmeterol; TIO=tiotropium; VI=vilanterol

Source: Section 4 of the submission, Utilisation and cost model workbook.

6.38 Table 10 summarises the estimated use and financial impact of the requested listing for MF/IND/GLY.

Table 10: Estimated use and financial implications to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine PBS/RPBS						
MF/IND/GLY FDC						
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS/RPBS cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
PBS/RPBS net cost (less copay)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimation of changes in use and financial impact of other comparators						
ICS/LABA FDC + LAMA						
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP/SAL 500/50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BUD/FOR 400/12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FF/VIL 200/25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TIO 2.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS/RPBS cost	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
PBS/RPBS net cost (less copay)	-$[redacted]	- $[redacted]	- $[redacted]	- $[redacted]	- $[redacted]	-$[redacted]
Estimated financial implications for the PBS/RPBS and the Health Budget*						
PBS/RPBS cost	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
PBS/RPBS net cost (less copay)	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

Abbreviations: BUD=budesonide; FOR=formoterol; FDC=fixed dose combination; FF=fluticasone furoate; FP=fluticasone propionate; GLY=glycopyrronium; ICS=inhaled corticosteroid; IND=indacaterol; LABA=long-acting beta2-agonst; LAMA=long-acting muscarinic receptor antagonist; MF=mometasone furoate; SAL=salmeterol; TIO=tiotropium; VI=vilanterol;
Source: Table 4.16, p120; Table 4.18, p123 of the submission; Utilisation and cost model workbook.

6.39 At the requested price (DPMQ=$[redacted]), the proposed listing of MF/IND/GLY was estimated to result in cost-savings to the PBS/RPBS over the first six years of listing. There would also be a reduction in the number of scripts processed by the DHS given two scripts is substituted for one script, but the number of Authority Required (STREAMLINED) scripts would remain unchanged.

6.40 The estimated net cost savings to the PBS/RPBS is driven by substitution with high dose FF/VI (200/25) + TIO (net cost = $94.06) because its net cost is higher than MF/IND/GLY (net cost = $[redacted]). In contrast, each unit substituted with high dose FP/SAL (500/50) + TIO ($83.83) and high dose BUD/FOR (400/12) + TIO ($86.11) results in a net cost to the PBS/RPBS.

6.41 Table 11 summarises sensitivity analyses presented in the submission (and conducted during the evaluation). Substitution with ICS/LABA MDI products was not explored, but the unit costs for MDIs are generally similar to DPI products.

Table 11: Sensitivity analysis of the financial implications to the PBS/RPBS

Sensitivity analysis	PBS/RPBS net cost (over 6 years)
Base case	[redacted]
Substitution rates 100% substitution with least costly high dose ICS/LABA DPI + LAMA 100% substitution with most costly high dose ICS/LABA DPI + LAMA	[redacted]
Comparator including medium dose ICS/LABA FDCs (BUD 800mcg per day or equivalent)# ICS/LABA (90% high dose and 10% medium dose) + LAMA ICS/LABA (80% high dose and 20% medium dose) + LAMA ICS/LABA (70% high dose and 30% medium dose) + LAMA	[redacted]
Proportion use in patients with controlled asthma on ICS/LABA (same total number of scripts) 10% substituting for ICS/LABA only 20% substituting for ICS/LABA only	[redacted]

Abbreviations: BUD=budesonide; DPI=dry powder inhaler; FF=fluticasone furoate; FOR=formoterol; ICS=inhaled corticosteroid; LABA=long-acting beta2-agonst; LAMA=long-acting muscarinic receptor antagonist; VI=vilanterol;
The sensitivity analysis presented in the submission included a programming error, where the DPMQs for BUD/FOR 400/12 and FF/VIL 200/25 were switched with each other (see cells C41:C42 on "Sensitivity testing" worksheet in "Utilisation-and-cost-model.xlsm")
Source: pp129-130 of the submission; 'Sensitivity testing' worksheet in "Utilisation-and-cost-model.xlsm".

6.42 The financial estimates were sensitive to:

- The substitution rates. Assuming more substitution with less costly alternatives resulted in a net cost to the PBS/RPBS, because the net cost of MF/IND/GLY was more than two of three included high dose ICS/LABA+LAMA comparators.
- The assumption that medium and high dose MF/IND/GLY will only substitute for high dose ICS/LABA + LAMA. Assuming ≥8% substitution with medium dose ICS/LABA + LAMA resulted in a net cost to the PBS/RPBS (all else constant), because medium dose ICS/LABA FDCs were less costly than high dose ICS/LABA FDCs.
- Leakage into the dual therapy market. Assuming ≥3% use in patients controlled on dual therapy results in a net cost to the PBS/RPBS (all else constant), because dual therapy was less costly than triple therapy.

