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

1 Purpose of submission

1.1 The Standard Re-entry resubmission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for mepolizumab for the treatment of chronic rhinosinusitis with nasal polyps (NP).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC).

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

Component	Description
Population	CRSwNP in adult (≥18 years-old) patients with a blood eosinophil count ≥300cells/µL (OR blood eosinophil count ≥150cells/µL if treated with OCS within previous 12 months) who have received prior NP surgery (or are unsuitable for surgery) and remain inadequately controlled [a] with intra-nasal corticosteroids (unless contra-indicated or not tolerated)
Intervention	Mepolizumab 100 mg SC injection by self-administration every 28 days
Comparator	Standard of care (including INCS (drops/sprays/rinses), saline rinses, short courses of OCS)
Outcomes	Primary endpoints: Total endoscopic nasal polyp score, nasal obstruction visual analogue scale (VAS) score. Secondary endpoints: Time to first actual nasal polyp 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 (reduced need for surgery, reduced polyp size, improved symptoms, improved QoL and reduced need for OCS) and comparable safety to standard of care for patients with recurrent severe bilateral nasal polyps who have received prior nasal polyp surgery

Source: Table 1-2, pp18-9 of the resubmission
Note - underlined text refers to changes from the previous submission
[a] The previous submission targeted patients inadequately controlled with intra-nasal corticosteroids (INCS) and oral corticosteroids (OCS) whereas the resubmission targeted patients inadequately controlled on INCS only.
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 Mepolizumab was TGA registered in January 2022 for add-on treatment in adult patients (18 years and above) with severe chronic rhinosinusitis with nasal polyps (CRSwNP) with an inadequate response to intranasal corticosteroids.

2.2 Mepolizumab is also currently TGA registered for severe eosinophilic asthma and relapsed or refractory eosinophilic granulomatosis polyangiitis.

Previous PBAC consideration

2.3 Mepolizumab for the treatment of CRSwNP in 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/µL was previously considered at the November 2021 PBAC meeting.

2.4 Table 2 summarises the key matters from the previous PBAC consideration and how the resubmission addressed those concerns.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical place in therapy	BEC threshold for access to mepolizumab should be increased from ≥150 cells/μL to ≥300 cells/μL (Paragraph 7.1, Nov 2021, PSD).	Addressed but the resubmission additionally included patients with BEC ≥150 cells whilst on OCS treatment, which may not be reasonable.
	The requirement for optimised therapy to include treatment with OCS…could lead to inappropriate use to meet the restriction criteria (Paragraph 3.8, Nov 2021, PSD)	Partially addressed – see Paragraph 3.5.
	The PBAC considered the inclusion of overall VAS score in the restriction may be appropriate (Paragraph 3.5, Nov 2021, PSD).	Addressed, however it is unclear whether the overall-VAS should also have been included to define response in the continuing treatment restriction.
	There were no restrictions around how many times a patient may retrial mepolizumab (Paragraph 3.3, Nov 2021, PSD).	Addressed, however the inclusion of 12-month treatment break in the initial restrictions may cause applicability issues - see Paragraph 3.7.
Continuing treatment requested restriction	There was no requirement in the continuing criteria to maintain response to treatment even though adequate response was defined (Paragraph 3.3, Nov 2021, PSD).	Addressed – see requested listing.
	It was unclear whether a patient who received NP surgery while on treatment with mepolizumab and fulfills the criteria for an 'adequate response' …should be eligible to continue treatment (Paragraph 3.3, Nov 2021, PSD).	Addressed, however the requirement for patients having undergone NP surgery to discontinue mepolizumab may cause equity issues – see Paragraph 3.6.
Economic evaluation	The PBAC considered a 5-year time horizon would be more appropriate given the SYNAPSE trial data was limited to 52 weeks (Paragraph 7.7, Nov 21, PSD).	Addressed
	An assumption of no loss of response was inappropriate given the reduction observed in SYNAPSE (Paragraph 7.7, Nov 21, PSD).	Addressed, however there are issues with the loss of response rates applied – see paragraph 6.39.
	The use of the SF-36 trial data to inform utilities would be preferable to the SNOT-22 (Paragraph 6.44, Nov 21, PSD)	Addressed
	The use of different utilities for different time points in the first 52 weeks of treatment was considered to be potentially unjustified and unnecessarily complicated (Paragraph 6.40, Nov 21, PSD)	Not addressed
	The SoC responder utility should be applied to [responders in] both arms from week 52, and applied to those who had effective surgery (Paragraph 6.54, Nov 21, PSD)	Addressed, however the mean utility across all responders was applied as opposed to the use of the SoC responder mean utility.
	Mepolizumab costs were based on patients remaining 'on treatment'…at each cycle. However, in clinical practice, patients …would remain on treatment until the next response assessment (every 24 weeks) (Paragraph 6.40, Nov 21, PSD).	Not addressed
	The cost of NP surgery may have been overestimated by the submission	Addressed, however there may still be issues with the unit cost applied – see paragraph 6.45
Financial estimates	The prevalence of CRS (10%) used in the previous submission was substantially overestimated, and the proportion of CRS patients with CRSwNP (30%) was likely overestimated (Paragraph 6.57, Nov 21, PSD).	Addressed – see Table 17

Component	Matter of concern	How the resubmission addresses it
	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 (Paragraph 6.64, Nov 21, PSD).	Addressed, but the value applied in the financial estimates is considered uncertain – see Table 17
	The initial uptake rates were considered potentially underestimated (Paragraph 6.57, Nov 21, PSD).	Addressed, however the uptake in patients unsuitable for surgery remains an important source of uncertainty – see Table 17
	The PBAC considered that if patients unsuitable for surgery were to be included in the proposed PBS population then a risk sharing agreement would be required to manage uncertainty associated with the uptake in this population (Paragraph 7.8, Nov 21, PSD).	Not addressed

Source: Sections 1-4 of the resubmission
BEC = blood eosinophil count; OCS = oral corticosteroids; PSD = Public Summary Document; VAS = visual analogue scale

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
MEPOLIZUMAB					
Mepolizumab 100mg/1mL injection, 1 mL pen device	Published price: $1,556.10 (public) $1,603.88 (private) Effective price: $[redacted] (public) $[redacted] (private)	1	1	5	Nucala

Category / Program: Section 100 - Highly Specialised Drugs Program (Private/Public)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required – In Writing
Condition: Chronic rhinosinusitis with nasal polyps (CRSwNP)
Indication: Chronic rhinosinusitis with nasal polyps
Treatment Phase: Initial treatment criteria
Clinical criteria:
Patient must have a diagnosis of CRSwNP confirmed and documented by nasal 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 must not be suitable for surgery as per written advice from at least two of the specialist prescribers listed above
AND
Clinical criteria:
Patient must have two of the following 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 polyps therapy; OR Patient must have a nasal obstruction visual analogue scale of >5 (out of a maximum score of 10) despite optimised nasal polyps therapy OR Patient must have an overall symptom visual analogue scale of >7 (out of a maximum score of 10) despite optimised nasal polyps therapy
AND
Clinical criteria:
Patient must not have received PBS-subsidised treatment with a biological medicine for CRSwNP; OR Patient must have had a 12-month break in treatment from the most recently approved PBS-subsidised mepolizumab treatment for CRSwNP 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 eosinophilic 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 300 cells per microlitre in the last 12 months; OR Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids in the last 12 months
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:
Optimised nasal polyps therapy includes: (i) Adherence to intranasal corticosteroid therapy for at least 2 months, unless contraindicated or not tolerated
Prescribing Instructions:
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
Prescribing Instructions:

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 Two of either baseline NP score obtained in the past 12 months; OR baseline nasal obstruction VAS score OR baseline overall VAS score

Category / Program: Section 100 - Highly Specialised Drugs Program (Private/Public)
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐
Restriction type: ☒Authority Required - Telephone
Condition: Chronic rhinosinusitis with nasal polyps
Indication: Chronic rhinosinusitis with nasal polyps
Treatment Phase: Continuing treatment criteria
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have achieved and sustained an adequate response to this drug, defined as 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.
AND
Clinical criteria:
Patient must not have undergone surgery for the removal of nasal polyps since the most recent 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.

3.1 A special pricing arrangement (SPA) was proposed by the Sponsor. The Sponsor proposed an effective ex-manufacturer price (EMP) of $ per pen. This represented a % reduction from the EMP of $ per pen proposed in the November 2021 submission. The pre-PBAC response proposed a further reduction with a revised EMP of $ per pen. This represented a % reduction from the EMP proposed in the November 2021 submission.

3.2 Mepolizumab is PBS-listed for uncontrolled severe asthma and is subject to an SPA.

3.3 The Sponsor stated a wish to work with the PBAC to agree on a separate grandfathering restriction for patients enrolled in a planned patient familiarisation program following TGA approval. No details for the proposed patient familiarisation program were provided and it was unclear if the enrolment in the familiarisation program would be aligned to the proposed PBS restriction. The Pre-Sub-Committee Response (PSCR) stated that a patient familiarisation program was currently recruiting

patients with the entry criteria not allowing patients outside of indication or the proposed PBAC criteria to be enrolled.

3.4 The resubmission additionally proposed a balance of supply restriction, similar to mepolizumab in severe asthma, be drafted post positive recommendation to account for patients who have received insufficient therapy under initial or continuing treatment restrictions to complete a 24-week treatment cycle.

3.5 The request for patients with a baseline BEC ≥150 but <300 cells/µL if they had received oral corticosteroid (OCS) in the past 12 months to access initial mepolizumab treatment was inconsistent with the PBAC consideration of the previous submission that the BEC threshold for access should be increased to ≥300 cells/µL (paragraph 7.1, mepolizumab Public Summary Document [PSD], November 2021 PBAC meeting) and may not be reasonable for the following reasons:

- ESC had previously considered that the inclusion of prior OCS use in the past 12 months as part of the restriction could lead to inappropriate use of OCS to meet the restriction criteria (paragraph 3.8, mepolizumab PSD, November 2021 PBAC meeting). The resubmission's proposed restriction would have a similar effect in that patients may be incentivised to use OCS even when it is not clinically appropriate in order to meet the lower baseline BEC threshold to become eligible for mepolizumab treatment; and
- The evidence used to inform the clinical claim, economic model and financial estimates in the resubmission utilised BEC ≥300 cells/µL subgroup data from the SYNAPSE trial. As such, the clinical, economic and financial data in the resubmission may not be applicable to the subset of patients with a BEC ≥150 but <300 cells/µL who have had treatment with OCS in the past 12 months. It was unclear how many patients, or what proportion of the requested population, would become eligible for mepolizumab under this clinical criterion.

The PSCR noted the proposed restriction would require patients to be on OCS treatment at the time of registering a BEC between ≥150 cells/µL and <300 cells/µL if they were to meet eligibility via this criterion. The PSCR reiterated that a retrospective longitudinal study (Ortega 2019) indicated BEC levels are suppressed by between 30-36% after systemic corticosteroid treatment and gradually return to near index levels by 3 months post-treatment. The ESC acknowledged the sensitivity of BEC to OCS and considered it may be reasonable for the restriction to include the BEC ≥150 cells/µL while on OCS criterion.

3.6 The requirement for patients to discontinue mepolizumab treatment after undergoing NP surgery may cause equity issues for patients who meet the continuing treatment response criteria but still require NP surgery. These patients may be forced to choose between continuing responsive mepolizumab treatment or potentially successful NP surgery. In the previous submission, ESC noted that symptomatic improvements can occur in patients without a change in the size of NPs (Paragraph 3.5, 6.04, mepolizumab PSD, November 2021 PBAC meeting) therefore NP surgery may still be

beneficial for patients who are responding to mepolizumab treatment. These patients would be unable to re-trial mepolizumab for at least 12 months under the requested restriction for initial treatment. In the pivotal SYNAPSE trial, patients could continue mepolizumab treatment after NP surgery, unlike the requested restrictions which would cause a patient to discontinue treatment. This may be an important applicability issue with the clinical evidence as 9% and 23% of mepolizumab and placebo-arm patients respectively underwent NP surgery in the 52-week treatment period of SYNAPSE (see Table 8). The PSCR stated that if the patient had surgery and the nasal polyps were removed, they would not require mepolizumab. Further the PSCR argued that if their nasal polyps or symptoms returned following surgery sufficient to meet the initiation criteria, they would be eligible to be treated with mepolizumab. The ESC agreed with the evaluation that there may be situations where patients responding to mepolizumab still require surgery.

