# 6.08 MEPOLIZUMAB, Injection 100 mg in 1 mL single dose pre-filled pen, Nucala®, GlaxoSmithKline Australia Pty Ltd.

## 1 Purpose of submission

1.1 The submission requested a Section 100 Highly Specialised Drugs Program, Authority Required (written restriction for initiation criteria, and a telephone/online restriction for the continuation criteria) listing for mepolizumab as add-on maintenance treatment for adults with uncontrolled chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype (defined by the submission as blood eosinophil count (BEC) ≥ 300 cells/µL), and on a stable combination of an inhaled corticosteroid (ICS), a long-acting beta-2 agonist (LABA), and a long-acting muscarinic agonist (LAMA).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus triple inhaled therapy (LABA + LAMA + ICS) alone. The components of the overall clinical claim addressed by the submission are summarised in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

| Component | Description |
|---|---|
| Population | Patients with uncontrolled COPD[a] characterised by an eosinophilic phenotype (BEC ≥ 300 cells/µL in the last 12 months) who continue to experience exacerbations (≥ 2 moderate[b] or ≥ 1 severe[c] exacerbation over 12 months) despite being optimised on triple inhaled therapy. |
| Intervention | Mepolizumab (100 mg administered SC once every four weeks) as add-on to triple inhaled therapy (ICS/LABA/LAMA) |
| Comparator | Triple inhaled therapy alone (ICS/LABA/LAMA) |
| Outcomes | Primary: annualised rate of moderate/severe exacerbations<br>Patient-relevant secondary: exacerbations requiring ED visit and/or hospitalisation<br>Safety: Rates of adverse events (AEs) and serious AEs (fatal and non-fatal) |
| Clinical claim | Mepolizumab is superior in terms of effectiveness compared to PBO as add-on treatment to triple inhaled therapy.<br>Mepolizumab is non-inferior in terms of safety compared to PBO as add-on treatment to triple inhaled therapy. |

*Source: Table 1-1 p19 of the submission.*

*AE = adverse events; BEC = blood eosinophil count; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; ED = emergency department; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA: long-acting muscarinic antagonist; PBO = placebo; SAE = severe adverse events; SC = subcutaneous.*

*[a] Uncontrolled COPD defined in terms of patient with moderate to severe air flow obstruction (post-bronchodilator $FEV_1$ < 80%) and who have experienced ≥ 2 moderate or ≥ 1 severe exacerbation.*

*[b] Moderate = exacerbations requiring systemic corticosteroids, antibiotics or both.*

*[c] Severe = exacerbations that result in hospitalisation for at least 24 hours or death.*

## 2 Background

### Registration status

2.1 Mepolizumab was approved by the Therapeutic Goods Administration (TGA) on 17 December 2025 for the following indication: 'add-on maintenance treatment for adult

patients with uncontrolled COPD with raised blood eosinophils on stable inhaler triple therapy (or, where clinically required, an equivalent regimen).' The TGA indication does not specify a cut-off for blood eosinophil level.

2.2 In Australia, mepolizumab is also TGA approved for the following indications:

- Add-on treatment for severe eosinophilic asthma in patients aged 12 years and over
- Add-on treatment for relapsing or refractory eosinophilic granulomatosis with polyangiitis in adult patients aged 18 years and over
- Add-on treatment in adult patients (18 years and above) with severe chronic rhinosinusitis with nasal polyps (CRSwNP) with an inadequate response to intranasal corticosteroids.

### Previous PBAC consideration

2.3 The PBAC has not previously considered mepolizumab for the treatment of uncontrolled COPD.

2.4 Mepolizumab is currently PBS-listed for:

- Initiation and continuation treatment for uncontrolled severe asthma.
- Initiation and continuation treatment of CRSwNP.

## 3 Requested listing

**Essential elements of the requested listing for mepolizumab (HSD Section 100, Public and Private)**

| Name, restriction, manner of administration, form | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Setting | Dispensed price for maximum quantity (under SPA) | Proprietary name and manufacturer |
|---|---|---|---|---|---|---|
| mepolizumab, Injection 100 mg in 1 mL single dose pre-filled pen | 1 | 1 | 6 (initial)<br>5 (continuing) | Public | $1556.10 (published)<br>$[redacted] (effective) | NUCALA, GlaxoSmithKline Australia Pty Ltd |
| | | | | Private | $1556.10 (published)<br>$[redacted] (effective) | |

*Source: Table 1-7 p37 of the submission.*
*HSD = Highly Specialised Drug; SPA = special pricing arrangement.*

| **Proposed initial treatment criteria** |
|---|
| **Category / Program:** Section 100 – Highly Specialised Drugs Program |
| Prescriber type: Medical Practitioner |
| Restriction type: Authority Required (Written; via HPOS upload) |
| Condition/PBS Indication: Chronic Obstructive Pulmonary Disease |
| **Treatment criteria** |
| Patient must be treated by a medical practitioner who is a respiratory physician or general physician experienced in the management of patients with COPD |
| **Clinical criteria** |
| Patient must be under the care of the same physician for at least 6 months; OR must have been diagnosed with COPD by a multidisciplinary team (MDT) |
| **AND**<br>Patient must not have received PBS-subsidised treatment with a biological medicine for COPD;<br>OR |

| **Proposed initial treatment criteria** |
|---|
| Patient must have had a 12-month break in treatment from the most recently approved PBS-subsidised MEPO treatment for COPD |
| **AND**<br>The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma |
| **AND**<br>Patient must have a duration of COPD of at least 1 year |
| **AND**<br>Patient must have failed to achieve adequate control with optimised triple inhaled therapy which has been documented.<br><br>Failure to achieve adequate control defined as:<br>(i) ≥2 moderate exacerbations requiring systemic glucocorticoids with or without antibiotics in the last 12 months; OR<br>(ii) ≥1 severe exacerbation (leading to hospitalization) in the last 12 months |
| **AND**<br>Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months |
| **AND**<br>Patient must not receive more than 28 weeks of treatment to demonstrate a response under this restriction |
| **Prescribing Instructions** |
| Optimised triple inhaled therapy includes:<br>(i) Adherence to use of ICS plus 2 additional COPD medications in the last 12 months, AND<br>(ii) In the last 3 months, adherence to use of triple inhaled therapy of an ICS (≥500mcg/day fluticasone propionate dose equivalent) plus LABA and LAMA, unless contraindicated or not tolerated<br><br>Where the patient has a contraindication or intolerance to LABA or LAMA or ICS, the reasons for the contraindication or intolerance should be documented in the patient's medical file. |
| **Population criteria:** |
| Patient must be aged 18 years or older. |

*Source: Table 1-8 pp 37-39 of the submission.*
*COPD = chronic obstructive pulmonary disease; HPOS= health professional online service; HSD = Highly Specialised Drug; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; MEPO = mepolizumab; PBS = Pharmaceutical Benefits Scheme.*

| **Restriction Summary [new] / Treatment of Concept: [new]** |
|---|
| **Category / Program:** Section 100 – Highly Specialised Drugs Program |
| **Prescriber type:** ☒Medical Practitioners |
| **Restriction type:** ☒ Authority Required (Telephone/Online) |
| **Indication:** COPD |
| **Treatment Phase:** Continuing |
| **Treatment criteria:** |
| Patient must be treated by a medical practitioner who is a respiratory physician or general physician experienced in the management of patients with COPD |
| **Clinical criteria:** |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition |
| **AND** |
| **Clinical criteria:** |
| Patient must have achieved and sustained an adequate response to this drug, defined as:<br><br>For patients with a history of **severe** exacerbation in the last 12 months, compared to the baseline level provided with the initial authority application:<br><br>• Patient has experienced **no change or a reduction in number of severe exacerbations AND**<br>• Patient has experienced **no increase in number of total exacerbations** over the past 12 months compared to baseline<br><br>For patients with a history of **moderate** exacerbation **only** in the last 12 months, compared to the baseline level provided with the initial authority application:<br><br>• Patient has experienced **no change or a reduction in number of moderate exacerbations** over the past 12 months compared to baseline **AND**<br>• Patient has experienced **no severe exacerbations** |
| **Population criteria:** |
| Patient must be aged 18 years or older. |

*Source: Table 1-10 p40 of the submission.*
*COPD = chronic obstructive pulmonary disease; PBS = Pharmaceutical Benefits Scheme.*

3.1 The submission requested a special pricing arrangement (SPA). The requested published ex-manufacturer price (EMP) was $[redacted] per 100 mg pre-filled pen and the requested effective EMP in the submission was $[redacted] per 100 mg pre-filled pen. The Pre-PBAC Response proposed a revised effective EMP of $[redacted] per 100 mg pre-filled pen.

3.2 The requested PBS criterion of 'Patient must have BEC ≥300 cells/µL in the last 12 months' is broader than the inclusion criteria used in the MATINEE trial, which required patients to have BEC ≥300 cells/µL at screening (within 6 weeks prior to treatment initiation) and ≥150 cells/µL during the last 12 months. An extension of the BEC validity window to 12 months aligns with current mepolizumab initiation criteria for uncontrolled severe asthma and CRSwNP. However, the efficacy demonstrated in the trial was based on specific selection criteria, and the benefits observed in the trial may not be realised in the intended PBS population if patients are able to access treatment under broader BEC criteria. The evaluation considered that a shorter window within which to assess BEC may be required for the PBS criteria as a means of better matching the conditions in the trial. The Pre-Sub-Committee Response (PSCR)

noted that for the consideration of uncontrolled severe allergic asthma, the PBAC previously recommended the extension of the validity period for BEC testing from 6 weeks to 12 months and noted clinical support indicated that this timeframe would allow timely access to mepolizumab treatment and reduce the logistical and administrative burden on patients and clinicians (paras 7.1–7.2, mepolizumab Public Summary Document [PSD], November 2017 PBAC Meeting). The PSCR highlighted that a 12 month validity window for COPD would similarly reduce logistical burden for patients and clinicians. The PSCR also noted a post-hoc exploratory analysis of pooled data from the mepolizumab COPD trials (METREX, METREO, MATINEE) demonstrated that for patients with BEC ≥300 cells/µL at any timepoint during the 12-month pre-randomisation period, mepolizumab led to 21% reduction in the annualised rate of moderate/severe exacerbations (relative risk [RR] = 0.79; 95% confidence interval [CI] 0.70, 0.90; p=0.001). The Sub-Committees considered that a 12 month time frame may be considered reasonable and agreed with the PSCR that it may allow for timely access to treatment. The Sub-Committees noted that a 12 month time frame would be consistent with current PBS restrictions for biologic medicines for the treatment of asthma. The PBAC agreed with the Sub-Committees that a 12 month validity window would be reasonable.

3.3 The proposed restriction defined 'Failure to achieve adequate control' with optimised triple inhaled therapy as: (i) ≥2 moderate exacerbations requiring systemic glucocorticoids with or without antibiotics in the last 12 months; OR (ii) ≥1 severe exacerbation (leading to hospitalisation) in the last 12 months. This is consistent with the MATINEE trial inclusion criteria. However, the trial further required that at least one exacerbation must have occurred while the patient was taking triple therapy (ICS + LAMA + LABA), or ICS-based dual therapy (ICS + LAMA or ICS +LABA) if either of the two bronchodilators were contraindicated. As the duration of optimised triple therapy was not defined, it is possible that some patients may qualify for PBS listed mepolizumab even though their exacerbations occurred prior to commencing LABA + LAMA + ICS treatment (i.e., exacerbations due to suboptimal management rather than resistant disease). It is suggested that, consistent with the trial, the wording of the PBS restriction include the duration of optimised triple therapy (minimum of 3 months use) and the requirement for at least one exacerbation to have occurred while the patient is taking triple therapy. The PSCR and Sub-Committees were supportive of these changes to the proposed restriction.

3.4 The MATINEE trial allowed use of ICS-based inhaled dual maintenance therapy (either ICS plus LABA or ICS plus LAMA) where intolerance or safety risk was documented for either LAMA or LABA. The trial did not include patients where ICS was contraindicated. However, the submission additionally requested to include patients with documented intolerance or safety concerns to ICS as ICS may pose a safety risk for certain subgroups of COPD patients particularly due to an increased risk of pneumonia. The Sub-Committees noted the MATINEE trial did not include patients where ICS was contraindicated. The Sub-Committees considered that the restriction should require patients to be taking a LABA, LAMA and an ICS. The Pre-PBAC Response maintained

that the restriction should include patients on dual therapy who are indicated for triple inhaled therapy. The Pre-PBAC Response noted that this would align with real-world practice, where not all patients tolerate triple therapy, and the current restriction criteria for uncontrolled severe asthma. The PBAC considered that intolerance or safety concerns associated with ICS were infrequent and mostly seen in patients with supratherapeutic doses of ICS. The PBAC considered that since the triple inhaler therapy should be 'optimised' without further specification of ICS dose, it was appropriate for the restriction to require patients to be taking a LABA, LAMA and an ICS. The PBAC considered that this would help reduce the risk of mepolizumab being used earlier in the treatment algorithm than intended.

3.5 Patients with severe COPD who had a post-salbutamol forced expiratory volume in 1 second ($FEV_1$) ≤ 20% were excluded from the MATINEE trial. When considering fluticasone furoate with umeclidinium and vilanterol for COPD, the PBAC advised that the $FEV_1$ requirement in the initial restriction be replaced with specification of exacerbation severity and a 12 month time period for the exacerbation history, to ensure consistency with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. It was noted that $FEV_1$ lacks precision to be used clinically as a predictor of exacerbations or mortality in patients with COPD and noted that history of previous exacerbations is regarded as the best predictor of future COPD episodes (paragraph 7.3, fluticasone furoate with umeclidinium and vilanterol, PSD, March 2019 PBAC meeting). The proposed PBS listing does not include an $FEV_1$ criterion. Excluding the $FEV_1$ threshold is consistent with the current PBS listings for fixed dose combination products for COPD. The evaluation also considered that the proportion of patients with $FEV_1$ ≤ 20% was likely to reflect a very small proportion of the eligible PBS population.

3.6 The submission requested a grandfather provision for patients that will be enrolled in a planned access program with restrictions aligned with the proposed initial PBS listing. Differences between the initial and grandfathering restriction are that grandfathered patients must have been using mepolizumab prior to the PBS listing date, and that the restriction is only valid from 12 months of the PBS listing date. The grandfathering restriction did not include a response assessment based on prior treatment. The PBAC considered the grandfathering phases should include clinical criteria requiring patients who have received at least 24 weeks of treatment to have both achieved and sustained an adequate response.

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

# 4 Population and disease

4.1 COPD is a heterogenous lung condition characterised by chronic respiratory symptoms (such as cough, dyspnoea and expectoration) and exacerbations, due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. While a broad range of genetic and environmental factors contribute to the risk of COPD developing, smoking remains

one of the most significant risk factors in high-income countries such as Australia. Clinically, there is considerable heterogeneity across patients with respect to symptoms, manifestations of parenchymal destruction and small airway damage, exacerbation frequency and co-morbidities.

4.2 The underlying inflammatory mechanism driving chronic airway inflammation in COPD can be broadly differentiated into type 1 and type 2 inflammation. An elevated BEC ('eosinophilic inflammation') is one of the established biomarkers of type 2 inflammation. Approximately 15% to 40% of the general COPD population are estimated to have signs of eosinophilic inflammation, as characterised by BEC ≥ 300 cells/µL. The submission stated that emerging evidence suggests these patients with COPD and BEC ≥ 300 cells/µL represent a distinct COPD phenotype ('eosinophilic phenotype') who are at increased risk of exacerbations and accelerated decline in lung function. While the concordance between blood and lung airways type 2 biomarkers do not strictly correlate, higher BEC in patients with COPD are associated with increased lung eosinophil numbers and the presence of higher levels of type 2 inflammation in the airways.

4.3 Mepolizumab is a humanised monoclonal antibody (IgG1, kappa) directed against human interleukin-5 (IL-5), a major cytokine responsible for the growth and survival of eosinophils. The submission proposed mepolizumab as add-on maintenance treatment for adults with uncontrolled COPD with an eosinophilic phenotype (BEC ≥300 cells/µL) and on a stable combination of an ICS, LABA and LAMA. This is in line with the GOLD Report 2026[1], however the proposed restriction also allows the use of mepolizumab as an add-on treatment in patients where LAMA, LABA or ICS are contraindicated.

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

# 5 Comparator

5.1 The submission estimated approximately 60% of patients with COPD who use triple inhaled therapy consisting of LABA + LAMA + ICS, continue to experience exacerbations, with 46% exhibiting BEC ≥ 300 cells/µL. This group of patients represents approximately 6% of the overall COPD population. There are currently no PBS subsidised pharmacological maintenance treatments available for these patients. The PBAC agreed with the Sub-Committees that the choice of triple inhaled therapy alone as the comparator in the submission was appropriate.

5.2 As an application for the consideration of dupilumab in the same population was submitted for the March 2026 PBAC Meeting, this may be considered a near market comparator. At the time of the evaluation, 2 published indirect treatment comparisons (ITCs) of mepolizumab versus dupilumab were available (see paragraph 6.26). The submission also provided a matching-adjusted indirect comparison (MAIC)

[1] *Global Initiative for Chronic Obstructive Lung Disease. 2025. https://goldcopd.org/2026-gold-report-and-pocket-guide*

comparing mepolizumab and dupilumab (see paragraphs 6.27 and 6.28). The PBAC considered that dupilumab was a relevant near market comparator.

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

# 6 Consideration of the evidence

## Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician stated that despite the availability of triple inhaled therapy, achieving optimal disease control in COPD patients remains challenging. The clinician highlighted that for this patient population, fewer and delayed exacerbations as observed for mepolizumab plus triple inhaled therapy vs triple inhaled therapy alone in the MATINEE trial, would be clinically meaningful for patients and provide cost and operational advantages for the health care system. The clinician stated that mepolizumab would improve the likelihood of stable COPD, preserve lung function and help to reduce exposure to systemic corticosteroids and antibiotics, thereby allowing patients to maintain independence and result in an overall improved quality of life. The clinician stated that from a system perspective, fewer exacerbations would likely translate into reduced emergency department and general practitioner presentations, lower rates of hospitalisations, and lead to an overall reduction in health care resource burden. The clinician highlighted that each exacerbation accelerates irreversible lung-function decline, and heightens the risk of subsequent events, often shortening the interval between them. The clinician stated that this exacerbation-driven cycle reflects the progressive nature of COPD, which distinguishes this population from patients with severe asthma, in whom lung function is largely reversible. The clinician also noted the demographic differences between COPD and severe asthma patients, where COPD patients are often older, more fragile and have more co-morbidities, such as cardiovascular disease, which increase susceptibility to exacerbations and amplify their clinical impact. The clinician also noted that for mepolizumab patients in the MATINEE trial, a waning in treatment effect was not observed and noted that there were strong theoretical reasons that indicate that the prevention of one exacerbation leads to the prevention of subsequent exacerbations, leading to a cascade of clinical benefit which would continue to be observed beyond 1 year.

