

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

1 Purpose of Application

- 1.1 The submission requested an Authority Required Section 100 listing for mepolizumab for treatment of chronic rhinosinusitis (CRS) with nasal polyps (NP; collectively CRSwNP) for patients who have received at least one previous surgery for the removal of NP (unless not suitable for surgery) and failed to achieve adequate control with optimised NP therapy (intranasal corticosteroids (INCS) unless contraindicated or not tolerated, and oral corticosteroids (OCS) unless contraindicated or not tolerated), with a blood eosinophil count (BEC) greater than or equal to 150 cells/ μ L. This was the first submission for mepolizumab for CRSwNP to be considered by PBAC. Mepolizumab is PBS listed for severe eosinophilic asthma.
- 1.2 The requested basis for listing is a cost-effectiveness analysis compared to standard of care (SoC) (Table 1).

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

Component	Description
Population	CRSwNP patients with a blood eosinophil count \geq 150cells/ μ L who have received prior NP surgery and remain inadequately controlled with standard of care (defined as INCS, saline rinses and short courses of OCS).
Intervention	Mepolizumab 100 mg SC injection per patient by self-administration every 28 days.
Comparator	Standard of care (including INCS (drops/sprays/rinses), saline rinses and short courses of OCS).
Outcomes	Primary endpoints: Total endoscopic nasal polyp (ENP) score, nasal obstruction visual analogue scale (VAS) score. Secondary endpoints: Time to first actual NP surgery, overall VAS score, change from baseline in SNOT-22 total score, proportion of patients requiring systemic steroids for nasal polyps, composite VAS, individual VAS symptom score for loss of smell, clinically significant asthma exacerbations, change in ACQ-5 score. Safety: Rates of adverse events (AEs) and serious AEs (fatal and non-fatal).
Clinical claim	Mepolizumab has superior efficacy and comparable safety to standard of care for patients with recurrent severe bilateral NP who have received prior NP surgery.

Source: Table 1-1, p16 of the submission.

ACQ-5= asthma control questionnaire; AE= adverse event; CRSwNP= chronic rhinosinusitis with nasal polyps; INCS= intranasal corticosteroids; NP= nasal polyps; OCS= oral corticosteroids; QoL= quality of life; SC= subcutaneous; SNOT-22= sino-nasal outcomes test (22 items); VAS= visual analogue scale.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was made under TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA Clinical Evaluation Report (CER) (round 1) was available with the submission. The submission stated that the delegate's decision was expected in January 2022.
- 2.2 The proposed indication was:
- Mepolizumab is indicated as add-on maintenance treatment of adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP).
- 2.3 The TGA evaluator concluded (TGA CER (round 1), p76) that it is appropriate to reword the indication to be more consistent with the inclusion criteria for the studies. The indication should be:
- Mepolizumab is indicated as add-on treatment in adult patients (18 years and above) with severe chronic rhinosinusitis with nasal polyps (CRSwNP) and an inadequate response to intranasal corticosteroids.
- 2.4 Mepolizumab is currently TGA registered for severe eosinophilic asthma and relapsed or refractory eosinophilic granulomatosis with polyangiitis.

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

3 Requested listing

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

Public Summary Document – November 2021 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed Price for Max. Qty	Available brands
MEPOLIZUMAB						
mepolizumab 100 mg/mL injection, 1 mL syringe	NEW public NEW private	1 1	1 1	5 5	Published price \$1,638.00 (public) \$1,685.74 (private) Effective price \$ [REDACTED] (public) \$ [REDACTED] (private)	Nucala
Restriction Summary [new] / Treatment of Concept: [new]						
Category / Program: Section 100 – Highly Specialised Drugs Program (public/private hospitals)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate assessment by Services Australia						
Administrative advice: No increase in the maximum quantity or number of units may be authorised.						
Administrative advice: Special Pricing Arrangements apply.						
Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)						
Treatment Phase: Initial treatment						
Treatment criteria:						
Patient must be treated by a respiratory physician, clinical immunologist, allergist, ear nose and throat specialist (ENT) or general physician experienced in the management of patients with CRSwNP.						
Clinical criteria:						
Patient must have a diagnosis of CRSwNP confirmed and documented by <i>nasal</i> endoscopy or computed tomography (CT) scan, OR Patient must have had a diagnosis of CRSwNP from at least two physicians and/or ENT surgeons experienced in the management of patients with CRSwNP.						
AND						
Clinical criteria:						
Patient must be under the care of the same physician for at least 6 months; OR must have been diagnosed with CRSwNP by a multidisciplinary team (MDT)						
AND						
Clinical criteria:						
Patient must have received at least one previous surgery for the removal of nasal polyps; OR Patient is must not be suitable for surgery as per written advice from <i>at least two of the specialist prescribers listed above</i> physicians or ENT in care or MDT.						
AND						
Clinical criteria:						
Patient must have a bilateral endoscopic nasal polyp score of ≥ 5 (out of a maximum score of 8, with a minimum score of 2 in each nasal cavity) despite optimised nasal polys therapy; OR Patient must have a nasal obstruction visual analogue scale of >5 (out of a maximum score of 10) despite optimised nasal polys therapy.						
AND						
Clinical criteria:						
Patient must not have received PBS-subsidised treatment with a biological medicine for CRSwNP; OR Patient must have had a break in treatment from the most recently approved PBS-subsidised mepolizumab treatment for CRSwNP.						

Public Summary Document – November 2021 PBAC Meeting

	OR The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for nasal polyps or severe asthma.
	AND
	Clinical criteria:
	Patient must have failed to achieve adequate control with optimised nasal polyps therapy which has been documented.
	AND
	Clinical criteria:
	Patient must have blood eosinophil count greater than or equal to 150cells/uL in the last 12 months.
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment to demonstrate a response under this restriction.
	Population criteria:
	Patient must be aged 18 years or older.
	Prescribing Instructions: Optimised nasal polyps therapy includes: (i) Adherence to <u>intranasal corticosteroid therapy</u> for at least 2 months, unless contraindicated or not tolerated; AND (ii) treatment with <u>oral corticosteroids</u> , <i>one course</i> in the past 12 months, unless contraindicated or not tolerated. AND The following initiation criteria indicate failure to achieve adequate control to optimised nasal polyps therapy and must be declared to have been met at the time of the application: Baseline endoscopic nasal polyp score of ≥ 5 (out of a maximum score of 8, with a minimum score of 2 in each nasal cavity), OR Baseline nasal obstruction VAS of >5 (out of a maximum score of 10) Surgical exception: details to be provided in a written application to seek an exemption include serious comorbid disease (e.g. cardiovascular, stroke) making the risk of surgery unacceptable. Any treating physician or MDT healthcare professional who would be making the decision to use a biologic and/or who is managing the patient can make the decision of whether the patient should be exempted from surgery. (With surgical exception, all other entry criteria need to be met for MEPO initiation) Evidence to provide in or with the application: 1. details of prior drug therapy (date of commencement and duration of therapy); AND 2. details of surgery (date and treatment); OR details of surgical exception AND 3. the eosinophil count and date; AND 4. Baseline NP score obtained in the past 12 months; AND 5. Baseline nasal obstruction VAS score
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia
	Administrative advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>
	Administrative advice: <i>Special Pricing Arrangements apply.</i>
	Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)
	Treatment Phase: Continuing treatment criteria
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this continuing treatment restriction.
	Patient must have previously received PBS-subsidised treatment with this drug for this condition

Public Summary Document – November 2021 PBAC Meeting

	AND
	Clinical criteria:
	Patient must have achieved an adequate response to this drug, defined as having at least one of: (i) an improvement in bilateral endoscopic NP score of ≥ 1.0 compared to the baseline level provided with the initial authority application, (ii) an improvement in nasal obstruction VAS score of ≥ 3.0 compared to the baseline level provided with the initial authority application. In absence of surgery, an adequate response to mepolizumab is defined as: An improvement in bilateral endoscopic NP score of ≥ 1.0 , OR An improvement in nasal obstruction VAS score of ≥ 3.0
	AND
	Clinical criteria:
	Patient must not have undergone surgery for the removal of nasal polyps since initiation of this drug for this condition.
	Treatment criteria:
	Patient must be treated by a respiratory physician, clinical immunologist, allergist, ear nose and throat specialist (ENT) or general physician experienced in the management of patients with CRSwNP.
	Population criteria:
	Patient must be aged 18 years or older.
	Prescribing Instructions:
	Evidence of each qualifying response measure to provide via telephone and to document in the patient's medical records for PBS compliance auditing purposes 1. NP score; OR 2. nasal obstruction VAS score

- 3.2 A special pricing arrangement (SPA) was proposed by the Sponsor. The sponsor proposed effective prices of \$ [REDACTED] for public and \$ [REDACTED] for private per vial, compared to published prices of \$1,638.00 for public and \$1,685.74 for private.
- 3.3 The proposed restriction omitted key information which may be important in determining the most appropriate use of mepolizumab in the proposed population:
- There were no restrictions around how many times a patient may re-trial mepolizumab. Based on the proposed restriction in the submission a patient may keep re-trialling mepolizumab as long as they had severe disease and a 'break in treatment' based on the initiation criteria. A minimum duration of the break in treatment was not provided by the submission. However, the proposed clinical criteria indicated that treatment must not be used within 4 weeks of another PBS-subsidised biological medicine prescribed for NPs or severe asthma and this may suggest a minimal period for a 'break in treatment'. It was unclear how this threshold of 4 weeks was determined as the reason was not provided by the submission. The pre-PBAC response clarified that the 4-week break in treatment refers to the washout period required following a previous biological agent for eosinophilic disease consistent with the severe asthma indication for biologic agents. The pre-PBAC response proposed that the recommended criteria for the re-initiation of mepolizumab is 6 months as per the initial listing of omalizumab in severe allergic asthma;
 - In the continuing criteria, the submission stated that in absence of surgery, an

adequate response to mepolizumab was defined as an improvement in bilateral endoscopic nasal polyp (ENP) score of ≥ 1 or an improvement in nasal obstruction (NO) visual analogue scale (collectively NO-VAS) score of ≥ 3 . However, there was no requirement in the continuing criteria to maintain response to treatment even though adequate response was defined; and

- It was unclear whether a patient who received nasal polyps (NP) surgery while on treatment with mepolizumab and fulfils the criteria for ‘an adequate response’ at a subsequent visit should be eligible to continue treatment with mepolizumab. The proposed restriction does not restrict use of mepolizumab in patients who have surgery whilst on treatment with mepolizumab (and it may be difficult to distinguish whether an adequate response was achieved due to mepolizumab or successful surgery). In the pivotal SYNAPSE trial, patients who underwent surgery were not required to discontinue from mepolizumab (or placebo). In the economic model any patient who received surgery was assumed to discontinue mepolizumab and no re-initiation was considered in the model or financial estimates. The Pre-Sub-Committee Response (PSCR) stated that the treatment continuation response criteria apply to patients who have not undergone NP surgery. The PSCR stated that patients undergoing NP surgery would discontinue treatment and be eligible to re-initiate treatment if they meet the initial clinical criteria at any stage following surgery.

3.4 The sponsor wished to work with the PBAC to agree on a separate grandfathering restriction for patients enrolled in a planned patient familiarisation program following TGA approval. The pre-PBAC response stated that any patient familiarisation program would align with the proposed PBS criteria.

3.5 The eligibility criteria in the pivotal SYNAPSE trial did not fully align with the requested restriction. The requested restriction was broader than the eligibility criteria in SYNAPSE, which required patients to have:

- Previous history of at least one prior NP surgery. Comparatively, patients deemed not suitable for surgery were allowed under the requested restriction;
- Previous treatment with INCS. Comparatively, patients with contraindication or intolerance to INCS could be treated under the requested restriction;
- Overall visual analogue scale (VAS) symptom score (>7). Overall VAS score not assessed under requested restriction. The PBAC considered inclusion of overall VAS score in the restriction may be appropriate; and
- Have both ENP score ≥ 5 and NO-VAS score >5 . The requested restriction required only satisfying the requirements from at least one of the two instruments. The ESC considered that the need for ongoing treatment should not be restricted to patients satisfying the requirements of both instruments as symptomatic improvement can occur without a change in the size of NPs.

The requested restriction’s criteria which required previous treatment with OCS (unless contradicted or not tolerated) and a BEC count of ≥ 150 cells/ μL were narrower than the eligibility criteria in SYNAPSE.

3.6 The requested restriction was also narrower than the indication recommended by the TGA evaluator (see paragraph 2.3), which did not restrict treatment with mepolizumab to patients:

- Who have received at least one previous surgery for the removal of nasal polyps (unless patient is not suitable for surgery);
- Who have received treatment with OCS in the past 12 months (unless contraindicated or not tolerated); or
- With a BEC ≥ 150 cells/ μ L in the last 12 months.

These criteria in the requested PBS restriction were aligned to the circumstances of use and efficacy results of subgroup analyses from the SYNAPSE trial. While the requested restriction allows access for patients deemed not suitable for surgery, it was noted that all patients in SYNAPSE must have had at least one surgery for the removal of NP within the previous 10 years. Thus, the efficacy and cost-effectiveness of mepolizumab in patients who were unsuitable for surgery was unknown. The pre-PBAC response argued that removing access to patients deemed to be unsuitable for prior surgery may create an inequity in access for this small subset of CRSwNP patients. The PBAC acknowledged that alternative treatment options are limited for patients considered unsuitable for surgery.