3.7 Under the requested restrictions, patients could re-trial mepolizumab after a 12-month treatment break. However there was no clinical, economic or financial evidence presented in the resubmission for this sub-set of patients and may be an important applicability issue. The PSCR stated that the requirement for a minimum break of 12 months was consistent with the PBS restriction criteria for mepolizumab in uncontrolled severe asthma. The ESC noted that one of the initial treatment clinical criteria for mepolizumab for uncontrolled severe asthma was 'Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug for severe asthma during the current treatment cycle'. The ESC considered that it may be appropriate for the initial treatment clinical criteria to be amended to include reference to the need to have 'have failed, or ceased to respond to' with respect to the treatment break.

3.8 The eligibility criteria in the pivotal SYNAPSE trial also did not fully align with the requested restrictions. The requested restrictions were broader than the eligibility criteria in SYNAPSE, which required patients to:

- Have all three of endoscopic nasal polyp (ENP) score ≥5, nasal obstruction (NO) VAS score >5 and overall VAS score >7. Comparatively, the requested restrictions required at least two of the three;
- Have received intra-nasal corticosteroids (INCS) for at least eight weeks prior to screening. The requested restrictions required patients to have received INCS for at least two months, without stating the recency of the two months, or to be contraindicated or intolerant to INCS. In addition, the ESC noted that the SYNAPSE trial included saline nasal douching, if required, as part of concomitant therapy and considered it may be appropriate to reference it in the prescribing instruction defining optimised nasal polyp therapy; and
- Have had at least one NP surgery in the past 10 years. However the requested restrictions allow patients to who were unsuitable for NP surgery to access mepolizumab. DUSC had previously considered that 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. (paragraph 6.62, mepolizumab PSD, November 2021 PBAC meeting)

3.9 The requested restrictions included only patients with a BEC ≥300 cells/µL (or BEC ≥150 cells/µL while on OCS), which was narrower than in SYNAPSE which did not include a BEC threshold requirement. However, restricting use of mepolizumab to this subgroup of patients was consistent with PBAC's previous consideration of the appropriate BEC threshold for eligibility to mepolizumab for the treatment of CRSwNP (paragraph 7.5, mepolizumab PSD, November 2021 PBAC meeting).

3.10 The requested restrictions were also narrower than the approved TGA indication which does not define 'severe' CRSwNP or 'inadequate response', does not require prior NP surgery and does not have a BEC requirement (see paragraph 2.1).

3.11 The ESC noted the clinical criteria that '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 eosinophilic asthma'. The ESC advised that combinations with biological medicines for indications other than NP or severe eosinophilic asthma, which may have efficacy for CRSwNP, should also be included as part of this criterion.

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 The target population in the resubmission 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), with a BEC ≥300 cells/µL or ≥150 cells/µL if treated with OCS within the past 12 months. This differed to the previous submission which targeted patients with a BEC ≥150 cells/µL and additionally required patients to be inadequately controlled on OCS treatment (unless contraindicated or not tolerated).

4.3 Mepolizumab is a humanised monoclonal antibody (IgG1, kappa) directed against human interleukin-5 (IL-5).

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

5 Comparator

5.1 The resubmission nominated SoC as the main comparator. SoC included background INCS therapy with intermittent usage of OCS and saline spray or rinses. This was the same nominated comparator as in the previous submission. The resubmission did not consider NP surgery as part of SoC, or as a relevant comparator to mepolizumab claiming that the place of therapy for mepolizumab was after a prior NP surgery. In the previous submission, ESC noted that "surgery was likely unreasonably omitted as part of the SoC" (Paragraph 5.2, 6.04, mepolizumab PSD, November 2021). Clinical evidence from SYNAPSE presented in the resubmission showed a lower proportion of mepolizumab patients underwent NP surgery than SoC patients (see Table 8), indicating NP surgery is a relevant comparator to mepolizumab.

5.2 Overall, whilst the nominated comparator of SoC is appropriate and has been previously accepted by the PBAC (7.3, mepolizumab PSD, November 2021 PBAC meeting), NP surgery was likely inappropriately omitted in the definition of SoC.

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 (2), health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals described the limitations of the treatment options currently available for CRSwNP. Input from health care professionals described the positive effects of mepolizumab on disease severity and overall Quality of Life (QoL). The comments noted improved efficacy and reduced risk of adverse events (AEs) of mepolizumab treatment compared to current treatment options, including recurrent surgeries, antibiotics, and systemic corticosteroids. One comment proposed a potential improvement in existing comorbidities, such as asthma or allergic rhinitis, as a result of treatment, and mentioned the disadvantages of the delivery of mepolizumab (by injection and with recurring appointments with specialists).

6.3 The PBAC noted the advice received from the Australasian Society of Clinical Immunology and Allergy (ASCIA) clarifying the likely use of mepolizumab in clinical practice. The PBAC specifically noted the advice that the use of mepolizumab may

decrease the number of patients requiring NP surgery and may have indirect health-economic benefits by improving the health related quality of life for patients, reducing absenteeism and increasing productivity. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 The resubmission 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 NP surgery and treatment with INCS for at least eight weeks. This was the same clinical trial used to inform the previous submission. However, the clinical claim of the resubmission was based on the SYNAPSE BEC ≥300 cells/µL sub-group whilst the clinical claim of the previous submission was based on the BEC ≥150 cells/µL sub-group. The placebo arm was considered to be a proxy for patients treated with SoC.

6.5 SYNAPSE comprised of a four-week run in period, followed by a 52-week treatment period. Details of the trial presented in the resubmission are provided in Table 3.

Table 3: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SYNAPSE	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).	CSR Dated 23 June 2020
	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.	*Lancet Respir Med* 2021; S2213-2600(21): 00097-7.
	Bachert C, Sousa AR, Han JK, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps: treatment efficacy by comorbidity and blood eosinophil count.	*J Allergy Clin Immunol* 2022; 149: 1711-21).
	Lipworth B, Chan R, Misiroys, R, Stewart K. Mepolizumab response in severe chronic rhinosinusitis with nasal polyps is dissociated from blood eosinophil levels (correspondence).	*J Allergy Clin Immunol*. 2022 May;149(5):1817
	Bachert C, Hellings P, Lund V et al. Improving quality of life and productivity in patients with chronic rhinosinusitis with nasal polyps treated with mepolizumab: SF-36 and WPAI results from SYNAPSE.	*Allergy: European journal of allergy and clinical immunology*:2021, 76 (110) 653-654
	Mullol J, Lund V, Wagenmann M et al. Mepolizumab Induced Loss of Smell Improvement in Patients With Chronic Rhinosinusitis With Nasal Polyps From the SYNAPSE Study.	*Journal of Allergy and Clinical Immunology.* 2022, 149(2): Supplement, Page AB160.

Source: Table 2-5 (p45-7) of the resubmission
Blue shaded cells indicate publications presented in previous submission

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, as stated in the previous submission (paragraph 6.24, mepolizumab PSD, November 2021 PBAC meeting), 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. Strictly speaking, the requested subgroup of BEC ≥300 cells/µL was not a pre-specified subgroup, but rather, the complement to the pre-specified ≤300 cells/µL subgroup. Regardless, no formal hypothesis testing was conducted for any of the subgroups and as such subgroup results should be considered exploratory.

Table 4: Key features of the included evidence

Trial, N	Design / duration / interventions	Risk of bias	Patient population	Main Outcomes	Use in modelled evaluation
SYNAPSE N=407 [a]	Phase 3, R, DB, PC, MC, PG Trial duration of treatment of 48 weeks (sufficient for 52 weeks of treatment). MEPO: 100mg, SC, Q4W vs. PLA: SC, Q4W	Low	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.	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	Co-primary outcomes of ENP and NO-VAS were used to in combination to inform responder status Yes No No Yes

Source: Table 2-6, p49 of the resubmission
a – Intent-to-treat population
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
Blue shaded cells indicate information presented in previous submission

6.7 In SYNPASE, patients could continue treatment with mepolizumab (or placebo) following courses of OCS or NP surgery without needing to discontinue treatment.

6.8 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.

6.9 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. With the exception of the SNOT-22, these secondary outcomes were all used to inform the economic model. SNOT-22 was used to inform the utilities in the economic model in the previous submission, however in the resubmission, utilities were informed by the Short-Form-36 (SF-36) exploratory outcome, which ESC had previously deemed preferable (paragraph 6.44, mepolizumab PSD, November 2021 PBAC meeting).

6.10 The resubmission proposed that the following minimal clinically important differences (MCIDs) for the primary outcomes, which were unchanged from the previous submission:

- Change from baseline in total ENP score: An ENP score responder was defined as a participant who had an improvement (decrease) of ≥1.0 point. The resubmission 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 analysis based on the SNOT-22 and overall symptoms VAS which were sufficiently correlated (r≥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.

6.11 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.

Comparative effectiveness

6.12 The results presented in the resubmission for the ITT population were unchanged. Median change from baseline, and difference in medians, at week 52 in ENP score and during weeks 49-52 in NO-VAS score were presented in the previous submission in the BEC <300 and ≥300 cells/µL subgroups, however the resubmission also presented additional clinical data for these subgroups for the co-primary outcomes, secondary outcomes and exploratory outcomes.

6.13 Table 5 and Table 6 summarises the change from baseline in the co-primary outcomes of ENP score change and NO-VAS score change.

Table 5: Analysis of change from baseline ENP score at week 52

	ITT		Baseline BEC < 300cells/µL		Baseline BEC ≥300cells/µL	
Total Endoscopic Score	**Placebo (N=201)**	**Mepolizumab (N=206)**	**Placebo (N=62)**	**Mepolizumab (N=67)**	**Placebo (N=139)**	**Mepolizumab (N=139)**
Change from Baseline, n (%)						
≥5-point improvement	2 (<1)	6 (3)	1 (2)	3 (4)	1 (<1)	3 (2)
4-point improvement	5 (2)	16 (8)	1 (2)	6 (9)	4 (3)	10 (7)
3-point improvement	11 (5)	23 (11)	3 (5)	7 (10)	8 (6)	16 (12)
2-point improvement	8 (4)	29 (14)	4 (6)	8 (12)	4 (3)	21 (15)
1-point improvement	31 (15)	30 (15)	9 (15)	10 (15)	22 (16)	20 (14)
No change	83 (41)	57 (28)	24 (39)	19 (28)	59 (42)	38 (27)
Worsening	61 (30)	45 (22)	20 (32)	14 (21)	41 (29)	31 (22)
Analysis of change from Baseline						
Median change from baseline	0.0	-1.0	0.0	-1.0	0.0	-1.0
p-value [d]		<0.001				
Adjusted treatment difference						
Difference in medians (95% CI) [e] p-value-		-0.73 (-1.11, -0.34) p<0·0001		-0.80 (-1.44, -0.16) p = NR		-1.00 (-1.50, -0.50) p = NR

Source: Table 2-20 (p76) of the resubmission

a. Participants with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty.

b. Participants with no nasal surgery/sinuplasty who withdrew from study prior to visit were assigned their worst observed score prior to study withdrawal.

c. Participants with missing visit data were assigned their worst observed score prior to the missing visit.

d. Based on Wilcoxon rank-sum test.

e. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

BEC = blood eosinophil count; CI = confidence interval; ENP = endoscopic nasal polyp

Blue shaded cells indicate information presented in previous submission

Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 6: Analysis of change from baseline NO-VAS score during weeks 49-52

	ITT		Baseline BEC < 300cells/µL		Baseline BEC ≥300cells/µL	
Nasal Obstruction VAS Score	**Placebo (N=201)**	**Mepolizumab (N=206)**	**Placebo (N=62)**	**Mepolizumab (N=67)**	**Placebo (N=139)**	**Mepolizumab (N=139)**
Change from Baseline, n (%)						
>5-point improvement	46 (23)	91 (44)	19 (31)	29 (43)	27 (19)	62 (45)
>3 to 5-point improvement	27 (13)	33 (16)	9 (15)	13 (19)	18 (13)	20 (14)
>1 to 3-point improvement	27 (13)	22 (11)	10 (16)	5 (7)	17 (12)	17 (12)
≤1-point improvement to ≤1-point worsening	95 (47)	57 (28)	21 (34)	20 (30)	74 (53)	37 (27)
>1-point worsening	6 (3)	3 (1)	3 (5)	0	3 (2)	3 (2)
Analysis of change from Baseline						
Median change from baseline	-0.82	-4.41	-1.93	-4.32	-0.33	-4.41
p-value [d]		<0.001		NR		NR
Adjusted treatment difference						
Difference in medians (95% CI) [e] p-value		-3.14 (-4.09, -2.18) p<0·0001		-2.10 (-4.12, -0.07) NR		-3.71 -4.79, -2.62 NR

Source: Table 2-23 (p73) of the resubmission

a. Participants with nasal surgery/sinuplasty prior to time period were assigned their worst observed score prior to nasal surgery/sinuplasty.

b. Participants with no nasal surgery/sinuplasty who withdrew from study prior to time period were assigned their worst observed score prior to study withdrawal.

c. Participants with missing time period data were assigned their worst observed score prior to the missing time period.

d. Based on Wilcoxon rank-sum test.

e. (ITT) Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.(BEC); Quantile regression with covariates of treatment group, geographic region and baseline score.