## Consumer inputs

6.2 The PBAC noted and welcomed input from individuals who would like access to mepolizumab (4), health care professionals (3) and organisations (3) via the Office of Health Technology Assessment Consultation Hub. Comments from individuals who would like access to mepolizumab described the impact that chronic respiratory symptoms (cough and shortness of breath) had on their ability to work, complete housework, and spend time with family. Individuals reported mixed experiences with inhaled therapies: one noted that inhaled triple therapy was ineffective, while another describes the cough and voice changes associated inhalation delivery methods.

6.3 Health care professional input described current inhaler and non-pharmacological interventions as insufficient for a subset of consumers with type 2 (eosinophilic) airway disease who continue to experience exacerbations despite optimised inhaled triple therapy. Comments stated that a significant proportion of these patients would benefit from IL-5 directed treatments, such as mepolizumab, and noted the positive results of mepolizumab vs placebo in the MATINEE trial. Health care professionals described COPD as a disabling condition associated with significant stigma and high mortality. COPD exacerbation symptoms were often described as feeling life-threatening. Health care professionals considered reducing exacerbations an important treatment outcome, noting that these events were associated with an increased risk of subsequent exacerbations, cardiovascular events, accelerated lung function decline and a higher risk of death. Health care professional input noted current standard of care for COPD exacerbations relies on oral corticosteroids which are associated with substantial side effects. Comments from health care professionals noted that disadvantages could arise from the PBS listing of mepolizumab, if patients with BEC < 200 cells/µL, or patients not yet receiving optimised triple therapy, access treatment.

6.4 Comments from Lung Foundation Australia, the Pharmaceutical Society of Australia and the Centres of Excellence in Treatable Traits and Severe Asthma expressed support for the proposed PBS listing of mepolizumab. Comments highlighted the high clinical need for patients with uncontrolled COPD despite optimised triple therapy and described the significant quality of life impacts associated with an increasing symptom burden that affects movement, daily activities and social engagements. Lung Foundation Australia noted that biologic medications have the potential to reduce reliance on oral corticosteroids, which are associated with significant morbidity and downstream health care costs. The Pharmaceutical Society of Australia noted that dupilumab was being considered at the March 2026 PBAC meeting and highlighted that standardisation of terminology or wording in the PBS listing criteria would be helpful to ensure consistency for prescribers.

## Clinical trials

6.5 The submission was based on one pivotal phase 3, multicentre, randomised, double-blind, placebo-controlled clinical trial, MATINEE (n=804), which compared mepolizumab as add-on to triple inhaled therapy (i.e., LABA + LAMA + ICS) to triple inhaled therapy alone in patients with uncontrolled COPD and an eosinophilic phenotype, over 52-weeks (with a 104-week extended duration to account for COVID-19).

6.6 Within MATINEE, uncontrolled COPD was defined as: history of ≥ 2 moderate (clinically significant exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics) or ≥ 1 severe (an event requiring hospitalisation for ≥ 24 hours) exacerbation within 12 months prior to inclusion, with one of these exacerbations

occurring while using triple inhaled therapy. This definition of moderate and severe exacerbation is consistent with the GOLD Report 2025[2].

6.7 The submission reported that exacerbations among individuals with COPD were considerably reduced in the MATINEE trial due to the adoption of non-pharmaceutical interventions such as physical distancing, lockdowns and masks due to the COVID-19 pandemic measures. To account for these effects, the MATINEE trial extended its treatment duration from 52 weeks to 104 weeks following regulatory approval (Protocol Amendment 6, approved 6 December 2021) to maximise the opportunity for collection of exacerbation data and maintain sufficient study power. The evaluation considered that it was unclear the extent to which the conduct of the trial during the COVID-19 pandemic may have affected the observed relative benefits of treatment with mepolizumab compared to placebo.

6.8 Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

| Study identifier | Citation | Publication citation |
|---|---|---|
| **Trials meeting the selection criteria** | | |
| MATINEE (NCT04133909) | A multi-centre, randomised, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657) | 24 October 2024 |
| | Sciurba, FC., Criner, GJ., Christenson, SA., et al. 2025. Mepolizumab to prevent exacerbations of COPD with an eosinophilic phenotype. | 30 April 2025<br><br>*New England Journal of Medicine, 392(17): 1710–1720.* |
| | Papi, SA. Christenson, J. Min, et al. (2025) Mepolizumab Is Efficacious Regardless of Severity of Prior Chronic Obstructive Pulmonary Disease Exacerbations: Post Hoc Analysis of the MATINEE Phase III Randomized Controlled Trial [abstract]. | 18 May 2025<br><br>*Am J Respir Crit Care Med 211:A1293.* |
| | Pavord, I., Jackson, DJ., Korn, S., et al. (2024). Clinical trial design of biologic therapies in COPD: MATINEE study of mepolizumab. | 30 October 2024<br><br>*European Respiratory Journal 2024 64(suppl 68): PA4789.* |
| METREX (NCT02105948) | Study to Evaluate Efficacy and Safety of Mepolizumab for Frequently Exacerbating Chronic Obstructive Pulmonary Disease (COPD) Patients (Study MEA117106). | - |
| | Study MEA117106: Mepolizumab vs. Placebo as add-on Treatment for Frequently Exacerbating COPD Patients. | - |
| | Sciurba, F., Chanez, P., Martinot, JB., et al. (2017). Late breaking abstract-mepolizumab reduces exacerbations in eosinophilic COPD. | 06 December 2017<br><br>*European Respiratory Journal 2017 50(suppl 61): OA3194.* |
| METREO (NCT02105961) | Efficacy and Safety of Mepolizumab as an Add-on Treatment in Chronic Obstructive Pulmonary Disease (COPD) (Study MEA117113) | - |

[2] *Global Initiative for Chronic Obstructive Lung Disease. 2024. https://goldcopd.org/wp-content/uploads/2024/11/GOLD-2025-Report-v1.0-15Nov2024_WMV.pdf p110*

| Study identifier | Citation | Publication citation |
|---|---|---|
| | Study MEA117113: Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level | - |
| | Pavord, ID., Kerstjens, HA., Korn, S., et al. (2017). Late Breaking Abstract-Dose-ranging study of mepolizumab in eosinophilic COPD. | 06 December 2017<br><br>*European Respiratory Journal 2017 50(suppl 61): PA1366.* |
| METREX/METREO pooled analysis | Pavord, ID., Chanez, P., Criner, GJ. et al. (2017). Mepolizumab for eosinophilic chronic obstructive pulmonary disease. | 26 October 2017<br><br>*New England Journal of Medicine, 377(17): 1613–1329.* |
| | Pavord, ID., Chapman, KR., Bafadhel, M., et al. (2021). Mepolizumab for eosinophil-associated COPD: analysis of METREX and METREO. | 16 June 2021<br><br>*International Journal of Chronic Obstructive Pulmonary Disease:16 1755–1770.* |
| | Condreay LD, Gao C, Bradford E, Yancey SW and Ghosh S. 2019. No genetic associations with mepolizumab efficacy in COPD with peripheral blood eosinophilia. | 05 July 2019<br><br>*Respiratory Medicine 155: 26–28.* |
| | Bafadhel, M., Sciurba, FC., Paggiaro, et al. (2018). Mepolizumab for eosinophilic chronic obstructive pulmonary disease (COPD): A meta-analysis of METREX and METREO exacerbation endpoints. | 22 May 2018 |
| | Chapman, KR., Pavord, ID., Paggiaro, et al. (2018). Mepolizumab for eosinophilic chronic obstructive pulmonary disease (COPD): a meta-analysis of METREX and METREO patient-reported outcomes, response to therapy and lung function. | 21 May 2018<br><br>*American Thoracic Society;197:A4230* |
| | Condreay L, Gao C, Bradford E, Yancey S and Ghosh S. 2019. No genetic associations were identified with mepolizumab efficacy in eosinophilic COPD. | 21 May 2019<br><br>*American Journal of Respiratory and Critical Care Medicine 199:A4550.* |
| | Criner, GJ., Hanania, NA., Maltais, F., et al. (2024). Efficacy of Mepolizumab in Patients With COPD and an Eosinophilic Phenotype With Chronic Bronchitis-A Post Hoc Analysis of the METREX & METREO Phase 3 Studies. In A27. Emerging Treatments and Therapeutic areas and Therapeutic Strategies in COPD. Results of Clinical Trials and Observational Studies. | 19 May 2024<br><br>*American Thoracic Society, 209:A1203.* |
| | Pavord, ID., Criner, G., Kerstjens, H., et al. (2018). Eosinophils as a predictor of mepolizumab treatment responses in COPD. | 19 November 2018<br><br>*European Respiratory Journal 2018 52(suppl 62): PA1992* |
| | Sciurba, FC., Han, ML., Korn, S et al. (2024). Efficacy of Mepolizumab in Patients With Chronic Obstructive Pulmonary Disease With or Without Chronic Bronchitis: Post Hoc Analysis of the METREX and METREO Phase 3 Trials | 21 May 2024<br><br>*American Thoracic Society. 209:A4976.* |

| Study identifier | Citation | Publication citation |
|---|---|---|
| | Vogelmeier, C., Stolz, D., Roche, N., et al. (2024). Mepolizumab response in patients with COPD and an eosinophilic phenotype with/without chronic bronchitis (CB): A METREX/METREO post hoc analysis. | 30 October 2024<br><br>*European Respiratory Journal 2024 64(suppl 68): PA4783* |
| COPD HELP (NCT04075331) | Flynn CA, McAuley HJC, Elneima O, Aung HWW, Ibrahim W, Ward TJC, Bourne M, Thornton TD, Mistry V, Gilbert HR and et al. 2025. Mepolizumab for COPD with Eosinophilic Phenotype following Hospitalization. NEJM evidence 4(6): EVIDoa2500012. | 30 April 2025<br><br>*NEJM Evidence:4(6)* |
| | Flynn, C., McAuley, HJC., Elneima, O., et al. (2025). COPD-HELP: A Randomised Controlled Trial of Mepolizumab Initiated Following Admission to Hospital for a Severe Exacerbation of Eosinophilic COPD. | 20 May 2025<br><br>*American Journal of Respiratory and Critical Care Medicine 2025;211:A5546* |

Source: Table 2-4 pp54-55 of the submission.
COPD = chronic obstructive pulmonary disease; MEPO= mepolizumab; SC = subcutaneous.

6.9 The key features of the randomised controlled trial (RCT), the MATINEE trial, are summarised in Table 3.

**Table 3: Key features of the included evidence from the MATINEE trial (mITT population)**

| N | Design/ duration | Overall risk of bias | Patient population | Outcomes | Use in modelled evaluation |
|---|---|---|---|---|---|
| *mITT*[a]<br>Mepolizumab, n=403<br>PBO, n=401 | R, DB<br>52 weeks | Low | Adults using LABA+LAMA+ICS for at least 3 months with uncontrolled COPD[b] with BEC ≥ 300 cells/µL at screening AND historical BEC ≥ 150 cells/µL in the previous 12 months | Primary: Annualised rate of moderate to severe exacerbation assessed up to 104 weeks | Annualised rate of moderate to severe exacerbation |
| | | | | Secondary: Time to first moderate or severe exacerbation assessed up to 104 weeks | |
| | | | | Secondary: Proportion of CAT responders (≥ 2-unit reduction from baseline) at Week 52 | |
| | | | | Secondary: Proportion of SGRQ total score responders (defined as ≥ 4-point reduction from baseline) at Week 52 | |
| | | | | Secondary: Proportion of E-RS: COPD responders (≥2-unit reduction from baseline) at Week 52 | |
| | | | | Secondary: Annualised rate of exacerbations requiring ED visit and/or hospitalisation assessed up to 104 weeks | |

*Source: Developed during the evaluation using Table 2-5 p58; Table 2-15 pp73-74; Table 2-17 p80; Table 2-18 p82; Table 2-19 p83 of the submission.*

*BEC = blood eosinophil count; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; DB = double blind; ED= emergency department; E-RS: COPD = Evaluating Respiratory Symptoms in COPD; FEV1 = forced expiratory volume in one second; ICS= inhaled corticosteroids; LABA = long-acting beta-2 agonist; LAMA = long-acting muscarinic antagonist; mITT = modified intention to treat; PBO= placebo; R = randomised; SGRQ = St George Respiratory Questionnaire.*

[a] *Patients who received ≥ 1 dose of study treatment.*

[b] *Uncontrolled COPD defined in terms of patient with moderate to severe air flow obstruction (post-bronchodilator FEV1 < 80%) and who have experienced ≥ 2 moderate (an exacerbation that requires systemic corticosteroids and/or antibiotics to treat, with one of the two requiring systemic corticosteroids) or ≥ 1 severe exacerbation (an exacerbation requiring hospitalisation).*

6.10 Overall, the risk of bias in the study was considered low across the domains of selection bias, performance bias, detection bias, attrition bias and reporting bias, as it was randomised, double-blinded with an independent committee that evaluated the safety and efficacy data, and adjudicated safety events.

6.11 The submission nominated a minimum clinically important difference (MCID) of ≥ 20% reduction in the relative treatment difference in the annualised rate of clinically significant exacerbations. The published MCIDs summarised by the submission varied between 4.4% to 42%, with no clear MCID for the evaluation of moderate or severe exacerbations. There is no validated MCID for exacerbations in COPD. Previously, the PBAC has considered an MCID of 9% to 54% for annual rates of all grades of exacerbations, but noted that the baseline rate, exacerbation severity and study duration were required for interpretation of the MCID (paragraph 6.10, fluticasone furoate with umeclidinium and vilanterol PSD, March 2019 PBAC Meeting).

6.12 Lung function was included as an exploratory end point in the MATINEE trial. The PBAC has previously considered $FEV_1$ as one measure of lung function that is a relevant patient outcome in COPD and accepted this as a surrogate measure. However, the PBAC considered that additional clinical outcomes such as frequency of exacerbations and hospitalisations would be informative as more direct, patient relevant measures of effect (paragraph 6.8, fluticasone vilanterol PSD March 2014 PBAC Meeting).

6.13 The submission used a ≥ 2-point decrease from baseline in the COPD Assessment test (CAT) score at Week 52 as the threshold for clinically meaningful improvement, based on the established MCID (Jones et al., 2009; Kon et al., 2014). The threshold for St George's Respiratory Questionnaire for COPD (SGRQ-C) total score was a ≥ 4-point decrease from baseline based on the established MCID reported by Meguro et al. (2007) and the nominated MCID for Evaluating Respiratory Symptoms in COPD (E-RS: COPD) was a ≥ 2-point decrease from baseline (Leidy et al., 2022).

6.14 In the MATINEE trial, of the 806 patients randomised, 804 (> 99%) received ≥ 1 dose of study treatment and were included in the modified intention to treat (mITT) analysis population for the efficacy assessment for primary and secondary end points. In the overall mITT population, 345 (42.9%) patients were enrolled for a fixed 52-week duration and 459 (57.1%) for an additional variable duration of 52 to 104 weeks.

6.15 All patients were required to complete a minimum of 52 weeks of treatment, where the maximum treatment period to 104 weeks was implemented due to the COVID-19 pandemic. Individual patient treatment duration was determined when they enrolled relative to when the overall study reached its event target, not by individual patient characteristics or response to treatment. Data were combined for the fixed 52-week duration group and the variable 52 to 104 weeks duration group. The evaluation considered that this was appropriate.

6.16 The evaluation considered that the baseline characteristics were balanced between the two arms and noted that exacerbation history is the best predictor of future exacerbations. Most participants (83%) had ≥ 2 moderate exacerbations and 21% had ≥ 1 severe exacerbation in the 12 months before screening, with an average of 2.3 prior moderate and/or severe exacerbations.

## Comparative effectiveness

Primary endpoint: annualised rate of moderate or severe exacerbation

6.17 Overall, mepolizumab led to a statistically significant reduction (21%; p=0.011) in the annualised rate per patient year of moderate or severe exacerbation compared to placebo (rate ratio), exceeding the nominated MCID of a ≥ 20% reduction (Table 4). The majority of patients in both the mepolizumab and placebo arms had < 1 exacerbation per year (65% versus 61% respectively), including no exacerbations in 50% of mepolizumab patients and 44% of placebo patients. The evaluation considered that where exacerbations did occur, the efficacy difference appeared to be driven by a subset of outlier patients (n = 6, 1.5% of the placebo arm) with ≥ 9 exacerbations; this makes the difference in the occurrence of exacerbations vulnerable to random

confounders, meaning the treatment effect could substantially change were the trial to be replicated. The evaluation considered it also suggests that part of the treatment benefit is derived from reducing repeat exacerbations in patients who exacerbate frequently, rather than preventing exacerbations across a larger number of patients.

6.18 The Sub-Committees noted that the PSCR disagreed that the treatment effect was sensitive to outlier patients with ≥ 9 exacerbations. The PSCR noted the following:

- The evaluation's definition of an outlier in the SoC arm, based on the avoidance of events in the mepolizumab arm, conflicts with the concept of a parallel trial design where there was a balanced distribution of treatment effect modifiers across both arms. It should be assumed that there would be a similar breakdown of exacerbations if the treatment arms were switched at randomisation.
- Patients with ≥ 9 exacerbations were not outliers. The exacerbation frequency in the 12 months prior to randomisation in the METREX and METREO trials ranged from 1 to 12, and ≥ 9/year was not uncommon.
- MATINEE accounted for patient variability by analysing annualised exacerbation rates and therefore accounted for high values.
- Treatment effect did not substantially change across similar trials (METREX and METREO).

However, the Sub-Committees noted that there were inconsistencies in the results in METREX and METREO, with METREO not showing a statistically significant difference in exacerbation rates in patients with screening BEC ≥ 300 cells/µL (RR = 0.85, 95% CI: 0.59–1.22; Table 5). The Pre-PBAC Response noted that METREX and METREO lacked statistical power for the BEC ≥ 300 cells/µL subgroup, with small sample sizes (N=172 and N=170, respectively), whereas MATINEE was designed and powered for this subgroup. The Pre-PBAC response argued that, in addition to the meta-analysis (N=1146, RR=0.79, 95%CI = 0.68,0.91, Table 5)[3], the MATINEE trial was a more reliable source of evidence.

6.19 The trial had a variable treatment duration of 52 to 104 weeks. Annualised exacerbation rates were used to account for this variability, resulting in an expression of an exacerbation rate per patient year of exposure (consistent with previous trials investigating treatments for COPD). However, this method assumes a constant event rate throughout the study period. The PSCR maintained that the use of annualised exacerbation rates was an appropriate approach to account for study duration variability and noted that although patient drop-off led to differences in event rates at Weeks 52 and 104, this did not influence the treatment difference between mepolizumab and placebo. The PSCR noted that the results for the primary endpoint up to week 52 (RR = 0.79, 95% CI: 0.65, 0.96) were consistent with the primary analyses up to week 104 (RR= 0.79, 95% CI: 0.66, 0.94).