3.7 The requested restriction also allowed for patients who could not use INCS or OCS due to contraindications or intolerances to be eligible for mepolizumab. This was inconsistent to SYNAPSE where all patients were treated with INCS for at least 8 weeks prior to screening and throughout the trial duration. The use of OCS was permitted in SYNAPSE and approximately 50% of patients had ≥ 1 course of OCS in previous 12 months. The requested restriction was likely consistent with the proposed TGA indication which specified “inadequately controlled CRSwNP”, but was broader than the restriction proposed by the TGA evaluator who suggested restricting use to patients with “an inadequate response to intranasal corticosteroids”.

3.8 The PSCR stated that while there is no consensus on an agreed BEC level at which systemic therapies for CRSwNP are required (Ho 2020)¹ there are an increasing number of studies recognising the role of blood/tissue eosinophilia as a marker for abnormal inflammatory state and risk for long term recurrence (McHugh T, Snidvongs K, Xie M & S, 2018)². The ESC considered that it may be reasonable for a BEC count cut-off to be included in the restriction and noted that the BEC threshold is currently set at ≥ 300 cells/ μ L for patients with uncontrolled severe asthma unless they have been receiving treatment with OCS (reduces to ≥ 150 cells/ μ L while receiving

¹ Ho J, Li W, Grayson JW, Alvarado R, Rimmer J, Sewell WA, Harvey RJ. Systemic medication requirement in post-surgical patients with eosinophilic chronic rhinosinusitis. *Rhinology*. 2021 Feb 1;59(1):59-65.

² McHugh T, Snidvongs K, Xie M, Banglawala S, Sommer D. High tissue eosinophilia as a marker to predict recurrence for eosinophilic chronic rhinosinusitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol*. 2018 Dec;8(12):1421-1429.

treatment with OCS). The ESC noted that OCS use was not an inclusion criterion for SYNAPSE and not all patients received a course of OCS during the trial (see paragraph 3.7). As such, the ESC considered the requirement for optimised NP therapy to include treatment with OCS in the past 12 months may not be reasonable and could lead to inappropriate use to meet the restriction criteria.

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

4 Population and disease

- 4.1 NP are chronic inflammatory outgrowths of the paranasal sinus mucosa (commonly the ethmoid sinuses) that present bilaterally along the middle and superior meatus and occur primarily in adults. NP greatly impact a patient's health related quality of life (HRQoL) through increases in nasal obstruction, loss of sense of smell, facial pain, facial pressure and nasal discharge; and the persistence of these symptoms leads to CRS. NP develop in the setting of chronic paranasal sinus inflammation and are therefore associated with CRS. In the last decade there has been a change in terminology in the medical literature and guidelines which acknowledges NP as a subtype of CRS (Hopkins, 2019) and the treatment algorithms for CRS depend mainly on the presence or absence of NP. While the pathogenesis of CRSwNP is not completely understood amidst significant microscopic and macroscopic disease heterogeneity, type 2 inflammation and eosinophils are thought to play a role (Schleimer 2017).
- 4.2 According to the European Position Paper on Rhinosinusitis and NP (EPOS) (Fokkens 2020) and consistent with the 2007 American Academy of Otolaryngology guideline (Rosenfeld 2007) the diagnosis of CRS (with or without NP) in adults was defined as:
- Inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
- ± facial pain/pressure
 - ± reduction or loss of smell
- for ≥12 weeks and either
- endoscopic signs of:
 - NP and/or
 - mucopurulent discharge primarily from middle meatus and/or
 - oedema/mucosal obstruction primarily in middle meatus and/or
 - computerised tomography (CT) changes:
 - mucosal changes within the ostiomeatal complex and/or sinuses.
- 4.3 It was noted that severe CRSwNP may be defined differently depending on the guidelines used. A comparison table was constructed during the evaluation to highlight these differences (Table 2).

Table 2: Thresholds for classification of severe CRSwNP

Instrument (range)	Requested restriction ^a	EPOS 2020	EUFOREA 2021 ^b	SYNAPSE trial ^c
ENP score (0-8)	≥5	NS	>4	≥5
NO-VAS score (0-10)	>5	NS	NS	>5
Overall symptom VAS (0-10)	NS	>7	≥5	>7
Nasal congestion score (0-3)	NS	NS	>2	NS
SNOT-22 score (0-110)	NS	NS	>35	NS
Loss of smell score (0-3)	NS	NS	>2	NS

Source: Complied during evaluation.

ENP= endoscopic nasal polyp; EUFOREA = European forum for research and education in allergy and airway diseases; NO-VAS= nasal obstruction-visual analogue scale; NS= not specified; SNOT-22= sino-nasal outcomes test (22 items); VAS= visual analogue scale.

a. Allowed for a choice of ENP score or NO-VAS score to be used (i.e. patient will not be required to satisfy both).

b. The presence of bilateral nasal polyps alone is not sufficient to define severe CRSwNP; the disease also needs to be clinically symptomatic: any of the listed patient reported outcomes can be used to define the severe phenotype (if available).

c. Need to satisfy all listed criteria

- 4.4 The target population for the submission were patients with CRSwNP who have received at least one previous surgery for the removal of NP (unless not suitable for surgery) and failed to achieve adequate control with optimised NP therapy (INCS unless contraindicated or not tolerated, and OCS unless contraindicated or not tolerated), with a BEC greater than or equal to 150 cells/ μ L.

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

5 Comparator

- 5.1 The submission nominated SoC as the main comparator. SoC included ongoing INCS usage with intermittent usage of other treatments like nasal saline irrigations and OCS (Fokkens 2020). The submission did not consider NP surgery as a relevant comparator to mepolizumab, and claimed that mepolizumab will not replace surgery as it is a progression event in the course of CRSwNP disease which could be required in patients on mepolizumab or SoC. This may not be appropriate. For the proportion of patients who are eligible for NP surgery, repeat NP surgery is a widely accepted and practiced for the treatment of CRSwNP, as acknowledged by the submission in their current treatment algorithm. Whilst repeat surgery may be viewed as a progression of CRSwNP, evidence presented by the submission indicated that patients with a prior history of NP surgery who were treated with mepolizumab had a 57% reduction in NP surgeries, suggesting that mepolizumab would therefore replace a proportion of NP surgeries. It was noted that the submission also implied that mepolizumab would be an alternative treatment option for (repeat) NP surgery in severe patients.
- 5.2 Overall, even though SoC (INCS usage with intermittent usage of other treatment like nasal saline irrigations and OCS) was likely the reasonable comparator, surgery was likely unreasonably omitted as part of SoC. SoC (including surgery) would be the most appropriate description of the comparator. The ESC considered SoC appropriate as the nominated comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with mepolizumab including an improvement in quality of life (QoL) due to a reduction in the impact of the condition on sleep, taste, smell, sinus congestion and associated chronic pain. The comments noted that a reduction in NP size does not always address the symptoms of this condition that impact on a patient's QoL. The comments also described the importance of having alternative treatment options available to patients with this condition who have often endured repeated NP removal surgeries.

Clinical trials

6.3 The submission was based on one head-to-head trial, SYNAPSE (intent-to-treat (ITT) N=407) comparing mepolizumab (N=206) to placebo (N=201), in adult (≥ 18 years of age) CRSwNP patients with uncontrolled symptoms after at least one surgery and treatment with INCS for at least eight weeks.

6.4 SYNAPSE comprised of a four-week run in period, followed by a 52-week treatment period. In addition, it was planned for up to the first 200 randomised participants to enter a six-month no-treatment follow-up period following their Week 52 visit in order to assess maintenance of response. It was noted that only a total of 134 patients entered the no-treatment follow-up phase, with 133 patients completing this period (mepolizumab N=68; placebo N=65). The reason for not meeting the recruitment target for the follow-up period was not explained.

6.5 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SYNAPSE	<p>Clinical Study Report: A randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab). Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, Smith SG, Martin N, Mayer B, Yancey SW, Sousa AR, Chan R, Hopkins C; SYNAPSE study investigators. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial.</p> <p>Hopkins C, Bachert C, Fokkens W, et al. Late Breaking Abstract - Add-on mepolizumab for chronic rhinosinusitis with nasal polyps: SYNAPSE study.</p> <p>Tabberer M, Trigg A, Busse W, et al. Mepolizumab reduces disease symptoms for patients with chronic rhinosinusitis with nasal polyps: Data from the SYNAPSE study.</p> <p>Bachert C. Mepolizumab for chronic rhinosinusitis with nasal polyps: comorbid asthma, NSAID exacerbated respiratory disease, eosinophil stratification.</p> <p>Lee SE, Tabberer M, Trigg A, et al. Mepolizumab improves health-related quality of life for patients with chronic rhinosinusitis with nasal polyps: Data from the SYNAPSE study.</p> <p>Chupp G., Albid I., Lugogo N., Kariyawasam HH., Bourdin A., et al., Mepolizumab Reduces Systemic Corticosteroid A1344: Use in Patients With Chronic Rhinosinusitis With Nasal Polyps.</p>	<p>CSR Dated 23 June 2020.</p> <p><i>Lancet Respir Med</i> 2021; S2213-2600(21): 00097-7.</p> <p>Poster presented at the 2020 ERS International Congress. <i>European Respiratory Journal</i> 2020 56: 4616.</p> <p>Poster presented at the American Academy of Allergy Asthma & Immunology Annual Meeting 2021.</p> <p>Poster presented at the American Academy of Allergy, Asthma & Immunology Annual Meeting 2020.</p> <p>Poster presented at the American Academy of Allergy Asthma & Immunology Annual Meeting 2021</p> <p>Online Abstract Issue of the <i>American Journal of Respiratory and Critical Care Medicine</i>, Volume 203, May 3, 2021</p>

Source: Table 2-4, p43 of the submission.

CSR= clinical study report

6.6 The key features of the direct randomised trial are summarised in Table 4. Overall, there was a low risk of bias in the SYNAPSE trial, however, the submission acknowledged that there were important protocol deviations that potentially affected the efficacy results, which led to removal of 26 (6%) patients from the per protocol (PP) population. The submission noted that the co-primary outcome results from the analysis of the PP population were similar to those from the ITT population. PP results were not available for other endpoints.

Table 4: Key features of the included evidence

Trial, N	Trial Design	Interventions	Population	Risk of bias	Main Outcomes	Used in modelled evaluation
SYNAPSE N=407*	Phase 3, R, DB, PC, MC, PG Trial duration of treatment of 48 weeks (sufficient for 52 weeks of treatment), followed by 24 week duration of follow-up (for patients entering this latter phase).	MEPO: 100mg, SC, Q4W vs. PLA: SC, Q4W	Adults with recurrent CRSwNP, a history of at least one prior surgery for NP, recurrent NP despite treatment with current SoC and in current need for NP surgery.	Low	Co-primary: Change from baseline total ENP score at week 52 Co-primary: Change from baseline mean NO-VAS score during the 4 weeks prior to week 52 Secondary: Time to first actual surgery Secondary: Change in VAS symptom score Secondary: SNOT-22 score Secondary: Requirement for systemic steroid use	Yes, in combination with co-primary outcome of NO-VAS score to determine responder status Yes, in combination with co-primary outcome of ENP score to determine responder status Yes No Yes, utilities were derived by mapping SNOT-22 results to the EQ-5D Yes

Source: Table 2-5, p47 of the submission.

CRSwNP= chronic rhinosinusitis with nasal polyps; DB= double blind; ENP= endoscopic nasal polyp; EQ-5D= European quality of life five dimension; MC= multicentre; MEPO = mepolizumab; MF= mometasone furoate; NO-VAS= nasal obstruction-visual analogue scale; NP= nasal polyps; PC= placebo-controlled; PG= parallel group; PLA= placebo; Q4W= every 4 weeks; R= randomised; SoC= standard of care; SNOT-22= Sino-nasal outcomes test (22 items); VAS= visual analogue scale

* Intent-to-treat population.

6.7 In addition to the study treatment, all patients were treated with the following concomitant therapy for CRSwNP throughout the study (run-in, treatment and no-treatment follow-up periods):

- Daily mometasone furoate (MF) intranasally; and
- If required: saline nasal douching, occasional short courses of high dose OCS and/oral antibiotics.

Patients could continue treatment with mepolizumab (or placebo) following courses of OCS or NP surgery.

6.8 In the primary analysis, patients who had nasal surgery/sinuplasty were assigned their worst observed score prior to surgery/sinuplasty and patients with missing data (due to study withdrawal or otherwise) were assigned their worst observed score prior to study withdrawal or missing visit. This approach may not be reasonable given any imbalance in the number of patients who had NP surgery or patients with missing data between the two treatment arms would result in bias in favour of the arm with less missing data. Two sensitivity analyses were conducted using alternative imputation methods. However, these sensitivity analyses assigned worse scores than the primary analysis and would therefore result in even larger biases (compared to the primary analysis) in favour of the arm with less missing data. Other approaches to the

treatment of missing data such as last observation carried forward or the censoring of patients did not appear to have been considered for the co-primary outcomes.