BEC = blood eosinophil count; CI = confidence interval; nasal obstruction visual analogue scale; SD = standard deviation; NO-VAS = nasal obstruction visual analogue score

Blue shaded cells indicate information presented in previous submission

Note that the results presented in Table 6 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.14 In the BEC ≥300 cells/µL subgroup a greater proportion of patients in the mepolizumab group than the placebo group demonstrated a ≥1-point improvement in ENP score (50% (70/139) compared with 28% (39/139), respectively). The unadjusted difference in median change in ENP score at week 52 between patients randomised to mepolizumab and SoC in the BEC ≥300 cells/µL subgroup was -1.0 and therefore met the MCID. The resubmission reasonably considered the odds of being a responder in the mepolizumab arm of the BEC ≥300 subgroup (OR 2.82; 95% CI 1.69, 4.70) was consistent with the ITT population which demonstrated statistical significance. However, as subgroup results were not formally tested, no p-values were reported for any differences in the subgroups and all results may be considered exploratory. Comparatively, while the unadjusted difference in median change in ENP score at week 52 between patients randomised to mepolizumab and SoC in the BEC <300 cells/µL subgroup was -1.0 and therefore met the MCID, the adjusted difference

of -0.80 (95%CI -1.44, 0.16) would not have met the MCID, which may support the decision to restrict use of mepolizumab in patients with BEC ≥300 cells/µL only[1].

6.15 In the BEC ≥300 cells/µL subgroup, 59% (82/139) and 32% (45/139) of mepolizumab and SoC patients respectively demonstrated a >3-point improvement from baseline (decrease) in their NO-VAS score, which was consistent with the ITT results. The absolute median change from baseline during weeks 49-52 NO-VAS score in the BEC ≥300 cells/µL subgroup and randomised to mepolizumab was also -4.41, and the point estimate for the adjusted median difference between treatment arms was -3.71 (95% CI -4.79, -2.62), which met the specified MCID and was consistent with the ITT population, though no subgroup results from SYNAPSE were formally tested and should be considered exploratory. Comparatively, the adjusted median difference between treatment arms in the BEC <300 cells/µL subgroup was -2.10 (95% CI -4.12, -0.07), which did not meet the nominated MCID, which may further support the requested restriction of limiting mepolizumab use to patients with a baseline of BEC ≥300 cells/µL only[2].

6.16 Table 7 summarises the results for response defined as ENP score change ≥1 OR NO-VAS score change ≥3 for the ITT and BEC subgroups in SYNAPSE. This definition of response aligned with the requested restrictions and data from the BEC ≥300 cells/µL sub-group was used to inform the economic model.

[1] *Note that the results presented in paragraph 6.14 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

[2] *Note that the results presented in paragraph 6.15 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

Table 7: Summary of ENP and/or NO-VAS responders in SYNAPSE (ITT and subgroups)

	ITT		BEC ≥ 150 cells/µL		BEC ≥ 300 cells/µL	
	Mepolizumab (N=206)	**Placebo (N=201)**	**Mepolizumab (N=186)**	**Placebo (N=185)**	**Mepolizumab (N=139)**	**Placebo (N=139)**
Total responder at Week 24, n (%)	144 (70)	95 (47)	129 (69.4)	86 (46.5)	101 (72.7)	66 (47.5)
Responders at Week 52						
ENP only, n (%)	22 (11)	22 (11)	NE	NE	19 (13.7)	21 (15.1)
NO-VAS only, n (%) [a]	42 (20)	38 (19)	NE	NE	31 (22.3)	27 (19.4)
Both responder, n (%)	82 (40)	35 (17)	NE	NE	51 (36.7)	18 (12.9)
Total responder, n (%)	146 (71)	95 (47)	NE	NE	101 (72.7)	66 (47.5)
Maintained response from Week 24, n/N (%)	125/144 (87)	65/95 (68)	112/129 (86.8)	58/86 (67.4)	86/101 (85.1)	44/66 (66.7)

Source: Calculated during evaluation using information from Table 2-22 (p72), Table 2-23 (p73) and 'variables' sheet economic model spreadsheet of resubmission, Table 2.5.7, 6.03.COM.74 November 2021 and Table 2.6.3, 6.03.COM.83 November 2021
ENP= endoscopic nasal polyp; NO-VAS= nasal obstruction visual analogue scale; n= number of participants with event; N= total participants in group, NE = not estimable
a. assume responder is number of patients with >3 point improvement as number of patients with ≥3 point improvement not reported
Blue shaded cells indicate information presented in previous submission
Note that the results presented in Table 7 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.17 The proportion of patients who were responders at week 24, and those who maintained response at week 52 from week 24, was higher in mepolizumab arm patients compared to patients treated with placebo, with a similar magnitude of difference across the ITT, BEC ≥150 cells/µL and BEC ≥300 cells/ µL populations.

6.18 Table 8 summarises the time to first nasal surgery. The percentage of patients with surgery at Week 24 was used in the economic model.

Table 8: Analysis of time to first nasal surgery

	ITT		Baseline BEC < 300cells/µL		Baseline BEC ≥300cells/µL	
	Placebo (N=201)	Mepolizumab (N=206)	Placebo (N=62)	Mepolizumab (N=67)	Placebo (N=139)	Mepolizumab (N=139)
Probability of surgery by Week 24, % (95% CI) [a]	9.1 (5.8, 14.0)	4.0 (2.0, 7.8)	8.1 (3.4, 18.3)	6.2 (2.4, 15.6)	9.5 (5.6, 15.8)	2.9 (1.1, 7.7)
Probability of surgery by Week 52, % (95% CI) [a]	23.6 (18.3, 30.3)	9.2 (5.9, 14.2)	17.8 (10.3, 29.8)	12.5 (6.5, 23.5)	26.4 (19.7, 34.8)	7.6 (4.1, 13.6)
Time to First Nasal Surgery						
Nasal surgery prior to Week 52, n (%)	46 (23)	18 (9)	11 (18)	8 (12)	35 (25)	10 (7)
No surgery prior to Week 52, n (%)	155 (77)	188 (91)	51 (82)	59 (88)	104 (75)	129 (93)
Hazard ratio (Mepolizumab/Placebo) (95% CI) [b]		0.43 (0.25, 0.76)		0.83 (0.33, 2.09)		0.31 (0.15, 0.64)
p-value		0.003		NR		NR

Source: Table 2-28 (p80-1) of the resubmission

a. Kaplan-Meier estimate.

b. 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).

Note: Includes data reported up to Week 52.

BEC = blood eosinophil count; CI = confidence interval

Blue shaded cells indicate information presented in previous submission

Note that the results presented in Table 8 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.19 The BEC ≥300 cells/µL subgroup results (hazard ratio: 0.31; 95% CI 0.15, 0.64) for time to first surgery were consistent with the ITT population, but the results were not statistically significant (i.e. 95% CI includes 1.00) in the complement subgroup of BEC <300 cells/µL (hazard ratio: 0.83, 0.33, 2.09).

6.20 A higher proportion of placebo arm patients (58/139, 42%) required ≥1 course of systemic steroids up to week 52 than mepolizumab arm patients (37/139, 27%) in the BEC ≥300 cells/µL sub-group (Odds Ratio to placebo: 0.49; 95% CI 0.28-0.86). These results showed a consistency between the ITT population and BEC ≥300 cells/µL subgroup, and ultimately supported the results of the ENP and NO-VAS. An annualised rate of systemic steroids use by responder status was used to inform the economic model.

6.21 The resubmission also reported results for the overall-VAS, change in SNOT-22 score and change in loss of smell VAS score for the ITT population, the BEC ≥300 cells/µL subgroup and, other than for the SNOT-22, the BEC <300 cells/µL subgroup. These results showed a consistency between the ITT population and BEC ≥300 cells/µL subgroup, and ultimately supported the results of the ENP and NO-VAS.

6.22 Table 9 presents the results of SF-36 mean score change in the BEC ≥300 cells/µL subgroup.

Table 9: Summary of SF-36 mean score changes at Week 52 in the BEC ≥300 subgroup

	LS mean (SE) change from baseline at Week 52			
	Placebo (n=136)	Mepolizumab (n=139)	Difference (Mepo - Placebo) (95% CI)	p-value
SF-36 domains (0–100)				
Physical functioning	2.17 (0.58)	5.99 (0.575)	3.82 (2.21, 5.43)	<0.001
Role limitation due to physical health	1.66 (0.669)	6.36 (0.662)	4.70 (2.85, 6.56)	<0.001
Bodily pain	1.50 (0.803)	5.96 (0.794)	4.46 (2.23, 6.68)	<0.001
General health	-0.07 (0.664)	5.74 (0.657)	5.81 (3.98, 7.65)	<0.001
Energy/fatigue (vitality)	1.42 (0.778)	6.82 (0.769)	5.40 (3.24, 7.56)	<0.001
Social functioning	0.73 (0.761)	5.38 (0.753)	4.64 (2.54, 6.75)	<0.001
Role limitation due to emotional problems	1.20 (0.798)	4.26 (0.789)	3.06 (0.85, 5.27)	0.007
Mental health (emotional well-being)	0.80 (0.788)	4.18 (0.779)	3.38 (1.20, 5.57)	0.003
SF-36 physical component summary	1.61 (0.58)	6.54 (0.57)	4.93 (3.32, 6.53)	<0.001
SF-36 mental component summary	0.71 (0.82)	4.22 (0.81)	3.51 (1.25, 5.77)	0.002

Source: Table 2-34 (p88) of the resubmission

Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, log(e) baseline blood eosinophil count, visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions. Subjects with nasal surgery/sinuplasty prior to visit, subjects who withdrew from study with no surgery/sinuplasty and subjects with missing visit data are assigned their worst observed score prior to nasal surgery/sinuplasty or study withdrawal or missing visit respectively.

Note: 3 Placebo subjects with missing baseline score are excluded from the analysis.

LS = least squares; SE = standard error; SF-36 = 36 item short-form survey

Note that the results presented in Table 9 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.23 Overall, patients with baseline BEC ≥300 cells/µL randomised to mepolizumab reported statistically significantly higher quality of life as measured using the SF-36 compared to patients randomised to placebo. The mean changes from baseline at week 52 for the SF-36 mental and physical component summary scores appeared consistent with the ITT population results presented in previous submission. In the ITT population, 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 ITT 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) (paragraph 6.20, mepolizumab PSD November 2021 PBAC meeting). SF-36 data for the BEC ≥300 cells/µL subgroup was converted to utility values using the Short-Form Six-Dimensions (SF-6D) and applied in the economic model.

Comparative harms

6.24 Table 10 presents a summary of adverse events (AEs) in the BEC ≥300 cells/µL and BEC <300 cells/µL subgroups in SYNAPSE. The safety data for these subgroups appeared consistent with the AE data for the SYNAPSE safety population presented in the previous submission and indicated that mepolizumab patients had comparable AEs compared to placebo patients.

Table 10: Adverse event overview and common AEs in BEC subgroups of SYNAPSE

	Baseline blood eosinophil count (cells/μL)					
	<300			≥300		
	Placebo (n=62)	Mepolizumab (n=67)	RD (95% CI)	Placebo (n=139)	Mepolizumab (n=139)	RD (95% CI)
Any AE, n (%) *	52 (83.9)	58 (86.6)	0.027 (-0.10, 0.17)	118 (84.9)	111 (79.9)	-0.05 (-0.14, 0.04)
AE related to study treatment, n (%)	2 (3.2)	7 (10.4)	0.072 (-0.02,0.17)	17 (12.2)	23 (16.5)	0.043 (-0.04, 0.13)
Any SAE, n (%) *	3 (4.8)	6 (9.0)	0.041 (-0.06, 0.14)	11 (7.9)	6 (4.3)	-0.036 (-0.10, 0.02)
Most common AE occurring in >10% of patients, n (%)						
Nasopharyngitis	13 (21.0)	15 (22.4)	0.014 (-0.13, 0.15)	33 (23.7)	37 (26.6)	0.029 (-0.07, 0.13)
Headache	12 (19.4)	10 (14.9)	-0.044 (-0.18, 0.09)	32 (23.0)	27 (19.4)	-0.036 (-0.13, 0.06)
Sinusitis	7 (11.3)	6 (9.0)	-0.023 (-0.14, 0.09)	15 (10.8)	4 (2.9)	-0.079 (-0.15, -0.02)
Acute sinusitis	5 (8.1)	7 (10.4)	0.024 (-0.09, 0.13)	8 (5.8)	6 (4.3)	-0.014 (-0.07, 0.04)
Epistaxis	5 (8.1)	8 (11.9)	0.039 (-0.07, 0.15)	13 (9.4)	9 (6.5)	-0.029 (-0.10, 0.04)
Nasal polyps	4 (6.5)	2 (3.0)	0.035 (-0.13, 0.05)	12 (8.6)	6 (4.3)	-0.043 (-0.11, 0.02)
Chronic sinusitis	2 (3.2)	1 (1.5)	-0.017 (-0.10, 0.05)	0 (0)	0 (0)	0.0 (-0.03, 0.03)
Upper respiratory tract infection	4 (6.5)	3 (4.5)	0.020 (-0.12, 0.07)	10 (7.2)	9 (6.5)	-0.007 (-0.07, 0.06)

Source: Table 2-49 (p108-9) of the resubmission.
*Includes data up to Week 52.
Note: The risk differences were analysed during the evaluation using statsdirect. Positive values refer to a higher risk in the mepolizumab arm
AE = adverse event; CI = confidence interval; RD = risk difference; SAE = serious adverse event.