[3] *Note that the results are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.20 The annualised rate of moderate exacerbations was assessed as a post hoc analysis where treatment with mepolizumab led to a 21% reduction (p=0.018) compared with placebo. The annualised rate of severe exacerbations was assessed as an exploratory outcome where treatment with mepolizumab led to a 34% relative reduction (p=0.055) compared to placebo. The results of the ad hoc analysis were consistent with the demonstrated primary outcome, showing a reduction in exacerbation rates (moderate or severe) that exceeded the MCID.

**Table 4: Annualised rate of moderate/severe exacerbations (mITT population) at 104 weeks**

| | Mepolizumab N = 403 | PBO N = 401 |
|---|---|---|
| **Primary outcome (moderate or severe exacerbations)** | | |
| **Number of moderate or severe exacerbations per year[a], n (%)** | | |
| 0 | 201 (50) | 175 (44) |
| >0-<1 | 62 (15) | 68 (17) |
| 1-<2 | 70 (17) | 77 (19) |
| 2-<3 | 30 (7) | 36 (9) |
| 3-<4 | 21 (5) | 16 (4) |
| 4-<5 | 8 (2) | 11 (3) |
| 5-<6 | 5 (1) | 6 (1) |
| 6-<7 | 3 (<1) | 2 (<1) |
| 7-<8 | 1 (<1) | 2 (<1) |
| 8-<9 | 2 (<1) | 2 (<1) |
| 9-<10 | 0 | 2 (<1) |
| ≥10 | 0 | 4 (<1) |
| Annualised rate of moderate or severe exacerbations (95% CI) | 0.80 (0.70, 0.91) | 1.01 (0.89, 1.15) |
| Rate ratio (95% CI); p value | **0.79 (0.66, 0.94); p = 0.011** | |
| **Individual components** | | |
| Rate ratio for moderate exacerbations (95% CI); nominal p value[b] | **0.79 (0.65, 0.96); p = 0.018** | |
| Rate ratio for severe exacerbations (95% CI); nominal p value[c] | 0.66 (0.43, 1.01); p = 0.055 | |

*Source: Table 2-17 p80 of the submission.*

*CI = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; mITT = modified intent-to-treat; PBO = placebo.*

*[a] Based on the crude annualised rate of exacerbations.*

*[b] Post hoc analysis. Note that these results are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

*[c] Exploratory analysis.*

*Analysis performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal), baseline % predicted FEV1 and smoking status (current versus former smoker), and with logarithm (time on- and off-treatment) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.*

*Bold indicates a statistically significant difference.*

6.21 The annualised rate of moderate or severe exacerbations during trial follow-up in the placebo arm (1.01) was substantially lower when compared to the rate reported in the 12 months prior to randomisation (unadjusted annualised rate of moderate/severe exacerbation = 2.3). Due to the COVID-19 pandemic, it is possible that stay-at-home and social distancing measures resulted in patients being less exposed to infection triggers. This may have affected the total number of exacerbations events observed in the trial. The Sub-Committees agreed with the evaluation that this was unlikely to have affected the difference between treatment arms in the occurrence of

moderate/severe exacerbation events, however considered it remained an uncertainty.

6.22 The time to first moderate or severe exacerbation was assessed as a secondary outcome. The Kaplan-Meier (KM) median time to the first moderate or severe exacerbation was longer in the mepolizumab group (419 days) compared to placebo (321 days). The time to first event analysis showed a statistically significant 23% reduction (hazard ratio [HR] = 0.77, 95% CI 0.64–0.93, p=0.009) in the hazard of the first exacerbation (moderate/severe exacerbation) event for mepolizumab compared with placebo. The risk was lower in the mepolizumab arm by 8 weeks, with the KM curves remaining divergent for the remainder of the study.

6.23 Treatment with mepolizumab led to a 35% relative reduction (p=0.032) in the annualised rate of exacerbations requiring an emergency department (ED) visit and/or hospitalisation compared with placebo. The evaluation considered that the rate reduction was driven by approximately 15 patients (less than 4% of the total cohort). This suggests that the aggregate benefit is derived from a small subset of patients. The PSCR considered that this would be an incorrect interpretation of the data which only considered those patients without an exacerbation (risk difference of 4% [17 patients]). Instead, the treatment benefit should be derived from reducing repeat exacerbations in patients who exacerbate frequently. The PSCR argued that mepolizumab consistently reduced the exacerbation frequency (ED visit/hospitalisation) compared to placebo, confirming the clinical benefit is driven by substantially more than 4% of the cohort.

6.24 Table 5 shows the exacerbation rates in patients across the MATINEE, METREX and METREO trials, and pooled results (as noted in the PSCR, p3).

**Table 5: Moderate/severe exacerbations in patients with screening BEC ≥300 cells/µL - MATINEE, METREX, METREO**

| | MATINEE[a] | | METERO[b] | | METREX[b] | | Pooled[c] | |
|---|---|---|---|---|---|---|---|---|
| | PBO (N=401) | MEPO (N=403) | PBO (N=87) | MEPO (N=83) | PBO (N=90) | MEPO (N=82) | PBO (N=578) | MEPO (N=568 |
| Exacerbations rate/year | 1.01 | 0.80 | 1.43 | 1.22 | 1.94 | 1.32 | 1.25 | 0.98 |
| Rate ratio (95% CI) | 0.79 (0.66, 0.94) | | 0.85 (0.59, 1.22) | | 0.68 (0.50, 0.92) | | 0.79 (0.68, 0.91) | |

*Source: Table 1. PSCR*
*Abbreviations: BEC = blood eosinophil count; CI = confidence interval; MEPO = mepolizumab; PBO = placebo*
*a Sciurba et al (2025)*
*b Sponsor Data on File. Note that the results in Table 5 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*
*c Vogelmeir et al (2025)*

QoL outcome changes[4]

6.25 The results in MATINEE did not meet any criteria for a meaningful difference in subjective quality of life as measured by three validated scales, as follows:

- The proportion of patients who achieved a CAT response at Week 52 (≥ 2-point decrease from baseline) between the mepolizumab and placebo treatment arms was 41% vs 46% (odds ratio [OR]=0.81; 95% CI 0.60, 1.09; p= 0.161). A 5%

[4] *Note that p values have not been adjusted for multiplicity*

difference for no change/worsening in the CAT score was noted in the mepolizumab arm compared to the placebo arm (mepolizumab = 43% vs placebo = 38%).

- The proportion of patients who achieved an SGRQ response at Week 52 (≥ 4-point decrease from baseline) between the mepolizumab and placebo treatment arms was 50% vs 46% (OR = 1.17; 95% CI 0.87, 1.57; p= 0.291).
- The proportion of patients who achieved an E-RS: COPD response (≥ 2-point decrease from baseline) between the mepolizumab and placebo groups was 31% vs 34% (OR = 0.82; 95% CI 0.60, 1.12; p=0.209).

ITC compared with dupilumab

6.26 The Sub-Committees noted that at the time of evaluation, 2 ITCs of mepolizumab compared to dupilumab had been published.

- Bhatt et al. (2025) conducted a placebo-adjusted Butcher ITC using aggregate clinical trial data from the BOREAS and NOTUS trials (dupilumab), and the METREX, METREO and MATINEE trials (mepolizumab). The study found that dupilumab provided a numerically favourable reduction (rate ratio of 0.82; 95% CI 0.66, 1.01) in the rate of moderate-to-severe exacerbations compared with mepolizumab (not statistically significant, METREO results not included in the primary ITC analysis). The placebo-adjusted Bucher ITC evaluating the change in pre-bronchodilator $FEV_1$ at week 52, the proportion of patients with SGRQ total score ≥ 4 points, and the proportion of patients with E-RS: COPD total score improvement ≥ 2 points significantly favoured dupilumab versus mepolizumab. The trials differed in their eosinophil count inclusion criteria. BOREAS and NOTUS required ≥ 300 cells/µL in the year prior. METREO allowed counts ≥ 150 cells/µL at screening but ≥ 300 cells/µL in the prior year. MATINEE required ≥ 300 cells/µL at screening and historical counts ≥ 150 cells/µL and METREX enrolled patients with and without elevated eosinophil counts. These variations may have influenced the trial outcomes.[5] The authors stated that a comparison of safety between dupilumab and mepolizumab was not included in the Butcher ITC because no meaningful differences in adverse events (AEs) or severe adverse events (SAEs) were observed in the studies. The PBAC recalled that in its consideration of dupilumab for uncontrolled severe eosinophilic or allergic asthma the Committee had considered a claim of non-inferior comparative safety versus the nominated comparators (which included mepolizumab) was reasonable (paragraph 7.7, dupilumab PSD, November 2020 PBAC Meeting).
- Suter et al. (2025) conducted an indirect comparison using published crude data for rate ratios or mean differences and their corresponding 95% CIs for dupilumab (BOREAS and NOTUS) and mepolizumab (MATINEE). The study concluded that both treatments were effective in reducing exacerbations. When comparing

[5] *Bhatt SP, Freemantle N, Soliman M, Heble J, Cabon Y, Mayen Herrera E, Yang J, Xu Y. Dupilumab Versus Mepolizumab for COPD: Evaluating Efficacy Outcomes Using Placebo-Adjusted Indirect Treatment Comparison. Pulmonary Therapy. 2025 Sep 26:1-7.*

crude 95% CI for the primary outcome, no difference between dupilumab and mepolizumab was apparent, although there was a numerically shorter time interval required to prevent an exacerbation in patients receiving dupilumab (2.3 years in NOTUS and 3.1 years in BOREAS, compared to 4.8 years in MATINEE).[6]

6.27 The Sub-Committees noted the submission had also presented a MAIC comparing mepolizumab and dupilumab (as noted in the PSCR p4). The PSCR noted that based on differences in eligibility criteria between the trials, 'restricted' analysis populations were identified from individual patient data from METREO, METREX, and MATINEE trials. Patients from the ITT population were included if they had BEC ≥300 cells/µL at screening, chronic bronchitis (per investigator-assessed or per response to SGRQ-C questionnaire), mMRC Dyspnoea Scale Score ≥2, and moderate to severe airflow limitation at baseline. The Sub-Committees noted that aggregate data from BOREAS and NOTUS had also been used. The MAIC was additionally adjusted for differences in the distribution of baseline characteristics across the trials deemed potential confounders/treatment effect modifiers, which included age, sex, race, geographic location, body mass index, number of moderate/severe exacerbations at baseline, having ≥1 severe exacerbation at baseline, smoking status, blood eosinophil count at screening, SGRQ-C total score at baseline, and E-RS:COPD score at baseline. The two subsets of patients presented were chronic bronchitis based on investigator assessment and the SGRQ-C questionnaire. The Sub-Committees considered that the weighted distribution appeared balanced between the two groups. Overall, the Sub-Committees considered the MAIC appeared to have been conducted in a methodologically sound manner.

6.28 The Sub-Committees noted that the MAIC demonstrated that there was no statistically significant difference between mepolizumab and dupilumab in reducing the annualised rate of moderate or severe exacerbations, the annualised rate of severe exacerbations or the time to first moderate or severe exacerbation, with all confidence intervals crossing zero (Table 6). The PSCR stated that the results demonstrate that mepolizumab is non-inferior to dupilumab in terms of efficacy. However, the Sub-Committees considered that it was unclear whether a conclusion of non-inferiority could be claimed, as no non-inferiority margin had been specified.

**Table 6: MAIC estimates of mepolizumab vs dupilumab, via placebo as the common reference arm**

| Restricted population | Annualised rate of moderate/severe exacerbations RR (95% CI) | Annualised rate of severe exacerbations RR (95% CI) | Time to first moderate or severe exacerbation HR (95% CI) |
|---|---|---|---|
| CB defined by investigator | 0.91 (0.60, 1.37) | 0.68 (0.27, 1.72) | 0.71 (0.46, 1.08) |
| CB based on SGRQ-C | 1.13 (0.80, 1.58) | 1.01 (0.47, 2.16) | 0.83 (0.61, 1.14) |

*Source: Figure A4 p217 submission, Table 3. PSCR*
*CB = chronic bronchitis; SGRQ = St. George Respiratory Questionnaire-COPD specific*

[6] *Suter P, Greig R, Chan R, Lipworth B. Efficacy of dupilumab and mepolizumab in eosinophilic COPD: insights from phase 3 trials. Respiratory Medicine. 2025 Sep 5:108343.*

## Comparative harms

6.29 Overall, mepolizumab was well tolerated with a safety profile similar to placebo (inhaled triple therapy alone). AEs were generally higher for the variable duration group (patients enrolled for up to 104 weeks) compared to the fixed duration group (patients enrolled for 52 weeks), which was considered consistent with longer treatment exposure. No new safety concerns were identified. An overview of AEs and SAEs in the overall safety population is presented in Table 7. The incidences of any AEs and SAEs during or after the treatment period were similar in both treatment arms.

**Table 7: Overview of AEs and SAEs (overall safety population)**

| Outcome | Mepolizumab N = 403 | PBO N = 401 | RR[a] (95% CI) | RD[a] (95% CI) |
|---|---|---|---|---|
| Any on/post-treatment AE | 301 (75%) | 308 (77%) | 0.97 (0.90, 1.05) | -0.02 (-0.08, 0.04) |
| AEs related to study treatment | 19 (5%) | 17 (4%) | 1.11 (0.59, 2.11) | 0.01 (-0.02, 0.03) |
| AEs leading to permanent discontinuation of study treatment | 14 (3%) | 18 (4%) | 0.77 (0.39, 1.54) | -0.01 (-0.04, 0.02) |
| AEs leading to withdrawal from the trial | 15 (4%) | 16 (4%) | 0.93 (0.47, 1.86) | 0.00 (-0.03, 0.02) |
| AEs leading to dose interruption/delay | 12 (3%) | 21 (5%) | 0.57 (0.28, 1.14) | -0.02 (-0.05, 0.01) |
| Any on/post-treatment SAE | 101 (25%) | 115 (29%) | 0.87 (0.70, 1.10) | -0.04 (-0.10, 0.03) |
| SAEs related to study treatment | 0 | 0 | 0 | 0 |
| Fatal SAEs | 11 (3%) | 11 (3%) | 1.00 (0.44, 2.27) | 0.00 (-0.02, 0.02) |
| Fatal SAEs related to study treatment | 0 | 0 | 0 | 0 |
| Any on-treatment AE | 299 (74%) | 307 (77%) | 0.97 (0.90, 1.05) | -0.02 (-0.08, 0.04) |
| Any on-treatment SAE | 99 (25%) | 112 (28%) | 0.88 (0.70, 1.11) | -0.03 (-0.09, 0.03) |
| Any post-treatment AE | 23 (6%) | 20 (5%) | 1.14 (0.64, 2.05) | 0.01 (-0.02, 0.04) |
| Any post-treatment SAE | 12 (3%) | 9 (2%) | 1.33 (0.57, 3.11) | 0.01 (-0.02, 0.03) |

Source: Table 2-25 p92 of the submission; Table 48 p183 MATINEE CSR.
AE = adverse event; RR = relative risk; RD = risk difference; PBO = placebo; SAE = serious adverse event.
[a] *Calculated during the evaluation; these results should be considered as indicative only as the underlying studies were not powered to detect differences in safety outcomes.*

6.30 A summary of adverse effects of special interest (AESI) is presented in Table 8. On-treatment AESI with a difference in incidence of ≥ 3% between treatment groups were all infections (higher in the mepolizumab arm 47% vs 43% for placebo) and cardiac disorders (higher in the placebo arm 11% vs 8% for mepolizumab). The most common infections across the treatment groups (Table 9), were COVID-19, nasopharyngitis, pneumonia, upper respiratory tract infection, and influenza. The AEs with > 2% difference between treatment groups were nasopharyngitis (10% in mepolizumab vs 8% in placebo) and urinary tract infection (4% in mepolizumab vs 2% in placebo).

**Table 8: AESI experienced during the treatment period (overall safety population) at 104 weeks**

| Outcome | Mepolizumab N = 403 | Placebo N = 401 |
|---|---|---|
| **Systemic reactions*** | 5 (1%) | 5 (1%) |
| Allergic (type I hypersensitivity) | 1 (<1%) | 0 |
| Other reactions* | 4 (<1%) | 4 (<1%) |
| **Anaphylaxis** | 0 | 0 |
| **Local site reactions** | 2 (<1%) | 3 (<1%) |
| **All Infections**[a] | 190 (47%) | 172 (43%) |
| Serious infections | 32 (8%) | 31 (8%) |
| **Potential opportunistic infections**[b] | 4 (<1%) | 7 (2%) |
| **Neoplasms**[a] | 9 (2%) | 17 (4%) |
| **Malignancies**[c] | 8 (2%) | 13 (3%) |
| **Cardiac Disorders**[a] | 31 (8%) | 44 (11%) |
| Serious cardiac disorders | 13 (3%) | 16 (4%) |
| **Serious CVT Events**[d] | 20 (5%) | 29 (7%) |
| Serious ischemic events[e] | 6 (1%) | 15 (4%) |

Source: Table 2-26 p93 of the submission; Table 66 p206 MATINEE CSR.
AESI = adverse event of special interest; CVT = cardiovascular thromboembolic; PBO = placebo; SMQ = Standard MedDRA query; SOC = System Organ Class.
[a] Infections from Infections and infestations SOC. Neoplasms from Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC. Cardiac disorders from Cardiac disorders SOC.
[b] Identified from SMQ or events with the preferred term of Herpes Zoster.
[c] Identified from SMQs.
[d] Serious CVT events identified from Cardiac disorders SOC, Vascular disorders SOC and SMQs.
[e] Subset of Serious CVT events identified through SMQs. *In the PBO group, there was 1 participant for whom information was not provided on the type of systemic reaction within their eCRF, therefore they had no value to count in the sublevel.

**Table 9: All infections reported in at least 1% of participants in any treatment group (safety population)**

| Preferred Term, n (%) | Mepolizumab N=403 | Placebo N=401 |
|---|---|---|
| **Infections and infestations, n (%)** | 190 (47) | 172 (43) |
| COVID-19 | 50 (12) | 49 (12) |
| Nasopharyngitis | 41 (10) | 32 (8) |
| Pneumonia | 30 (7) | 27(7) |
| Upper respiratory tract infection | 25 (6) | 20 (5) |
| Influenza | 19 (5) | 19 (5) |
| Urinary tract infection | 18 (4) | 7 (2) |
| Bronchitis | 8 (2) | 11 (3) |
| Sinusitis | 9 (2) | 7 (2) |
| Lower respiratory tract infection | 7 (2) | 7 (2) |
| Rhinitis | 7 (2) | 5 (1) |
| Respiratory tract infection | 3 (<1) | 8 (2) |
| Pharyngitis | 6 (1) | 4 (<1) |

*Source: Table 71, p212 MATINEE CSR.*

6.31 Although the overall incidence of adjudicated major adverse cardiovascular events (MACE) was balanced between groups (11 events in each arm), there was a numeric imbalance in deaths from a cardiovascular cause (6 (1.5%) in the mepolizumab group vs. 3 (0.7%) in the placebo group). The evaluation considered that given the low total number of events and the lack of statistical power for rare safety endpoints, it is difficult to determine if this imbalance represents a genuine safety signal or random variation.