Quality Use of Medicines

6.43 The submission did not report quality use of medicine information for MF/IND/GLY. Neither IND nor GLY are currently included in the Australian Asthma Handbook or GINA guidelines as treatments for asthma, but they are available on the PBS for COPD via the Breezhaler® device: Onbrez® containing IND, Seebri® containing GLY, and Ultibro® FDC containing IND/GLY.

6.44 There is potential that MF/IND/GLY could be inappropriately prescribed in children and adolescents, given triple therapy with ICS/LABA+TIO is PBS listed from 6 years of age but listing of MF/IND/GLY is sought for adults. The draft PI stated that the safety and efficacy of MF/IND/GLY in patients aged below 18 years had not been established. For Atectura® Breezhaler® (MF/IND), the sponsor requested listing in patients 12 years and over. The PBAC considered that confirmation that a patient is aged 18 years and over as part of an Authority Required (Telephone/Electronic/Emergency) listing may assist in minimising this potential quality use of medicines issue.

6.45 In 2015, DUSC considered that given there were '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 bromide, DUSC ADV July 2015 PBAC meeting). For many patients, MF/IND/GLY would be the first asthma inhaler that requires capsules to be loaded into the inhaler prior to use, which may add to this confusion. Unlike in COPD, there is only one other product listed for asthma that require capsules to be loaded into a device (Foradile® dry powder capsules containing formoterol), but it is rarely prescribed[10]. At the same time, a single inhaler has the potential to improve quality use of medicines compared to multiple inhalers; particularly given correcting inhaler technique is a major factor for severe asthma management.

6.46 In 2017, DUSC considered that the PBS-listing of Trelegy® would mean that a product in an Ellipta® device would be available at all stages of the COPD stepwise management plan and '[w]hile it may contribute to the correct use of the device, it may also facilitate more rapid escalation to triple therapy, which may not be warranted.' (fluticasone furoate + umeclidinium + vilanterol FDC, DUSC ADV December 2017 PBAC meeting). Similarly, if Atectura® Breezhaler® (MF/IND) were also recommended for listing at the July 2020 meeting, there would be a product in a Breezhaler® device available at Steps 3 to 5 of the clinical management algorithm, which may prompt rapid step-up to triple therapy.

6.47 The ESC considered that the stepwise approach to asthma therapy remained appropriate. The PBAC agreed with the ESC and evaluation that rapid escalation to triple therapy could be a significant QUM issue if MF/IND/GLY were to be listed, particularly if MF/IND was listed as well.

6.48 Further, dosing confusion could occur given the dose of ICS in the medium dose MF/IND (160mcg) is numerically the same as the dose of ICS in the high dose MF/IND/GLY (160mcg) because of differences in the physicochemical properties of the two products. The pre-PBAC response argued that with the changes to the labelling of dosing required by the TGA, this confusion would be mitigated, as the delivered doses of MF/IND and MF/IND/GLY are different.

Financial Management – Risk Sharing Arrangements

6.49 No risk sharing arrangement was proposed. The submission argued the proposed listing is not expected to expose the Commonwealth to any significantly greater risk or expenditure than that posed by the currently listed drugs. Neither special pricing arrangement nor expenditure caps currently apply to any asthma product.

6.50 During the evaluation, it was considered that as the first triple ICS/LABA/LAMA FDC available for asthma, there is a risk that clinicians may prescribe MF/IND/GLY to patients with less severe asthma (i.e. patients controlled on dual ICS/LABA FDC) with financial implications. The PBAC previously considered a risk sharing arrangement was

[10] Total PBS & RPBS services for Foradile® (item 8136F) in 2019 was 2814. Sourced from PBS statistics.

appropriate for the first triple ICS/LABA/LAMA FDC in COPD (Trelegy® Ellipta®) for a similar reason (paragraph 6.64, fluticasone furoate with umeclidinium and vilanterol FDC, PSD December 2017 PBAC meeting).

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

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of mometasone furoate (MF), with indacaterol acetate (IND), and glycopyrronium (GLY) fixed dose combination (FDC) for maintenance therapy of severe asthma as it was unclear if TGA registration would include medium dose MF/IND/GLY. However, the PBAC was of a mind to recommend the listing of high dose MF/IND/GLY for this indication on a cost-minimisation basis with the least costly combination of high dose inhaled corticosteroid (ICS) with long-acting beta2 agonist (LABA) FDC plus long-acting muscarinic antagonist (LAMA).