6.25 Drug-related AEs were comparable across treatment arms but 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, though the PBAC noted that injection site reactions were not significant in either arm of the SYNAPSE trial and that a claim of non-inferior safety was reasonable (paragraph 7.6, mepolizumab PSD, November 2021 PBAC meeting).

Benefits/harms

6.26 A summary of comparative benefits for mepolizumab versus placebo is presented in Table 11 below.

Table 11: Summary of comparative benefits for mepolizumab versus placebo (BEC ≥300 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 [a]	86/139	44/139	NR	61.9	31.7	30.2 (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	139	0.0	NR	139	-1.0	NR	-1.00 (-1.50, -0.50)
NO-VAS	139	-4.41	NR	139	-0.33	NR	-3.71 (-4.79, -2.62)

Source: Table 2-23 (p73) of the resubmission; Table 2-20 (p76) of the resubmission; Cells D12:E12, 'Calculations' sheet, Large Files – GSK-Nucala-Resubmission-Final.xlsm

a – Estimated as proportion of patients who maintained response at week 52 after responding at week 24 in the BEC ≥300 cells/µL subgroup

ENP = Endoscopic Nasal Polyp score; NO-VAS = Nasal Obstruction Visual Analogue Scale; RD = risk difference; SoC = standard of care

Note that the results presented in Table 11 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.27 On the basis of direct evidence presented by the submission, for every 100 patients in with BEC ≥300 cells/µL treated with mepolizumab in comparison to placebo and over a treatment duration of 52 weeks:

- approximately 30 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 for BEC ≥300 cells/µL patients resulted in:

- approximately a 1.00-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 3.71-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.

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

Clinical claim

6.29 The resubmission described mepolizumab as superior in terms of effectiveness compared with SoC in patients with a baseline BEC ≥300 cells/µL (or BEC ≥150 cells/µL if they have had OCS in the previous 12 months). This was based on the consideration that the BEC ≥300 cells/µL subgroup results demonstrated treatment differences that were clinically meaningful to patients, including the secondary outcome of time to NP surgery. The resubmission further justified the claim by stating in the BEC ≥300 cells/µL subgroup ENP median score change from baseline at week 52 in mepolizumab patients was -1.0 compared to 0.0 for placebo and the median NO-VAS

score change in the weeks 49-52 period was -4.41 in mepolizumab compared to -0.33 in placebo (in excess of the nominated MCID of ≥3).

6.30 The resubmission also stated the ITT population demonstrated clinically meaningful and statistically significant changes in the secondary endpoints of HRQoL (as measured by the SNOT-22) and systemic steroid use as well as in the exploratory analysis of the SF-36. The BEC ≥300 cells/µL subgroup were consistent with the ITT population for these outcomes.

6.31 In November 2021, the PBAC accepted the claim of clinical superiority of mepolizumab in the BEC ≥300 subgroup based on SYNAPSE trial evidence in the previous submission (paragraph 7.5, mepolizumab PSD, November 2021 PBAC meeting). However, results for the BEC ≥300 cells/µL subgroup were not formally statistically tested and therefore results should be considered exploratory, with no tests for subgroup interactions conducted to show that BEC ≥300 cells/µL was a treatment effect modifier.

6.32 Clinical evidence was not presented in the resubmission for patients:

- who had a BEC ≥150 but <300 cells/µL while receiving treatment with OCS in the last 12 months;
- who were contraindicated to INCS and/or NP surgery; and
- who had previously discontinued mepolizumab but reinitiated mepolizumab treatment after a 12-month break.

However these subsets of patients were all included in the requested restrictions, and as such the effectiveness of mepolizumab in these patients was unknown. The PSCR noted the proposed restriction would require patients to be on OCS treatment at the time of registering a BEC between ≥150 cells/µL and <300 cells/µL if they were to meet eligibility via this criterion.

6.33 The submission described mepolizumab as comparable in terms of safety compared to SoC. This claim was likely reasonable, and the PBAC has previously accepted that a claim of non-inferior safety was reasonable (paragraph 7.6, mepolizumab PSD, November 2021 PBAC meeting).

6.34 The PBAC considered that the claim of superior comparative effectiveness was reasonable compared with SoC in patients with a baseline BEC ≥300 cells/µL.

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

Economic analysis

6.36 The resubmission 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 value expected analysis. The economic model presented remained structurally the same as the previous submission but differed based on certain key inputs (time-horizon; maintenance of response; source of utility values;

assumptions regarding utility values for responders and 'effective surgery' patients after week 52; and numerous unit costs). Additionally, the economic model in the resubmission was largely informed by the BEC ≥300 cells/µL subgroup from SYNAPSE, compared to the BEC ≥150 cells/µL subgroup in the previous submission. Despite this, the transition probabilities in the model of the resubmission were relatively similar to the corresponding transition probabilities in the previous model (with the exception of loss of response). A trial-based cost per responder analysis based on the results of SYNAPSE was also conducted during the evaluation.

6.37 There were several translational issues which were not considered nor adjusted for by the resubmission that could affect the cost effectiveness of mepolizumab in the proposed PBS population. As discussed in paragraph 6.32, even though the requested restriction allowed access for patients who had a BEC ≥150 cells/µL but <300 cells/µL if they were treated with OCS in the last 12 months; who were deemed unsuitable for surgery; who were contraindicated or intolerant to INCS; and patients who had previously discontinued mepolizumab treatment, no clinical evidence was presented to inform the efficacy of mepolizumab in these patients and no consideration of these subgroups were made in the resubmission's economic evaluation. Additionally, the proportion of patients with co-morbid 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 (paragraph 6.39, mepolizumab PSD, November 2021 PBAC meeting).

6.38 Table 12 presents a summary of the model structure used in the economic evaluation presented in the resubmission

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Time horizon	5 years in the model base-case (vs 1 year in the key SYNAPSE trial)
Outcomes	LYs, QALYs, number of surgeries, weeks waiting for surgery, number of asthma exacerbations.
Methods used to generate results	Markov model incorporating a cohort expected value analysis
Health states	6 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
Transition probabilities	0-52 weeks: SYNAPSE clinical trial, response measured at week 24 and week 52. After-52 weeks: extrapolation of SYNAPSE trial data where maintenance of response was informed by the inverse of the loss of response between week 24 and week 52 in SYNAPSE independently for each treatment arm.
Extrapolation method	Loss of response per-arm between week 24 and week 52 in SYNAPSE converted to annual loss of response rates and applied from week 52 onwards.
Health related quality of life	SF-36 SYNAPSE data converted to SF-6D utility data using an Australian value set. Previous submission was based on SNOT-22 results. Baseline – 0.564 (previous submission: 0.534) Responder (week 52+) / Effective Surgery: 0.785 (previous submission: SoC: 0.704, mepolizumab: 0.742) Non-responder (week 52+): 0.551 (previous submission: 0.566)

Source: Table 3-2 (p128) of the resubmission
Note - underlined text refers to differences from the previous submission
LY = life years; QALYs = quality-adjusted life years

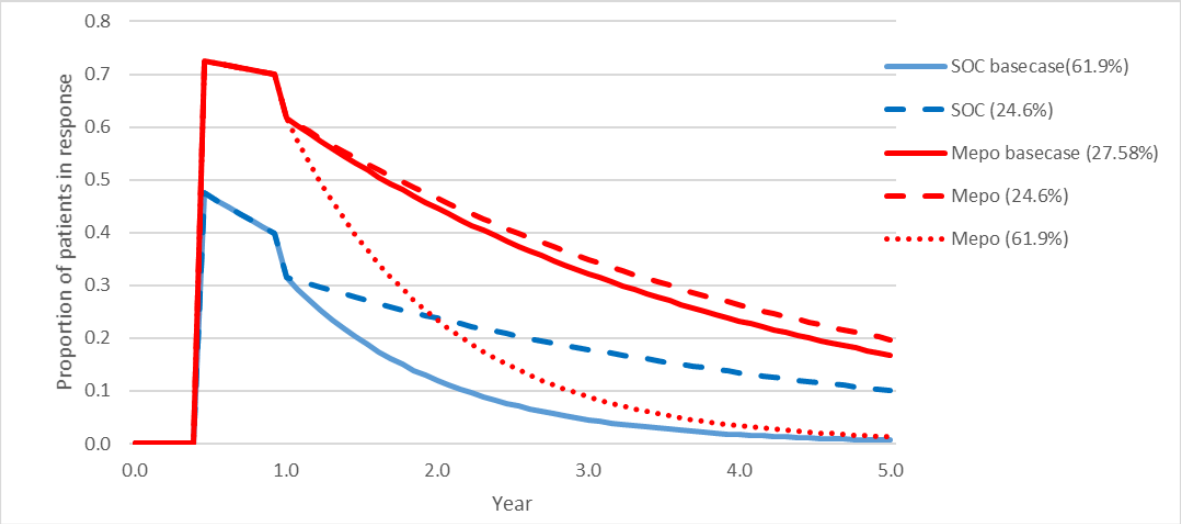
6.39 Different to the previous submission, at week 52 in the resubmission's economic model, a proportion of patients who were responders were assumed to experience a loss of response based on the rate at which responders became non-responders between week 24 to week 52 in SYNAPSE. In the previous submission, no loss of response was assumed after week 52. The PBAC previously considered that an assumption of no loss of response was inappropriate given the reduction observed in SYNAPSE (paragraph 7.7, mepolizumab PSD, November 2021 PBAC meeting). ESC considered a 24.6% loss of response should be applied to both arms, whereby 24.6% was derived from the proportion of mepolizumab BEC ≥150 cells/µL responders at Week 24 who maintained their response at Week 52 (paragraph 6.54, mepolizumab PSD, November 2021 PBAC meeting).

6.40 The resultant annual loss of response rates applied in the resubmission were 27.6% to mepolizumab patients and 61.9% to SoC patients. The mepolizumab arm value of 27.6% differed from the 24.6% value noted as being appropriate by ESC in the previous submission due to a change in requested population to patients with BEC ≥300 cells/µL. It may have been inappropriate to have assumed these transitions were different between treatment arms. The resubmission's approach favoured mepolizumab as an analysis that assumes no loss of response led to an increase of

ICER by 30%. One-way sensitivity analyses applying the mepolizumab annual loss of response (27.6%) and the SoC loss of response (61.9%) to both arms increased the ICER by 71% and 222% respectively. These variables, and the differential between maintenance of response rates between arms, are key model drivers. The PSCR stated the observation of differential loss of response seen in SYNAPSE was plausible as one treatment arm had an active treatment and argued that its application in the base-case resulted in similar loss of response gradients (see Figure 1). The PSCR considered that the additional analysis conducted during the evaluation whereby loss of response rate for SoC were applied to mepolizumab patients resulted in an implausible proportion of responders at the end of Year 2 (approximately 25%) (see Figure 1). The PSCR further considered that applying the same loss of response rates in each arm resulted in an accelerated loss of response in the mepolizumab treated patients compared to SoC as it has an exponential impact on response rates. The ESC questioned whether the almost 100% loss of response by Year 4 in the SOC arm of the base-case was clinically appropriate. The ESC recalled that in November 2021 the PBAC considered the application of a 24.6% loss of response applied to both arms was appropriate as part of a re-specified base-case to address the concerns identified with the economic model (paragraph 7.7, mepolizumab PSD, November 2021 PBAC meeting). The ESC considered that the application of a 27.6% loss of response rate applied to both arms was consistent with the November 2021 PBAC recommendations in the revised BEC ≥300 cells/µL population. The pre-PBAC response stated that as part of the SYNAPSE trial follow-on, 134 patients receiving either mepolizumab or SoC were followed between week 52 and 76, while off treatment. At week 76, a loss of response was seen in 5 of 23 SoC patients (with a BEC ≥300 cells/µL at baseline) who were responders at week 52. This is a loss of response of 21.7% over 24 weeks or 47.1% annually. The pre-PBAC response proposed a 47.1% annual loss of response for the SoC arm claiming it was supported by the analysis of response post week 52 and has greater plausibility than using the same loss as response as mepolizumab (Figure 2)[3].