## Benefits/harms

6.32 A summary of the comparative benefits and harms for mepolizumab versus placebo is presented in Table 10.

**Table 10: Summary of comparative benefits and harms for mepolizumab versus placebo**

| Benefits | | | | | | |
|---|---|---|---|---|---|---|
| **Outcome** | **Mepolizumab (95% CI)** | **Placebo (95% CI)** | **Rate ratio (95% CI)** | **Event rate/100 patient-yrs[b]** | | **Rate difference[b]** |
| | | | | **Mepolizumab** | **Placebo** | |
| **[a]Annualized rate of moderate/severe exacerbation (on & off treatment)** | | | | | | |
| Moderate/ severe | 0.80 (0.70, 0.91) | 1.01 (0.89, 1.15) | **0.79 (0.66, 0.94)** | 80 | 101 | -0.21 |
| **Outcome** | **Mepolizumab n/N** | **Placebo n/N** | **Risk ratio[b] (95% CI)** | **Event rate/100 patients** | | **Risk difference[b] (95% CI)** |
| | | | | **Mepolizumab** | **Placebo** | |
| **Patients with exacerbations (on & off treatment)** | | | | | | |
| Moderate/ severe | 202/403 | 226/401 | 0.89 (0.78, 1.01) | 50 | 56 | -0.06 (-0.13, 0.01) |
| **Harms** | | | | | | |
| Any AEs | 301/403 | 308/401 | 0.97 (0.90, 1.05) | 75 | 77 | -0.02 (-0.08, 0.04) |
| Any SAEs | 101/403 | 115/401 | 0.87 (0.70, 1.10) | 25 | 29 | -0.04 (-0.10, 0.03) |
| Fatal SAEs | 11/403 | 11/401 | 1.00 (0.44, 2.27) | 3 | 3 | 0.00 (-0.02, 0.02) |

Source: Table 2-17 p80, Table 2-25 p92 of the submission; Table 23 p124, Table 24 p126, Table 48 p183 MATINEE CSR.
AE= adverse event; CI = confidence interval; n = number of patients with event; N = total patients in group; SAE= severe adverse event.
[a] Analysis performed using a negative binomial model with covariates of treatment group, geographic region, number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal), baseline % predicted FEV1 and smoking status (current versus former smoker), and with logarithm (time on- and off-treatment) as an offset variable. Estimates based on weighting applied to each level of class variable determined from observed proportions.
[b] Calculated during the evaluation.
Bold indicates a statistically significant difference.

6.33 On the basis of the evidence presented by the submission, for every 100 patients treated with mepolizumab plus triple inhaled therapy for 52 weeks, compared with triple inhaled therapy alone:

- Approximately 21 fewer moderate/severe COPD exacerbations per year.
- Approximately 6 fewer patients would have a moderate or severe exacerbation.
- There were no differences noted in the occurrence of harms.

## Clinical claim

6.34 The submission described mepolizumab plus triple inhaled therapy as superior in terms of effectiveness compared to triple inhaled therapy alone, in patients with uncontrolled COPD with an eosinophilic phenotype. The Sub-Committees considered that the evidence provides support for the efficacy claim, however noted that the evaluation considered that the magnitude and generalisability of the treatment effect was uncertain given that the majority of the difference in the rate ratio was driven by the avoidance of events among a small subset of outlier patients (n=6, 1.5% of the placebo arm) with ≥ 9 exacerbations.

6.35 The Sub-Committees noted that the PSCR disagreed that the treatment effect was sensitive to outlier patients with ≥ 9 exacerbations and noted that there was a balanced distribution of treatment effect modifiers across both arms. The PSCR noted

that it should be assumed that there would be a similar breakdown of exacerbations if the treatment arms were switched at randomisation (also see paragraph 6.18). The PSCR also argued that the treatment effect did not change substantially across similar trials (METREX and METREO). However, the Sub-Committees noted that there were inconsistencies in the results in METREX and METREO, with METRO not showing a statistically significant difference in exacerbation rates (RR = 0.85, 95% CI: 0.59–1.22).[7] Overall, the Sub-Committees considered that while the evidence provides support for superior efficacy of mepolizumab plus triple inhaled therapy vs triple inhaled therapy, the magnitude of effect was marginal and subject to some uncertainty. The Pre-PBAC Response stated that the clinical hearing and consumer comments provided in support of the current submission (paragraphs 6.1–6.4) help to frame the clinical importance of a 21% reduction in annual rate of moderate/severe exacerbations, as observed in the MATINEE trial.

6.36 While the efficacy of mepolizumab was demonstrated through the primary outcome, it is not clear to what extent the experience of COVID-19 during the trial conduct impacted on the absolute occurrence of moderate/severe exacerbation events in the treatment arms, and whether the treatment effect for mepolizumab observed during the trial is likely to be observed in clinical practice. The Sub-Committees considered that the pandemic was unlikely to have affected the difference between treatment arms in the occurrence of moderate/severe exacerbation events, however considered it remained an uncertainty.

6.37 The submission claimed that mepolizumab plus triple inhaled therapy was non-inferior in terms of safety, compared to triple inhaled therapy alone, in patients with uncontrolled COPD with an eosinophilic phenotype. The Sub-Committees considered that this claim was adequately supported in the trial. No new safety concerns were identified in MATINEE and the safety data in COPD patients remained consistent with the known safety profile of mepolizumab. The Sub-Committees considered that a longer duration of follow-up is needed to adequately capture the long-term safety of mepolizumab in COPD patients.

6.38 The PBAC considered that the claim of superior comparative effectiveness for mepolizumab plus triple inhaled therapy versus triple inhaled therapy alone was reasonable but the magnitude of treatment benefit was subject to some uncertainty.

6.39 The PBAC considered that the claim of non-inferior comparative safety for mepolizumab plus triple inhaled therapy versus triple inhaled therapy alone was reasonable.

## Economic analysis

6.40 The submission presented a modelled cost-utility analysis comparing mepolizumab plus triple inhaled therapy with triple inhaled therapy alone utilising inputs from the

[7] *Note that these results are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

MATINEE trial and the literature. A summary of the key components of the economic evaluation is provided in Table 11.

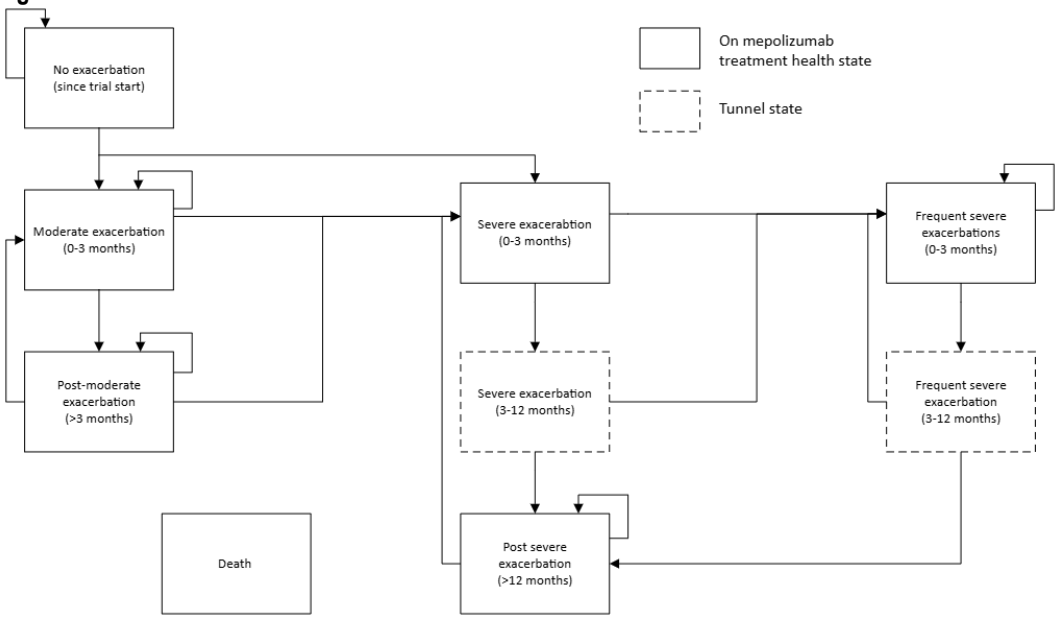
**Table 11: Summary of model structure, key inputs and rationale**

| Component | Summary |
|---|---|
| Treatments | Mepolizumab plus triple inhaled therapy vs triple inhaled therapy alone |
| Time horizon | 15 years in the model base case versus 104 weeks in trial |
| Outcomes | Life years, QALYs, moderate COPD exacerbations, severe COPD exacerbations |
| Methods used to generate results | Markov model |
| Health states | No exacerbations, moderate exacerbation (0-3 months), severe exacerbations (0-3 months), severe exacerbations (3-12 months), frequent severe exacerbations (0-3 months), frequent severe exacerbations (3-12 months), post severe exacerbations (>12 months), dead (8 states in total). Mepolizumab arm had these health states on-treatment and post-discontinuation. |
| Cycle length | 3 months |
| Transition probabilities | Background rates of moderate and severe exacerbations (MATINEE calibrated values reflective of exacerbation history at study entry).<br><br>RR (vs baseline) of subsequent moderate and severe exacerbations after an initial exacerbation (pooled MATINEE, METREX, MERTREO, IMPACT, and ECPLISE trials).<br><br>Age adjusted CFR (15.6%). Age adjustment was calculated using a relative risk per year 1 year increment of 1.041 after the age of 69 years. These values were based on Hoogendoorn et al 2011.<br>SMR: 2.5x vs general population (Samyshkin 2014).<br><br>Mepolizumab treatment efficacy: RR of moderate/severe exacerbations vs triple inhaled therapy alone for overall (Yr1) & responder sub-population (Yr2+) – MATINEE.<br><br>Stopping rule: Proportion meeting response definition at 6 & 12 months – MATINEE<br>Mepolizumab discontinuation rates: Overall (Yr1) & responder sub-populations (Yr2+) – MATINEE. |
| Health-related quality of life | Baseline utility: 0.738 (“no exacerbation” health state) based on MATINEE EQ-5D-3L.<br>Disutilities by health state relative to baseline (applied to both treatment arms) based on pooled COPD trials EQ-5D-3L (MATINEE, METREX, MERTREO, and IMPACT).<br>Resulting utilities by health state:<br>Moderate exacerbation: 0.72<br>Severe exacerbation 0-3 months: 0.68<br>Severe exacerbation 3+ months: 0.69<br>Frequent severe exacerbations 0-3 months: 0.63<br>Frequent severe exacerbations 3+ months: 0.66<br>Post severe exacerbations >12 months: 0.65 |
| Costs | • Mepolizumab requested price and administration training.<br>• Triple inhaled therapy alone including ICS, LABA and LAMA.<br>• Exacerbation treatment per moderate and severe, including hospitalisation, outpatient treatment, and ED visits.<br>• Disease monitoring by healthcare professionals. |

*Source: Table 3-1, pp108-109 of the submission.*
*CFR – case fatality rate; COPD = chronic obstructive pulmonary disease; ED = emergency department; EQ-5D-3L = EuroQoL 5-dimension 3-level questionnaire; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; QALY = quality-adjusted life year; RR = risk ratio; SC = subcutaneous; Yr = year.*

6.41 The submission presented a Markov model to assess the long-term impact of mepolizumab compared with triple inhaled therapy alone. The model structure is summarised in Figure 1. All individuals enter the model in the 'no exacerbations' health state where they remain until they either experience an exacerbation event (moderate or severe), discontinue from treatment (mepolizumab), or die. Severe and moderate exacerbations were captured in separate health states, while discontinuation from mepolizumab treatment was captured through parallel health states with ongoing exacerbation risk equal to the comparator arm. The model tracks short-term (0–3 months) and longer-term (> 3 months moderate; 3–12 months/> 12 months severe) impacts of each exacerbation through separate health states. Patients who have experienced an exacerbation are at increased risk of experiencing further exacerbations. Any patient experiencing a second severe exacerbation within 12 months moves to the frequent severe exacerbation-related health states. This model structure differed from a large proportion of published economic evaluations in COPD, which are commonly based on the GOLD grades of severity based on airflow obstruction using post-bronchodilator $FEV_1$. Model structures based on disease severity are well-supported by the literature and better align with clinical guidelines, and previous COPD economic models considered by the PBAC (paragraph 6.29, fluticasone furoate with umeclidinium and vilanterol PSD, March 2019 PBAC meeting), given that GOLD stages accurately reflect lung function, symptoms and risk of exacerbation, which directly impacts patient-related costs, health-related quality of life and disease progression. Therefore, the evaluation considered that it would have been more appropriate if the model had accounted for the GOLD severity grades in its structure. The PSCR maintained that the model structure was appropriate, noting that prior exacerbations are the most reliable predictor of future exacerbations and $FEV_1$ alone is an unreliable surrogate measure. The PSCR noted that lung function was explored in MATINEE (exploratory endpoint). There was no significant difference between mepolizumab and placebo observed in the change from baseline in pre-bronchodilator FEV1 at Week 52, and therefore the PSCR stated it was not feasible to develop a model based on GOLD severity stages in the model. The Sub-Committees considered that while the exclusion of $FEV_1$ was a simplistic approach, $FEV_1$ and exacerbations were correlated outcomes and therefore the approach taken was likely reasonable, and possibly conservative and removes the risk of double-counting.

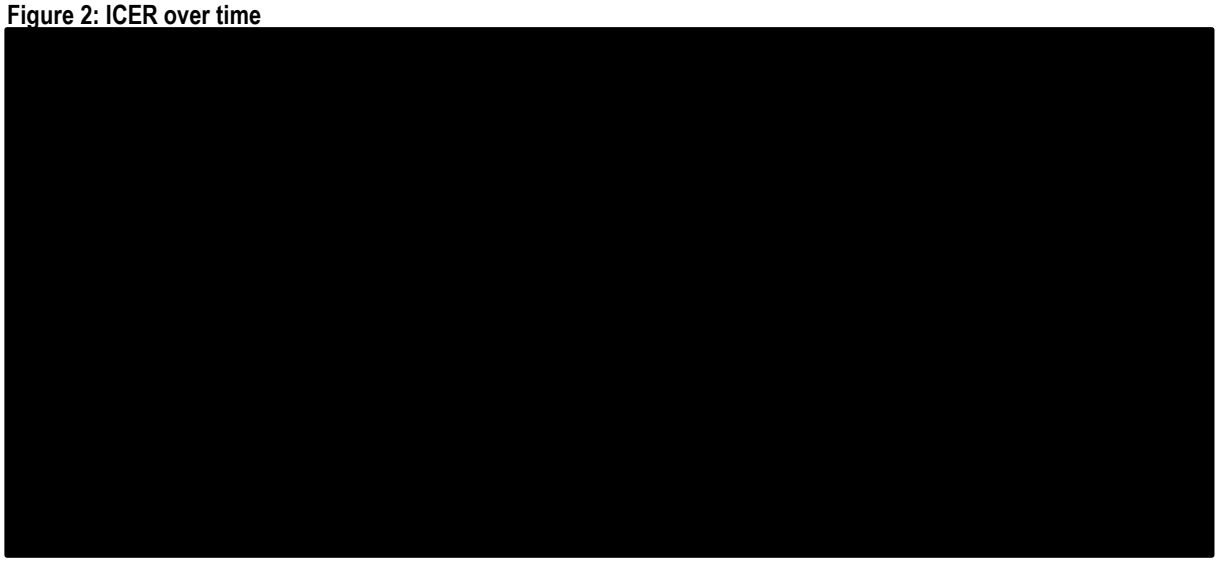
**Figure 1: Model structure**




*Source: Figure 3-3, p123 of the submission.*

6.42 The submission proposed a 15-year time horizon, given that the MATINEE trial mean age was approximately 65 years and the median age of death for chronic lower respiratory diseases is approximately 80 years (Australian Bureau of Statistics [ABS], 2023). The PBAC previously accepted a 10-year time horizon for the economic model evaluating triple therapy for the treatment of patients with moderate to severe COPD with frequent exacerbations (paragraph 7.9, fluticasone furoate with umeclidinium and vilanterol, PSD, March 2019 PBAC meeting). The model was sensitive to using a 10-year time horizon, increasing the incremental cost-effectiveness ratio (ICER) from $55,000 to < $75,000 per quality-adjusted life year (QALY) gained to $75,000 to < $95,000/QALY gained (+[redacted]%). The impact on the ICER of varying the time horizon is shown in Figure 2. The ICER becomes relatively stable at Year 6. The Sub-Committees considered that 10 years remained the most appropriate time horizon for this patient group. The Pre-PBAC response proposed a revised base case which included a 10 year time horizon (see paragraph 6.55).

**Figure 2: ICER over time**



*Source: Compiled during the evaluation from Attachment 'Nucala (Mepolizumab) COPD Mar 26 CUA' of the submission.*
*ICER = incremental cost-effectiveness ratio; QALY = quality=adjusted life year.*

6.43 The submission noted that the MATINEE trial had a disproportionately lower exacerbation rate during trial follow-up compared to the triple inhaled therapy alone eosinophilic subgroups in the METREX and METREO trials, which also evaluated mepolizumab. The submission claimed that this was due to the impact on the MATINEE trial of the COVID-19 pandemic. The model therefore used data from the 12 months prior to randomisation from MATINEE to source baseline exacerbation rates. The Sub-Committees agreed with the evaluation that this was likely to be reasonable as triple therapy for the prior 12 months was part of the inclusion criteria of MATINEE, noting the impact of the pandemic on the MATINEE trial outcomes was uncertain. However, the Sub-Committees noted that it was not possible to test the baseline exacerbation rates during trial follow-up, as the submission did not provide these by the occurrence of moderate and severe exacerbations (as required as inputs into the model). The submission conducted a sensitivity analysis using baseline exacerbation rates from pooled COPD trials (MATINEE, METREX, METREO, IMPACT, and ECLIPSE), which were lower for both moderate (1.702 vs. 0.920) and severe (0.201 vs. 0.170)[8] exacerbations compared to the base case. The model was sensitive to using the pooled COPD trials' baseline exacerbation rates, increasing the ICER from $55,000 to < $75,000/QALY gained to $75,000 to < $95,000/QALY gained (+ [redacted]%).

6.44 The submission also pooled data from COPD trials (MATINEE, METREX, METREO, IMPACT, and ECLIPSE) to inform the estimates of subsequent exacerbations. The

[8] *Data from METREX, METREO, IMPACT, ELIPSE were limited to subgroup with ≥2 moderate or ≥1 severe exacerbation in the prior year and BEC ≥300 cells/µL while on optimised inhaled therapy. Only the mepolizumab dosage of 100mg SC from the METREO trial was included. Note that exacerbation rates derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

submission applied the inclusion criteria from MATINEE (i.e., patients with ≥ 2 moderate or ≥ 1 severe exacerbation in the year prior and BEC of ≥ 300 cells/μL) to select participants from the additional trials. The evaluation considered that this was reasonable. The pooled population included patients from both treatment arms from MATINEE, METREX and METREO. Subsequent exacerbations could have been impacted by the effect of mepolizumab as it was used as treatment in MATINEE, METREX, and METREO.