7.2 The PBAC noted the TGA delegate file note stating that the submitted data indicated a positive risk-benefit profile of high dose MF/IND/GLY for the proposed use, but did not support the proposed used of medium dose MF/IND/GLY. The PBAC noted the registration application would be considered at the August 2020 Advisory Committee on Medicines (ACM) meeting.

7.3 The PBAC noted the nomination of high dose fluticasone propionate with salmeterol (FP/SAL) FDC plus tiotropium (TIO) as the primary comparator for both medium and high dose MF/IND/GLY and the submissions argument that the most likely replacements would be within dry powder inhaler (DPI) formulations. The PBAC considered that some patients may to step-up from a medium dose ICS/LABA to a medium dose ICS/LABA plus LAMA, rather than to a high dose ICS/LABA LAMA. As such, the PBAC considered that the appropriate comparator for each strength of MF/IND/GLY would be comparable doses of ICS/LABA FDC plus LAMA. In addition, the PBAC reaffirmed that DPI and metered dose inhalers (MDI) are relevant comparators for each other (see paragraph 5.4).

7.4 The PBAC noted the primary evidence to support the clinical claim that both medium and high dose MF/IND/GLY were non-inferior to high dose FP/SAL plus TIO was from the Argon trial. The PBAC considered the risk of bias in Argon to be high and to potentially favour MF/IND/GLY over FP/SAL plus TIO for the reasons outlined in paragraph 6.9. The PBAC agreed with ESC that the primary outcome, the Asthma Quality of Life Questionnaire (AQLQ), was subjective and at a high risk of bias due to the partial open label nature of the trial. As such, the PBAC considered the AQLQ results of Argon trial were not a reliable measure to inform the clinical claim.

7.5 The PBAC considered the risk of bias in the Iridium trial to be low. The PBAC noted the results showed medium and high dose MF/IND/GLY had a significantly larger improvement in the primary outcome (trough forced expiratory volume in one second (FEV1)) compared to medium and high dose MF/IND, respectively. The PBAC agreed with the ESC that, although the incremental benefit in terms of FEV1 was below the

minimal clinically important difference (MCID) of 100 mL, the lung function improvements for MF/IND/GLY were comparable with those demonstrated in other studies evaluating the benefit of LAMA in addition to LABA/ICS (Kerstjens et al 2012). The PBAC considered the incremental benefit of triple therapy MF/IND/GLY versus dual therapy MF/IND were further supported by the proportion of patients with improvement of ≥ 100 mL in trough FEV1 results reported in Iridium (see Table 7). The PBAC considered these data suggested that medium dose MF/IND/GLY is comparable to medium dose ICS/LABA plus LAMA and high dose MF/IND/GLY is comparable to high dose ICS/LABA plus LAMA.

7.6 On balance, the PBAC considered the clinical claim that medium and high dose MF/IND/GLY is non-inferior to high dose FP/SAL plus TIO to be uncertain for medium dose MF/IND/GLY and reasonable for high dose MF/IND/GLY.

7.7 The PBAC noted the submission proposed an equal price for medium and high dose MF/IND/GLY, which was based on cost-minimisation with high dose FP/SAL plus TIO with an additional price premium. The PBAC noted the price premium was based on the claim that high dose MF/IND/GLY was statistically better than high dose FP/SAL plus TIO for a number of secondary outcomes in the ARGON trial. The PBAC agreed with the ESC that the price premium for the high dose was not justified, as the ARGON trial had a high risk of bias in favour of MF/IND/GLY and the magnitude of the effects reported were unlikely to be clinically important. The PBAC considered that, if recommended for listing on the PBS, medium and high dose MF/IND/GLY should be priced no higher than the lowest cost combination of respective medium and high dose ICS/LABA plus LAMA combinations.

7.8 The PBAC noted the concerns raised regarding the financial estimates sensitivity to substitution rates and the assumption that medium and high dose MF/IND/GLY will only substitute for high dose ICS/LABA plus LAMA. The PBAC considered that, if recommended for listing on the PBS, these concerns would be addressed by the Committee's recommendation that it would be on a cost-minimisation basis against the least costly combination of ICS/LABA plus LAMA as outlined in paragraph 7.7. However, the PBAC remained concerned about the risk of inappropriate use in patients with less severe asthma otherwise managed on ICS or ICS/LABA. The PBAC considered a higher restriction level (Authority Required – Telephone/Electronic /Emergency) would be appropriate to minimise this risk.