[3] *Note that the results presented in paragraph 6.40 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for SYNAPSE. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

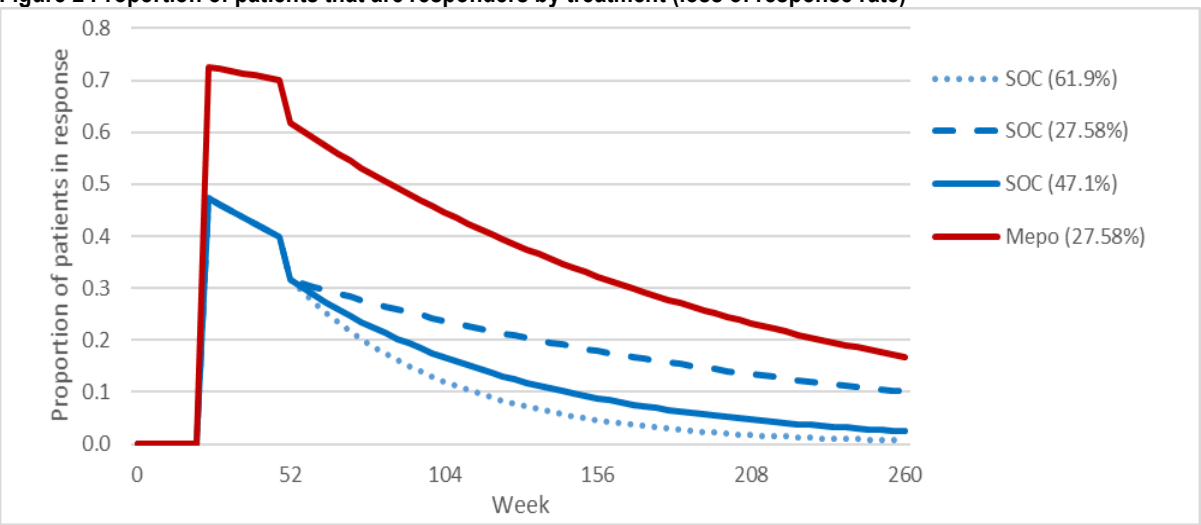
Figure 1 Proportion of patients that are responders by treatment (loss of response rate)



Source: Figure 1, p3, of the PSCR

Note that the plots depicted in Figure 1 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Figure 2 Proportion of patients that are responders by treatment (loss of response rate)



Source: Figure 1, p2, of the pre-PBAC response

Note that the plots depicted in Figure 2 are presented specifically for the purposes of informing the PBAC consideration. Their interpretation and application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.41 After week 52 in the model, a proportion of responders (in both treatment arms) transitioned to non-responders at the end of every four-week cycle, with mepolizumab non-responders in the model assumed to discontinue treatment immediately, accruing no costs of treatment. However, the ESC agreed with the evaluation that in practice, patients who experience loss of response in between assessments (which was expected to occur every 24 weeks based on the number of requested repeats in the proposed elements), would likely continue treatment until their next assessment and as such, usage of mepolizumab in patients in the

mepolizumab arm of the model who transition from responder to non-responder may be underestimated. An evaluator-conducted scenario analysis that assumed mepolizumab responder patients who transitioned to an off-treatment (but alive) health state after week 52 would receive an additional 12 weeks of treatment (i.e., half of the 24 weeks of total treatment per prescription, for an additional $) instead of discontinuing immediately increased the ICER by 5.9%. The pre-PBAC response considered that this change to the model was appropriate.

6.42 Within each treatment arm, different utility values were applied at different time points in the first 52 weeks of treatment in the model. This was an unjustified and unnecessarily complex approach. The utility change-from-baseline (CFB) in the SoC arm for 'in trial' and 'responder patients' all have overlapping 95% CIs during the first 52 weeks, which further suggests this approach was unjustified. The approach of applying different utility values over different time points in the first 52 weeks of treatment was also used in the previous submission and was considered to be potentially unjustified and unnecessarily complicated (paragraph 6.40, mepolizumab PSD, November 2021 PBAC meeting).

6.43 Additionally, differential utilities between the treatment arms were applied in the model up to week 48. This may not be supported as the 95% confidence intervals in the observed differences between mepolizumab and SoC between weeks 4-20 all included 0, indicating that there was no difference between treatment arms. The assumption of differential utilities for responders between arms between weeks 24-48 was also inconsistent with the approach from week 52 onwards which assumed that all responders had the same utility, irrespective of treatment. A multi-variate sensitivity analysis conducted during the evaluation using more conservative assumptions by applying the mean baseline utility in both arms until week 24 and applying the SoC responder utilities between weeks 24-48 to responders in both arms, increased the ICER by 14.2%. The PSCR disagreed that the application of differential utility values between arms between weeks 0-24 was inappropriate based on the justification that setting the utility values to be the same across the treatment arms from weeks 4-24 implies that the quality of life benefit of treatment only manifest after week 24. The PSCR further justified this view by stating mepolizumab patients in SYNAPSE maintained greater improvements than SoC patients over 52 weeks in SF36 physical function and mental summary scores, ENP score, NO-VAS score, loss of smell VAS score and SNOT-22 score. The ESC considered that applying the mean baseline utility in both arms until week 24 was likely too conservative as there will be some differences due to response rates. However, the ESC considered that it may be appropriate to apply the same responder and non-responder utility values to both arms post 24 weeks.

6.44 Compared to the previous submission, the utility values estimated and applied in the resubmission were systematically higher for all 'in trial' and all 'responder' health states, regardless of time point and treatment arm. However, the opposite was true for all non-responder health states (except 'non-responder' at week 24) whereby

utility values applied in the resubmission were systematically lower than the 'non-responder' utility values applied for the corresponding time points in the previous submission's model. This difference favours the mepolizumab arm given mepolizumab has a higher rate of response than SoC. The cause for this difference was unclear and could be due to one (or both) of the use of different HRQoL measure (SNOT-22 or SF-36) or because of the difference in BEC subgroup and may represent an important source of uncertainty in the model.

6.45 The cost of NP surgery may have been overestimated in the previous submission (paragraph 6.47, mepolizumab PSD, November 2021 PBAC meeting). In the resubmission, a different separation-weighted AR-DRG cost of surgery based on DRG D06Z (55%) and D10Z (45%) was used to estimate the cost of NP surgery. This revised weighting reduced the unit cost to $8,453.32 in the resubmission (from $9,600.43 previously). The ESC considered this unit cost remained a source of uncertainty in the economic model. The resubmission's economic model estimated that there will be 0.213 fewer NP surgeries in the mepolizumab arm (0.281 surgery count, undiscounted) than in the SoC arm (0.494 surgery count, undiscounted), therefore any overestimate of the cost of NP surgery would favour mepolizumab. The ESC advised that there were unfortunately long wait times for NP surgery in the public hospital setting. The ESC noted the resubmission assumed a wait time of 52 weeks for NP surgery, however the ESC considered a minimum of 3 years to be more reflective of the current situation in the public hospital setting. The ESC noted that increasing the surgery wait time from 52 weeks to 3 years for the public hospital setting had a minimal impact on the ICER.

6.46 The resubmission claimed that a compliance rate of 94.56% was applied to mepolizumab dosage costs to align with the compliance rate applied in the financial estimates. However, this rate did not appear to have been applied in the base-case analysis. The application of this rate decreased the ICER by 6.3%. The pre-PBAC response agreed with the evaluation that this rate should have been applied in the resubmission base-case and suggested it would be appropriate to include as part of the base-case re-specification.

6.47 Table 13 summarises the key drivers of the model.

Table 13: Key drivers of the model

Description	Method/Value	Impact
Differential loss of response	Annual loss of response = 61.9% mepolizumab; 27.6% SoC	High, favours mepolizumab. Using SoC rate in both arms increases ICER by 222%. Assuming no loss of response in either arm increased ICER by 30.1%.
Differential utility values during weeks 4-48	Between weeks 4 and 24 utility values based on total arm values, between weeks 28-42 utility values for responder applied based on values observed per arm in SYNAPSE	Moderate, favours mepolizumab. Applying mean baseline utility equally between arms in week 4-24 and applying SoC arm responder utility to responders in both arms between weeks 28-42 increased the ICER by 14.2%.
SoC non-responder utility week 52+ [a]	Change from baseline in utility: -0.013 (resultant utility value applied: 0.551)	Moderate, favours mepolizumab given the base-case value is lower than baseline utility. Using the 95% confidence intervals (upper 0.645, lower 0.457) changed the ICER by -15.3% and +22.0%, respectively
Responder / effective surgery utility week 52+ [b]	Change from baseline in utility: 0.221 (resultant utility value applied: 0.785)	Moderate, favours mepolizumab given ESC requested the use of the lower SoC responder utility value. Using the 95% confidence intervals (upper0.836, lower 0.734) changed the ICER by +19.4% and -14.0% respectively

Source: Compiled during the evaluation from Section 3 of the resubmission.

a. This was applied to non-responders in either arm after week 52, but was derived from the SoC arm in SYNAPSE

b. This was applied to patients in these health states in either arm after week 52

6.48 Table 14 summarises the results of the economic evaluation presented in the resubmission. A cost per responder analysis for the within trial period (52 weeks) was conducted during the evaluation. The pre-PBAC response provided a re-specified base case incorporating: (1) a revised mepolizumab price ($), (2) differential loss of response (mepolizumab 27.6%, SoC 47.1%), (3) 50% of 24 week mepolizumab cost allocated for mepolizumab week 52+ non-responders, (4) application of 94.56% compliance for mepolizumab.

Table 14: Results of the economic evaluation

Step and component	Mepolizumab	Standard of care	Increment
Trial-based (52 weeks) costs and outcomes (responders)			
Costs [a] ($)	[redacted]	$1,820	[redacted]
Response rate	0.617	0.316	0.301
Incremental cost/extra responder gained ($)			[redacted][1]
Time horizon extended to 5 years (QALYs)			
Costs ($)	[redacted]	$5,252	[redacted]
LYs	4.436	4.436	0.000
QALYs	2.957	2.778	0.179
Incremental cost/extra QALYs gained (base-case) ($)			[redacted][2]
Pre-PBAC response re-specified base-case			
Costs ($)	[redacted]	$5,154	[redacted]
LYs	4.436	4.436	0.000
QALYs	2.957	2.803	0.154
Incremental cost/extra QALYs gained (revised base-case) ($)			[redacted][2]
Previous submission (November 2021, 30-year time horizon)			
Costs ($)	[redacted]	$9,714	[redacted]
QALYs	9.692	8.876	0.905
Incremental cost/extra QALYs gained (base-case) ($)			[redacted][2]

Source: Table 3-28, p180 of the submission, Table 3, p3 pre-PBAC response
a. includes all costs accrued up to 52 weeks as estimated by the economic model
LY = life year; QALY= quality-adjusted life year
Blue shaded cells indicate values previously considered by PBAC
The redacted values correspond to the following ranges:
[1] *$5,000 to < $15,000/QALY*
[2] *$55,000 to < $75,000/QALY*

6.49 The largest contribution to the incremental cost in the model was drug acquisition costs (116% of total incremental cost). Surgery had a larger contribution to the incremental cost (-15.6%) than in the previous submission (-6.4%). This was expected given no loss of response after 52 weeks was applied in the previous submission, and only patients who were non-responders could have surgery after 52 weeks. Overall, the base-case ICER decreased by $5,000 to < $10,000 per QALY from the previous submission.