6.45 The submission applied a standardised mortality ratio (SMR) of 2.5 to background mortality to reflect the increased probability of death for severe COPD patients, which excluded exacerbation-related mortality (Samyshkin et al. (2014)). This may have overestimated background mortality as 43.4% of the MATINEE population had moderate COPD. At the same time, it did not account for the SMR for very severe COPD reported in Samyshkin et al. (2014) of 3.85. The model also included allowance for short-term increased mortality after a severe exacerbation by applying case-fatality rates (CFRs) to severe exacerbations in the first cycle post-exacerbation. The submission sourced a CFR of 15.6% (95% CI 10.9, 20.3) for a hospitalised exacerbation from a meta-analysis of Hoogendoorn et al. (2011). The approach by the submission resulted in the magnitudes of the SMRs being uncertain as it combined sources from different years and settings with unclear applicability to Australia in 2026. Given that the SMR excluded exacerbation-related mortality, including a CFR for exacerbation did not result in double counting. The submission also applied a multiplier for additional mortality risk per additional year, reported by Hoogendoorn et al. (2011) (RR = 1.041; 95%CI 1.037, 1.045), starting at 69 years, as the mean age of the meta-analysis. The evaluation noted that this may double count deaths due to exacerbations as the CFR (noted above) accounts for all ages. The model was not sensitive to removing the additional mortality risk per additional year.

6.46 Estimates of treatment efficacy were sourced from the MATINEE trial and applied as follows:

- Rate ratios (RR) were applied to the triple inhaled therapy alone probabilities in Year 1 of the model for moderate and severe exacerbations, separately. The evaluation considered that this was reasonable. The RRs (see Table 12) were informed by the relative reduction in the overall exacerbation rate per person, i.e., first and subsequent exacerbations. This was consistent with the primary outcome of the MATINEE trial but may have underestimated the RR for frequent exacerbations, as the primary outcome of the trial combined single with frequent exacerbations.
- To account for non-responders in Year 1, to which a stopping rule was applied, a separate treatment effect was applied to responders from Year 2 onwards. The evaluation considered that non-responders in Year 1 should have the same treatment effect as triple inhaled therapy alone as they would have never responded to mepolizumab. The PSCR argued that it would not be appropriate to apply the data from the triple inhaled therapy alone arm to the mepolizumab arm

during the observed trial period in patients who remain on treatment. The PSCR stated that in Year 1, the model applied the treatment effect observed in the overall mepolizumab cohort which included both responders and non-responders, despite the stopping rule being applied in Month 6 which removed a proportion of non-responders from the modelled mepolizumab arm. The PSCR considered this to be a conservative approach.

- Patients who discontinued would not have a residual treatment effect. The evaluation considered that this was reasonable.
- Exacerbation RR for moderate events in Year 1 and Year 2+, as well as severe events in Year 2+ were not presented in the CSR. These could not be verified during the evaluation. The model results were sensitive to the application of the upper bound of the CI for the treatment effect (rate ratio) on severe exacerbations in Year 2+ (0.63). At this value, the ICER increased from $55,000 to < $75,000/QALY gained to $95,000 to < $115,000/QALY gained (+[redacted]%). The PSCR clarified that the annualised rate of moderate exacerbations and responder subgroup analyses were conducted post-hoc to inform the economic evaluation. The Sub-Committees considered the rates for moderate (year 1 and year 2+) and severe events (year 2+) applied in the base case of the model appeared reasonable.

**Table 12: Relative treatment efficacy of mepolizumab vs triple inhaled therapy alone against 1st and subsequent moderate & severe exacerbations**

| Exacerbation severity, RR (95% CI) | Overall population (Year 1) | Responder sub-population (Year 2+) |
|---|---|---|
| Moderate | 0.79 (0.65, 0.96)[a] | 0.65 (0.53, 0.81)[a] |
| Severe | 0.66 (0.43, 1.01) | 0.33 (0.17, 0.63)[a] |

*Source: Table 3-21, p142 of the submission.*
*CI = confidence interval; RR = rate ratio.*
*[a] Could not be verified in the evaluation. Clarified in the PSCR (see paragraph 6.46)*
*Note that the rate ratios in Table 12 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.47 The submission proposed a stopping rule of 'no worsening' for consistency with the PBS restriction, for which mepolizumab was continued if there was no change in the number of total exacerbations (moderate + severe) and no change in severe exacerbations compared to the last 12 months. The model applied the stopping rule at 6 and 12 months, then for Years 2+ it was applied every 3 months as discontinuation. See paragraph 6.48 for discussion of Years 2+ stopping rule application. Responders based on the requested PBS restriction from the MATINEE trial are presented in Table 13.

**Table 13: Proportion meeting the R1 response criteria (MATINEE)**

| Timepoint | N | Meeting R1 response criteria, n | % responders / non-responders |
|---|---|---|---|
| Baseline | 403 | 403 | 100.0% / 0.0% |
| 0-6 months | 370 | 352 | 95.1% / 4.9% |
| 6-12 months | 330 | 291 | 88.2% / 11.8% |
| 12-24 months | 80 | 72 | 90.0% / 10.0% |

*Source: p142 of the submission; Table 3-22, p143 of the submission.*
*N = number of patients remaining on treatment with mepolizumab at this time point; n = number of subjects meeting response definition at this time point; R1 = 'No worsening' response definition.*
*Note that number and proportion meeting R1 response criteria values were derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.48 From Year 2, the submission used different estimations for discontinuations in the following:

- No prior exacerbations: using the MATINEE mepolizumab responder sub-population annual discontinuation rate between weeks 52 to 104 of 0.055 per person-year, a 1.37% discontinuation probability per cycle (3 months) was applied. The sub-population annual discontinuation rate was not presented in the CSR and could not be verified during the evaluation.

- All other states: the submission applied the stopping rule criteria from year 2 using trial data from 12 to 24 months, yielding a cycle probability of 2.6% applied every 3 months. The Sub-Committees agreed with the evaluation that it was reasonable to apply the stopping rule in Year 2+, although it would have been more appropriate to be applied every 6 months as in Year 1 of the model. The Sub-Committees also noted that the stopping rule probability (2.6%) applied to all other states as treatment discontinuation likely did not fully reflect those discontinuing treatment. This was because it did not account for trial-observed treatment discontinuation, likely reflecting discontinuation due to AEs. This was only accounted for in the no exacerbation health state. Failing to account for discontinuation in addition to the stopping rule overestimated mepolizumab use and its effect. The PSCR acknowledged that it may be reasonable to include the additive impact of treatment discontinuation per 3-month cycle and the loss of response stopping rule on a 6-monthly basis. However, the PSCR did not agree with the approach taken by the evaluation which applied the 12-month stopping rule discontinuation. The PSCR proposed using the stopping rule derived from non-responders in Year 2 of MATINEE (5.13% over 6 months) which yielded an ICER of $55,000 to < $75,000/QALY gained. The Sub-Committees noted that the alternate probabilities proposed by the evaluation ranged between 12.64–42.57% in different exacerbation health states and were derived from overall non-responders at 0–6 months (4.9%), and 6–12 months (11.8%). The Sub-Committees also noted the PSCR's approach applied 5.13% to each exacerbation health state, rather than re-estimating it for each health state as in the base case. The Sub-Committees considered that this approach would underestimate the ICER and considered that, overall, the approach taken by the evaluation to be more appropriate. The Pre-PBAC response provided a revised base case analysis which

included a treatment discontinuation probability of 1.37% every 3 months to all health states, a Year 2+ 6-month stopping rule and revised loss of response probabilities for Year 2+ according to health state (paragraph 6.55).The calculations for the revised loss of response probabilities applied as a 6-monthly stopping rule in the Pre-PBAC Response are based on the observed loss of response in Months 12–24 (10.0%) in the MATINEE trial (Table 14).

**Table 14: Year 2+ loss of response calculations for the mepolizumab arm in the revised base-case model**

| Health state | Month 0–12 | | Month 12–24 | | | |
|---|---|---|---|---|---|---|
| | Over 12 months | | Over 12 months | | Over 6 months | |
| | Continue | Discontinue | Continue | Discontinue | Continue | Discontinue |
| No exacerbations | 100.00% | 0.00% | 100.00% | 0.00% | 100.00% | 0.00% |
| Moderate exacerbations | 80.00% | 20.00% | 83.08% | 16.92% | 91.15% | 8.85%[b] |
| Severe / post-severe exacerbations | 40.91% | 59.09% | 50.00% | 50.00% | 70.71% | 29.29%[b] |
| Frequent severe exacerbations | 50.00% | 50.00% | 57.69% | 42.31% | 75.96% | 24.04%[b] |
| Overall | 88.18% | 11.82% | 90.00% | 10.00%[a] | 94.87% | 5.13%[c] |
| Reference | A | B | C | D | E | F |
| Calculation | - | | 1 - D | B x (10 /11.82%) | 1 - F | $-C^{1/2} + 1$ |

*Source: Pre-PBAC Response*

*[a] 291 mepolizumab responders at 12 months → 80 with 24 months of follow-up → 72 maintained their response from 12–24 months: = 1 - (72/80).*

*[b] Applied to revised based case of the Pre-PBAC Response.*

*[c] As suggested in the PSCR.*

*Note that the loss of response values were derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.49 The model sourced base case utilities from the MATINEE trial (no exacerbations) and from the pooled analysis (MATINEE, METREX, MERTREO, and IMPACT, applied as absolute decrements to no exacerbation utility) of the EQ-5D-5L results. The evaluation considered that this was reasonable. The Sub-Committees noted that the results were mapped to the 3-level version and scored using Canadian tariffs. The Sub-Committees agreed with the evaluation that scoring the 5-level version with an Australian algorithm[9] would have been more appropriate and obviated the need for the mapping step. The model was not sensitive to the variations in the utility values.

6.50 The submission noted the MATINEE trial did not present resource utilisation data per exacerbation severity. Therefore, the MATINEE trial was not suitable as the source of resource use data for the model. The submission utilised a 1-year prospective Canadian study (Mittmann et al. 2008) reporting on moderate and severe exacerbations, including ED, inpatient care, and outpatient management. The Sub-Committees agreed with the evaluation that it was unclear how this study, which used Canadian data from 2001–02, applied to the current (24 years later) Australian setting.

*[9] Norman R, Mulhern B, Lancsar E, Lorgelly P, Ratcliffe J, Street D, Viney R. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. Pharmacoeconomics. 2023 Apr;41(4): pp427-438*

6.51 The mean cost of treating a moderate or severe exacerbation was estimated at $323.37 and $9,671.37, respectively. The cost of treating a severe exacerbation double counted ED costs, as these were already included in the hospitalisation costs as per the Australian Refined Diagnostic-Related Groups. However, the model was not sensitive to removing ED costs from severe exacerbations.

6.52 The economic model did not include the cost of administration, only a one-off cost of training for self-administration ($86.80, MBS item 82215 [updated cost not applied, as was done for the cost and utilisation model]), however the evaluation noted that not all patients will be able to self-administer or have a carer and will therefore require administration by a healthcare professional. The Sub-Committees noted that if any additional support for mepolizumab would be required, the ICER would be underestimated. The PBAC considered that the inclusion of only a one-off cost of training for self-administration was appropriate.

6.53 Key model drivers are presented in Table 15.

**Table 15: Key drivers of the model**

| Description | Method/Value | Impact<br>Base case: $[redacted][1]/QALY gained. |
|---|---|---|
| Treatment efficacy on severe exacerbations Year 2+ | RR estimated from MATINEE trial data (0.33)[a]. The Sub-Committees considered the rate used for severe exacerbations Year 2+ appeared reasonable. | High, favours mepolizumab<br>Use of the upper CI (0.63) increased the ICER to $[redacted][2]/QALY gained. |
| Time horizon | Assumed 15 years given MATINEE trial mean age was approximately 65 years. The Sub-Committees considered a 10 year time horizon was appropriate. | High, favours mepolizumab<br>Use of 10 years increased the ICER to $[redacted][3]/QALY gained. |
| Baseline exacerbation rate | MATINEE trial pre 12-month baseline rates calibrated. The Sub-Committees considered the approach taken by the submission for this input was likely appropriate. | High, favours mepolizumab<br>Use of estimate from pooled COPD trials increased the ICER to $[redacted][3]/QALY gained. |
| Treatment efficacy on severe exacerbations Year 1 | RR estimated from MATINEE trial data (0.66). | Moderate, favours mepolizumab<br>Use of the upper CI (1.01) increased the ICER to $[redacted][1]/QALY gained. |
| Case fatality rate | Assumed 15.6% from Hoogendoorn et al. (2011). | Moderate, favours mepolizumab<br>Use of Hoogendoorn et al. (2011) lower CI (10.9%) increased the ICER to $[redacted][1]/QALY gained. |

Source: Compiled in the evaluation from Section 3 of the submission.
CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RR = rate ratio.
[a] Could not be verified in the evaluation.
*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000*
[2] *$95,000 to < $115,000*
[3] *$75,000 to < $95,000*

6.54 Results of the stepped economic evaluation conducted during the evaluation are presented in Table 16. The submission did not justify the exclusion of a stepped economic evaluation.

**Table 16: Results of the stepped economic evaluation [a]**

| Step and component | Mepolizumab | Triple inhaled therapy alone | Increment |
|---|---|---|---|
| **Step 1: trial-based costs and exacerbations avoided** | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| Exacerbations | 1.747 | 2.187 | -0.440 |
| Incremental cost/exacerbation avoided | | | $[redacted] [1] |
| **Step 2: trial-based costs and LYG** | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| LYG | 0.983 | 0.951 | 0.032 |
| Incremental cost/extra LYG gained | | | $[redacted] [2] |
| **Step 3: time horizon extended to 15 years** | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| LYG | 8.510 | 6.914 | 1.596 |
| Incremental cost/extra LYG gained | | | $[redacted] [3] |
| **Step 4: discounting (5%) included** | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| LYG | 6.583 | 5.535 | 1.048 |
| Incremental cost/extra LYG gained | | | $[redacted] [4] |
| **Step 5: utility weights applied** | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| QALYs | 4.586 | 3.807 | 0.779 |
| Incremental cost/extra QALY gained (base case) | | | $[redacted] [5] |

Source: Table 3-46, pp168-169 of the submission; Attachment 'Nucala (Mepolizumab) COPD Mar 26 CUA' of the submission.
LYG = life-year gained; QALY = quality-adjusted life year.
[a] Calculated during the evaluation as a stepped economic evaluation was not presented by the submission.
*The redacted values correspond to the following ranges:*
[1] *$25,000 to < $35,000*
[2] *$355,000 to < $455,000*
[3] *$35,000 to < $45,000*
[4] *$45,000 to < $55,000*
[5] *$55,000 to < $75,000*

6.55 The results of key univariate / multivariate sensitivity analyses are summarised in Table 17. The Sub-Committees considered a revised base case was required to address a number of unsupported assumptions and included: the stopping rule changed from every 3 months to every 6 months in Year 2+, inclusion of a discontinuation rate for responders in Year 2+ (1.37%) and a 10-year time horizon. The Sub-Committees noted that these changes to the model increased the ICER to $75,000 to < $95,000 per QALY gained.

6.56 The Pre-PBAC Response agreed with the revisions recommended by the Sub-Committees but adjusted the 6-monthly stopping rule probabilities for Year 2+ to be based on data from Months 12–24 of the MATINEE trial (Table 14), not Months 0–12 as conducted by the evaluation. These changes to the model resulted in a similar ICER to the Sub-Committee's revised base case analysis (Sub-Committee's: $75,000 to < $95,000/QALY gained, pre-PBAC Response: $75,000 to < $95,000/QALY gained). The Pre-PBAC Response also proposed a revised effective EMP for mepolizumab of $[redacted] per 100 mg pre-filled pen. With the reduced price and revisions to the economic model, as proposed in the Pre-PBAC Response, the ICER was $55,000 to < $75,000/QALY gained.

**Table 17: Sensitivity analyses**

| Analyses | Incremental cost | Incremental QALY | ICER | % change to ICER |
|---|---|---|---|---|
| **Base case** | $[redacted] | **0.779** | $[redacted][1] | - |
| **Stopping rule (base case from Year 2 onwards 2.6% per 3 month cycle)** | | | | |
| Stopping rule every 6 months (1) [a,b] | $[redacted] | 0.438 | $[redacted][1] | [redacted]% |
| No stopping rule | $[redacted] | 0.601 | $[redacted][2] | [redacted]% |
| **Discontinuation Year 2+ (base case 2.6% for exacerbation health states)** | | | | |
| Discontinuation from Year 2 responders (no exacerbation) 1.37% (2) [a] | $[redacted] | 0.906 | $[redacted][1] | [redacted]% |
| **Time horizon (base case 15 years)** | | | | |
| 10 years (3) | $[redacted] | 0.548 | $[redacted][3] | [redacted]% |
| **Case fatality rate for severe exacerbations (base case 15.6%)** | | | | |
| Lower CI:10.9% | $[redacted] | 0.677 | $[redacted][1] | [redacted]% |
| 0%[a] | $[redacted] | 0.020 | $[redacted][4] | [redacted]% |
| No added mortality per age [a] | $[redacted] | 0.776 | $[redacted][1] | [redacted]% |
| **Discount rate (base case: 5%)** | | | | |
| 0% | $[redacted] | 1.171 | $[redacted][5] | -[redacted]% |
| 3.5% | $[redacted] | 0.876 | $[redacted][1] | -[redacted]% |
| **Baseline exacerbation rates (base case MATINEE calibrated)** | | | | |
| Pooled COPD trials [c] | $[redacted] | 0.686 | $[redacted][3] | [redacted]% |
| **Treatment efficacy severe exacerbation Year 1 (base case 0.66)** | | | | |
| Lower CI severe 0.43 [a] | $[redacted] | 0.858 | $[redacted][1] | -[redacted]% |
| Upper CI severe 1.01 [a] | $[redacted] | 0.661 | $[redacted][1] | [redacted]% |
| **Treatment efficacy severe exacerbation Year 2 (base case 0.33)** | | | | |
| Lower CI severe 0.17 [a] | $[redacted] | 0.913 | $[redacted][5] | -[redacted]% |
| Upper CI severe 0.63 [a] | $[redacted] | 0.475 | $[redacted][2] | [redacted]% |
| **Multivariate analyses[a]** | | | | |
| Stopping rule every 6 months (1) [b] + Discontinuation from Year 2 responders (no exacerbation) 1.37% (2) | $[redacted] | 0.468 | $[redacted][1] | [redacted]% |
| Discontinuation from Year 2 responders (no exacerbation) 1.37% (2) + 10-year time horizon (3) | $[redacted] | 0.606 | $[redacted][3] | [redacted]% |
| Stopping rule every 6 months [b] (1) + Discontinuation from Year 2 responders (no exacerbation) 1.37% (2) + 10-year time horizon (3) | $[redacted] | 0.375 | $[redacted][3] | [redacted]% |
| **Pre-PBAC Response** | | | | |
| Stopping rule every 6 months [d] + Discontinuation from Year 2 responders (no exacerbation) 1.37% (2) + 10-year time horizon (3) | $[redacted] | 0.418 | $[redacted][3] | [redacted]% |
| Stopping rule every 6 months [d] + Discontinuation from Year 2 responders (no exacerbation) 1.37% (2) + 10-year time horizon (3) + Price reduction ($[redacted] per 100 mg pre-filled pen) | $[redacted] | 0.418 | $[redacted][1] | [redacted]% |