- 6.9 The efficacy of mepolizumab in the SYNAPSE trial was assessed using co-primary outcomes of change from baseline in total ENP score (0-8) at Week 52 and change in mean NO-VAS symptom score (0-10), which was assessed daily, during the 4 weeks prior to Week 52.
- 6.10 Key secondary outcomes presented in the submission included time to first nasal surgery; impact on quality of life (QoL) measured by the 36-item short form health survey (SF-36) version 2 (v2) and the sino-nasal outcome test (22 items) (SNOT-22); proportion of participants requiring systemic steroids; and clinically significant asthma exacerbations. These secondary outcomes were used to inform the economic model.
- 6.11 In order to provide strong control of type I error when making inferences for the pre-defined secondary endpoints, multiplicity was controlled using a hierarchical closed testing approach in the following order (dependent on statistical significance having been achieved for the two co-primary endpoints first): time to first nasal surgery; change from baseline in overall VAS symptom score; change from baseline in SNOT-22 total score (a QoL measure); proportion of participants requiring systemic steroids for nasal polyps; change from baseline in the mean composite VAS score; change from baseline in mean individual VAS symptom score for loss of smell.
- 6.12 The submission proposed that the following minimal clinically important differences (MCIDs):
- Change from baseline in total ENP score (centrally read): An ENP score responder was defined as a participant who had an improvement (decrease) of ≥ 1.0 point. The submission claimed this was based on Bachert 2021, however a MCID was never explicitly stated in this article (the proportion of patients who achieved a reduction of the ENP score by at least 1 point was reported but it was not stated whether this was clinically meaningful);
 - Change from baseline in NO-VAS symptom score: A responder in the assessment of NO-VAS symptom score was defined as a participant who had an improvement (decrease) from baseline of ≥ 3 points. This was based on advisory board advice (panel indicated an improvement of 2-3 points would be clinically meaningful), in the absence of a validated MCID in the literature. The submission claimed this was further supported by a psychometric analyses based on the SNOT-22 and overall symptoms VAS which were sufficiently correlated ($r \geq 0.3$) to indicate a meaningful within-patient change thresholds (Tabberer M, Trigg A, 2021). This could not be independently verified, however as a MCID of ≥ 3 would represent at least a 30% change the MCID may be reasonable.
 - Change from baseline in SNOT-22 total score: The MCID for the QoL SNOT-22 measurement was a ≥ 8.9 change in SNOT-22 score (Hopkins 2009). A SNOT-22 responder was defined as a participant who had a SNOT-22 score decrease of ≥ 8.9 from baseline at Week 52.

The PBAC has not previously considered these outcomes for CRSwNP. It was not clear whether the nominated MCIDs should be applied to point estimate of the results in SYNAPSE or, more conservatively, to the lower or upper bounds of the 95% confidence intervals. It was assumed that it would be applied to the point estimates during evaluation.

- 6.13 The change from baseline of ENP score and NO-VAS were not used in the economic model. Instead, the number of responders based on either an ENP score change of ≥ 1.0 point from baseline or NO-VAS score change of ≥ 3.0 points from baseline were the key efficacy input in the economic evaluation. This was in line with the requested restriction which required response on one of either ENP score (≥ 1) or NO-VAS score (≥ 3) to continue treatment.
- 6.14 No formal hypothesis testing in subgroups of the population was performed. The ESC noted the PSCR provided the demographics for the BEC ≥ 150 cells/ μL subgroup and considered they appeared generally comparable to the ITT population.

Comparative effectiveness

- 6.15 Table 5 and Table 6 summarise the co-primary and key secondary results of SYNAPSE, respectively. It was noted that all primary and secondary endpoints achieved statistical significance at the two-sided 5% level adjusted for multiplicity in the ITT population.

Public Summary Document – November 2021 PBAC Meeting

Table 5: Summary of co-primary outcome results in SYNAPSE

	ITT			BEC \geq 150 cells/ μ L		
	PLA	MEPO	Difference (95%CI); p-value	PLA	MEPO	Difference (95%CI); p-value
Change from baseline in total ENP score (centrally read)						
Median change at Week 52 ^a	0.0	-1.0	-0.73 (-1.11, -0.34); <0.0001	0.0	-0.5	-0.75 (-1.21, -0.29); NR
Responder Week 52, n/N (%) ^b	57/201 (28)	104/206 (50)	NR	NR	NR	NR
Change from baseline in NO-VAS symptom score						
Median change at Week 49-52 ^a	-0.82	-4.41	-3.14 (-4.09, -2.18); <0.0001	-0.75	-4.32	-3.36 (-4.27, -2.44); NR
Responder Week 52, n/N (%) ^c	73/201 (36)	124/206 (60)	NR	NR	NR	NR
Any Responder (ENP and/or NO-VAS)						
Total responder at Week 24, n/N (%)	95/201 (47)	144/206 (70)	NR	86/185 (47)	129/186 (69)	NR
Total responder at Week 52, n/N (%)	95/201 (47)	146/206 (71)	NR	NR	NR	NR
Maintained response at Week 52 from Week 24, n/N (%)	65/95 (68)	125/144 (87)	NR	58/86 (67)	112/129 (87)	NR

Source: Table 2-19, 2-21, 2-22, pp 65, 67-69 of the submission; calculated during evaluation using information from Table 2-19, p65, Table 2-22, p68-69 and Table 2-52, p102 of submission; and cells H8:J16 and H84:J91, "Defaults" sheet, and F21:I36, "Inputs" sheet, Attachment 5-Mepolizumab CEM.xlsm

ENP= endoscopic nasal polyp; NO-VAS= nasal obstruction visual analogue scale; n= number of participants with event; N= total participants in group; NR = not reported; SNOT-22= sino-nasal outcomes test (22 items)

a. Difference refers to the adjusted difference. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count; p-value based on Wilcoxon rank-sum test.

b. Defined as a participant with a \geq 1-point improvement from baseline in the absence of surgery/sinuplasty prior to that visit.

c. Defined as a participant who had an improvement (decrease) from baseline of \geq 3 points. Responder status was calculated during the evaluation

Values in bold indicate statistical significant differences, values in italics indicate values extracted during evaluation

Table 6 Summary of secondary outcome results in SYNAPSE

	ITT			BEC \geq 150 cells/ μ L		
	PLA	MEPO	Difference (95%CI); p-value	PLA	MEPO	Difference
<u>Time to first nasal surgery</u>						
Probability of surgery by Week 24 (95% CI) ^a	9.1 (5.8, 14.0)	4.0 (2.0, 7.8)	NR	9.7 (7.6, 11.9)	4.3 (2.8, 5.8)	NR
Probability of surgery by Week 52 (95% CI) ^a	23.6 (18.3, 30.3)	9.2 (5.9,14.2)	0.43 (0.25, 0.76); 0.003 ^b	23.8 (20.7, 26.9)	9.1 (7.0,11.3)	NR
Proportion of responders at Week 24 needing surgery by Week 52	16/95 (17)	6/144 (4)	NR	15/86 (17)	5/129 (4)	NR
Proportion of non-responders at Week 24 needing surgery by Week 52	12/88 ^c (14)	NR	NR	11/81 ^c (14)	NR	NR
<u>Proportion of participants requiring systemic steroids up to Week 52</u> ^d						
Number of participants with \geq 1 course, n/N (%)	74/201 (37)	52/206 (25)	0.58 (0.36, 0.92); 0.020 ^e	NR	NR	NR
Total number of courses	124	82	NR	NR	NR	NR
<u>Change from baseline in SNOT-22 total score</u>						
Median change at Week 52	-14.0	-30.0	-16.49 (-23.57, -9.42); <0.001	NR	NR	NR
Responder, n/N (%) ^f	106/198 (54)	150/205 (73)	2.44 (1.60, 3.73); <0.001	NR	NR	NR
<u>Clinically significant asthma exacerbations</u> ^g						
Subjects with at least one exacerbation, n/N (%)	11/149 (7)	6/140 (4)	NR	NR	NR	NR
Total exacerbations	20	6	NR	NR	NR	NR
Exacerbation rate/year (95% CI)	0.15 (0.08, 0.26)	0.05 (0.02,0.12)	0.33 (0.12, 0.95) ^h	NR	NR	NR

Source: Table 2-31, 2-35, 2-37, 2-39, pp 81, 85, 87-89 of the submission;

a. Kaplan-Meier estimate

b. Difference refers to the hazard ratio. Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).

c There should be 106 non-responders (201 total – 95 responders in 24 weeks) for ITT and 99 non-responders (185 total – 86 responders at 24 weeks) for BEC \geq 150 cells/ μ L, it was unclear how missing data was treated.

d. Courses of systemic steroids separated by <7 days were considered a continuation of the same course.

e. Difference refers to the odds ratio. Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.

f. Defined as a participants with a \geq 8.9-point improvement (decrease) from baseline in SNOT-22 total score in the absence of surgery/sinuplasty prior to that visit. Difference refers to odds ratio. Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count. 1 Mepolizumab and 3 Placebo participants with missing baseline score were excluded from the analysis.

g. An asthma exacerbation is defined as worsening of asthma requiring systemic corticosteroids (i.v. or oral steroid) for at least 3 days or a single IM CS dose and/or emergency department visit, or hospitalization. The denominator of percentages is the number of subjects with concurrent asthma.

h. Difference refers to rate ratio. Estimated from a negative binomial model with covariates of treatment group, geographic region, log(e) baseline blood eosinophil count and number of exacerbations in the previous year (0, 1, >=2 as ordinal), and with logarithm of time (year) on-study up to Week 52 as an offset variable.

Values in bold indicate statistical significant differences, values in italics indicate values extracted during evaluation

6.16 In the ITT population, at the end of the 52-week treatment period, a greater proportion of patients randomized to mepolizumab compared to patients randomized

to placebo demonstrated a ≥ 1 -point improvement from baseline (responder status, as defined by the submission) in their total ENP score (50% compared with 28%, respectively). Though a greater proportion of patients treated with mepolizumab experienced improvement, it was noted that 50% of patients experienced no change or worsening of symptoms and were thus classified as non-responders. While the median change from baseline to Week 52 total ENP score for patients treated with mepolizumab was -1.0 and met the MCID, 102/206 patients were non-responders and the median change from baseline was very close to zero or no change (i.e. if two more patients reported no change or worsening the median in the mepolizumab arm would be zero). It was unclear why median and not mean results were used. Based on the point estimates for mean change from baseline the unadjusted difference in mean change between the two treatment groups was -0.8 (-0.1 in placebo and -0.9 in mepolizumab), which would not meet the proposed MCID of ≥ 1.0 point change. The PSCR presented a post hoc analysis of the mean change from baseline in which patients with nasal surgery prior to the visit/time period were assigned the worst possible score and a mixed model repeated measures with covariates of treatment group, geographic region, baseline score and $\log(e)$ baseline blood eosinophil count, visit/time period, interaction terms for visit/time period by baseline and visit/time period by treatment was used, resulting in a mean change from baseline at week 52 of 0.98 for the mepolizumab group. The ESC considered that while this was closer to meeting the -1.0 MCID, assigning the worst possible scores in the sensitivity analysis may further bias the result in favour of the arm with less missing data (i.e. mepolizumab).

- 6.17 In the ITT population, at the end of the 52-week treatment period, a greater proportion of patients randomised to mepolizumab compared to placebo demonstrated a >3 -point improvement from baseline (decrease) in their NO-VAS score (124 patients (60%) compared to 73 patients (36%) respectively). It appeared that the definition of responder in the assessment of NO-VAS symptom score was nominated post hoc by the submission based on the advice from their advisory board. This may have introduced bias with regards to the reliability of the NO-VAS responder results and the total responder analysis. The median change from baseline NO-VAS score in the mepolizumab arm was -4.41 ($p < 0.0001$), and the point estimate for the adjusted median difference between treatment arms was -3.14, which met the specified MCID. It was unclear why median and not mean results were used. Based on the point estimates for mean change from baseline the unadjusted difference in mean change between the two treatment groups was -1.7 (-2.5 in placebo and -4.2 in mepolizumab), which would not meet the proposed MCID of ≥ 3.0 point change.
- 6.18 Overall, patients tended to perform more favourably in the co-primary outcome of median change from baseline in NO-VAS score (subjective, patient assessed) compared to the co-primary outcome of median change from baseline in total ENP score (objective, clinician assessed), as 60% of patients randomised to mepolizumab were considered to be responders via improvement in NO-VAS score, compared to

50% for the total ENP score. It was estimated during evaluation that only 82/146 (56.2%) of responders in the mepolizumab arm and 35/95 (36.8%) of responders in the placebo arm reported response to both ENP and NO-VAS suggesting that the correlation between the two measures may not be high. The ESC advised that due to the inflammatory component of CRSwNP symptomatic improvement can occur without a change in the size of NPs.

- 6.19 The time to first NP surgery was a key secondary endpoint in SYNAPSE. For time to first nasal surgery up to Week 52, the probability of undergoing surgery at any time prior to Week 52 was statistically significantly lower in the mepolizumab group than for participants in the placebo group (hazard ratio: 0.43, 95% CI: 0.25, 0.76; $p=0.003$). Similarly, a statistically significant reduction in the mepolizumab arm compared to the placebo arm in the odds of requiring systemic corticosteroid treatment was reported (odds ratio: 0.58, 95% CI: 0.36, 0.92; $p=0.020$) was reported. No MCIDs were nominated by the submission for these endpoints and it was unclear whether or not these differences were clinically meaningful.
- 6.20 For the secondary endpoint of the change from baseline in SNOT-22 total score at Week 52, the median change from baseline in the mepolizumab arm was -30.0 compared with -14.0 in the placebo arm. Notably, both treatment arms met the nominated MCID of ≥ 8.9 points. The submission relied on the mapping of the SNOT-22 results from responders and non-responders in SYNAPSE to EQ-5D (using Canadian tariffs) to derive the utilities applied in the economic model. With regards to the SF-36, the median change from baseline at Week 52 for the physical and mental component summary scores were 0.0 for the placebo group. For the mepolizumab group, there was a larger median change from baseline in the physical component summary score (6.8) than the mental component summary score (1.2). It was unclear why the SF-36 v2 was not used by the submission despite this data being collected in SYNAPSE.
- 6.21 The rate of exacerbations in patients with asthma was 67% lower in the mepolizumab group than the placebo group (rate ratio: 0.33, 95% CI: 0.12, 0.95). Overall the results in SYNAPSE regarding mepolizumab and asthma symptoms were consistent with the PBAC's previous opinion that mepolizumab was superior to standard of care in the treatment of severe eosinophilic asthma (Mepolizumab Public Summary Document (PSD), March 2016, paragraph 7.7).
- 6.22 The submission presented a subgroup analysis of the co-primary outcomes based on baseline BEC and claimed that these supported the efficacy of mepolizumab in patients with $\text{BEC} \geq 150$ cells/ μL , in line with the requested restriction, as the difference in median ENP and NO-VAS between mepolizumab and placebo was higher in patients with elevated baseline BEC of ≥ 150 cells/ μL . Given the mechanism of action of mepolizumab as an interleukin-5 inhibitor, this was biologically plausible. Only limited results for the $\text{BEC} \geq 150$ cells/ μL subgroup (and the complement) were reported by the submission and none of them could be independently verified.