6.50 The results of key univariate and multivariate sensitivity analyses are summarised in Table 15.

Table 15: Results of sensitivity analyses

Variable	Base-case	Scenario	Increment cost ($)	Increment QALY	ICER $/QALY	% change
Base-case			[redacted]	**0.179**	[redacted][1]	**-**
Univariate analyses						
Application of mepolizumab costs after week 52 to 'responders'	Patients able to transition out of 'responder' HS in any cycle and no longer receive mepolizumab costs	The 43.6% of responders who transitioned out of 'response' (but remained alive) receive an additional 50% of mepolizumab costs for a 24-week treatment block ($1,398.21) [a]	[redacted]	0.179	[redacted][1]	+5.9%
Response rate at week 24	Mep - 72.7%	68.9% (lower 95%CI)	[redacted]	0.164	[redacted][1]	+4.9%
		76.4%(upper 95%CI)	[redacted]	0.194	[redacted][1]	-4.1%
	SoC - 47.5%	43.2% (lower 95%CI)	[redacted]	0.187	[redacted][1]	-4.8%
		51.7% (upper 95%CI)	[redacted]	0.170	[redacted][1]	+5.3%
Loss of response after 52 weeks	Mep – 27.6% SoC – 61.9%	Mep – 31.6% [b] SoC – 61.9%	[redacted]	0.157	[redacted][1]	+8%
		Use Mep rate (27.6%) in both arms	[redacted]	0.11	[redacted][2]	+70.7%
		Use SoC rate (61.9%) in both arms	[redacted]	0.04	[redacted][3]	+222%
		No loss of response	[redacted]	0.21	[redacted][5]	+30.1%
Utility	Utility value for non-responder at week 52 onwards = 0.551	Baseline utility value (0.564) applied instead	[redacted]	0.174	[redacted][1]	+2.5%
	Mean of responder utility in both arms (0.785) used to inform both arms of 'responders' after week 52, and 'effective surgery'	SoC responder utility (0.780) used	[redacted]	0.176	[redacted][1]	+1.6%
	SoC CFB utility non-responder week 52+ : -0.013	Lower 95% CI: -0.107	NR	NR	[redacted][4]	-15.3%
		Upper 95% CI: 0.081	NR	NR	[redacted][1]	+22.0%
	Responder / effective surgery CFB utility week 52+ [c] : 0.221	Lower 95% CI: -0.170	NR	NR	[redacted][1]	+19.4%
		Upper 95% CI: 0.272	NR	NR	[redacted][4]	-14.0%
Surgery unit cost	$8,453.32 (based on 55% : 45% split of AR-DRG D067 and D10Z codes).	Assumed cost of surgery to be $790.84 based on previous submission evaluation of MBS items proposed by advisory board	[redacted]	0.179	[redacted][1]	+14.1%
		Assumed cost applied in the previous submission ($9,600.43)	[redacted]	0.179	[redacted][1]	-2.1%

Variable	Base-case	Scenario	Increment cost ($)	Increment QALY	ICER $/QALY	% change
Surgery public/private setting	-Surgery wait time: private = 4 weeks, public = 52 weeks	-Surgery wait time: private = 4 weeks, public = 3 years	[redacted]	0.184	[redacted][1]	-2.1%
Mepolizumab compliance rate	100% [d]	94.56%		0.179	[redacted][1]	-6.3%
Discount rate	5% costs and effects	0%		0.202	[redacted][1]	-3%
		3.5%		0.185	[redacted][1]	-1%
Multivariate analyses						
Utility values during weeks 4-48	Between weeks 4 and 24 utility values based on total arm values, between weeks 28-42 utility values for responder applied based on values observed per arm	Between weeks 4 and 24 mean baseline value applied equally to both arms, between weeks 28-42 SoC arm responder utility applied to responders in both arms		0.157	[redacted][1]	+14.2%
Re-specified base-case requested by ESC during previous submission [e]	(A) Annual loss of response after 52 weeks = 27.6% (mep) and 61.9% (SoC). Responder week 52+ / effective surgery utility = 0.785 in both arms	(B) Annual loss of response after 52 weeks = 27.6% applied to both arms Responder week 52+ / effective surgery utility = 0.780 in both arms (derived from SoC arm responders in SYNPASE)		0.11	[redacted][2]	+72.7%
Re-specified base-case requested by ESC during resubmission	(A) + Mep non-responders do not receive full 24 week mep costs if transitioning before the end of a 24-week cycle	(B) + 50% of 24 week mep cost for mep week 52+ non-responders		0.106	[redacted][2]	+82.3%

Source: Table 3-30 (p184) of the resubmission & OWSA" sheet, resubmission economic model spreadsheet

BEC= blood eosinophil count; CFB = change from baseline; ICER= incremental cost effectiveness ratio; HS = health state; ITT= intent-to-treat; Mep = mepolizumab; QALY= quality-adjusted life years; SoC= standard of care

a. In order to crudely account for mepolizumab responders who transition out of a responder health state (but remaining alive) not being applied the remainder of any of the allowed 24-week treatment amount under the proposed essential elements. This was calculated as the proportion of mepolizumab responders at week 52 (61.7%) minus the proportion of mepolizumab responders at year 5 (16.8%) minus the proportion of mepolizumab arm patients who had died by Year 5 (1.3%) all multiplied by the cost of 12 weeks' of mepolizumab treatment ($1,398.21 = 3 x $466.07). This value was then added to the total costs of the mepolizumab arm.

b. The change to mepolizumab annual loss of response was done to make the absolute loss of response between Years 1 and 2 equal between arms.

c. This was applied to week 52+ responders / effective surgery patients in both arms

d. The resubmission stated a compliance rate of 94.56% was applied to mepolizumab doses, however this does not appear to have been applied in the model

e. As per paragraph 6.54, mepolizumab PSD, March 2021 PBAC meeting

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*
[2] *$95,000 to < $115,000*
[3] *$155,000 to < $255,000*
[4] *$45,000 to < $55,000*
[5] *$75,000 to < $95,000*

6.51 The model was not particularly sensitive to changes to response rate at week 24, likely because of the assumption of loss of response being a key driver of the model.

6.52 Overall, the structure of the economic model presented remained reasonable. However, the results of the economic evaluation were highly sensitive to many of the values and assumptions used for maintenance of response rates and for utility values. An evaluator-conducted multivariate sensitivity analysis using the conditions requested by ESC for a re-specified base-case in the previous submission increased the ICER by 72.7% to $95,000 to < $115,000/QALY, which illustrates that the model inputs and assumptions in the resubmission may have been optimistic. The ESC noted the impact of inclusion of appropriate mepolizumab costs for non-responders and considered it should be included in the re-specified base-case in addition to the factors identified in November 2021. The ESC noted that this increased the base-case ICER by 82% from $55,000 to <$75,000/QALY to $95,000 to <$115,000/QALY gained.

6.53 The pre-PBAC response re-specified base-case differed from the ESC re-specified base case in that it included a revised mepolizumab price, a differential loss of response across treatment arms and application of 94.56% compliance for mepolizumab (see paragraph 6.48). The pre-PBAC response stated the revised base-case ICER was $55,000 to < $75,000/QALY gained.

Drug cost/patient/year

6.54 Drug acquisition costs of mepolizumab are summarised in Table 16 below. The resubmission stated a mepolizumab compliance rate of 94.56% was applied in the economic model, however this did not appear to be applied in the actual economic model, though a 94.56% compliance rate was applied to the financial estimates. This inconsistency in the application of compliance rate between the economic model and the financial estimates (as well as the inclusion of private mark ups used in the financial estimates) explained the differences in cost/patient/year reported in Table 16. The pre-PBAC response re-specified base-case economic model included the application of a 94.56% compliance rate.

Table 16: Drug cost per patient for mepolizumab (based on price of $[redacted] as proposed in the resubmission)

	Trial dose and duration	Economic Model	Financial estimates
Mean dose	100mg Q4W	100mg Q4W	100mg Q4W
Mean duration	11.3 months	2.24 years	116.5 weeks [c]
Cost/patient/year ($)	[redacted] [a]	[redacted] [b]	[redacted] [d]

Source: Table 21, p 70 of the Clinical Study Report and the economic model Excel spreadsheet.
a. estimated as (365.25 days ÷ 12 months) × (11.3 months ÷ 28 days) × $[redacted]/dose
b. estimated by dividing the undiscounted drug acquisition cost in the model ($[redacted] by the mean duration of treatment
c. 24 weeks initial treatment plus 92.46 weeks continuing treatment
d. estimated as 12.34 doses (94.56% compliance of 13.04 doses, given every 28 days over 365.25 days) × $[redacted]/dose (weighted private/public)

6.55 The pre-PBAC response proposed a revised EMP of $[redacted] per pen (see paragraph 3.1).

Estimated PBS usage & financial implications

6.56 This resubmission was not considered by DUSC. DUSC considered the previous submission, and overall believed the estimates were overestimated due to a substantial overestimation of CRSwNP prevalence and due to the inclusion of patients with CRSwNP who may already be accessing mepolizumab for severe asthma (paragraph 6.62, mepolizumab PSD, November 2021 PBAC meeting). However, DUSC considered that the treatment uptake rates used in the previous submission were underestimated (paragraph 6.62, mepolizumab PSD, November 2021 PBAC meeting).

6.57 The resubmission 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 17.

Table 17: Key inputs for financial estimates

Data	Value and source	Comment
Eligible population		
Prevalence of CRSwNP	0.51% Source: Mean of UK CPRD-HES database study (GSK 213951) and Starry et al (2022)	The use of 0.51% for prevalence of CRSwNP in resubmission was likely reasonable and aligns with DUSC's consideration of likely prevalence (0.38% - 0.77%) during the previous submission.
Proportion with baseline BEC ≥300 cells/μL	68.3% Source: SYNAPSE trial (BEC ≥300 cells/μL subgroup)	Reasonable other than for the omission of patients with BEC ≥150 cells/μL if treated with OCS within last 12 months. The PBAC considered that patients with BEC ≥150 cells/μL but <300 cells/μL whilst receiving OCS treatment would not be eligible for PBS subsidised treatment.
Proportion requiring (first) NP surgery	47% Source: Chen et al 2020.	May be under-estimated due to the potentially unjustified removal of one outlier study from a systematic literature review.
Proportion suitable or 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 in the advisory board feedback. 'Patient preference' and 'access' were reasons provided for unsuitability by an advisory board member, whereas such reasons may not be adequately justified.
Proportion who experiences NP regrowth post-surgical removal	21% Source: Hopkins et al 2009	Decreased from 61% in the previous submission. The resubmission stated this was due to the attending clinicians to the advisory board not believing the 61% value obtained from the advisory board feedback was accurate. 21% was taken from a UK hospital audit study but may be an underestimation.

<table>
<tr><th>Data</th><th>Value and source</th><th>Comment</th></tr>
<tr><td>Proportion of CRSwNP patients who are already prescribed another PBS-listed biologic for severe asthma [a]</td><td>10.78%
Source: SYNAPSE; Adelphi Real World 2020; Albers 2018</td><td>Derived from assuming 77% of CRSwNP patients eligible for mepolizumab have comorbid asthma (based on SYNAPSE), 70% of comorbid asthma patients would have severe asthma (based on an Adelphi Panel) and 20% of comorbid severe asthma patients had severe eosinophilic asthma (based on an observational study (n=670) of the phenotypes of severe asthma patients (Albers 2018)). There is uncertainty in the values from the Adelphi panel and from Albers 2018.</td></tr>
<tr><td colspan="3">Treatment utilisation</td></tr>
<tr><td>Uptake rate for initial patients</td><td>Yr 1: 48.00 % [b]
Yr 2: 52.00%
Yr 3: 56.00%
Yr 4: 60.00%
Yr 5: 64.00%
Yr 6: 68.00% [c]
Source: Adelphi panel</td><td>Substantially increased from the previous submission (5% Year 1 dropping to 3.5% Year 6). A value of 68% was derived from the Adelphi panel, but it is unclear why the resubmission only applied this at year 6. The resubmission did not apply differential initial uptake rates by patients suitable and unsuitable for NP surgery. The PBAC considered that an uptake rate of 48% across all 6 years to be more appropriate.</td></tr>
<tr><td>Uptake rate for continuing patients</td><td>Yr 1: 34.85%
Yr 2: 37.75%
Yr 3: 40.66%
Yr 4: 43.56%
Yr 5: 46.64%
Yr 6: 49.37%
Source: Calculated by applying a 72.6% responder rate based on patients responding at the 24-week mark in the base-case economic model for the given year.</td><td>Substantially increased from the previous submission (3.5% Year 1 dropping to 2.45% Year 6).</td></tr>
<tr><td>Dosing and duration for mepolizumab assumed</td><td>Compliance: 94.56% assumed
Source: SYNAPSE trial

Dosing and duration used by the submission:<table><tr><th></th><th>Initiating</th><th>Continuing</th></tr><tr><td>Duration</td><td>24 wks</td><td>92.46 wks</td></tr><tr><td>Doses/wk</td><td>0.25</td><td>0.25</td></tr><tr><td>Scripts/yr</td><td>5.67</td><td>12.29 [d]</td></tr></table>Total duration 116.46 weeks (2.24 years)</td><td>The time on treatment reported in the economic model base-case was 2.1798 years (113.74 weeks), which would result in a time on treatment of 89.74 weeks after the subtraction of the 24-week initial treatment period. However, this value was derived from an economic model with a 5-year time horizon. Varying the economic model to a 6-year time horizon results in a time on treatment of 2.3174 years, which represents 96.92 weeks of continuing treatment (i.e., after the 24 weeks of initial treatment). The PBAC noted the 24 weeks of initiating treatment was incorrectly assumed to be out of a possible 52 weeks of treatment. This led to an underestimate of use. The PBAC also noted patients on treatment for more than 1 year were not excluded from the prevalent pool of patients and thus the uptake rates were applied to a pool of patients which included patients already on treatment. This led to a substantial overestimate of the use of mepolizumab.</td></tr>
</table>

Data	Value and source	Comment
Setting – PBS/RPBS split; PBS/RPBS weighted co-payment; Public-private split	PBS: 98.63%; RPBS: 1.37% PBS: $22.75; RPBS: $4.02 Public: 69.63%; Private: $30.37% Source: PBS dispensing data for mepolizumab item codes for severe eosinophilic asthma dispensed over the 12-month period from Jan 2020-Dec 2020.	Reasonable. It appeared 2 item codes used (12073K and 12030E) were no longer on the current PBS schedule.