*Source: Table 3-51, pp174-175 of the submission. Text in italics was estimated in the evaluation using Attachment 'Nucala (Mepolizumab) COPD Mar 26 CUA' of the submission.*

*CI = confidence interval; COPD = chronic obstructive pulmonary disease; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year.*

[a] *Calculated during the evaluation and during the preparation of the ESC DUSC advice.*

[b] *The 0 to 12-month stopping rule discontinuation probabilities (moderate = 12.64%, Severe/Post-Severe = 42.57%; Frequent Severe = 34.74%) applied every 6 months.*
[c] *Pooled COPD trials comprise pooled data from MATINEE, METREX, METREO, IMPACT, ECLIPSE, where data from METREX, METREO, IMPACT, ELIPSE were limited to subgroup with ≥2 moderate or ≥1 severe exacerbation in the prior year and BEC ≥300 cells/µL while on optimised inhaled therapy. Only the mepolizumab dosage of 100mg SC from the METREO trial was included.*
[d] *12-24 month stopping rule discontinuation probabilities (moderate = 8.85%, Severe/Post-Severe = 29.29%; Frequent Severe = 24.04%) applied every 6 months.*
*The redacted values correspond to the following ranges:*
[1] *$55,000 to < $75,000*
[2] *$95,000 to < $115,000*
[3] *$75,000 to < $95,000*
[4] *> $1,055,000*
[5] *$45,000 to < $55,000*

6.57 The ICERs for PBAC recommendations for related conditions include $40,000 - $45,000 per QALY for omalizumab for uncontrolled severe allergic asthma (omalizumab PSD, November 2010 PBAC Meeting) and $45,000 to < $55,000 per QALY gained for tezepelumab for non-eosinophilic and non-allergic severe uncontrolled asthma (paragraph 7.11, tezepelumab PSD, November 2025 PBAC Meeting). The net cost to the PBS/RPBS for omalizumab was estimated by the submission to be less than $10 million in any of the first 5 years (omalizumab PSD, November 2010 PBAC Meeting). The net cost to the PBS/RPBS for of listing tezepelumab was estimated by the submission to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing (paragraph 6.84, tezepelumab PSD, November 2025 PBAC Meeting). The PBAC has previously suggested lower acceptable ICERs for other conditions with larger numbers of eligible patients and larger estimated net costs to the PBS/RPBS than those reported for omalizumab and tezepelumab. An ICER of less than $15,000 - $45,000 per QALY was accepted for evolocumab (paragraph 5.8, evolocumab PSD, November 2019 PBAC Meeting), an ICER in the order of $30,000 per QALY gained was considered appropriate in the PBAC's deferral of tirzepatide for the treatment of adult patients with inadequately controlled type 2 diabetes (paragraph 7.9, tirzepatide PSD, July 2025 PBAC Meeting), and an ICER of up to $25,000 per QALY gained for semaglutide for use in patients with established cardiovascular disease with obesity accepted (paragraph 7.12, semaglutide PSD, November 2025 PBAC Meeting).

## Mepolizumab cost/patient/year

6.58 The cost/patient/year estimated in the evaluation is presented in Table 18. For the economic model and financial estimates, the stopping rule at 6 and 12 months was applied per Table 13.

6.59 The Pre-PBAC Response proposed a revised effective EMP of $[redacted] per 100 mg pre-filled pen.

**Table 18: Drug cost per patient for mepolizumab and triple inhaled therapy alone**

| | Trial dose and duration | Economic model | Financial estimates |
|---|---|---|---|
| Mean dose | 100 mg every 4 weeks | | |
| Mean duration (months) | 15.1 | 45.6 (3.8 years) | |
| Continuing patients incorporating stopping rule | No | 95.1% months 0-6<br>88.2% months 6-12 | |
| Drug cost (effective DPMQ) | Submission = $[redacted][a] / Pre-PBAC Response = $[redacted] | | |
| Cost/patient/month [b] | Submission = $[redacted] / Pre-PBAC Response = $[redacted] | | |
| Cost/patient/year [b] | Submission = $[redacted] / Pre-PBAC Response = $[redacted] | Submission = $[redacted][c]/ Pre-PBAC Response = $[redacted][c] | |

DPMQ = Dispensed price for maximum quantity

Source: Table 2-12, p66 of the submission; Table 3-22, p143 of the submission; Table 3-45, p168 of the submission

[a] Weighted using 2024 prescription data from mepolizumab for severe eosinophilic asthma, estimated as $[redacted] = 60.47% (public) x $[redacted] + 39.53% (private) x $[redacted]. Pre-PBAC Response: $[redacted] = 60.47% (public) x $[redacted] + 39.53% (private) x $[redacted].

[b] Does not account for compliance.

[c] Estimated by applying 95.1% to the first 6 months and 95.1%*88.2% = 83.9% to the last 6 months.

## Estimated PBS usage & financial implications

6.60 This submission was considered jointly by DUSC and ESC.

6.61 The submission adopted an epidemiological approach to derive the number of patients who would meet the proposed eligibility criteria for mepolizumab under the proposed PBS indication and to estimate the financial impact of its listing. The evaluation considered this was reasonable. Inputs used in the financial model are presented in Table 19.

**Table 19: Key inputs for financial estimates**

| Data | Value | Source | Evaluators comment<br>Sub-Committees Comment |
|---|---|---|---|
| **Eligible population** | | | |
| Number of prevalent COPD patients on triple inhaled therapy | Submission:<br>Yr 1: [redacted]1<br>Yr 2: [redacted]1<br>Yr 3: [redacted]1<br>Yr 4: [redacted]1<br>Yr 5: [redacted]1<br>Yr 6: [redacted]1<br><br>Pre-PBAC Response:<br>Yr 1: [redacted]1<br>Yr 2: [redacted]1<br>Yr 3: [redacted]1<br>Yr 4: [redacted]1<br>Yr 5: [redacted]6<br>Yr 6: [redacted]6 | 10% PBS sample data analysis.<br>Projection based on the number of prevalent COPD patients on triple inhaled therapy from January 2021 to December 2024.<br>[redacted]1 patients on triple therapy in 2025 with projections calculated by applying the average annual growth of [redacted] patients observed during the January 2021 to December 2024 period. | The Sub-Committees considered that this estimate was uncertain. The Sub-Committees noted that the [redacted]1 patients reported by the submission to be on triple therapy in 2025 was based on patients receiving single inhaler FDC triple therapy and those receiving open triple therapy. The submission stated that according to the 10% PBS sample data analysis, [redacted]% of COPD patients receiving triple therapy were on single inhaler FDC triple therapy and [redacted]% were on open triple therapy. The Sub-Committees noted that based on the 100% PBS sample, the number of prevalent patients who had received at least one prescription for single inhaler FDC triple therapy in 2025 was 186,168 (see Table 21). The Pre-PBAC Response proposed updated estimates incorporating a triple inhaled prevalent population based on the actual number of prevalent patients on single inhaled triple therapy (PBS 100%) with additional estimates for open triple inhaled therapy patients (relative market share, PBS 10%). A linear projection is applied. |
| Proportion of COPD patients who are indicated for triple therapy, but are using dual therapy due to intolerance to LAMA, LABA or ICS component | [redacted]% | Clinical expert opinion (GSK Mepolizumab COPD Advisory Board, 2025) | The accuracy of expert opinion was uncertain.<br><br>The Sub-Committees considered that the restriction should require patients to be taking a LABA, LAMA and ICS and hence this input should be removed. The Pre-PBAC Response did not agree to exclude this parameter (see paragraph 3.4). However, the PBAC agreed with the Sub-Committees that the restriction should require patients to be taking a LABA, LAMA and ICS. |
| Proportion on triple inhaled therapy who have experienced ≥ 2 moderate or ≥ 1 severe exacerbations in the past 12 months | 60.54% | Benson et al. (2019), Figure 1 | The Sub-Committees considered that it was unclear how relevant the Benson et al (2019) study was to the Australian population, particularly given that the data were collected in 2017, and single inhaler FDC triple therapy was not introduced until 2018. The Sub-Committees considered that patient estimates based on open triple therapy may not suitably translate to the single inhaler FDC triple therapy setting without further analysis. The Pre-PBAC Response maintained that this parameter was appropriate. |

| Data | Value | Source | Evaluators comment<br>Sub-Committees Comment |
|---|---|---|---|
| Proportion of patients who are optimised on triple therapy, i.e., ≥ 3 months of use (among those with ≥ 2 moderate or ≥ 1 severe exacerbation over recent 12 months while on triple inhaled therapy) | 74.81% | Benson et al. 2019; Sensitivity analysis 2 | The evaluation noted that the estimates calculated were from different subpopulations and were therefore not comparable.<br>As outlined above, the Sub-Committees considered that it was unclear how relevant the Benson et al (2019) study was the to the Australian population. |
| Proportion with BEC ≥ 300 cells/μL (among those with ≥2 moderate or ≥1 severe exacerbation over recent 12 months while on triple inhaled therapy) | 45.93% | Benson et al. (2019) Figure 1 | The Sub-Committees considered that the proportion with BEC ≥ 300 cells/μL was likely overestimated. The Sub-Committees noted that the results of an Australian study of COPD patients in outpatient clinics (Hiles et al. 2021) estimated 29.4% of patients have a BEC ≥ 300 cells/μL.[10] The Pre-PBAC response proposed a weighted average of 40.94% (see paragraph 6.64). |
| Eligible patients | Submission:<br>Yr 1: [redacted]2<br>Yr 2: [redacted]3<br>Yr 3: [redacted]3<br>Yr 4: [redacted]3<br>Yr 5: [redacted]4<br>Yr 6: [redacted]4<br><br>Pre-PBAC response:<br>Yr 1: [redacted]2<br>Yr 2: [redacted]2<br>Yr 3: [redacted]3<br>Yr 4: [redacted]3<br>Yr 5: [redacted]4<br>Yr 6: [redacted]4 | Calculated | |
| **Grandfather population** | | | |
| Grandfathered patients | [redacted]5 | Assumption.<br>Grandfathered patients considered to be a subset of the eligible patient population and were assumed to have the same discontinuation rates as initiating patients. | |

[10] *Hiles SA, Gibson PG, McDonald VM. Disease burden of eosinophilic airway disease: Comparing severe asthma, COPD and asthma-COPD overlap. Respirology. 2021;26(1):52-61. doi:10.1111/resp.13841*

| Data | Value | Source | Evaluators comment<br>Sub-Committees Comment |
|---|---|---|---|
| **Treatment utilisation** | | | |
| Uptake rate | Yr 1: [redacted]%<br>Yr 2: [redacted]%<br>Yr 3: [redacted]%<br>Yr 4: [redacted]%<br>Yr 5: [redacted]%<br>Yr 6: [redacted]% | Yr 6 was sourced from clinical expert opinion, Yr 1 was an assumption, and Yrs 2-5 were a linear extrapolation between Yrs1 and 6. | The Year 1 uptake rates were not justified by the submission. |
| Treatment persistence | Submission:<br>Yr 1: 100%<br>Yr 1 (6 month): 83.2%<br>Yr 2: 66.9%<br>Yr 3: 58.4%<br>Yr 4: 50.4%<br>Yr 5: 43.3%<br>Yr 6: 37.0%<br><br>Pre-PBAC response:<br>Yr 1: 100%<br>Yr 1 (6 month): 83.2%<br>Yr 2: 67.6%<br>Yr 3: 50.0%<br>Yr 4: 36.2%<br>Yr 5: 25.9%<br>Yr 6: 18.3% | Economic model | The submission and pre-PBAC response revised estimates applied a stopping rule (83.2% per the economic model) at 6 months. |
| Compliance | 98.7% | MATINEE trial | The Sub-Committees noted that the submission assumed that compliance in the MATINEE trial (98.7%) would follow through to the real-world experience, however the Sub-Committees considered that this was unlikely. The Sub-Committees considered a compliance of 93% may be more appropriate. The Pre-PBAC Response noted that there was no source to support the 93% and maintained that 98.7% was appropriate. The PBAC noted the compliance rate of 93% was consistent with that considered appropriate by DUSC in the consideration of tezepelumab for non-eosinophilic and non-allergic severe uncontrolled asthma population (Table 20, tezepelumab PSD, November 2025 PBAC meeting). |
| **Costs** | | | |
| Mepolizumab (DPMQ) | $[redacted]<br>$[redacted]<br>$[redacted]<br>$[redacted] | Published price public<br>Published price private<br>Effective price public<br>Effective price private | As per the submission. The Pre-PBAC Response proposed a revised effective EMP of $[redacted] per 100 mg pre-filled pen (public DPMQ $[redacted] / private DPMQ = $[redacted]). |

| Data | Value | Source | Evaluators comment<br>Sub-Committees Comment |
|---|---|---|---|
| Section 100 Private/Public split | 33.8% / 66.2% | PBS/RPBS mepolizumab script services for uncontrolled severe asthma indication (Jan 2024 to Dec 2024) | The evaluation considered that this was reasonable. |
| Patient training for self-administration by a nurse practitioner | $88.90 | MBS item 82215, used 80% total fee and was assumed once per initiator. | The evaluation noted that not all patients will be able to self-administer or have a carer and will therefore require administration by a healthcare professional. |

*Source: Table 4-1, pp177-178 of the submission.*
*BEC = blood eosinophil count; COPD = chronic obstructive pulmonary disease; FDC = fixed-dose combination; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Yr = year.*
*The redacted values correspond to the following ranges:*
[1] *200,000 to < 300,000*
[2] *40,000 to < 50,000*
[3] *50,000 to < 60,000*
[4] *60,000 to < 70,000*
[5] *< 500*
[6] *300,000 to < 400,000*

6.62 The estimated use and financial implications of listing mepolizumab on the PBS as presented in the submission and Pre-PBAC Response are presented in Table 20.

**Table 20: Estimated use and financial implications (effective price)**

| | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | Total |
|---|---|---|---|---|---|---|---|
| **Estimated extent of use - Submission** | | | | | | | |
| Number of patients treated | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | - |
| Number of scripts dispensed | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][3] | [redacted][3] | [redacted][3] | - |
| **Net financial implications – Submission (DPMQ public $[redacted], DPMQ private $[redacted])** | | | | | | | |
| Net cost to PBS/RPBS | $[redacted][4] | $[redacted][4] | $[redacted][5] | $[redacted][5] | $[redacted][5] | $[redacted][5] | $[redacted][6] |
| Net cost to MBS | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] |
| Net cost to Government | $[redacted][4] | $[redacted][4] | $[redacted][5] | $[redacted][5] | $[redacted][5] | $[redacted][5] | $[redacted][6] |
| **Estimated extent of use – Pre-PBAC Response** | | | | | | | |
| Number of patients treated | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | [redacted][8] | - |
| Number of scripts dispensed | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | - |
| **Net financial implications – Pre-PBAC Response (DPMQ public $[redacted], DPMQ private $[redacted])** | | | | | | | |
| Net cost to PBS/RPBS | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][9] |
| Net cost to MBS | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] |
| Net cost to Government | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][4] | $[redacted][9] |

Source: Compiled from Section 4 of the submission. Pre-PBAC Response.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme.
*The redacted values correspond to the following ranges:*
[1] *10,000 to < 20,000*
[2] *100,000 to < 200,000*
[3] *200,000 to < 300,000*
[4] *$100 million to < $200 million*
[5] *$200 million to < $300 million*
[6] *> $1 billion*
[7] *$0 to < $10 million*
[8] *10,000 to < 20,000*
[9] *$900 million to < $1 billion*

6.63 The total cost to the PBS/RPBS of listing mepolizumab was estimated in the submission base case to be $200 million to < $300 million in Year 6, and a total of > $1 billion million in the first 6 years of listing.

6.64 The submission identified Benson et al. (2019) as the only suitable study with sufficient granularity of exacerbations and BEC data to estimate the eligible patient population distribution. Benson et al. (2019) reported findings from a survey conducted among primary care physicians or respiratory specialists in France, Germany, Italy, Spain and the UK in 2017. Although Benson et al. (2019) applied an adjustment for confounding, the possibility of bias cannot be ruled out, as 5 patients per physician were recruited

consecutively over a short period. Based on this study the submission assumed the following:

- Among patients receiving treatment with triple therapy, 60.54% (13.5% / 22.3%) experienced ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the past 12 months.
- A treatment course of ≥ 3 months was taken as indicating treatment optimisation.
- Among patients on triple therapy and experiencing ≥ 2 moderate or ≥ 1 severe exacerbation(s), 74.81% (10.1%/13.5%) had been treated with triple therapy for ≥ 3 months (in the figure of 10.1% was from sensitivity analysis 2 of Benson et al. (2019)). The evaluation considered that this estimate was misleading; the 13.5% included patients with BEC <150 cells/µL, whereas the 10.1% was estimated for patients with BEC ≥ 150 cells/µL, such that the 74.81% reflects the proportion continuing treatment between BEC categories.
- Among patients in triple therapy with ≥ 2 moderate or ≥ 1 severe exacerbation(s) in the preceding 12 months, 45.9% (6.2%/13.5%) had a BEC of ≥ 300 cells/µL. The Sub-Committees considered that the proportion with BEC ≥ 300 cells/µL was likely overestimated. The Sub-Committees noted that the results of an Australian study of COPD patients in outpatient clinics (Hiles et al. 2021) estimated 29.4% of patients have a BEC ≥ 300 cells/µL. The Pre-PBAC Response noted that this percentage was based on the overall COPD population, whereas the Benson et al estimate was based on a patient population taking triple inhaled therapy and experiencing frequent exacerbations, and argued it was therefore more clinically relevant. The Pre-PBAC Response also noted that a recent Australian-based study (Menon 2026, not yet published) observed 37.7% of 53 patients admitted with a COPD exacerbation [redacted][11] at a tertiary hospital in Western Australia over September 2022 to October 2023 had a BEC ≥300 in the last 12 months. To address the Sub-Committee's recommendation for respecifying the proportion with BEC ≥300 and considering the applicability limitations across studies (Benson 2019, Hiles 2021, Menon 2026), the Pre-PBAC response proposed a weighted average of 40.94%.

6.65 The submission included [redacted]% uptake in Year 1. The evaluation considered that this was uncertain and not supported by evidence or expert opinion. Uptake was assumed to reach a maximum of [redacted]% in Year 6, which the submission considered a conservative estimate based on expert opinion from an advisory board, and indicated that 20% of eligible patients would not be prescribed a biologic treatment due to barriers including needle phobia, need for a lifelong support program and access to specialists.