- 6.23 In patients with baseline BEC of ≥ 150 cells/ μL , while the difference in median NO-VAS score at Week 49-52 from baseline (-3.36, 95%CI -4.27, -2.44) met the proposed MCID of ≥ 3.0 points of change in the baseline, the difference in median ENP score at Week 52 from baseline (-0.75, 95%CI -1.21, -0.29) did not meet the proposed MCID of ≥ 1.0 point of change. Comparatively, the results in the complement subgroup (difference = -0.40, 95%CI -1.78, 0.98 for ENP and difference = -0.39, 95%CI -4.59, 3.81 for NO-VAS) were not significantly different (difference included zero in confidence interval).
- 6.24 It was noted that the requested restriction was limited to patients with a BEC ≥ 150 cells/ μL , a subset of the ITT population in which the trial was neither powered nor designed for. However, there may be significant issues with the applicability of this subgroup as:
- In SYNAPSE the pre-specified subgroups for BEC were ≤ 300 cells/ μL ; >300 to ≤ 500 cells/ μL ; >500 to ≤ 700 cells/ μL and >700 cells/ μL , and the 150 cells/ μL threshold appeared to be a post hoc subgroup;
 - As noted in paragraph 6.14, subgroups were not formally assessed in SYNAPSE and as such no statistical significance could be concluded for any outcome in the BEC ≥ 150 cells/ μL subgroup; and
 - The complement subgroup (BEC < 150 cells/ μL) was small (only 20 patients randomised to mepolizumab and 16 patients randomised to placebo had BEC < 150 cells/ μL) therefore the lack of efficacy of mepolizumab in this subgroup may be due to the lack of sample size. While the results in the BEC < 150 cells/ μL subgroup do not appear to be different between treatment arms (95% confidence interval of difference in medians included zero), it was noted that the point estimate for change from baseline for both ENP and NO-VAS in the mepolizumab arm was actually higher in the BEC < 150 cells/ μL subgroup (-1.0 and -6.35 for ENP and NO-VAS, respectively) than in the BEC ≥ 150 cells/ μL subgroup (-0.5 and -4.32 for ENP and NO-VAS, respectively), with a similar proportion of ENP responders (11/20 [55%] for BEC < 150 cells/ μL and 93/185 [50%] for BEC ≥ 150 cells/ μL). NO-VAS responders were not reported for these subgroups.

Therefore it was unclear if a BEC of ≥ 150 cells/ μL was clinically meaningful or if the results using this threshold should be relied upon. The PSCR maintained that the nomination of BEC ≥ 150 cells/ μL was an appropriate subgroup for the requested restriction and, as these patients made up over 90% of the ITT population, the results presented for the BEC ≥ 150 subgroup are applicable and supported by the results in the ITT population. In addition, the PSCR argued that the sample of the BEC < 150 cells/ μL subgroup is too small to generate reliable results. The ESC agreed with the evaluation that the proposed BEC ≥ 150 cells/ μL threshold appeared to be a post hoc subgroup. The ESC considered the BEC < 150 cells/ μL complement subgroup also appeared to demonstrate a trend towards increased efficacy for the mepolizumab

arm but agreed with the PSCR that the sample size was too small to be able to draw meaningful conclusions.

6.25 The ESC noted the PSCR argued that based on physiological grounds and other indications for mepolizumab that a cut-off for BEC was appropriate (see paragraph 3.8). The ESC considered that it may be reasonable that a cut-off be present and noted that it is currently set at ≥ 300 cells/ μL for patients with uncontrolled severe asthma (see paragraph 3.8). The ESC noted the outcomes reported by the pre-specified baseline BEC levels provided in Table 7. The ESC considered that the median NO-VAS scores at Weeks 49-52 supported a BEC threshold of ≥ 300 cells/ μL and that in the absence of strong evidence to the contrary it may be reasonable to maintain consistency across CRSwNP and uncontrolled severe asthma indications. The pre-PBAC response argued that if alignment with the asthma indication was considered appropriate then the BEC cut-off should be set at ≥ 300 cells/ μL or ≥ 150 cells/ μL for those receiving treatment with OCS in the last 12 months. The pre-PBAC response considered this OCS criterion appropriate as OCS use causes EOS suppression and is consistent with the results from the SYNAPSE study which included a proportion who took OCS.

Table 7 Outcomes for subgroups based on baseline blood eosinophil count

	Median total ENP score at Week 52			Median NO-VAS score at Weeks 49–52		
	Placebo	MEPO	Difference (95% CI)	Placebo	MEPO	Difference (95% CI)
Baseline BEC (cells/μL)						
< 300 ^a	0.0	-1.0	-0.80 (-1.43, -0.17)	-2.37	-4.31	-1.88 (-3.89, 0.13)
300-500 ^b	0.0	0.0	-0.33 (-1.05, 0.38)	-1.36	-5.87	-4.30 (-6.37, -2.24)
500-700 ^c	1.0	-1.0	-2.00 (-3.16, -0.84)	-0.14	-3.35	-3.58 (-5.84, -1.32)
> 700 ^d	0.0	0.0	0.00 (-0.68, 0.68)	0.00	-4.40	-3.55 (-5.40, -1.71)

Source: Table 2.9 pp 389-392 and Table 2.22, pp480-483 of the Clinical Study Report.

BEC= blood eosinophil count; ENP= endoscopic nasal polyp; MEPO = mepolizumab; NO-VAS= nasal obstruction visual analogue scale; μL = microliter

^a MEPO n = 69, Placebo n = 66

^b MEPO n = 60, Placebo n = 59

^c MEPO n = 28, Placebo n = 26

^d MEPO n = 49, Placebo n = 50

6.26 The PBAC considered the data presented in Table 8 indicated that the number of previous surgeries was not a treatment effect modifier.

Table 8 Outcomes for subgroups based on number of previous surgeries

	Median total ENP score at Week 52			Median NO-VAS score at Weeks 49–52		
	Placebo	MEPO	Difference (95% CI)	Placebo	MEPO	Difference (95% CI)
Number of previous surgeries						
1 ^a	0.0	-1.0	-1.00 (-1.51, -0.49)	-2.15	-4.47	-2.46 (-3.94, -0.97)
2 ^b	0.0	0.0	0.00 (-0.80, 0.80)	-0.75	-4.31	-0.77 (-3.21, 1.72)
> 2 ^c	0.0	0.0	-2.0 (-0.86, 0.46)	-0.22	-3.49	-3.50 (-4.90, -2.10)

Source: Table 25, p 79 and Table 27, p 86 of the Clinical Study Report

^a MEPO n = 108, Placebo n = 81

^b MEPO n = 47, Placebo n = 47

^c MEPO n = 51, Placebo n = 73

Comparative harms

6.27 Table 9 presents a summary of adverse events (AEs) in SYNAPSE.

Table 9: Adverse event overview

	PLA (N=201)	MEPO (N=206)	OR (95% CI)*	RD (95% CI)*
On-treatment and post-treatment^a – AEs				
Any on/post-treatment AE	170 (85)	169 (82)	0.83 (0.48, 1.45)	-0.03 (-0.10, 0.05)
AEs related to study treatment	19 (9)	30 (15)	1.63 (0.85, 3.19)	0.05 (-0.01, 0.12)
AEs leading to permanent discontinuation of study treatment	4 (2)	4 (2)	0.98 (0.18, 5.31)	-0.001 (-0.03, 0.03)
AEs leading to withdrawal from the study	1 (<1)	0	0.33 (0.01, 76.96)	-0.01 (-0.03, 0.01)
AEs leading to drug interruption/delay	4 (2)	2 (<1)	0.48 (0.04, 3.42)	-0.01 (-0.04, 0.02)
Any on-treatment AE	168 (84)	169 (82)	0.90 (0.52, 1.55)	-0.02 (-0.09, 0.06)
Any post-treatment ^a AE	14 (7)	6 (3)	0.40 (0.12, 1.14)	-0.04 (-0.09, 0.002)
On-treatment and post-treatment^a – SAEs				
Any on/post-treatment SAE	14 (7)	12 (6)	0.83 (0.34, 1.98)	-0.01 (-0.06, 0.04)
SAEs related to study treatment	1 (<1)	0	0.33 (0.01, 76.96)	-0.01 (-0.03, 0.01)
Fatal SAEs	0	0	NA	0.00 (-0.02, 0.02)
Fatal SAEs related to study treatment	0	0	NA	0.00 (-0.02, 0.02)
Any on-treatment SAE	13 (6)	12 (6)	0.89 (0.36, 2.19)	-0.01 (-0.06, 0.04)
Any post-treatment ^a SAE	1 (<1)	1 (<1)	0.98 (0.01, 76.96)	-0.0001 (-0.02, 0.02)
No treatment follow-up period^b				
Any AE	26 (40)	32 (46)	1.30 (0.62, 2.73)	0.06 (-0.10, 0.23)
Any SAE	4 (6)	2 (3)	0.46 (0.04, 3.32)	-0.03 (-0.12, 0.05)
Fatal SAE	1 (2)	0	0.32 (0.01, 75.00)	-0.02 (-0.08, 0.04)

Source: Table 2-45, p94 of the submission.

AE= adverse event; CI= confidence interval; MEPO= mepolizumab; OR= odds ratio; PLA= placebo; RD= risk difference; SAE= serious adverse event

*Calculated during evaluation via StatsDirect (version3.3.3), using the random effects model.

a. For participants who did not enter the no-treatment follow-up period after Week 52, an event was post-treatment if the start date was more than 28 days after the investigational product stop date. For participants who entered the no-treatment follow-up period after Week 52, an event was post-treatment if the start date was more than 28 days after the investigational product stop date but before the Week 52 visit date.

b. Placebo n=65; mepolizumab n=69. For participants who entered the no-treatment follow-up period only, an event was reported as during the follow-up period if the start date was after the Week 52 visit date.

6.28 The most frequently reported on-treatment AEs ($\geq 10\%$ in either treatment group) were nasopharyngitis (25% and 23% of patients in the mepolizumab and placebo groups, respectively), headache (18% and 22%) and sinusitis (5% and 11%). No other AEs were reported for more than 10% of participants in either treatment group.

6.29 Results indicated patients treated with mepolizumab had comparable AEs compared to patients treated with placebo. It should be noted that mepolizumab will likely have an inferior safety profile to SoC in the proposed PBS population as Australian patients would not be currently experiencing any injection site reactions related to a placebo injection.

6.30 The TGA CER (p73) evaluated mepolizumab based on two trials (SYNAPSE and NCT01362244, also known as MPP111782). The TGA evaluator concluded that

“overall, the safety profile is consistent with that described for the approved indications and no new safety issues were identified.”

Benefits/harms

6.31 A summary of comparative benefits for mepolizumab versus placebo is presented in Table 10. A summary of the comparative harms was presented in Table 9.

Table 10: Summary of comparative benefits for mepolizumab versus placebo (BEC ≥150 cells/μL)

Trial	Mepolizumab n/N	Placebo (SoC) n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)	
				Mepolizumab	Placebo (SoC)		
Benefits							
Any responder at 52 weeks							
ENP or NO-VAS responder	NR	NR	NR	60.2	31.4	28.8 (NR)	
Median change from baseline							
	Mepolizumab			Placebo (SoC)			Median difference: Mepolizumab vs placebo (SoC) (95% CI)
	N	Median Δ baseline	SD	N	Median Δ baseline	SD	
ENP	186	-0.5	NR	185	0.0	NR	-0.75 (-1.21, -0.29)
NO-VAS	186	-4.32	NR	185	-0.75	NR	-3.36 (-4.27, -2.44)

ENP = Endoscopic Nasal Polyp score; NO-VAS = Nasal Obstruction Visual Analogue Scale; RD = risk difference; SoC = standard of care
Source: Figure 2-12 p74 and figure 2-14, p76 of the resubmission, Cells D12:E12, 'Calculations' sheet, Attachment 5-Mepolizumab CEM.xlsm

6.32 On the basis of direct evidence presented by the submission, for every 100 patients with BEC ≥150 cells/μL treated with mepolizumab in comparison to placebo and over a treatment duration of 52 weeks:

- approximately 29 more patients will be a responder based on ENP (≥1.0 point improvement from baseline) and/or NO-VAS (≥3.0 point improvement from baseline);

On the basis of direct evidence presented by the submission, the comparison of mepolizumab and placebo resulted in:

- approximately a 0.75-point reduction in ENP score over 52 weeks of follow-up. It was considered that a reduction of ≥1.0 point was clinically significant; and
- approximately a 3.36-point reduction in NO-VAS score over 52 weeks of follow-up. It was considered that a reduction of ≥3.0 point was clinically significant.