Source: Section 4 of the resubmission
a – note, this variable was described as 'patients who do not have comorbid severe eosinophilic asthma' in the resubmission and given the value of 89.22% (i.e., 100 % - 10.78%). The variable and value were reported differently in this table to better show how this variable was calculated.
b – this value was applied as 48.00% in the financial workbook, but inconsistently stated as 48.04% and 48.00% in the resubmission
c – this value was applied as 68.00% in the financial workbook, but inconsistently stated as 68.04% and 68.00% in the resubmission
d – for a full year of continuing treatment
OCS = oral corticosteroids;
Blue shaded cells indicate information presented in previous submission

6.58 The SYNAPSE BEC ≥300 cells/µL subgroup was used to inform the financial estimates. The estimated financial impact of PBS listing mepolizumab presented in the resubmission is summarised in Table 18.

Table 18: Estimated use and financial implications presented in the resubmission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS and RPBS)						
Prevalence of CRSwNP (0.51%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients eligible for NP surgery [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients ineligible for NP surgery [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total eligible patients [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients electing treatment						
Eligible for NP surgery (initial)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ineligible for NP surgery (initial)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible for NP surgery (continuing)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ineligible for NP surgery (continuing)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total electing treatment (initial) [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total electing treatment (continuing) [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts (mepolizumab)						
Patient-years (initial) [e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient-years (continuing) [f]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PBS/RPBS scripts (initial) [g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PBS/RPBS scripts (continuing) [h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PBS/RPBS scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBS/RPBS cost less co-pay						
Total (eff) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
Total cost of replaced medicines (pub/eff) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for the PBS/RPBS						
Net cost to PBS/RPBS (eff) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for the health budget						
Net change in scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net MBS costs ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to Government health budget (eff) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous submission						
Total electing treatment (initial)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total electing treatment (continuing)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS (eff) ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to health budget ($)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables 4-5 to 4-16 (p193-200) of the resubmission and table 17, 6.04 mepolizumab PSD PBAC November 2021

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

a - Patients eligible for surgery were those: with BEC ≥300 cells/μL (68.3%); CRSwNP patients requiring surgery (47.0%); CRSwNP patients suitable for surgery (93.0%); CRSwNP patients who will experience NP regrowth post-surgical removal (21.0%); Patients who do not have comorbid severe eosinophilic asthma (89.22%).

Patients ineligible for surgery were those: with BEC ≥300 cells/μL (68.3%); CRSwNP patients requiring surgery (47.0%); CRSwNP patients unsuitable for surgery (7.0%); Patients who do not have comorbid severe eosinophilic asthma (89.22%).

b sum of patients eligible and ineligible for surgery.

c. The sum of all (eligible for surgery and ineligible for surgery) patients initiating mepolizumab for the given year.

d. The sum of all (eligible for surgery and ineligible for surgery) patients continuing mepolizumab for the given year after responding to initial treatment.

e. patient years calculated as total initial patients each year multiplied by 24 weeks / 52 weeks (0.4615), whereby 24 weeks represents the time allowed on initial treatment before response assessment. However, 0.4615 is slightly inaccurate due to 365.25 days in a year. The accurate number is 0.4600 (168 days / 365.25), leading to a slight overestimation of mepolizumab costs in the resubmission.
f. patient-years for continuing patients applied 92.46 weeks on treatment which was assumed to apply for the remainder of the first year after initial treatment and then continue into a second and partially into a third year. There were issues with the value of 92.46 weeks applied (see Table 17).
g. Calculated by applying patient-years (initial) by 5.67 scripts per year
h. Calculated by applying patient-years (continuing) by 12.29 scripts per year
Blue shaded cells indicate information presented in previous submission

The redacted values correspond to the following ranges:
[1] 100,000 to < 200,000
[2] 5,000 to < 10,000
[3] 500 to < 5,000
[4] 10,000 to < 20,000
[5] 50,000 to < 60,000
[6] 20,000 to < 30,000
[7] 60,000 to < 70,000
[8] 70,000 to < 80,000
[9] 80,000 to < 90,000
[10] 90,000 to < 100,000
[11] $10 million to < $20 million
[12] $20 million to <$30 million
[13] $30 million to < $40 million
[14] $40 million to < $50 million
[15] $0 to < $10 million

6.59 The PBAC considered the approach taken by the resubmission to estimate the total number of eligible patients was appropriate. The PBAC noted that the prevalent pool of eligible patients was 5,000 to < 10,000 in Year 1 increasing to 5,000 to < 10,000 in Year 6. However, the PBAC noted the subsequent approach applied in the estimates in which the uptake was applied to the total prevalent pool including those already on treatment resulted in 20,000 to < 30,000 patients initiating treatment over 6 years (Table 18, row labelled 'Total electing treatment (initial)') out of a pool of prevalent patients of between 5,000 to < 10,000 and 5,000 to < 10,000. The PBAC considered this was inappropriate.

6.60 The uptake rate in the November 2021 submission was 5% in Year 1 dropping to 3.5% Year 6. The resubmission applied an uptake rate for initial patients of 48% increasing to 68%. The resubmission did not apply differential initial uptake rates by patients suitable and unsuitable for NP surgery. The PBAC noted the value of 68% was derived from the Adelphi panel but considered it likely overestimated. As noted above, it was also applied incorrectly in the resubmission. The PBAC acknowledged the difficulty in determining the uptake rate but considered percentage of enrolled versus randomised patients from the SYNAPSE (48%, 414/854), POLYP 1 (39%, 138/355)[4] and POLYP 2 (39%, 127/329)[1] trials indicated an overall uptake rate of 48% may be appropriate and advised this should be applied across all 6 years using the methodology outlined in the following paragraph and Table 19.

[4] Gevaert P, Omachi T.A., Corren J, Mullol J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomised phase 3 trials. J Allergy Clin Immunol 2020: 146; 595-605

6.61 The resubmission assumed a total treatment duration of 116.46 weeks (2.24 years). The PBAC noted that as the uptake was being applied to a prevalent pool of patients each year, the total treatment duration should not be used to estimate continuation of treatment from one year to the next. This resulted in patients initiating treatment in year 1 being eligible to initiate treatment again in year 2 (and year 3) even though they were already on treatment. The PBAC noted that accounting for 94.6% compliance and a response rate of 72.6%, patients receive an average 21.5 prescriptions over the 2.24 years which is equivalent to an average of 9.6 scripts per year. Noting the estimated total eligible patients to be appropriate, the PBAC considered the financial estimates should be revised to include a 48% uptake rate applied across Year 1 to Year 6 with an average of 9.6 scripts per patient treated. The revised estimated financial impact of PBS listing mepolizumab is summarised in Table 19.

Table 19 Revised estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (PBS and RPBS)						
Prevalence of CRSwNP (0.51%)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients eligible for NP surgery [a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Patients ineligible for NP surgery [a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total eligible patients [b]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion of patients treated (uptake)	48%	48%	48%	48%	48%	48%
Total electing treatment (includes initiating and continuing patients)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total PBS/RPBS scripts [c]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]
PBS/RPBS cost less co-pay						
Total (eff) ($)	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
Total cost of replaced medicines (pub/eff) ($)	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Estimated financial implications for the PBS/RPBS						
Net cost to PBS/RPBS (eff) ($)	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]

Source: Tables 4-5 (p193) of the resubmission and prepared per PBAC respecified estimates

a. Patients eligible for surgery were those: with BEC ≥300 cells/μL (68.3%); CRSwNP patients requiring surgery (47.0%); CRSwNP patients suitable for surgery (93.0%); CRSwNP patients who will experience NP regrowth post-surgical removal (21.0%); Patients who do not have comorbid severe eosinophilic asthma (89.22%).

Patients ineligible for surgery were those: with BEC ≥300 cells/μL (68.3%); CRSwNP patients requiring surgery (47.0%); CRSwNP patients unsuitable for surgery (7.0%); Patients who do not have comorbid severe eosinophilic asthma (89.22%).

b. Sum of patients eligible and ineligible for surgery.

c. Total electing treatment multiplied by 9.6 scripts (based on an average of 21.5 scripts over 2.24 years)

Average of 21.5 scripts based on sum of scripts in Year 1 (Initial 5.6736 (6 x 0.9456) + Continuing 4.8055 (7 x 0.9456 x 0.726)) plus Year 2 (Continuing 8.9246 (13 x 0.9456 x 0.726)) plus Year 3 (Continuing 2.1385 (3.115 x 0.9456 x 0.726))

The redacted values correspond to the following ranges:

[1] 100,000 to < 200,000

[2] 5,000 to < 10,000

[3] 500 to < 5,000

[4] 30,000 to < 40,000

[5] 40,000 to < 50,000

[6] $10 million to < $20 million

[7] $0 to < $10 million

6.62 The revised total cost to the PBS/RPBS of listing mepolizumab was estimated to be $10 million to < $20 million in Year 6, and a total of $90 million to < $100 million in the first 6 years of listing.

6.63 The PBAC considered it was reasonable to accept the revised financial estimates as the basis of a risk sharing arrangement (RSA).

Quality Use of Medicines

6.64 The Sponsor plans to offer an educational program on CRSwNP (meetings and materials), including how to use the pre-filled pen and who is an appropriate candidate for treatment. The Sponsor will provide healthcare professionals with patient-materials (e.g., videos) to support/train patients to self-administer the pre-filled pen. The Sponsor is currently sponsoring a patient support program (via Sonic Healthcare), which includes a program nurse providing training on how to self-administer for patients with severe eosinophilic asthma (TGA and PBS listed).

Financial Management – Risk Sharing Arrangements

6.65 The resubmission did not propose an RSA. In November 2021, 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 uncertainty associated with the uptake in this population (paragraph 7.8, mepolizumab PSD, November 2021 PBAC meeting). The resubmission included patients unsuitable for surgery in the requested population. The PSCR considered the potential sources of uncertainty in the eligible population to be those with BEC ≥150 and <300 cells/µL, patients re-initiating following a treatment break and patients not eligible for surgery. The PSCR stated the Sponsor is willing to propose annual caps in an RSA equal to the estimated net effective cost to the PBS/RPBS.

6.66 The PSCR further stated that an appropriate rebate for mepolizumab expenditure above these proposed caps would be %. The PSCR derived this value based on the difference between the annual net cost of mepolizumab per patient in the financial estimates ($ including co-payments and compliance) and the average annual cost of nasal polyp surgery avoided in the financial estimates ($2,255.44 – calculated as cost of surgery ($8,543.32) multiplied by the annual risk of surgery before week 52 for SoC patients (26.4%)), as a proportion of the annual net cost of mepolizumab per patient. The ESC disagreed with the assumption made by the PSCR that any use above the caps would still be cost-effective and considered that a 100% rebate would be more appropriate given the potential sources of uncertainties in the financial estimates. The PBAC noted the revised financial estimates presented in Table 19 and considered them to be an appropriate basis of a RSA.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of mepolizumab for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP), on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program). The PBAC considered that the blood eosinophil count (BEC) threshold for access to mepolizumab should be ≥300 cells/µL. The PBAC is satisfied that mepolizumab provides, for some patients, a significant improvement in efficacy over standard of care (SoC). The PBAC considered that due to the limitations of the treatment options currently available the addition of mepolizumab offered high added therapeutic value.

7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of mepolizumab would be acceptable at the price proposed in the pre-PBAC response, and with a risk sharing arrangement (RSA) to address the uncertainty associated with including patients unsuitable for surgery in the proposed PBS population.