6.66 The Sub-Committees noted the analysis of the 100% PBS sample undertaken by the Drug Utilisation Section, which reported the number of incident and prevalent patients and the scripts for PBS listed single inhaler triple therapies for COPD during

[11] *The redacted information is intended for publication in a forthcoming article in European Respiratory Journal Open Research.*

2023–2025 (Table 21). The Sub-Committees considered a market share approach based on the actual number of treated prevalent patients supplied triple therapy would likely provide more certain estimates for the utilisation of the single inhaler triple therapies. The Sub-Committees noted that there would also be an additional open triple inhaled therapy population.

**Table 21: Number of incident and prevalent patients, and scripts for PBS listed single inhaler triple therapies for COPD**

| Year/Drug/Item Code | Incident patients | Prevalent patients | Scripts |
|---|---|---|---|
| **Total 2023** | **46,654** | **138,169** | **857,453** |
| Beclometasone + formoterol + glycopyrronium (item code 12468F) | 11,133 | 27,473 | 148,005 |
| Budesonide + glycopyrronium + formoterol (item code 12672Y) | 10,021 | 20,164 | 100,709 |
| Fluticasone furoate + umeclidinium + vilanterol (item code 11379X) | 25,500 | 90,532 | 608,739 |
| **Total 2024** | **48,179** | **160,545** | **965,113** |
| Beclometasone + formoterol + glycopyrronium (item codes 12468F and 14310E) | 13,252 | 38,054 | 202,852 |
| Budesonide + glycopyrronium + formoterol (item codes 12672Y and 14536C) | 11,601 | 29,945 | 155,633 |
| Fluticasone furoate + umeclidinium + vilanterol (item codes 11379X and 14346C) | 23,326 | 92,546 | 606,628 |
| **Total 2025** | **47,736** | **186,168** | **993,497** |
| Beclometasone + formoterol + glycopyrronium (item codes 12468F and 14310E) | 13,952 | 48,438 | 228,186 |
| Budesonide + glycopyrronium + formoterol (item codes 12672Y and 14536C) | 12,309 | 40,543 | 190,492 |
| Fluticasone furoate + umeclidinium + vilanterol (item codes 11379X and 14346C) | 21,475 | 97,187 | 574,819 |

Source: Authorities data and prescriptions data was extracted on the 9 February 2026 from the prescription database and Authorities database maintained by the Department of Health, Disability and Ageing, processed by Services Australia from between 1 January 2023 and 31 December 2025, respectively. Data were extracted based on the date of supply. The number of incident patients, prevalent patients, and scripts dispensed was determined by counting the number of people supplied at least one PBS prescription using person specific numbers (non-identifying) in the data for the time period 1 January 2023 and 31 December 2025. Patient initiation was defined as the date of supply of the first PBS or RPBS prescription.

6.67 The Sub-Committees considered that revised financial estimates were required and suggested these could be provided in the pre-PBAC response. The Sub-Committees considered a market share approach based on the actual number of treated prevalent patients supplied triple therapy outlined in Table 21 with an additional estimate for the open triple inhaled therapy population would be appropriate. The Sub-Committees advised that a linear projection to forecast the eligible population would be appropriate. The Sub-Committees considered the percentage of patients with BEC ≥ 300 cells/µL from Hiles et al (2021) was likely appropriate. The Sub-Committees considered that as it was unclear how relevant the Benson et al (2019) study was to the Australian population and an alternative source to determine the proportion at high risk of exacerbations would likely be more appropriate. The Sub-Committees considered that compliance assumptions should be as outlined by the Sub-Committees in Table 19. The Sub-Committees considered that sensitivity analyses

varying assumptions around the percentage of patients with BEC ≥ 300 cells/µL along with those for compliance and uptake rates would also be informative.

6.68 The pre-PBAC response provided revised financial estimates which:

- Incorporated a linear projection, based on the 100% PBS data, to forecast the single triple inhaler therapy population. It was noted that the open triple therapy population (based on the PBS 10% sample) had reduced significantly across time with the introduction of single inhaler triple therapy. A trend of decreasing open triple therapy was assumed with an additional open triple inhaled therapy population included in Year 1 only.
- Continued to include an adjustment ([redacted]% increase in projected number of COPD patients on triple therapy) to account for patients who are indicated for triple therapy but are using dual therapy due to intolerance to LAMA, LABA or ICS component.
- Continued to use Benson et al (2019) to determine the percentage of patients on triple inhaled therapy who have experienced ≥ 2 moderate or ≥ 1 severe exacerbations in the past 12 months. In the absence of an alternative source suggested by the Sub-Committees the pre-PBAC response argued that the 60.54% from Benson et al (2019) remained appropriate. The pre-PBAC response stated that it was the only study identified that adequately informs the eligibility proportions across the progressively enriched cohorts in the financial model.
- Decreased the percentage of patients with EOS ≥ 300µL from 45.9% to 40.94% based on a weighted average across Benson et al (2019), Hiles et al (2021) and Menon et al. (submitted for publication) (see paragraph 6.64).
- Maintained that the 98.7% compliance rate remained appropriate given a source was not provided for the 93% compliance rate recommended by the Sub-Committees.
- Updated treatment persistence rates to be consistent with the revised economic model provided with the pre-PBAC response (see Table 19).
- Incorporated a revised effective EMP of $[redacted] per 100 mg pre-filled pen.

Uptake rates in the revised estimates submitted with the pre-PBAC response remained consistent with the submission base case with rates applied cumulatively. The net cost to the PBS/RPBS was reported as $100 million to < $200 million in Year 6 and $900 million to < $1 billion in the first 6 years of listing.

## Quality Use of Medicines

6.69 The submission noted that it will conduct routine pharmacovigilance and risk minimisation activities. This was not described. Additional risk minimisation activities proposed by the submission included educational meetings for healthcare professionals, a patient support program, and administration videos. The Sub-Committees noted that the submission assumed one nurse practitioner visit for 40

minutes for patient education on administration and then all future treatments are self-administered. The Sub-Committees considered that it is likely that repeat education on administration will be required for some patients and noted that there will be additional resources available through the patient support program.

### Financial Management – Risk Sharing Arrangements

6.70 The submission did not present a risk-sharing arrangement.

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

## 7 PBAC Outcome

7.1 The PBAC recommended the listing of mepolizumab as an add-on maintenance treatment for adults with uncontrolled chronic obstructive pulmonary disease (COPD) and type 2 inflammation (defined by the submission as blood eosinophil count (BEC) ≥ 300 cells/µL). The PBAC was satisfied that mepolizumab provides, for some patients, a significant improvement in efficacy over triple inhaled therapy alone. The PBAC noted that mepolizumab plus triple inhaled therapy significantly reduced the annualised rate of moderate/severe exacerbations and significantly extended the time to the first occurrence of a moderate/severe exacerbation compared to triple inhaled therapy alone, however noted that the magnitude of benefit was subject to some uncertainty. The PBAC considered that the incremental cost-effectiveness ratio (ICER) was high and uncertain however that with revisions to the economic model and a price reduction mepolizumab could be considered cost-effective. The PBAC considered that further revisions to the financial estimates provided in the mepolizumab pre-PBAC Response were required. The PBAC considered that with these revisions, the remaining uncertainties could be managed with a risk sharing arrangement (RSA).

7.2 The PBAC noted comments from individuals who would like access to mepolizumab, health care professionals and organisations which expressed support for the proposed PBS listing of mepolizumab. The comments highlighted that patients with COPD who continue to exacerbate despite optimised triple inhaled therapy represent a group with a persisting unmet clinical need, as ongoing exacerbations are strongly associated with accelerated disease progression. Comments noted that treatment options for this patient group remain limited and long-term use of oral corticosteroids carries substantial risks associated with toxicity. Comments stated that exacerbations significantly limited daily functioning, contributed to a reduced quality of life, and increase the likelihood of future events. The PBAC noted the input highlighted the importance of additional treatment options, such as mepolizumab, to help manage disease burden, reduce reliance on oral corticosteroids, and ultimately improve long-term outcomes.

7.3 With respect to the proposed restriction, the PBAC proposed that:

- A Section 100, Highly Specialised Drug Program Authority Required (Written) listing was appropriate for both the Initial and Grandfathering treatment

phases. A Section 100, Highly Specialised Drugs Program Authority Required (Telephone/Online) listing was appropriate for the continuing treatment phase. The initial treatment restriction should have 6 repeats with 5 repeats for the continuing and grandfathering treatment phases.

- The indication for treatment should be uncontrolled COPD.
- Initial treatment criteria requiring a patient to be under the care of the same physician for at least 6 months or to have been diagnosed with COPD by a multidisciplinary team was not required.
- For patients who had not achieved or who had not sustained a response to treatment, a re-trial after a 12-month break was considered appropriate.
- As per paragraph 3.2, a BEC of at least 300 cells/µL in the 12 months prior to commencing treatment was appropriate.
- As per paragraph 3.3, clinical criteria specifying that patients must not have achieved adequate control with at least 3 months of an optimised triple inhaled therapy was required in both the initial and grandfathering treatment phases. Triple inhaled therapy was considered to consist of treatment with a long-acting muscarinic agonist (LAMA), long-acting beta-2 agonist (LABA) and inhaled corticosteroid (ICS).
- Patients must have experienced at least one severe COPD exacerbation, or at least two moderate COPD exacerbations in the 12 months prior to treatment. At least one of those exacerbations must have occurred while the patient was taking triple inhaled therapy.
- As per paragraph 3.4, the PBAC considered that each treatment phase should require mepolizumab to be taken in combination with triple inhaled therapy.
- Given the age profile of patients with COPD a criteria restricting use to patients aged 18 years and older was not required.
- Both the continuing and grandfathering phases should include clinical criteria requiring patients who have received at least 24 weeks of treatment to have both achieved and sustained an adequate response. An adequate response is defined as maintenance (i.e. no change) or a reduction in the number of moderate and/or severe exacerbation/s compared to the baseline levels provided with the initial authority application.
- Should a second biologic be listed for this indication, flow on changes to the restriction in paragraph 8.1 as outlined in paragraph 8.2 were considered appropriate.
- Flow on changes to all PBS-subsidised biological medicine listed for nasal polyps, uncontrolled severe allergic asthma, and uncontrolled severe asthma

to prevent concomitant therapy with another biologic listed for these indications including uncontrolled COPD as outlined in paragraph 8.3.

7.4 The PBAC considered that the proposed comparator of triple inhaled therapy was appropriate. The PBAC also considered that dupilumab was a relevant near market comparator, and noted dupilumab was also considered by the Committee for the same indication at its March 2026 meeting.

7.5 The PBAC noted that the submission was based on one head-to-head clinical trial, MATINEE (n=804), which compared mepolizumab as add-on to triple inhaled therapy (i.e., LABA + LAMA + ICS) to triple inhaled therapy alone in patients with uncontrolled COPD and an eosinophilic phenotype. The PBAC noted that mepolizumab resulted in a statistically significant reduction in the annualised rate of moderate or severe COPD exacerbations compared to placebo (relative risk [RR] = 0.79, 95% confidence interval [CI] = 0.66–0.94, p=0.011). The PBAC also noted there was a statistically significant reduction in the time to first moderate or severe exacerbation of COPD in patients treated with mepolizumab compared with placebo (hazard ratio [HR] = 0.77, 95% CI 0.64–0.93, p=0.009). The PBAC noted that there were no meaningful differences in quality of life between the mepolizumab and placebo treatment arms, as measured by three validated scales in the MATINEE trial. The PBAC noted that the Sub-Committees considered that the magnitude of treatment benefit of mepolizumab versus placebo was subject to uncertainty given that much of the difference in the rate ratio was driven by the avoidance of events among a subset of patients with ≥ 9 exacerbations. Overall, the PBAC considered that the claim of superior comparative effectiveness compared to triple inhaled therapy alone was reasonable, but the magnitude of treatment benefit was subject to some uncertainty.

7.6 The PBAC noted that mepolizumab was generally well tolerated in the MATINEE trial and had a similar safety profile to the placebo arm. The PBAC noted that no new safety concerns had been identified. The PBAC noted that while the overall incidence of adjudicated major adverse cardiovascular events (MACE) was balanced between groups (11 events in each arm), there was a numeric imbalance in deaths from a cardiovascular cause (6 (1.5%) in the mepolizumab group vs. 3 (0.7%) in the placebo group). The PBAC agreed with the evaluation that given the lack of statistical power for rare safety endpoints, it is difficult to determine if this imbalance represented a genuine safety signal or random variation. Overall, the PBAC considered the claim of non-inferior comparative safety versus placebo was reasonable. The PBAC noted that the Sub-Committees considered that a longer duration of follow-up was needed to adequately capture the long-term safety of mepolizumab in COPD patients.

7.7 The PBAC noted that 2 literature-based indirect treatment comparisons (ITCs) had been identified comparing mepolizumab and dupilumab (see paragraph 6.26). The PBAC noted the primary ITC analysis undertaken by Bhatt et al. (2025) found that dupilumab provided a numerically favourable but not statistically significant reduction (rate ratio = 0.82, 95% CI 0.66–1.01) in the rate of moderate or severe COPD exacerbations compared with mepolizumab. The PBAC noted that the ITC analysis

undertaken by Suter et al. (2025) restricted trials to those that required patients to have a BEC 300 cells/µL at inclusion. Suter et al. (2025) reported both dupilumab and mepolizumab were associated with significant reductions in annual exacerbation rates versus placebo, with overlapping 95% confidence intervals. The PBAC also noted that the submission presented a matched-adjusted indirect treatment comparison (MAIC) comparing mepolizumab and dupilumab. The PBAC agreed with the Sub-Committees that the MAIC demonstrated that there was no statistically significant difference between mepolizumab and dupilumab in reducing the annualised rate of moderate or severe exacerbations, the annualised rate of severe exacerbations or the time to first moderate or severe exacerbation, with all confidence intervals crossing zero (see Table 6). The PBAC recalled that it had previously accepted a claim of non-inferior comparative safety for dupilumab and mepolizumab in its consideration of dupilumab for uncontrolled severe eosinophilic or allergic asthma (see paragraph 6.26). Overall, the PBAC advised that the totality of the data suggested that mepolizumab and dupilumab have similar clinical effectiveness and safety, and that a claim of non-inferior comparative effectiveness and safety would be reasonable.

7.8 The PBAC noted that the submission presented a cost-utility analysis to support the cost-effectiveness of mepolizumab plus triple inhaled therapy versus triple inhaled therapy alone. The PBAC acknowledged the key concerns raised by the Sub-Committees (see paragraph 6.55). The PBAC noted that the Sub-Committees had advised that to align with the proposed restriction, treatment discontinuation due to a loss of response (stopping rule) should occur every 6 months, not every 3 months in Years 2+ of the model. The Sub-Committees advised that treatment discontinuation, for reasons not related to a response (e.g. adverse events), should be applied to all health states in the model, not only those related to responders ('no exacerbation' health state). The Sub-Committees considered that 10 years was the most appropriate time horizon for this patient group. The PBAC also noted that the economic model relied on a modest magnitude of treatment benefit which was subject to some uncertainty. The PBAC considered that while the rate of exacerbation is regarded as an important clinical endpoint which is directly experienced by patients and represent important changes in symptoms and health status, when used to project longer-term outcomes, such as mortality and long-term decline, such measures function similar to an intermediate or surrogate measure.

7.9 The PBAC noted that the Pre-PBAC Response had addressed the main concerns related to the economic model raised by the Sub-Committees (paragraph 6.56). The PBAC also noted that the Pre-PBAC Response proposed a revised effective price for mepolizumab of $[redacted] per 100 mg pre-filled pen (ex-manufacturer price). The PBAC noted that with the reduced price and revisions to the economic model, as proposed in the Pre-PBAC Response, the ICER was $55,000 to < $75,000/QALY gained. The PBAC considered that the ICER remained high. The PBAC considered that in light of uncertainties related to the model's reliance on surrogate endpoints and its unknown long-term clinical impact along with the ICERs accepted in similar contexts (see paragraph 6.57), mepolizumab would be cost-effective based on the Pre-PBAC model

and a price reduction which achieved an ICER of less than $25,000 to < $35,000 per QALY gained.

7.10 The PBAC noted the current near market comparator dupilumab was also considered for the same indication at its March 2026 meeting, and that as per paragraph 7.7 the Committee considered a claim of non-inferior comparative effectiveness and safety was reasonable. The PBAC recommended that if both dupilumab and mepolizumab are listed on the PBS, the following equi-effective doses would be appropriate for a cost-minimisation approach for the subsequent therapy listed:

- Mepolizumab 100 mg by subcutaneous injection every 4 weeks (13 doses over 1 year)
- Dupilumab 300 mg by subcutaneous injection every 2 weeks (26 doses over 1 year).

7.11 The PBAC noted the submission used 10% PBS sample data to determine the number of prevalent patients on triple inhaled therapy and agreed with its Sub-Committees that the estimate was uncertain. The PBAC noted the analysis of the 100% PBS sample which reported the number of prevalent patients for PBS listed single inhaler triple therapies for COPD (Table 21). The PBAC agreed with its Sub-Committees that an approach based on the actual number of treated prevalent patients supplied triple therapy was appropriate and noted the additional suggested revisions to inputs outlined in paragraph 6.67.

7.12 The PBAC noted the pre-PBAC response provided revised financial estimates based on the number of treated prevalent patients supplied triple therapy with inputs as outlined in paragraph 6.68. The PBAC considered the approach taken to forecasting both the single triple inhaler therapy (based on 100% PBS data) and open triple inhaler therapy (based on PBS 10% sample) populations was appropriate. However, as per paragraph 7.3, the PBAC considered that mepolizumab should be taken in combination with triple inhaled therapy. As such, the PBAC recommended the removal of the [redacted]% increase in the projected number of COPD patients on triple therapy to account for intolerance to LAMA, LABA or ICS.

7.13 The PBAC noted the Sub-Committees concern that the use of the Benson et al (2019) study inputs were a source of uncertainty due to concerns regarding applicability to the Australian population. The PBAC noted that an alternative source was not proposed by its Sub-Committees and the pre-PBAC response argument that despite applicability concerns the use of Benson et al (2019) remained appropriate. The PBAC accepted the use of Benson et al (2019) to inform the proportion on triple therapy who have experienced ≥ 2 moderate or ≥ 1 severe exacerbation and the proportion who are optimised on triple therapy. The PBAC agreed with the Sub-Committees that Benson et al (2019) likely overestimates the proportion with BEC ≥ 300 cells/µL. The PBAC noted the approach taken by the pre-PBAC response which reduced the proportion with BEC ≥ 300 cells/µL from 45.9% to 40.94% and considered that this remained optimistic but acceptable in the context of the overall eligibility inputs.

7.14 The PBAC agreed with its Sub-Committees that a compliance rate of 93% should be applied and noted that this was consistent with that considered appropriate by DUSC in the consideration of tezepelumab for non-eosinophilic and non-allergic severe uncontrolled asthma population (Table 20, tezepelumab PSD, November 2025 PBAC meeting).

7.15 The PBAC considered the methodological approach taken to applying uptake rates in the submission and pre-PBAC response estimates was appropriate. The PBAC considered the uptake rate of [redacted]% in Year 1 was appropriate but considered it likely that the cumulative uptake rate in Year 6 may be marginally higher than [redacted]%.