6.33 A comparison of harms for mepolizumab versus placebo in SYNPASE has not been described given comparable safety.

Clinical claim

6.34 The submission described mepolizumab (in addition to SoC) as superior in terms of effectiveness compared with placebo (in addition to SoC) in patients with CRSwNP and a BEC ≥150 cells/μL. The therapeutic conclusion was based on the results of SYNPASE with both co-primary outcomes having met the nominated MCIDs and all primary and secondary endpoints achieved statistical significance at the two-sided 5% level

adjusted for multiplicity in the ITT population. The submission claimed that the efficacy of mepolizumab was higher in patients with elevated baseline BEC of ≥ 150 cells/ μL . However, this claim may not be adequately supported because:

- The threshold for BEC of ≥ 150 cells/ μL appeared to have been nominated post hoc and was not part of the formal statistical assessment, and the difference in median ENP score from baseline in the ≥ 150 cell/ μL subgroup (-0.75, 95%CI -1.21, -0.29) did not meet the proposed MCID of ≥ 1.0 point of change. The complementary subgroup (BEC < 150 cells/ μL) also had a very small number of patients (36 out of a total of 407 patients had BEC < 150 cells/ μL) and therefore the results from the complement subgroup was likely biased towards the null and was unlikely to show any difference between treatments. Further, no test for subgroup interactions was conducted. As such, it was unclear that a BEC ≥ 150 cells/ μL was an appropriate clinical threshold. The ESC noted the PSCR argued that based on physiological grounds and other indications for mepolizumab that a cut-off for BEC is appropriate (see paragraph 3.9). The ESC considered that a BEC threshold of ≥ 300 cells/ μL , which is consistent with the listing of mepolizumab for uncontrolled severe asthma, may be appropriate (see paragraph 6.25); and
- In the ITT population, while the unadjusted median change from baseline to Week 52 total ENP score for patients treated with mepolizumab (median difference -1.0, $P < 0.001$) met the proposed MCID of ≥ 1.0 point of change, 102/206 (49.5%) of patients experienced no change or worsening of symptoms. Therefore, the observed median change from baseline was in actuality very close to zero. The adjusted difference in median ENP (Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count) was -0.73 (95%CI -1.11, -0.34) which did not meet the proposed MCID. Using the point estimates for the mean (rather than median) change from baseline in ENP score, the difference was -0.8 points which also did not meet the MCID. Similarly, the point estimate of the mean (rather than median) change from baseline in NO-VAS score (-1.7) also did not meet the MCID of ≥ 3.0 points. The PSCR noted that the SYNAPSE trial reported a statistically significant 57% reduction for the mepolizumab treated group compared to placebo in the risk of having surgery, significant improvements in overall VAS symptom scores and a clinically significant improvement in HRQoL. The PSCR argued that these are considered as clinically significant improvements and important benefits to patients. The ESC acknowledged the concerns raised by the evaluation that the claim of superior effectiveness may not be adequately supported by the data provided in the submission but considered that overall it was likely that mepolizumab was more effective than placebo.

- 6.35 With regard to safety, the submission claimed mepolizumab was comparable to SoC. This may not be reasonable. Given that current SoC does not include any subcutaneous injections, unlike in SYNAPSE which included placebo injections, there would be no injection site reactions associated with the comparator in the proposed

PBS population currently treated with SoC. However, the overall safety of mepolizumab in SYNAPSE was consistent with the known safety profile of the product, which has been marketed since 2016, and its use in approved indications of severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis (EGPA). The TGA noted (TGA CER, p74) that “overall, the safety profile is consistent with that described for the approved indications and no new safety issues were identified.” The ESC acknowledged that in practice there would be no injections for SoC but noted that data showed that injection site reaction events were not significant in either group in SYNAPSE. The ESC considered the claim of comparable safety was likely reasonable.

- 6.36 The PBAC considered that the claim of superior comparative effectiveness was reasonable patients with CRSwNP. However, the PBAC considered the BEC threshold for access to mepolizumab should be increased from ≥ 150 cells/ μ L to ≥ 300 cells/ μ L.
- 6.37 The PBAC considered that the claim of non-inferior safety was reasonable.

Economic analysis

- 6.38 The submission presented a modelled economic evaluation based on the SYNAPSE trial. The type of economic evaluation presented was a cost-utility Markov model incorporating a cohort expected value analysis. The base case analysis incorporated the subpopulation of patients who had a BEC ≥ 150 cells/ μ L at baseline (90% and 92% of patients in the SYNAPSE mepolizumab and SoC arms, respectively), consistent with the proposed restriction. A scenario analysis was also presented where the ITT population (irrespective of BEC) from SYNAPSE was modelled. A trial based cost per responder analysis based on the results of SYNAPSE was also conducted during the evaluation.
- 6.39 It was noted that there were several translational issues which were not considered nor adjusted for by the submission that could affect the efficacy of mepolizumab in the proposed PBS population and the results of the economic evaluation. In particular, the requested restriction allowed access for patients who were deemed unsuitable for surgery and patients who were contraindicated or intolerant to INCS. These represented potential applicability issues given these are not consistent with the trial criteria (and economic model), and the efficacy (and cost-effectiveness) of mepolizumab for these patients was unknown. The proportion of patients with comorbid asthma and gender may also be different between the trial setting and Australian setting, and these were identified as potential treatment effect modifiers in SYNAPSE.
- 6.40 Table 11 presents a summary of the model structure used in the economic evaluation presented in the submission.

Public Summary Document – November 2021 PBAC Meeting

Table 11: Summary of model structure and rationale

Component	Summary	Evaluation comments
Time horizon	30 years in the model base case vs 52 weeks in the SYNAPSE trial.	Possibly optimistic. See paragraph 6.41.
Outcomes	Life years, quality-adjusted life years, number of surgeries, weeks waiting for surgery, number of asthma exacerbations	Appropriate
Health states	Seven health states, including: -“In trial” - corresponding to first six cycles of treatment - Response: responds to initial treatment with mepolizumab or SoC; - Non-response: does not respond to initial treatment with mepolizumab or SoC; - Response post-NP surgery: patients who respond to surgery; - Recurrence post-NP surgery: patients who responded to surgery but subsequently show recurrence of CRSwNP; combined with - Non-response post-NP surgery: patients who do not respond to surgery (base case assumes 100% of patients respond to surgery); and - Death.	Health states in the economic model were inconsistent with the health states described in the submission. The economic model ultimately consisted of six health states: in trial; responder; non-responder (including waiting for surgery); effective surgery; recurrence or failed surgery (including waiting for additional surgery); and dead.
Cycle length	4 weeks	Reasonable. This was aligned to the dosing regimen of mepolizumab (once every 4 weeks).
Methods used to generate results	Between 0-52 weeks, transition probabilities were based on SYNAPSE trial data for estimating the transitions between response, non-response, and surgery within the trial period. Patients who received surgery were considered treatment non-responders and were assumed to discontinue treatment and transition to the post-surgery health state. After 52 weeks (i.e. from week 56), extrapolation of SYNAPSE trial data was applied until the time horizon of 30 years where patients who were responders to treatment at Week 52 were assumed to maintain their response to treatment with no loss of efficacy. The model accounted for all-cause mortality among the cohort by applying life table data for the Australian population, stratified by age and sex. The proportion of patients treated with mepolizumab (or SoC) was assumed to be the same as the proportion of responders in the SYNAPSE trial. Ongoing CRSwNP-related costs for patients who were ‘responders’ differed by treatment arm with monitoring costs applied to mepolizumab arm, but were the same for ‘non-responders’ across both treatment arms. These were assigned depending on the proportion of patients in each health state. SoC was assumed to have no drug acquisition costs as INCS are not PBS listed.	The extrapolation assumptions may not be reasonable. See paragraph 6.43. Mepolizumab drug costs were based on patients remaining ‘on treatment’ in the ‘responder’ health state at each cycle. However, in clinical practice, patients would not be assessed every four weeks and would remain on treatment until the next response assessment (every 24 weeks). The utilisation of mepolizumab was therefore likely underestimated by the submission which favoured mepolizumab. Health state costs were assumed to be zero in the model base case, under the assumption that known CRSwNP-related health resource utilisation and costs were modelled explicitly through asthma exacerbations, OCS use, and antibiotic use.

Public Summary Document – November 2021 PBAC Meeting

Component	Summary	Evaluation comments
	Utilities were assigned depending on the proportion of patients in each health state and also varied by the cycle. See paragraph 6.45.	
Utilities	<p>Utility scores used in the economic model were derived by mapping the SNOT-22 scores to the EQ-5D-3L instrument.</p> <p>All patients entered the model with baseline utility based on the pooled trial population at the start of the trial (0.534). Between Week 0 and Week 24, utilities were modelled by least squares mean change from baseline (CFB) by treatment arm at each assessment timepoint (i.e., each 4-week cycle). At Week 24, response was measured, and patients were classified as responders and non-responders. Starting at Week 24, utilities for responders were modelled as CFB by treatment arms that were directly observed in SYNAPSE. Non-responders in the mepolizumab arm were assumed to discontinue mepolizumab and have the same utility as the SoC non-responder arm.</p> <p>The responder utility from Week 52 onwards was based on responders at Week 52 who were also responders at Week 24 for each arm (mepolizumab arm: 0.742, SoC arm: 0.704). Non-responders from Week 52 for both the SoC and mepolizumab arms are based on the utility of non-responders at Week 52 in the SoC arm.</p>	<p>It was unclear why SF-36 v2 outcomes were not used by the submission to calculate SF-6D utilities despite this data being collected in SYNAPSE. See paragraph 6.44.</p> <p>Using different utilities for different timepoints in the first 52 weeks of treatment may not be justified and was likely unnecessarily complicated. Further, differences between treatment arms may not be justified as the confidence intervals reported may not be reliable as the utility analysis was an unplanned analysis in an unplanned subgroup (BEC\geq150 cells/μL) and was not adjusted for multiplicity (with a comparison made every four weeks).</p> <p>It was noted that a higher proportion of patients underwent surgery, experienced asthma exacerbations and OCS use in the SoC arm compared to the mepolizumab arm. See paragraph 6.45.</p> <p>Overall the submission's method risked overestimating the benefits of mepolizumab compared to a more conservative approach of applying an overall utility for responders (across both treatment arms).</p>

Source: Table 3-1, p108 of the submission, and compiled during the evaluation.

BEC= blood eosinophil count; CRSwNP= chronic rhinosinusitis with nasal polyps; EQ-5D-3L= European quality of life five dimension three levels; ICER= incremental cost effectiveness ratio; NP= nasal polyps; OCS= oral corticosteroids; PBS= pharmaceutical benefits scheme; SoC= standard of care; SF-36= 36-item short form health survey; SNOT-22= Sino-nasal outcomes test (22 items); v2= version 2

6.41 Though CRSwNP is a lifelong chronic condition, the chosen time horizon of 30 years may be considered optimistic given SYNAPSE trial data was limited to 52 weeks. It was noted that in the submission for mepolizumab for the treatment of severe eosinophilic asthma in which a lifetime horizon was presented, the PBAC (Mepolizumab PSD, March 2016, paragraph 6.44) previously considered that the results of the economic model may be unreliable in part due to the extrapolation of trial data (Week 16 to 32) to the life duration of the model. The ESC considered a shorter time horizon of 5 years may be more appropriate given the trial data available. The pre-PBAC response stated that treatment with SoC with or without add-on mepolizumab is expected to be required indefinitely for this population. Further, the pre-PBAC response argued that the time horizon of 30 years is consistent with the SYNAPSE patient mean age of 48 years and with the typical onset of CRSwNP occurring in middle-age.

6.42 The approach used for the transition probabilities in the economic model was reasonable, though inconsistent with the requested restriction which does not preclude mepolizumab treatment to patients who choose to undergo surgery whilst

on treatment and does not prevent patients from re-trialling mepolizumab if they fail to respond previously. The potential for these scenarios was not considered in the economic model presented by the submission which may underestimate usage of mepolizumab with an unknown effect on the ICER.

- 6.43 Extrapolation of patient outcomes was performed from cycle 15/Week 56 (given the end of the SYNAPSE trial was at Week 52) to the end of the modelled time horizon of 30 years. The economic model assumed that patients who were responders to treatment at Week 52 would continue to maintain their response to treatment with no loss of efficacy, while non-responders could progress to requiring surgery each cycle, and patients who had already received a surgery could progress to recurrence post-surgery in each cycle. However, the assumption that responders at Week 52 will remain in the responder health state (unless they die) for up to 30 years may not have been appropriate and was likely optimistic and favoured mepolizumab. The PSCR argued that a sustained and progressive response to mepolizumab treatment in ENP score and NO-VAS was observed in the 52-week SYNAPSE trial, as well as no observed plateauing or waning of treatment benefit. The PSCR stated that any analysis considering loss of response should apply this to both treatment arms. The ESC agreed with the evaluation that the assumption of a sustained response may not be appropriate given that a reduction in response was observed in SYNAPSE (only 125/144 (86.8%) of patients who achieved response at week 24 maintained response at week 52, see Table 5).
- 6.44 Utility scores used in the economic model were derived by mapping the SNOT-22 scores to the EQ-5D-3L instrument using an established mapping algorithm (Crump 2017) and the Canadian value set. It was noted that the adjusted R^2 observed for Crump's model used only explained 34% of the variance in the model, though Crump 2017 argued that these findings were consistent with models mapping condition-specific measures onto utility values generated from a generic measure. Crump's analysis was also based on 232 patients with CRS on the waitlist for bilateral endoscopic sinus surgery, with a median baseline SNOT-22 global score of 42.0 (compared to CRSwNP patients enrolled in SYNAPSE who appeared to have more severe disease with a median SNOT-22 global score of 64.0 at baseline). This may introduce some uncertainty into the applicability of Crump 2017 to the current submission. It was unclear why SF-36 v2 outcomes were not used by the submission despite this data being collected in SYNAPSE. The SF-36 may be particularly useful given it is possible to convert SF-36 to SF-6D Australian value set³ as opposed to Canadian values used in the submission. It was unclear how the utilities derived from SF-36 would have differed to the utilities derived from SNOT-22 used in the economic model. The PSCR argued the benefit of estimating utility weights with the SNOT-22

³ Mulhern, B., Norman, R. & Brazier, J. Valuing SF-6Dv2 in Australia Using an International Protocol. *PharmacoEconomics* (2021). <https://doi.org/10.1007/s40273-021-01043-4>

measure compared to a generic measure such as SF-36 was an improved sensitivity to changes in disease-specific symptoms that are directly relevant to the disease states and patient HRQoL. The ESC disagreed with the PSCR and considered that any potential benefits in terms of sensitivity to changes in disease-specific symptoms with the use of SNOT-22 would likely be lost once utility scores are mapped to the EQ-5D-3L instrument. The ESC considered that use of the trial SF-36 v2 outcomes which can be converted to an SF-6D Australian value set would be preferable.