7.9 The PBAC advised it would finalise its advice on whether or not to recommend MF/IND/GLY at its next available opportunity following provision of the ACM advice and Delegate's decision (if required) and clarity on whether the TGA registration would include medium dose MF/IND/GLY.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

During the TGA evaluation the recommendation was that the MF/IND/GLY 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/GLY 80/150/50 is now 68/114/46 and MF/IND/GLY 160/150/50 is now MF/IND/GLY 136/114/46.

Addendum to the July 2020 PBAC Minutes:

10 Background

10.1 At its July 2020 meeting, the PBAC deferred making a recommendation regarding the listing of mometasone furoate (MF), with indacaterol acetate (IND), and glycopyrronium (GLY) fixed dose combination (FDC) for maintenance therapy of severe asthma as it was unclear if TGA registration would include medium dose MF/IND/GLY. However, the PBAC was of a mind to recommend the listing of high dose MF/IND/GLY for this indication on a cost-minimisation basis with the least costly combination of high dose inhaled corticosteroid (ICS) with long-acting beta2 agonist (LABA) FDC plus long-acting muscarinic antagonist (LAMA).

10.2 TGA approval for both medium dose MF/IND/GLY and high dose MF/IND/GLY was granted on the 9 October 2020.

11 PBAC Outcome

11.1 The PBAC recommended the Authority Required (Telephone/Electronic/Emergency) listing of mometasone furoate (MF), with indacaterol acetate (IND), and glycopyrronium (GLY) fixed dose combination (FDC) for maintenance therapy of severe asthma. Noting the TGA has registered both both medium dose MF/IND/GLY and high dose MF/IND/GLY for this indication, the PBAC was satisfied the remaining outstanding issues relating to this application were satisfactorily resolved.

11.2 The PBAC considered that medium and high dose MF/IND/GLY should be priced no higher than the lowest cost combination of respective medium and high dose ICS/LABA plus LAMA combinations.

11.3 The PBAC remained concerned about the risk of inappropriate use in patients with less severe asthma otherwise managed on ICS or ICS/LABA and considered a higher restriction level (Authority Required – Telephone/Electronic /Emergency) would be appropriate to minimise this risk.

11.4 The PBAC recommended that MF/IND/GLY should not be treated as interchangeable on an individual patient basis with any other drugs.

11.5 The PBAC advised that MF/IND/GLY is suitable for prescribing by nurse practitioners.

11.6 The PBAC recommended that the Early Supply Rule should apply.

11.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because MF/IND/GLY is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over FP/SAL plus TIO, 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.

11.8 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

Outcome:
Recommended

12 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	Available brands
INDACATEROL + GLYCOPYRRONIUM + MOMETASONE indacaterol 114 microgram + glycopyrronium 46 microgram + mometasone furoate 68 microgram, powder for inhalation, 30 capsules	NEW	1	30	5	Enerzair Breezhaler 114/46/68
indacaterol 114 microgram + glycopyrronium 46 microgram + mometasone furoate 136 microgram, powder for inhalation, 30 capsules	NEW	1	30	5	Enerzair Breezhaler 114/68/136

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
Restriction type / Method: ☒ Authority Required – Telephone/Electronic /Emergency
Severity: Severe
Condition: asthma
Indication: Severe asthma
Clinical criteria:
Patient must have experienced at least one severe exacerbation, which has required documented use of systemic corticosteroids, in the previous 12 months while receiving optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented.
Population criteria:
Patient must be aged 18 years or over
Prescribing Instructions: Optimised asthma therapy includes adherence to the maintenance combination of an inhaled corticosteroid (at least 800 micrograms budesonide per day or equivalent) and a long acting beta-2 agonist.
Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
Administrative Advice: This drug is not PBS-subsidised for the treatment of chronic obstructive pulmonary disease (COPD).
Administrative Advice: This product is not indicated for the initiation of treatment in asthma.
Administrative Advice: The treatment must not be used in combination with an ICS/LABA, LABA/LAMA or LAMA, LABA or ICS monotherapy.
Administrative Advice: A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.
Administrative Advice: A LABA includes olodaterol, indacaterol, salmeterol, formoterol or vilanterol.
Administrative Advice: An ICS includes fluticasone propionate, fluticasone furoate, budesonide, beclometasone or ciclesonide.

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

13 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.

14 Sponsor's Comment

The sponsor had no comment.