7.3 The PBAC noted the input from individuals, health care professionals and organisations that described the limitations of the treatment options currently available for CRSwNP along with the positive effects of mepolizumab on disease severity and Quality of Life (QoL). The PBAC also noted the advice from ESC regarding the long wait times for nasal polyp (NP) surgery. The PBAC considered there was a high clinical need for effective treatments for CRSwNP.

7.4 With regard to the requested listing and restriction, the PBAC advised that:

- A Section 100 Highly Specialised Drugs Program listing is appropriate, noting that this was consistent with the current restriction for mepolizumab for uncontrolled severe asthma.
- Reference to patients with a baseline BEC ≥150 but <300 cells/µL while receiving treatment with oral corticosteroid (OCS) in the past 12 months be removed from the restriction. The PBAC considered there was no clinical, economic or financial evidence presented in the resubmission to inform this sub-group of patients. The PBAC acknowledged the sensitivity of BEC to OCS as raised by ESC but considered the inclusion of such a criterion could lead to inappropriate use of OCS to meet the restriction criteria.
- It was reasonable to include overall VAS in the continuing treatment restriction as one of the options for demonstrating an adequate response to therapy (≥2.5 points improvement from baseline).
- The PBAC agreed with the ESC that there may be situations where patients responding to mepolizumab still require surgery and hence the requirement for patients to discontinue mepolizumab treatment after undergoing NP surgery should be removed from the restriction (see paragraph 3.6).

- The PBAC noted the ESC suggestion to include reference to the need to have 'have failed or ceased to respond to' with respect to the 12 month treatment break in the initial treatment criteria (see paragraph 3.7). The PBAC noted this would mean the criteria would be 'Patient must have had a 12 month break in PBS subsidised therapy after having failed or ceased to respond to treatment with a biological medicine for this condition'. The PBAC was concerned that, for this condition, such wording may reduce adherence to the 12 month treatment break and hence advised it should not be included in the restriction.
- The clinical criteria that the '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)' was not required given the proposed restriction also required patients to have a diagnosis of CRSwNP by nasal endoscopy or CT scan or from at least two physicians and/or ENT surgeons experienced in the management of CRSwNP.
- A grandfathering restriction is appropriate.
- A Written/Electronic - full assessment via the Online PBS Authorities (OPA) system is appropriate.

7.5 The PBAC reaffirmed its November 2021 advice that the nominated comparator of SoC was appropriate (7.3, mepolizumab PSD, November 2021 PBAC meeting).

7.6 The resubmission was based on the SYNAPSE trial (N=407) comparing mepolizumab to placebo in patients with CRSwNP patients with uncontrolled symptoms after at least one NP surgery and treatment with intranasal corticosteroids (INCS), with the clinical claim based on the SYNAPSE BEC ≥300 cells/µL sub-group. The PBAC reaffirmed its November 2021 advice that the Committee accepted the claim of clinical superiority of mepolizumab in the BEC ≥300 subgroup based on SYNAPSE trial evidence (paragraph 7.5, mepolizumab PSD, November 2021 PBAC meeting).

7.7 The PBAC reaffirmed its November 2021 advice that the claim of non-inferior safety was reasonable (paragraph 7.6, mepolizumab PSD, November 2021 PBAC meeting).

7.8 The PBAC recalled that in November 2021, it had agreed with the ESC that a respecified base case incorporating a 5 year time horizon, an assumption of 24.6% loss of response (27.6% for the BEC ≥300 cells/µL sub-group, see paragraph 6.40) and the SoC responder utility applied to both arms from Week 52 and applied to those who had effective surgery would be appropriate (paragraph 7.7, mepolizumab PSD, November 2021 PBAC meeting). The PBAC noted the resubmission provided a respecified base case that incorporated both the 5 year time horizon and the requested approach to SoC responder utility inputs. However, the PBAC considered the loss of response assumptions applied in the resubmission were not consistent with the Committee's November 2021 advice and favoured mepolizumab (see paragraphs 6.39 and 6.40). The PBAC noted the pre-PBAC response argument regarding the plausibility of assuming a 47.1% annual loss of response for the SoC arm (see paragraph 6.40) and considered it was reasonable. The PBAC agreed with ESC advice

that appropriate mepolizumab costs for non-responders should be included in the economic model (see paragraph 6.52). The PBAC noted the pre-PBAC response provided a re-specified base-case incorporating:

- a revised mepolizumab price (see paragraph 3.1),
- differential loss of response (mepolizumab 27.6%, SoC 47.1%),
- 50% of 24 week mepolizumab cost allocated for mepolizumab week 52+ non-responders,
- application of 94.56% compliance for mepolizumab.

The PBAC considered the pre-PBAC response re-specified base-case along with the revised price submitted in the pre-PBAC response addressed previous concerns regarding the cost-effectiveness of mepolizumab.

7.9 The PBAC considered the resubmission financial estimates addressed November 2021 PBAC meeting concerns raised by DUSC regarding prevalence rates of chronic rhinosinusitis 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 (paragraph 7.8, mepolizumab PSD, November 2021 PBAC meeting). The PBAC considered the approach taken by the resubmission to estimate the total number of eligible patients was appropriate. However, the PBAC expressed concern regarding the approach taken to determining the total number of patients electing treatment and subsequent estimates (see paragraphs 6.59 to 6.61). Noting the estimated total eligible patients to be appropriate, the PBAC advised that the financial estimates be revised to include a 48% uptake rate applied across Year 1 to Year 6 with an average of 9.6 scripts per patient treated (see paragraph 6.61). The PBAC noted that grandfathered patients were accounted for in the prevalence based approach used to determine the financial estimates.

7.10 The PBAC recalled that in November 2021 it had considered that if patients unsuitable for surgery were to be included in the proposed PBS population, then a RSA would be required to manage uncertainty associated with the uptake in this population (paragraph 7.8, mepolizumab PSD, November 2021 PBAC meeting). The PBAC noted the resubmission included patients unsuitable for surgery in the requested population and that an RSA was proposed in the Pre-Sub-Committee Response. The PBAC considered an RSA would be appropriate, with financial caps set at the level of the revised estimates, as presented in Table 19. In addition, the PBAC agreed with the ESC that a 100% rebate for any use above the caps would be appropriate to mitigate any residual uncertainties regarding uptake in patients unsuitable for surgery.

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

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

7.13 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were met.

Specifically, the PBAC found that in the circumstances of its recommendation for mepolizumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of change from baseline in endoscopic nasal polyp score (see paragraph 6.14) and nasal obstruction visual analogue scale score (see paragraph 6.15) along with the impact seen on time to first nasal surgery (see paragraph 6.19) and improvements in QoL (see paragraph 6.23);
b) The treatment is expected to address a high and urgent unmet clinical need due to the limitations of the treatment options currently available;
c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

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

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
MEPOLIZUMAB					
mepolizumab 100 mg/mL injection, 1 mL pen device	NEW public NEW private	1 1	1 1	5 5	Nucala
Restriction Summary [new] / Treatment of Concept: [new]					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒ Authority Required (in writing only via post/HPOS upload)				
	Prescribing Rule level Administrative Advice				
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative advice: No increase in the maximum number of repeats may be authorised.				
	Administrative advice: Special Pricing Arrangements apply.				
	Administrative advice: The length of a break in therapy is measured from the date that the relevant PBS-subsidised medicine listed for this PBS indication is ceased during the most recent treatment cycle until the date of the subsequent application for treatment under a new treatment cycle				
	Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)				
	Treatment Phase: Initial treatment				
	Treatment criteria:				

	Patient must be treated by a medical practitioner who is either a: (i) respiratory physician, (ii) clinical immunologist, (iii) allergist, (iv) ear nose and throat specialist (ENT), (iv) general physician experienced in the management of patients with CRSwNP.
	Clinical criteria:
	Patient must have a diagnosis of CRSwNP confirmed by at least one of: (i) nasal endoscopy, (ii) computed tomography (CT) scan, with the results documented in the patient's medical records.
	Patient must have a diagnosis of CRSwNP from at least two physicians of the above mentioned prescriber types.
	AND
	Clinical criteria:
	Patient must have undergone surgery for the removal of nasal polyps; or
	Patient must have the written advice from at least two physicians of the above mentioned prescriber types demonstrating inappropriateness for surgery.
	AND
	Clinical criteria:
	Patient must have, despite optimised nasal polyp therapy, at least two of: (a) bilateral endoscopic nasal polyp score of at least 5 (out of a maximum score of 8, with a minimum score of 2 in each nasal cavity), (b) nasal obstruction visual analogue scale (VAS) score greater than 5 (out of a maximum score of 10), (c) overall symptom VAS score greater than 7 (out of a maximum score of 10).
	AND
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with a biological medicine for this condition; or
	Patient must have had a 12 month break in PBS-subsidised treatment with a biological medicine for this condition.
	AND
	Clinical criteria:
	The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma.
	AND
	Clinical criteria:
	Patient must have failed to achieve adequate control with optimised nasal polyp therapy which has been documented.
	AND
	Clinical criteria:
	Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months.
	Population criteria:
	Patient must be at least 18 years of age.
	Prescribing Instructions: Optimised nasal polyp therapy includes: (a) adherence to intranasal corticosteroid therapy for at least 2 months, unless contraindicated or not tolerated; and (b) if required, nasal irrigation with saline.

	Where the patient has a contraindication or intolerance to intranasal corticosteroid therapy, document the reasons for the contraindication or intolerance in the patient's medical file.
	The authority application must be made in writing and must include: (a) a completed authority prescription form, (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), (c) details (date of commencement and duration of therapy) of prior optimised nasal polyp medicine treatment, (d) details (date and treatment) of nasal polyp surgery; OR (e) if applicable, details of surgical exception including serious comorbid disease (e.g. cardiovascular, stroke) making the risk of surgery unacceptable, (f) the eosinophil count and date, (g) two of the following, measured within the past 12 months: (i) baseline bilateral endoscopic nasal polyp score, (ii) baseline nasal obstruction VAS score, (iii) baseline overall VAS score.
	Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (telephone/electronic via PBS Authorities system)
	Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)
	Treatment Phase: Continuing treatment
	Treatment criteria:
	Patient must be treated by a medical practitioner who is either a: (i) respiratory physician, (ii) clinical immunologist, (iii) allergist, (iv) ear nose and throat specialist (ENT), (v) general physician experienced in the management of patients with CRSwNP.
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have both demonstrated and sustained an adequate response to this drug, defined as having at least one of: (i) an improvement in bilateral endoscopic nasal polyp score of at least 1.0 compared to the baseline level provided with the initial authority application, (ii) an improvement in nasal obstruction visual analogue scale (VAS) score of at least 3.0 compared to the baseline level provided with the initial authority application, (iii) an improvement in overall symptom VAS score of at least 2.5 compared to the baseline level provided with the initial authority application.
	Population criteria:

	Patient must be at least 18 years of age.
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒ Authority Required (in writing only via post/HPOS upload):
	Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements
	Treatment criteria:
	Patient must be treated by a medical practitioner who is either a: (i) respiratory physician, (ii) clinical immunologist, (iii) allergist, (iv) ear nose and throat specialist (ENT), (v) general physician experienced in the management of patients with CRSwNP.
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this PBS indication prior to [Listing date]
	AND
	Clinical criteria:
	Patient must have had a diagnosis of CRSwNP confirmed by at least one of: (i) nasal endoscopy, (ii) computed tomography (CT) scan, prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have undergone at least one previous surgery for the removal of nasal polyps prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have had, prior to initiating non-PBS-subsidised treatment with this drug for this condition, at least two of: (a) bilateral endoscopic nasal polyp score of at least 5 (out of a maximum score of 8, with a minimum score of 2 in each nasal cavity), (b) nasal obstruction visual analogue scale (VAS) score greater than 5 (out of a maximum score of 10), (c) overall symptom VAS score greater than 7 (out of a maximum score of 10).
	AND
	Clinical criteria:
	The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for any of: (i) nasal polyps, (ii) uncontrolled severe allergic asthma, (iii) uncontrolled severe asthma.
	AND
	Clinical criteria:

	Patient must have failed to achieve adequate control with optimised nasal polyp therapy which has been documented.
	AND
	Clinical criteria:
	Patient must have had a blood eosinophil count of at least 300 cells per microlitre in the 12 months prior to initiating non-PBS-subsidised treatment with this drug for this condition
	Population criteria:
	Patient must be at least 18 years of age.
	Prescribing Instructions: Optimised nasal polyp therapy includes: (a) adherence to intranasal corticosteroid therapy for at least 2 months, unless contraindicated or not tolerated. (b) if required, nasal irrigation with saline. Where the patient has a contraindication or intolerance to intranasal corticosteroid therapy, document the reasons for the contraindication or intolerance in the patient's medical file.
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

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

9 Context for Decision

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

through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.