- 6.45 Different utilities for patients in the ‘in trial’ and ‘responder’ health state were applied via treatment arm in the economic model, with higher utility in the mepolizumab arm than the SoC arm. However, utilities for ‘non-responders’, ‘effective surgery’, and ‘recurrence post-surgery’ (and ‘failed surgery’) were the same across both arms. Disutilities associated with CRSwNP-related events were considered in the economic model. It was noted that a higher proportion of patients underwent surgery, experienced asthma exacerbations and OCS use in the SoC arm compared to the mepolizumab arm. Hence, at least part of the differential utility observed via treatment arm may have been attributable to this difference. The submission’s further application of disutilities associated with these events may lead to potential double counting, favouring mepolizumab. The PSCR presented new information regarding the SNOT-22 scores by responder status in the ITT population and claimed that patients receiving treatment with mepolizumab saw improvement in their SNOT-22 total score relative to SoC in SYNAPSE, and hence, responders in the mepolizumab arm of the model included an improved utility compared to SoC. The ESC noted the additional information was not evaluated. The ESC noted that the differential utility applied for the responder health state depending on the treatment arm was a key driver of the economic model. The ESC also noted the utility value applied for individuals undergoing effective surgery differed from values applied for responders to either mepolizumab or SoC. The ESC considered that differences between treatment arms may not be justified as it was not clear if these three utility values were truly different. The ESC considered that the application of the same utility values for responders to mepolizumab, SoC or surgery would be appropriate.
- 6.46 Table 12 summarises the key drivers of the economic model.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Utilities	Values for model health states taken from SYNAPSE by mapping the SNOT-22 scores to the EQ-5D-3L instrument using an established mapping algorithm (Crump 2017) and Canadian value set. Differential utility applied for the responder health state depending on treatment arm and disutilities associated with CRSwNP-related events were further applied.	High, favours mepolizumab. Assuming no differential utility (i.e. 0.704 for responders and 0.566 for non-responders from week 52 onwards) between treatment arms increased the ICER by 51.9%.
Efficacy	Relied on point estimate of all ENP and/or NO-VAS responders in BEC ≥ 150 cells/ μ L in SYNAPSE.	Moderate. Using lower 95% for mepolizumab and upper 95% for SoC increased ICER by 22.96%
Time horizon	Base case time horizon was 30 years, but a shorter time horizon of (e.g. 5 years) may be more appropriate given the trial data available (52 weeks).	Moderate, favoured mepolizumab. Changing time horizon to 5 years increased the ICER by 17.1%.

Source: Compiled during evaluation.

CRSwNP= chronic rhinosinusitis with nasal polyps; ENP= endoscopic nasal polyp; EQ-5D-3L= European quality of life five dimension three levels; ICER= incremental cost effectiveness ratio; NO-VAS= nasal obstruction visual analogue scale; SNOT-22= Sino-nasal outcomes test (22 items)

- 6.47 The cost of NP surgery may have been overestimated by the submission. The submission assumed the cost of each surgery was \$9,600.43 based on AR-DRG codes. Comparatively, the submission’s advisory board reported the following MBS items as routinely used for NP surgery: 41716 fee: \$307.70; 41737 fee: \$502.85; 41752 fee: \$307.70; and 41668 fee: \$228.85. Using the multiple operation rule and assuming all MBS items were claimed, the cost of surgery would be \$790.84 based on the advisory board’s opinion, which was substantially less than the estimated surgical costs assumed in the model. However, surgery costs did not have a large impact on the ICER in the submission’s model – assuming a cost of \$790.84 for surgery increased ICER by only 5.85%, but should still be considered a source of uncertainty in the model. The model also estimated more surgeries in the SoC arm (1.528, undiscounted) compared to the mepolizumab arm (0.860, undiscounted) suggesting that mepolizumab may replace surgery in SoC even though the submission did not consider surgery as part of the comparator.
- 6.48 It was unclear whether the inclusion of asthma outcomes in the economic model was appropriate, as the requested restriction was for treatment of CRSwNP. However the inclusion of asthma outcomes had minimum effect on the ICER (exclusion of asthma outcome increased the ICER by <1%).
- 6.49 Table 13 summarises the results of the economic evaluation presented in the submission. A cost per responder analysis for the within trial period (52 weeks) was conducted during the evaluation.

Public Summary Document – November 2021 PBAC Meeting

Table 13: Results of the economic evaluation

Step and component	Mepolizumab	Standard of care	Increment
Trial-based (52 weeks) costs and outcomes (responders)			
Costs (\$)	██████	\$1,792	██████
Response rate	0.602	0.314	0.289
Incremental cost/extra responder gained			██████ ¹
Time horizon extended to 30 years (QALYs)			
Costs (\$)	██████	\$9,714	██████
QALYs	9.692	8.876	0.905
Incremental cost/extra QALYs gained (base case)			██████ ²

Source: Table 3-35, p149 of the submission, Attachment 5- Mepolizumab CEM.xlsm.

QALY= quality-adjusted life year

Text in italics indicate values calculated during evaluation.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$55,000 to < \$75,000

6.50 The majority of the incremental cost was the cost of mepolizumab (105% of incremental cost) with the largest offset from the cost of surgery assumed (-6.4% of incremental cost). There was a minor difference in the life years between the two treatment arms due to the assumption of potential death from surgery, and with more patients in the SoC arm having surgery, the overall life years in the SoC arm was (very slightly) lower compared to the mepolizumab arm despite the submission's statement that mepolizumab has no effect on mortality.

6.51 Univariate sensitivity analyses performed by the submission, and univariate and multivariate sensitivity analyses conducted during the evaluation are summarised in Table 14. The PBAC noted that Table 14 had been updated to address an error in the percentage of patients reported to lose response to treatment as identified by the pre-PBAC response.

Table 14: Results of sensitivity analyses

Variable	Base case	Scenario	Increment cost (\$)	Increment QALY	ICER	percent change
Base case			██████	0.905	██████ ¹	-
Univariate analyses						
Time horizon	30 years	Within trial (52 weeks)*	██████	0.037	██████ ²	+107.4%
		5 years*	██████	0.243	██████ ³	+17.1%
Discount rate	5% costs and effects	0%	██████	1.781	██████ ¹	-3.4%
		3.5%	██████	1.093	██████ ¹	-1.1%
Population	Baseline BEC ≥150 cells/μL	ITT population	██████	0.817	██████ ¹	+11.8%
Response rate at Week 24 and at Week 52	Mepolizumab – Week 24: 69.4%; Week 52: 60.2% SoC – Week 24: 46.5%; Week 52: 31.4%	Use upper 95% CI for both*	██████	0.936	██████ ¹	+4.87%
		Use lower 95% CI for both*	██████	0.873	██████ ¹	-4.61%
		Use lower 95% for mepolizumab and upper 95% for SoC*	██████	0.690	██████ ³	+22.96%
Loss of effect after 52 weeks	Assume 0% loss of response	Assume 24.6%† loss of response (corresponds to 13.2% loss of response)	██████	0.219	██████ ¹	+12.68%

Public Summary Document – November 2021 PBAC Meeting

Variable	Base case	Scenario	Increment cost (\$)	Increment QALY	ICER	percent change
		from Week 24 to 52 in SYNAPSE)*				
Utility	Differed by responder status and treatment arm	SoC responder utility applied to both arms from Week 52*	██████	0.596	██████ ⁴	+51.9%
Utility	Differed by responder status and treatment arm, and effective surgery differed from responder	SoC responder utility applied to both arms from Week 52, and applied to those who had effective surgery	██████	0.535	██████ ⁴	+69.1%
Blood eosinophil count	≥150 cells/μL	≥300 cells/μL	Unable to be explored due to lack of data (e.g. transition probabilities such as response rates and probability of surgery, and utilities were not available for a blood eosinophil count threshold of ≥300 cells/μL)			
Multivariate analyses						
Time horizon and loss of effect after 52 weeks	Time horizon of 30 years and assume 0% loss of response	Time horizon of 5 years and assume 24.6% [†] loss of response*	██████	0.158	██████ ³	+28.2%
Time horizon and utility	Time horizon of 30 years and utility differed by responder status and treatment arm	Time horizon of 5 years and SoC responder utility applied to both arms from Week 52*	██████	0.164	██████ ⁴	+73.9%
Time horizon and utility	Time horizon of 30 years and utility differed by responder status and treatment arm, and effective surgery differed from responder	Time horizon of 5 years and SoC responder utility applied to both arms from Week 52, and applied to those who had effective surgery	██████	0.143	██████ ²	+99.7%
Time horizon, loss of effect after 52 weeks and utility	Time horizon of 30 years, assume 0% loss of response and utility differed by responder status and treatment arm	Time horizon of 5 years, assume 24.6% [†] loss of response and SoC responder utility applied to both arms from Week 52*	██████	0.109	██████ ²	+85.3%
Time horizon, loss of effect after 52 weeks and utility	Time horizon of 30 years, assume 0% loss of response and utility differed by responder status and treatment arm, and effective surgery differed from responder	Time horizon of 5 years, assume 24.6% [†] loss of response and SoC responder utility applied to both arms from Week 52, and applied to those who had effective surgery	██████	0.090	██████ ⁵	+125.2%

Public Summary Document – November 2021 PBAC Meeting

Source: Tables 3-37 & 3-38, pp151-152 of the submission.

BEC= blood eosinophil count; ICER= incremental cost effectiveness ratio; ITT= intent-to-treat; QALY= quality-adjusted life years; SoC= standard of care

*Indicate sensitivity analyses conducted during evaluation

†The pre-PBAC response correctly identified that the proportion of patients who would lose response to treatment annually should be 24.6% instead of 21.5%. Table 14 has been updated with the correct proportion.

The redacted values correspond to the following ranges:

- ¹ \$55,000 to < \$75,000
- ² \$115,000 to < \$135,000
- ³ \$75,000 to < \$95,000
- ⁴ \$95,000 to < \$115,000
- ⁵ \$135,000 to < \$155,000

6.52 The ESC noted the assumption of differential utility based on treatment arm and the extrapolation to a 30-year time horizon from ‘within trial’ in the base case had the largest potential impacts on the ICER. Multivariate sensitivity analyses combining two scenarios assuming the same utilities across treatment arms and a five-year time horizon increased the estimated ICER by 73.9%. This, combined with the loss of treatment effect further increased the estimated ICER by 85.3%. Overall, the ESC considered the base case ICER was likely underestimated based on the use of optimistic inputs (differential utility) and assumptions (extrapolation to 30 years with no loss of effect) which favoured mepolizumab.

6.53 The ESC noted that as SF-36/SF-6D utilities via responder status were not available in the Clinical Study Report nor provided by the submission, the impact of these could not be explored in the sensitivity analysis.

6.54 The ESC considered that a respecified base case incorporating the following amendments was required to address concerns identified:

- a 5 year time horizon
- an assumption of 24.6% loss of response
- the SoC responder utility applied to both arms from Week 52, and applied to those who had effective surgery.

The ESC noted that incorporating the above amendments increased the ICER from \$55,000 to < \$75,000/QALY to \$135,000 to < \$155,000/QALY.

Drug cost/patient/year

6.55 Drug acquisition costs of mepolizumab are summarised in Table 15.

Table 15: Drug cost per patient for mepolizumab

	Trial dose and duration	Model	Financial estimates
Mean dose	100mg Q4W	100mg Q4W	100mg Q4W
Mean duration	11.3 months	16.90 years	Lifelong
Cost/patient/year (\$)	██████ ^a	██████	██████ ^b

Source: Table 21, p 70 of the Clinical Study Report and Attachment 5- Mepolizumab CEM.xlsm.

^a estimated as (365.25 days ÷ 12 months) × (11.3 months ÷ 28 days) × \$██████/dose

^b estimated as 12.22 doses (94% compliance of 13 doses per 52 weeks) × \$██████/dose (weighted private/public)

Estimated PBS usage & financial implications

6.56 This submission was considered by DUSC.

6.57 The submission used an epidemiological approach to estimate the utilisation and financial impact of listing mepolizumab on the PBS for CRSwNP. A summary of the key assumptions used to calculate the financial estimates is presented in Table 16.