7.16 The PBAC considered that, with the above amendments and with the price reduction required to achieve cost effectiveness outlined in paragraph 7.9 it would be reasonable to accept the pre-PBAC response revised financial estimates.

7.17 The PBAC considered that the risk of use outside of the proposed patient population (particularly in patients not optimised on triple inhaled therapy) was high and that this along with the remaining uncertainties in the financial estimates could be managed through an RSA with a [redacted]% rebate for expenditure above the annual caps. Should the near market comparator dupilumab be listed on the PBS before mepolizumab is able to proceed to listing, it would be appropriate for mepolizumab to join any established RSA with no increase in the caps.

7.18 The PBAC advised that mepolizumab is not suitable for prescribing by nurse practitioners.

7.19 The PBAC recommended that the Early Supply Rule should not apply.

7.20 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for mepolizumab:

a. The treatment is expected to provide a clinically relevant improvement in the rate and time to next moderate or severe exacerbation over inhaled triple therapy alone, however the magnitude of benefit was subject to some uncertainty, and no changes in long-term outcomes such as survival have been established;

b. The treatment is not expected to address a high and urgent unmet clinical need as there are therapies listed on the PBS that can be used in the management of exacerbations. However, the persistent clinical need for therapies that can reduce both exacerbations and reliance on oral corticosteroids in the management of exacerbations was acknowledged;

c. It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.21 The PBAC advised that this submission would not be eligible for an Independent Review as it received a positive recommendation.

**Outcome:**
Recommended

# 8 Recommended listing

8.1 Add new listing (new indication) as follows:

Initial treatment

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| MEPOLIZUMAB | | | | | |
| mepolizumab 100 mg/mL injection, 1 mL pen device | NEW (HSD PUBLIC)<br>NEW (HSD PRIVATE)<br>MP | 1 | 1 | 6 | Nucala |

| | |
|---|---|
| | **Category / Program:** Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) |
| | **Prescriber type:** Medical Practitioners |
| | **Restriction type:** Authority Required (FULL assessment) in writing only via OPA/post/HPOS upload |
| | **Authority type:** Complex Authority Required (CAR) |
| | **Administrative Advice:**<br>The length of a break in therapy is measured from the date that the relevant PBS-subsidised medicine listed for this PBS indication is ceased during the most recent treatment cycle, until the date of the subsequent application for treatment under a new treatment cycle. |
| | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised |
| | **Administrative Advice:** No increase in the maximum number of repeats may be authorised |
| | **Administrative Advice:** Special Pricing Arrangements apply |
| | **Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).<br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |
| | **Indication:** Uncontrolled chronic obstructive pulmonary disease (COPD) |
| | **Treatment Phase:** Initial treatment (New patients; or Recommencement of treatment in a new treatment cycle following a break in PBS subsidised biological medicine therapy) |
| | **Clinical criteria:** |
| | Patient must not have received PBS-subsidised treatment with a biological medicine for this condition; **OR** |
| | Patient must have had at least a 12-month break from the most recently approved PBS-subsidised biological medicine for this condition |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have a blood eosinophil count of at least 300 cells per microlitre in the 12 months prior to commencing treatment with this drug in this treatment cycle. |
| | **AND** |

| | |
|---|---|
| | **Clinical criteria:** |
| | Patient must not have achieved adequate control with at least 3 months of an optimised triple inhaler therapy consisting of: (i) long-acting muscarinic antagonist (LAMA), (ii) a long-acting beta-2 agonist (LABA), (iii) an inhaled corticosteroid (ICS), despite formal assessment of and adherence to correct inhaler technique which has been documented in the patient's medical records. |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have experienced at least one severe COPD exacerbation, or at least two moderate COPD exacerbations in the 12 months prior to commencing treatment with this drug in this treatment cycle. |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be in combination with all of (i) LAMA, (ii) LABA, (iii) ICS in an optimised triple inhaler therapy |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma, (iv) uncontrolled chronic obstructive pulmonary disease. |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must not receive more than 28 weeks of treatment under this restriction |
| | **Treatment criteria:** |
| | Must be treated by a medical practitioner who is either a (i) respiratory physician, (ii) general physician experienced in the management of patients with this condition. |
| | **Prescribing Instructions:**<br>For the purpose of administering this restriction, COPD exacerbations in the 12 months prior to starting treatment in this treatment cycle are defined as experiencing:<br>i. at least 1 severe COPD exacerbation which required hospitalisation AND/OR<br>ii. 2 or more moderate COPD exacerbations, of which at least:<br>a. one required treatment with systemic corticosteroids and<br>b. one required treatment with systemic corticosteroids or antibiotics.<br>At least one of the moderate or severe exacerbations must have occurred while the patient was taking all of (i) LAMA, (ii) LABA, and (iii) ICS in an optimised triple inhaler therapy. |
| | **Prescribing Instructions:**<br>The authority application must be via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include the following:<br>a. the blood eosinophil count and date;<br>b. details of the optimised triple inhaler therapy with the combination of LAMA, LABA and ICS (name of treatment, dosage, date of commencement, and duration of therapy); and<br>c. details of the number and severity of COPD exacerbation(s) experienced in the 12 months prior to commencing treatment with this drug in this treatment cycle including:<br>(i) no. of moderate exacerbations requiring treatment with systemic corticosteroids<br>(ii) no. of moderate exacerbations requiring treatment with antibiotics<br>(ii) no. of severe exacerbation/s which required hospitalisation.<br><br>The details of the number and the severity of COPD exacerbations are to inform the basis of determining if an adequate response to treatment has been achieved under the continuing treatment restriction. In addition to stating the above details in the authority application, document them in the patient's medical records. |
| | **Prescribing Instruction:**<br>If the application is submitted through HPOS form upload or mail, it must include:<br>i. details of the proposed prescription; and<br>ii. a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |

Continuing and Grandfather treatment:

| MEDICINAL PRODUCT<br>medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| MEPOLIZUMAB | | | | | |
| mepolizumab 100 mg/mL injection, 1 mL pen device | NEW | 1 | 1 | 5 | Nucala |

| | |
|---|---|
| | **Category / Program:** Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) |
| | **Prescriber type:** Medical Practitioners |
| | **Restriction type:** Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues) |
| | **Authority type:** Complex Authority Required (CAR) |
| | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised |
| | **Administrative Advice:** No increase in the maximum number of repeats may be authorised |
| | **Administrative Advice:** Special Pricing Arrangements apply |
| | |
| | **Indication:** Uncontrolled chronic obstructive pulmonary disease (COPD) |
| | **Treatment Phase:** Continuing treatment |
| | **Clinical criteria:** |
| | Patient must have received PBS-subsidised treatment with this biological medicine for this condition |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have both achieved and sustained an adequate response to this drug, defined as maintenance (i.e. no change) or a reduction in the number of moderate and/or severe exacerbation/s compared to the baseline levels provided with the initial PBS authority application. |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be in combination with all of (i) LAMA, (ii) LABA, (iii) ICS in an optimised triple inhaler therapy |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma, (iv) uncontrolled chronic obstructive pulmonary disease. |
| | **Treatment criteria:** |
| | Must be treated by a medical practitioner who is either a (i) respiratory physician, (ii) general physician experienced in the management of patients with this condition. |
| | **Prescribing Instructions:**<br>The following must be provided in each continuing PBS authority application and be documented in the patient's medical records:<br>details of the current number and severity of exacerbations compared to baseline levels provided in the initial authority application of this treatment cycle including:<br>(i) no. of moderate exacerbations requiring treatment with systemic corticosteroids<br>(ii) no. of moderate exacerbations requiring treatment with antibiotics<br>(ii) no. of severe exacerbation/s which required hospitalisation |
| | **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |

| | |
|---|---|
| **Restriction type:** ☒ Authority Required – Authority Required (FULL assessment) in writing only via OPA/post/HPOS upload | |
| | **Indication:** Uncontrolled Chronic obstructive pulmonary disease (COPD) |
| | **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply- Grandfather arrangements |
| | **Clinical criteria:** |
| | Patient must have previously received non-PBS subsidised treatment with this biological medicine for this PBS indication prior to [listing date] |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a blood eosinophil count of at least 300 cells per microlitre in the 12 months prior to commencing non-PBS subsidised treatment with this drug for this condition. |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must not have achieved, prior to commencing non-PBS subsidised treatment with this drug for this condition, adequate control with at least 3 months of optimised triple inhaled therapy consisting of: (i) long-acting muscarinic antagonist (LAMA),(ii) a long-acting beta-2 agonist (LABA), (iii) an inhaled corticosteroid (ICS), despite formal assessment of and adherence to correct inhaler technique which has been documented in the patient's medical records. |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have experienced at least one severe COPD exacerbation, or at least two moderate COPD exacerbations in the 12 months prior to commencing non-PBS subsidised treatment with this drug for this condition. |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be in combination with all of (i) LAMA, (ii) LABA, (iii) ICS in an optimised triple inhaler therapy |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have both achieved and sustained an adequate response to this drug, defined as maintenance (i.e. no change) or a reduction in the number of moderate and/or severe exacerbation/s compared to the baseline levels provided with this authority application, if they received at least 24 weeks of treatment with this drug for this condition. |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma, (iv) uncontrolled chronic obstructive pulmonary disease. |
| | **Treatment criteria:** |
| | Must be treated by a medical practitioner who is either a (i) respiratory physician (ii) general physician experienced in the management of patients with this condition. |
| | **Prescribing Instructions:**<br>For the purpose of administering this restriction, COPD exacerbations in the 12 months prior to commencing non-PBS subsidised treatment with this drug for this condition, are defined as experiencing:<br>(i) at least 1 severe COPD exacerbation which required hospitalisation AND/OR<br>(ii) 2 or more moderate COPD exacerbations, of which at least:<br>a. one required treatment with systemic corticosteroids and<br>b. one required treatment with systemic corticosteroids or antibiotics. |

| | |
|---|---|
| | At least one of the moderate or severe exacerbations must have occurred while the patient was taking all of (i) LAMA, (ii) LABA, and (iii) ICS. |
| | **Prescribing Instructions:**<br>The authority application must be via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include the following:<br>a. the blood eosinophil count and date;<br>b. details of therapy with a combination of LAMA, LABA and ICS (name of treatment, dosage, date of commencement, and duration of therapy prior to commencing non-PBS subsidised treatment with this drug for this condition);<br>c. **Baseline exacerbation history**<br>details of the number and severity of COPD exacerbations experienced in the 12 months immediately prior to commencement of this drug as non-PBS-subsidised therapy for this condition, including:<br>i. number of moderate exacerbations requiring treatment with systemic corticosteroids<br>ii. number of moderate exacerbations requiring treatment with antibiotics<br>iii. number of severe exacerbations requiring hospitalisation; and<br>d. **Assessment of response to treatment where applicable (for patients who have received at least 24 weeks of treatment)**<br>details of the current number and severity of COPD exacerbations, compared with the baseline information supplied in this authority application, including:<br>i. number of moderate exacerbations requiring treatment with systemic corticosteroids<br>ii. number of moderate exacerbations requiring treatment with antibiotics<br>iii. number of severe exacerbations requiring hospitalisation<br><br>The details of the number and the severity of COPD exacerbations are to inform the basis of determining if an adequate response to treatment has been achieved under the continuing treatment restriction.<br>In addition to stating the above details in the authority application, document them in the patient's medical records. |
| | **Prescribing Instruction:**<br>If the application is submitted through HPOS form upload or mail, it must include:<br>i. details of the proposed prescription; and<br>ii. a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Administrative Advice:** A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria. |
| | **Administrative Advice:** This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
| | **Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).<br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |

8.2 Flow on changes to listing. Should a second biologic be listed for this indication, amend the treatment phase: Initial treatment to state: Initial treatment – *initial 1*, add Initial 2 (change of treatment) restriction and the long Administrative Advice as follows.

| MEDICINAL PRODUCT<br>medicinal product pack | PBS item code | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| MEPOLIZUMAB | | | | | |
| mepolizumab 100 mg/mL injection, 1 mL pen device | Initial item code (HSD PUBLIC)<br>Initial item code (HSD PRIVATE)<br>MP | 1 | 1 | 6 | Nucala |

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| | | **Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS) |
| | | **Prescriber type:** ☒Medical Practitioners |
| | | **Restriction type:** ☒ Authority Required (FULL assessment) in writing only via OPA/post/HPOS upload |
| | | **Authority type:** ☒ Complex Authority Required (CAR) |
| | | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised |
| | | **Administrative Advice:** No increase in the maximum number of repeats may be authorised |
| | | **Administrative Advice:** Special Pricing Arrangements apply |
| | | **Administrative Advice:** Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).<br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |

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| | **Indication:** Uncontrolled chronic obstructive pulmonary disease (COPD) |
| | **Treatment Phase:** Initial treatment – Initial 2 (Change of treatment) |
| | **Clinical criteria:** |
| | Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have either: (i) not previously received this drug for this condition in the current treatment cycle, (ii) previously received this drug in the current treatment cycle and demonstrated/maintained an adequate clinical response. |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must be in combination with all of (i) LAMA, (ii) LABA, (iii) ICS in an optimised triple inhaler therapy |
| | **AND** |
| | **Clinical criteria:** |

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| | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma, (iv) uncontrolled chronic obstructive pulmonary disease. |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must not receive more than 28 weeks of treatment under this restriction |
| | **Treatment criteria:** |
| | Must be treated by a medical practitioner who is either a (i) respiratory physician, (ii) general physician experienced in the management of patients with COPD this condition. |
| | **Prescribing Instructions:**<br>The authority application must be via the Online PBS Authorities System, or in writing via HPOS form upload or mail and must include the following:<br>a. details (date and duration of treatment) of prior biological medicine treatment; and<br>b. The reason for switching therapy (e.g. not achieving adequate response with prior biological therapy, partial response to prior therapy, adverse event to prior therapy)<br>All supporting evidence must be documented in the patient's medical records |
| | **Prescribing Instruction:**<br>If the application is submitted through HPOS form upload or mail, it must include:<br>i. details of the proposed prescription; and<br>ii. a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |

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| | **Administrative Advice:**<br>**TREATMENT OF PATIENTS WITH UNCONTROLLED CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**<br>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines for Uncontrolled COPD. Where the term biological medicine appears in the following notes and restrictions it refers to all PBS benefits with the specific PBS indication of 'Uncontrolled COPD'<br>A patient is eligible for PBS-subsidised treatment with only one biological medicine for 'Uncontrolled COPD' at any one time.<br>Under these arrangements, within a treatment cycle, a patient may receive long-term treatment with a biological medicine as long as they sustain a response to therapy.<br>A patient currently receiving PBS-subsidised treatment as of (first biologic for COPD listing date X/X/XXXX ) is considered to have started a cycle of treatment.<br>Within the same treatment cycle, a patient cannot trial and not achieve response, or cease to respond to, the same PBS-subsidised biological medicine more than once.<br>Therefore, in cases where the patient does not achieve the response criteria for a PBS-subsidised biological medicine, they must change to an alternate biological medicine if they wish to continue PBS-subsidised biological treatment.<br>In cases where the patient does not achieve or sustain the response criteria to treatment two times, they are deemed to have completed a single treatment cycle. They must have at least a 12-month break in PBS-subsidised biological medicine therapy before they are eligible to recommence another new treatment cycle [further details are under 'Recommencement of treatment after a treatment break in PBS-subsidised therapy' below].<br>The length of the break in therapy is measured from the date the most recent treatment with a PBS-subsidised biological medicine is ceased until the date of the first application for recommencement of treatment with a biological medicine under the new treatment cycle.<br>There is no limit to the number of treatment cycles that a patient may undertake in their lifetime.<br><br>How to prescribe PBS-subsidised biological medicine treatment for 'Uncontrolled COPD'<br>(1) Initial treatment:<br>Applications for initial treatment should be made where: |

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| | (i) a patient has not received prior PBS-subsidised biological medicine treatment and wishes to commence such therapy (Initial 1 restriction); or<br>(ii) a patient has received prior PBS-subsidised treatment with a biological medicine and wishes to recommence a new treatment cycle with this biological medicine following a mandatory treatment break in PBS-subsidised therapy (Initial 1 restriction); or<br>(iii) a patient has received prior PBS-subsidised biological medicine therapy and wishes to trial an alternate biological medicine within the same treatment cycle (Initial 2 restriction) - [further details are under 'Swapping therapy' below].<br>All applications for initial treatment will be limited to provide for a maximum of up to 28 weeks of therapy of a biological medicine. It is recommended that a patient be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological medicine supply.<br><br>(2) Grandfather patients<br>A patient who commenced treatment with a biological medicine for 'Uncontrolled COPD' prior to [the relevant biological medicine's listing date, specified in the restrictions] and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.<br>A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment will be authorised under this restriction. Following completion of the first PBS-subsidised course, further subsidised treatment must be prescribed under the continuing treatment restriction of the relevant biological medicine.<br><br>(3) Continuing treatment:<br>Following the completion of an initial treatment course with a specific biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that biological medicine providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing biological medicine treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. It is recommended that a patient be reviewed the month prior to completing their current course of treatment to ensure uninterrupted biological medicine supply.<br>(4) Swapping therapy within the same treatment cycle.<br>Once initial treatment with the first PBS-subsidised biological medicine is approved, a patient may swap to an alternate biological medicine at any time by qualifying under an Initial 2 restriction.<br>However, they cannot swap to a particular biological medicine if they did not achieve response to prior treatment with that drug within the same treatment cycle.<br>Within the same treatment cycle a patient may alternate between therapy with any biological medicine of their choice (1 at a time) providing:<br>(i) they have not received PBS-subsidised treatment with that particular biological medicine previously; or<br>(ii) they have demonstrated an adequate response to that particular biological medicine if they have previously trialled it on the PBS; and<br>(iii) they have not previously ceased to respond to treatment with all 2 biological medicines in this treatment cycle.<br>(5) Re-commencement of a new treatment cycle after a treatment break in PBS-subsidised therapy:<br>A patient who wishes to trial a second or subsequent new treatment cycle, following a mandatory break in PBS-subsidised therapy of at least 12 months (in patients who have not achieved or ceased to sustain a response to treatment 2 times within a treatment cycle), must re-qualify through an Initial 1 restriction. |

8.3 Flow on changes to all PBS-subsidised biological medicine listed for nasal polyps, uncontrolled severe allergic asthma, and uncontrolled severe asthma to prevent concomitant therapy with another biologic listed for these indications including uncontrolled COPD.

Amend the following clinical criterion with the addition of the text in italics:

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| | **Clinical criteria:** |

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| | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma, (*iv) uncontrolled chronic obstructive pulmonary disease*. |

***These restrictions 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

GSK welcomes the PBAC's recommendation to list mepolizumab (NUCALA®) on the PBS as an add-on maintenance treatment for adults with uncontrolled chronic obstructive pulmonary disease (COPD) and type 2 inflammation (defined by the submission as blood eosinophil count (BEC) ≥ 300 cells/µL). GSK is working through the conditions of the recommendation.