Table 16: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value and Source	Comment
Eligible population		
Prevalence of CRSwNP	10% have CRS and of these 30% have CRSwNP Source: National Health Survey 2014-2015 and Australian Public Assessment Report for Omalizumab (TGA 2021).	It was noted that the prevalence of 'chronic sinusitis' in 2017-2018 remained the same as the 2014-2015 estimates. Incident patients were assumed to be part of the prevalent population. DUSC considered the submission substantially overestimated disease prevalence of CRS and overestimated the percentage who have CRSwNP.
Proportion with baseline BEC \geq 150 cells/ μ L	91% Source: SYNAPSE trial	Aligned to requested restriction.
Proportion who see a specialist	35% Source: Sponsor internal estimates based on local market research	Possible source of double counting and underestimate of eligible patients.
Proportion requiring (first) NP surgery	61% Source: Advisory board feedback (n=7), based on question "what proportion of CRSwNP patients require nasal polyp surgery during the course of their disease?" A large variance in responses (range: 30-100%) was noted, with the mean of 61% used.	Given that response was not limited to patients seen by specialists but CRSwNP patients in general, there may be potential double counting with proportion of patients who see specialists. This value used was consistent with the observed percentage of patients who had undergone surgery in five Western countries which ranged from 43-84% ⁴ .
Proportion suitable/unsuitable for surgery	Suitable: 93% Unsuitable: 7% Source: Advisory board feedback (n=7), "... what proportion of CRSwNP patients are unsuitable for surgery?" The definition of 'unsuitable' was unclear. 'Patient preference' and 'access' were reasons provided for unsuitability by an advisory board member, whereas such reasons may not be adequately justified.	The submission implicitly assumed that all patients suitable for surgery would undergo the surgery (100% uptake rate of surgery).
Proportion who experience NP	61%	Along with proportion of patients with prior surgery who have a high level of symptoms was used as a proxy for the requested

⁴ Chen S, Zhou A, Emmanuel B, Thomas K, Guiang H. Systematic literature review of the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyposis. *Curr Med Res Opin.* 2020;36(11):1897-1911. doi:10.1080/03007995.2020.1815682

Public Summary Document – November 2021 PBAC Meeting

Data	Value and Source	Comment												
regrowth post-surgical removal	Source: Advisory board feedback (n=7) "What proportion of CRSwNP patients require more than one nasal polyp surgery?"	initiation criteria. Possible source of double counting and underestimate of eligible patients.												
Proportion with prior surgery who have a high level of symptoms	45% Source: Adelphi real world 2021 (p18), based on US sample of patients with 1+ surgeries (n=181). Based on physician-perceived 'high' level of symptoms, which was not clearly defined in the submission.	Along with the proportion who experience NP regrowth post-surgery, was used as a proxy for the requested initiation criteria. It was unclear how this response by clinicians aligned with the initiation criteria, but was likely more closely aligned to the requested restriction criteria compared to the 'proportion who experience NP regrowth post-surgical removal'. Possible source of double counting and underestimate of eligible patients.												
Grandfathered patients	Yr 1: 90 Yr 2: 90 Yr 3: 90 Yr 4: 90 Yr 5: 90 Yr 6: 90 Source: Anticipated by the submission (p158).	No details regarding patient familiarisation program or current patient numbers. The inclusion of grandfathered patients may not be appropriate given a prevalence based approach was used to estimate the number of eligible patients by the submission and there may be an element of double counting. However, it was noted that the number of grandfathered patients (90) was relatively small and represented 90 out of 39,536 eligible patients (30,887 + 8,469 eligible and ineligible for surgery; see Table 17) in Year 1 overall.												
Treatment utilisation														
Uptake rate for initial patients	Yr 1: 5.00% Yr 2: 4.50% Yr 3: 4.00% Yr 4: 3.50% Yr 5: 3.50% Yr 6: 3.50% Source: Uptake rates deemed reasonable by the PBAC for dupilumab for atopic dermatitis (November 2020).	Potentially underestimated. The uptake rate for patients unsuitable for surgery should be high (100%) given patients deemed suitable for surgery were assumed to have a 100% uptake rate for surgery and given there exist no alternative line of therapy available to those unsuitable for surgery who have an inadequate response.												
Uptake rate for continuing patients	Yr 1: 3.50% Yr 2: 3.15% Yr 3: 2.80% Yr 4: 2.45% Yr 5: 2.45% Yr 6: 2.45% Source: Calculated by applying a 70% responder rate based on patients responding at the 24-week mark in the base case economic model for the given year.	Inconsistent with economic model as did not consider patients who may have a loss of response at week 52 or have surgery while being treated with mepolizumab.												
Dosing and duration for mepolizumab assumed	Compliance: 94% Source: SYNAPSE trial Dosing and duration used by the submission: <table border="1" data-bbox="440 1839 930 1953"> <thead> <tr> <th></th> <th>Duration</th> <th>Doses/mth</th> <th>Scripts/yr</th> </tr> </thead> <tbody> <tr> <td>Initiating</td> <td>3 mths</td> <td>1.09</td> <td>3.07</td> </tr> <tr> <td>Continuing (1st year)</td> <td>3 mths</td> <td>1.09</td> <td>3.07</td> </tr> </tbody> </table>		Duration	Doses/mth	Scripts/yr	Initiating	3 mths	1.09	3.07	Continuing (1 st year)	3 mths	1.09	3.07	The compliance rate used was inconsistent with the economic model which did not appear to consider compliance (i.e. 100% compliance assumed). The submission claimed the treatment duration for initiating patients was 6 months (even though 3 months was applied in the
	Duration	Doses/mth	Scripts/yr											
Initiating	3 mths	1.09	3.07											
Continuing (1 st year)	3 mths	1.09	3.07											

Public Summary Document – November 2021 PBAC Meeting

Data	Value and Source	Comment																				
	<table border="1" data-bbox="443 309 932 331"> <tr> <td>Continuing</td> <td>12 mths</td> <td>1.09</td> <td>12.26</td> </tr> </table> <p data-bbox="437 338 938 394">Population split: 78% surgical and 22% ineligible surgical patients.</p> <p data-bbox="437 427 938 573">The dosing, duration and population split used in the submission's financial model were inaccurate. These were rectified during the evaluation. The table below contain revised values, in line with the requested restriction:</p> <table border="1" data-bbox="443 580 932 719"> <thead> <tr> <th></th> <th>Duration</th> <th>Doses/wk</th> <th>Scripts/yr</th> </tr> </thead> <tbody> <tr> <td>Initiating</td> <td>24 wks</td> <td>0.25</td> <td>5.64</td> </tr> <tr> <td>Continuing (1st year)</td> <td>28 wks</td> <td>0.25</td> <td>5.64</td> </tr> <tr> <td>Continuing</td> <td>52 wks</td> <td>0.25</td> <td>12.26</td> </tr> </tbody> </table> <p data-bbox="437 725 938 808">Population split of 100% should be used given the number of patients were already grouped appropriately.</p>	Continuing	12 mths	1.09	12.26		Duration	Doses/wk	Scripts/yr	Initiating	24 wks	0.25	5.64	Continuing (1 st year)	28 wks	0.25	5.64	Continuing	52 wks	0.25	12.26	<p data-bbox="948 309 1417 544">financial model) and 72 months for continuing patients. The treatment duration for initiating patients was inconsistent with the requested restriction for initial patients which would be sufficient for 24 weeks (24/52=0.46 years). It appeared the duration of treatment of 6 years for continuing patients was aligned to the lifelong treatment of mepolizumab.</p>
Continuing	12 mths	1.09	12.26																			
	Duration	Doses/wk	Scripts/yr																			
Initiating	24 wks	0.25	5.64																			
Continuing (1 st year)	28 wks	0.25	5.64																			
Continuing	52 wks	0.25	12.26																			
Setting – public/private split	<p data-bbox="437 817 938 851">Public: 69.63%</p> <p data-bbox="437 857 938 891">Private: 30.37%</p> <p data-bbox="437 898 938 990">Source: PBS dispensing data for mepolizumab item codes for severe eosinophilic asthma dispensed over the 12-month period from Jan 2020-Dec 2020.</p>	<p data-bbox="948 862 1417 952">Reasonable. It appeared 2 item codes used (12073K and 12030E) were no longer on the current PBS schedule.</p>																				

Source: Tables 4-2, 4-4, 4-6, 4-8, 4-14 & 4-15, pp 156,157,159,160, 163 &164 of the submission.

BEC= blood eosinophil count; CT= computed tomography; NP= nasal polyps; ENP= endoscopic nasal polyp; NO-VAS= nasal obstruction-visual analogue scale; MBS= Medicare benefits schedule; PBS= pharmaceutical benefits scheme; SoC= standard of care.

- 6.58 The financial model did not account for patients who may have had surgery whilst on mepolizumab treatment. This was inconsistent with the economic model, where those who received surgery were regarded as non-responders and removed from mepolizumab treatment. The financial model also assumed that the 70% response rate at Week 24 was maintained throughout the treatment duration by all patients and did not consider the potential loss of response at Week 52 (87% of responders at Week 24 maintained response at Week 52 in SYNAPSE) which was applied in the economic model (where maintenance of response was assumed from Week 52 onwards). This may have led to an overestimation of the number of patients in the financial model.
- 6.59 The submission's use of i) the proportion of patients with CRSwNP who would see a specialist (35%) along with proportion who require NP surgery (61%) and ii) proportion who experience NP regrowth post-surgical removal (61%) as well as proportion with prior surgery who have a high level of symptoms (45%) to estimate eligible patients likely included some double counting which resulted in an underestimate of the number of eligible patients. Further, an incorrect number of scripts was used by the submission in their calculation of mepolizumab scripts required (3.07 scripts per year used in the submission compared to 6.07 scripts per year required). This led to an underestimation of mepolizumab scripts and an underestimation of the resulting costs. This error was rectified during the evaluation.

6.60 The estimated financial impact of PBS listing mepolizumab is summarised in Table 17.

Public Summary Document – November 2021 PBAC Meeting

Table 17: Estimated use and financial implications of the proposed mepolizumab listing

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian pop ≥18 years of age	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Prevalence of CRS ≥18 years of age (10%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Proportion with CRSwNP (30%)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Patients eligible for NP surgery	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Patients ineligible for NP surgery	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Grandfathered patients	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Patients electing treatment						
Eligible for NP surgery (initial)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Ineligible for NP surgery (initial)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Eligible for NP surgery (continuing)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Ineligible for NP surgery (continuing)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Ongoing grandfathered patients (continuing)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Total electing treatment (initial)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Total electing treatment (continuing)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁵	█ ⁵
Number of scripts (mepolizumab) ^a						
Eligible for NP surgery (initial)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Ineligible for NP surgery (initial)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Eligible for NP surgery (continuing – first year of treatment)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Ineligible for NP surgery patients (continuing – first year of treatment)	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Total treated (continuing – second year of treatment onwards)	█ ⁶	█ ⁸	█ ⁴	█ ⁹	█ ¹⁰	█ ¹¹
Grandfathered	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷	█ ⁷
Total volume of scripts	█ ¹²	█ ⁴	█ ⁹	█ ¹³	█ ¹¹	█ ¹⁴
PBS/RPBS cost less co-pay						
Total (eff)	█ ¹⁵	█ ¹⁵	█ ¹⁶	█ ¹⁷	█ ¹⁷	█ ¹⁸
Total cost of replaced medicines (pub/eff)	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Net cost to PBS/RPBS (eff)	█ ¹⁵	█ ¹⁵	█ ¹⁶	█ ¹⁷	█ ¹⁷	█ ¹⁸
Net MBS costs ^b	█ ¹⁹	█ ¹⁹	█ ¹⁹	█ ¹⁹	█ ¹⁹	█ ¹⁹
Net cost to Government health budget	█ ¹⁵	█ ¹⁵	█ ¹⁶	█ ¹⁷	█ ¹⁷	█ ¹⁸

CRS= chronic rhinosinusitis; CRSwNP= chronic rhinosinusitis with nasal polyps; eff=effective; MBS= Medicare benefits schedule; NP= nasal polyps; PBS= pharmaceuticals benefits scheme; pub= published

Public Summary Document – November 2021 PBAC Meeting

^a The dosing, duration and population split used in the submission's financial model were inaccurate. These were rectified during the evaluation.

^b The MBS costs presented by the submission were incorrect for continuing patients where costs were not calculated for the total number of continuing patients (i.e. only newly continuing patients were considered for that given year). This was rectified during the evaluation.

The redacted values correspond to the following ranges:

¹ > 10,000,000

² 2,000,000 to < 3,000,000

³ 600,000 to < 700,000

⁴ 30,000 to < 40,000

⁵ 5,000 to < 10,000

⁶ < 500⁷ 500 to < 5,000

⁸ 10,000 to < 20,000

⁹ 40,000 to < 50,000

¹⁰ 50,000 to < 60,000

¹¹ 70,000 to < 80,000

¹² 20,000 to < 30,000

¹³ 60,000 to < 70,000

¹⁴ 80,000 to < 90,000

¹⁵ \$10 million to < \$20 million

¹⁶ \$20 million to < \$30 million

¹⁷ \$30 million to < \$40 million

¹⁸ \$40 million to < \$50 million

¹⁹ \$0 to < \$10 million

6.61 The estimated net cost to the government budget of listing mepolizumab on the PBS/RPBS at the proposed effective price was \$10 million to < \$20 million in Year 1, increasing to \$40 million to < \$50 million in Year 6 after correcting the doses of mepolizumab per patient per year. The total cost over the six year period was \$100 million to < \$200 million.

6.62 DUSC considered that overall the estimates presented in the submission are overestimated. The main issues are:

- The restrictions are narrower than the TGA registered indication but broader than the SYNAPSE trial eligibility criteria on which the submission is based.
- The submission substantially overestimates the disease prevalence of CRS.
- The submission overestimates the percentage of CRS patients with NP.
- The submission does not address patients who have CRSwNP and severe asthma, leading to an overestimation of the eligible population if patients are already accessing mepolizumab for severe asthma.
- The submission underestimates treatment uptake rates.
- As CRSwNP prevalence is greater in people aged 60 years and over, there could be a large population of patients who are unsuitable for surgery and eligible for mepolizumab treatment.

6.63 DUSC considered that the submission prevalence rates of CRS at 10% and a prevalence of CRSwNP rate of 30% were overestimated. DUSC noted the CRS prevalence in Europe is around 2.1% to 4.3% (based on studies conducted in between 1996 and 2005). DUSC further noted that a 1996 Finnish study used a postal survey of approximately 4,300 people with very targeted questions about doctor-diagnosed CRS and a 2005 French study used robust field epidemiology to ascertain CRS diagnoses. While these studies were not contemporary, DUSC considered they are more specific about the

prevalence of CRS than the 2014-2015 and 2017-2018 National Health Surveys that asked a relatively open-ended question about ‘any long-term conditions lasting or expected to last 6 months or more’; here sinusitis or sinus allergy were assumed to be equivalent to CRS. DUSC also considered the 30% estimated proportion of CRSwNP is likely to be overestimated as it is based on self-assessment. DUSC noted that Benjamin (2019) had a CRSwNP rate of 18% based on a medical chart audit of a US academic hospital. The pre-PBAC response accepted a CRS prevalence rate of 2.1%. However, the pre-PBAC response argued the rate of 18% supplied by DUSC from Benjamin (2019) was uncertain as it was from one hospital compared to the systematic literature review proposed by the submission. The pre-PBAC response suggested it may be pragmatic to use the middle value considering the uncertainty from both sources, and proposed a CRSwNP rate of 25%.

- 6.64 The financial estimates did not consider the proportion of CRSwNP patients who were already prescribed another PBS-listed biologic for severe asthma thereby assuming there would be no overlap of these patients. The requested restriction prohibits the use of mepolizumab in combination with another PBS-subsidised biological medicine prescribed for severe asthma, a known co-morbidity of CRSwNP. 20,315 items were reported for mepolizumab (items 12073K, 12021Q, 12064Y, 12007Y, 12030E, 12043W, 12052H, 12051G, 10980X, 10996R, 11839D, 11014Q, 11003D and 11829N), between July 2020 and June 2021. It was likely that a proportion of these scripts would have been used by patients with CRSwNP and severe asthma. As these patients were not accounted for in the financial model, it was likely to have led to the potential overestimation of patient numbers. The proportion of patients with severe eosinophilic asthma currently treated with PBS subsidised mepolizumab and CRSwNP was unknown. The pre-PBAC response stated the Adelphi CRSwNP real world data reported that 70% of the comorbid asthma patients had severe asthma, and 70% of the SYNAPSE patients (i.e., mepolizumab eligible patients) had comorbid asthma. Assuming 20% of the comorbid severe asthma patients had severe eosinophilic asthma based on IDEAL study (Albers 2018), the pre-PBAC response estimated 10% (70% \times 70% \times 20%) of the total mepolizumab eligible CRSwNP patients are also eligible for severe eosinophilic asthma treatment with mepolizumab and may already be receiving mepolizumab (or an alternative biologic) on the PBS.
- 6.65 The uptake of mepolizumab used in the submission’s financial model was based on uptake rates deemed reasonable by the PBAC for dupilumab for atopic dermatitis (November 2020). The submission claimed dupilumab was a first-in-class biologic for atopic dermatitis and hence uptake was anticipated to be analogous to mepolizumab, also a first-in-class biologic for a disease with non-life threatening outcomes. While dupilumab was a first-in-class biologic for a disease with non-life threatening outcomes, dupilumab for atopic dermatitis involved a very different patient group from the one anticipated in this submission. Dupilumab was considered for adults with severe atopic dermatitis who have had an inadequate response to topical therapies (i.e. patient’s choice of dupilumab via SC injection would be more invasive compared

to topical treatment). Comparatively, in the current submission, patients have already consented to a more invasive procedure (prior surgery) and mepolizumab via SC injection likely represented a less invasive treatment compared to potential repeat surgery. DUSC considered that the initial and continuing treatment uptake rates were underestimated. DUSC noted that more people are able to administer injectable treatments themselves, and that there are not the same barriers to this type of treatment that there were previously. DUSC further noted that people are waiting for this treatment and will use it as soon as it is available. DUSC noted that the uptake rate for initial patients did not consider uptake in people unsuitable for surgery. In addition, DUSC also considered that patients are more likely to replace surgery with mepolizumab due to the risk/benefit ratio. The pre-PBAC response acknowledged that the submission uptake rate was starkly different to estimated biologic use in CRSwNP seen in survey data from Adelphi (Adelphi Group, 2020). The pre-PBAC response argued the data from Adelphi represents a different clinical setting than Australia with different prescribing practices and suggested it may be reasonable to assume a lower peak uptake rate than the American setting.

- 6.66 The pre-PBAC response presented revised financial estimates with the following changes: the modelled treatment duration of mepolizumab was reduced from 76 months to 34.99 months; the disease prevalence of CRS was reduced from 10% to 2.1%; the percentage of CRSwNP patients was reduced from 30% to 25%; patients with CRSwNP with severe asthma already receiving mepolizumab removed (10%); uptake rates increased to 10-20% for patients eligible for surgery or to 20%-30% for those not eligible for surgery. The PBAC noted the revised financial estimates presented in the pre-PBAC response had not been verified. The PBAC considered there was insufficient detail in the pre-PBAC response on how the changes stated in Table 1 of the response were applied in the financial estimates model.

Quality Use of Medicines

- 6.67 The submission did not present quality use of medicines issues however DUSC commented that:
- the criteria regarding specialist access could create inequity issues.
 - mepolizumab can be self-administered if a healthcare professional deems appropriate with patient or caregiver trained in injection techniques.
 - the PI states 'in line with clinical practice, monitoring of patients after administration of biological agents is recommended' with no further detail regarding monitoring requirements provided.
- 6.68 The pre-PBAC response stated the sponsor is committed to providing and supporting education to healthcare professionals to improve the quality use of medicines and is currently undertaking an assessment on the educational/training needs of health care professionals and patients with CRSwNP, which includes self-injection training.

Financial Management – Risk Sharing Arrangements

6.69 A risk sharing arrangement was not proposed by the submission.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend mepolizumab for treatment of chronic rhinosinusitis (CRS) with nasal polyps (NP; collectively CRSwNP) for patients who have received at least one previous surgery for the removal of NP. Overall, the PBAC considered the clinical claim of superior effectiveness compared SoC was reasonable in patients with CRSwNP. However, the PBAC considered the blood eosinophil count (BEC) threshold for access to mepolizumab should be increased from ≥ 150 cells/ μL to ≥ 300 cells/ μL . The PBAC considered that the submission had underestimated the incremental cost-effectiveness ratio (ICER) due to reliance on optimistic assumptions and inputs in the economic model. The PBAC considered the revised base case proposed by ESC was appropriate and that the resulting revised ICER high and uncertain at the proposed price. The PBAC considered the financial estimates were highly uncertain and advised that a risk sharing arrangement (RSA) would be required if patients unsuitable for surgery were to be included.
- 7.2 The PBAC noted the input from individuals, health care professionals and organisations that reported improvements in symptoms such fatigue and sense of smell were key quality of life (QoL) benefits associated with mepolizumab that do not always correspond with a reduction in NP size.
- 7.3 The PBAC agreed with the ESC that standard of care (SoC) was an appropriate comparator.
- 7.4 The PBAC noted that the primary clinical evidence supporting the clinical claim was the SYNAPSE trial (N=407) which compared mepolizumab with placebo in patients with CRSwNP and uncontrolled symptoms after at least one prior surgery and treatment with intranasal corticosteroids (INCS). For the co-primary outcome of Endoscopic Nasal Polyps (ENP) score, the adjusted difference in median at week 52 in the intent-to-treat (ITT) population (-0.73 [95%CI -1.11, -0.34]) did not meet nominated MCID of ≥ 1.0 change when applied to the point estimate. The MCID (≥ 3.0 change from baseline) was met for the other co-primary outcome, nasal obstruction visual analogue scale (NO-VAS) in the ITT population when assessed using the median change (-3.14, [95%CI -4.09, -2.18]). The PBAC acknowledged the ENP was more objective and less prone to bias as it was clinician assessed whereas NO-VAS was potentially more subjective and prone to bias as it was patient assessed. However, the PBAC agreed with the ESC that due to the inflammatory component of CRSwNP symptomatic improvement can occur without a change in the size of NPs. In addition, the PBAC noted that the secondary endpoints reported in Table 6 all achieved statistical significance.

- 7.5 The submission presented a subgroup analysis of the co-primary outcomes based on baseline BEC ≥ 150 cells/ μL , in line with the requested restriction. The PBAC considered that while the difference in median NO-VAS score for this subgroup (-3.36, 95%CI -4.27, -2.44) met the proposed MCID, the difference in median ENP score (-0.75, 95%CI -1.21, -0.29) did not meet the proposed MCID of ≥ 1.0 point of change. The PBAC also agreed with the ESC that the BEC < 150 cells/ μL complement subgroup sample size was too small to be able to draw meaningful conclusions regarding efficacy (see paragraph 6.24). The PBAC noted that in SYNAPSE the pre-specified subgroups for BEC were ≤ 300 cells/ μL ; > 300 to ≤ 500 cells/ μL ; > 500 to ≤ 700 cells/ μL and > 700 cells/ μL , and the 150 cells/ μL threshold appeared to be a post hoc subgroup. The PBAC considered that the median NO-VAS score data presented in Table 7 for the pre-specified BEC subgroups indicated no clear effect modification beyond 300 cells/ μL with similar data not presented for the 150 cells/ μL threshold. The PBAC agreed with the ESC that based on physiological grounds and other indications for mepolizumab that a cut-off for BEC is appropriate. The PBAC considered that a BEC threshold of ≥ 300 cells/ μL , which is consistent with the listing of mepolizumab for uncontrolled severe asthma, would be appropriate. Overall, the PBAC considered the clinical claim of superior effectiveness compared SoC was reasonable for patients with CRSwNP and a BEC ≥ 300 cells/ μL .
- 7.6 The PBAC acknowledged that unlike mepolizumab there would be no injection site reactions associated with the comparator in the proposed PBS population currently treated with SoC. However, the PBAC noted that injection site reactions were not significant in either arm of the SYNAPSE trial and as such agreed with the ESC that the claim of non-inferior safety was reasonable.
- 7.7 The PBAC noted the submission presented a cost-utility model which assumed a sustained response to mepolizumab over a 30 year time horizon along with differential utilities applied for responder health states depending on the treatment arm and for individuals undergoing effective surgery. The PBAC agreed with the ESC that a 5 year time horizon would be more appropriate given the SYNAPSE trial data were limited to 52 weeks. The PBAC also agreed with the ESC that the assumption of no loss of response across with mepolizumab treatment may not be appropriate given that a reduction was observed in the SYNAPSE trial (see paragraph 6.43). Finally, the PBAC noted that the differential utility applied for the responder health state depending on the treatment arm was a key driver of the economic model. The PBAC also noted the utility value applied for individuals who undergo effective surgery differed from values applied for responders to either mepolizumab or SoC (see paragraph 6.45). The PBAC considered that differences between treatment arms may not be justified as it was not clear if these three utility values were truly different. As such, the PBAC agreed with the ESC that a respecified base case incorporating the following amendments would be appropriate to address the concerns identified:
- a 5 year time horizon;
 - an assumption of 24.6% loss of response;
 - the SoC responder utility applied to both arms from Week 52, and applied to those

who had effective surgery.

The PBAC noted that incorporating the above amendments increased the ICER from \$55,000 to < \$75,000/QALY to \$135,000 to < \$155,000/QALY. The PBAC considered the revised ICER was high and uncertain at the proposed price.

- 7.8 The PBAC agreed with DUSC that overall the estimates presented in the submission were likely overestimated primarily due to the prevalence rates of CRS and CRSwNP used in the submission along with the inclusion of a proportion of CRSwNP patients already prescribed a PBS-listed biologic for severe asthma (see paragraphs 6.63 and 6.64). The PBAC considered the initial and continuing uptake rates were underestimated and agreed with DUSC that that this was particularly evident for patients unsuitable for surgery (see paragraph 6.65). The PBAC agreed with DUSC that more people are able to administer SC injections themselves reducing the barriers to uptake of such treatments. The PBAC considered that the favourable risk/benefit profile of mepolizumab, along with current wait times for NP surgery, would likely see patients eligible for surgery commencing mepolizumab. The PBAC considered the potential for such use a major source of uncertainty in the financial estimates. The PBAC noted that one option would be to restrict use to patients who had received at least one prior surgery for the removal of NP. However, the PBAC agreed with the pre-PBAC response that removing access for patients deemed to be unsuitable for prior surgery may create an inequity for this subset of CRSwNP patients given that alternative treatment options are limited. As such, the PBAC considered that if patients unsuitable for surgery were to be included in the proposed PBS population then an RSA would be required to manage the uncertainty associated with uptake in this population.
- 7.9 The PBAC advised that a resubmission, which included the revised base case outlined in paragraph 7.7, that provided updated utilisation and financial impact estimates, and which presented a proposed RSA to manage the uncertainty associated with inclusion of patients unsuitable for surgery in the proposed PBS population, may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway. The PBAC considered that there were multiple outstanding issues which needed to be resolved and therefore that a standard re-entry pathway was appropriate.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in

relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

GSK notes that table 5 shows a differential loss of response between treatment arms with a greater maintenance of response observed for mepolizumab versus standard of care. Analyses conducted through the evaluation did not include the observed maintenance of response for standard of care which would have improved the incremental cost-effectiveness ratio.

GSK looks forward to working with the PBAC to ensure timely access to mepolizumab (Nucala) for people with chronic rhinosinusitis with nasal polyps (CRSwNP), a persistent condition with limited treatment options currently available in Australia.