

6.03 OMALIZUMAB,**Injection 75 mg in 0.5 mL single dose prefilled syringe,****Injection 150 mg in 1 mL single dose prefilled syringe,****Injection 300 mg in 2 mL single dose prefilled syringe,****Injection 75 mg in 0.5 mL single dose prefilled pen,****Injection 150 mg in 1 mL single dose prefilled pen,****Injection 300 mg in 2 mL single dose prefilled pen,****Xolair[®],****Novartis Pharmaceuticals Australia Pty Limited.****1 Purpose of submission**

- 1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for omalizumab for the initial treatment and an Authority Required (Telephone/Online) listing for the continuing treatment of patients with chronic rhinosinusitis with nasal polyps (CRSwNP).
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus mepolizumab.

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

Component	Description
Population	Adult patients (≥18 years of age) for the treatment of severe CRSwNP with inadequate response to INCS and IgE ≥30 IU/mL.
Intervention	Omalizumab SC injection, every 2 to 4 weeks - appropriate dose and dosing frequency is determined by baseline IgE (IU/mL), and body weight (kg) (see Table 1 of the TGA Product Information ¹).
Comparator	Mepolizumab 100 mg SC injection by self-administration every 28 days
Outcomes	Change from baseline in NPS, NCS, and SNOT-22
Clinical claim	In adult patients with severe CRSwNP with inadequate response to INCS, omalizumab is non-inferior to mepolizumab in terms of comparative effectiveness and safety.

Source: Table 1.1, p13 of the submission.

CRSwNP, chronic rhinosinusitis with nasal polyps; IgE, immunoglobulin E; INCS, intranasal corticosteroids; SC, subcutaneous; NPS, Nasal Polyp Score; NCS, Nasal Congestion Score; SNOT-22, Sinonasal Outcome Test Score.

¹ <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2009-PI-00304-3>

2 Background

Registration status

2.1 Omalizumab was TGA registered on 12 March 2021 for the following indication:

“[Omalizumab] is indicated as add-on treatment in adult patients (18 years of age and above) for the treatment of severe CRSwNP with inadequate response to intranasal corticosteroids. Recommended dosing is determined by serum immunoglobulin E levels and body weight corresponding to the recommended dose range in the Product Information”.

2.2 Omalizumab currently has TGA approval for CRSwNP, chronic spontaneous urticaria, and allergic asthma.

Previous PBAC consideration

2.3 The nominated comparator, mepolizumab, was recommended for listing for the treatment of CRSwNP in adult patients in the November 2022 PBAC meeting. 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, and with a risk sharing arrangement (RSA) to address the uncertainty associated with including patients unsuitable for surgery in the proposed PBS population (para 7.2, mepolizumab, Public Summary Document [PSD], November 2022 PBAC meeting). The PBAC considered financial caps set at the level of the revised financial estimates and a ██████% rebate for any use above the caps would be appropriate (para 7.10, mepolizumab, PSD, November 2022 PBAC meeting).

3 Requested listing

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

Initial treatment phase:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
OMALIZUMAB					
omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe	NEW/ Public	1	1	65	Xolair
omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe	NEW/ Private	1	1	65	Xolair
omalizumab 150 mg/mL injection, 1 mL syringe	NEW/ Public	1	1	65	Xolair
omalizumab 150 mg/mL injection, 1 mL syringe	NEW/ Private	1	1	65	Xolair
<i>omalizumab 300 mg/ 2 mL injection, 2 mL syringe</i>	<i>NEW/ Private</i>	1	1	5	<i>Xolair</i>
Restriction Summary / Treatment of Concept:					

Public Summary Document - May 2025 PBAC Meeting

	<p>Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)</p>
	<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
	<p>Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)</p>
	<p>Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>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.</p>
	<p>Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)</p>
	<p>Treatment Phase: Initial treatment</p>
	<p>Clinical criteria:</p>
	<p>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</p>
	<p>OR</p>
	<p>Patient must have had a diagnosis of CRSwNP from at least two physicians of the above mentioned prescriber types</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have undergone surgery for the removal of nasal polyps</p>
	<p>OR</p>
	<p>Patient must have the written advice from at least two physicians of the above mentioned prescriber types demonstrating inappropriateness for surgery,</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have, despite optimised nasal polyp therapy, at least two of: (i) 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), (ii) nasal obstruction visual analogue scale (VAS) score greater than 5 (out of a maximum score of 10), (iii) overall symptom VAS score greater than 7 (out of a maximum score of 10),</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must not have received PBS-subsidised treatment with a biological medicine for this condition;</p>
	<p>OR</p>
	<p>Patient must have had a 12-month break in PBS-subsidised treatment with a biological medicine for this condition</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>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,</p>
	<p>AND</p>
	<p>Clinical criteria:</p>

Public Summary Document - May 2025 PBAC Meeting

	Patient must have failed to achieve adequate control with optimised nasal polyp therapy which has been documented
	AND
	Clinical criteria:
	Patient must have a total serum immunoglobulin E level greater than or equal to 30 IU/mL in the last 12 months
	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) or (v) general physician experienced in the management of patients with CRSwNP
	Population criteria:
	Patient must be aged at least 18 years or older. of age
	Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate maximum quantity and number of repeats to provide for an initial course of omalizumab consisting of the recommended number of doses for the baseline IgE level and body weight of the patient (refer to the TGA-approved Product Information) to be administered every 2 or 4 weeks.
	Prescribing Instructions: Optimised nasal polyps 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: a) A completed authority prescription form, b) A completed authority application form relevant to the indication and treatment phase 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 free serum immunoglobulin E level 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 the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can 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

Public Summary Document - May 2025 PBAC Meeting

Continuing treatment phase:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OMALIZUMAB					
omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe	NEW/ Public	1	1	65	Xolair
omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe	NEW/ Private	1	1	65	Xolair
omalizumab 150 mg/ mL injection, 1 mL syringe	NEW/ Public	1	1	65	Xolair
omalizumab 150 mg/ mL injection, 1 mL syringe	NEW/ Private	1	1	65	Xolair

Restriction Summary / Treatment of Concept:

	Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/electronic via PBS Authorities system)
	Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: The length of a break in therapy is measured from the date that the relevant PBS-subsidised medicine listed for this PBS indication is ceased during the most recent treatment cycle, until the date of the subsequent application for treatment under a new treatment cycle.
	Administrative Advice: Medical practitioners should request the appropriate maximum quantity and number of repeats to provide for an initial course of omalizumab consisting of the recommended number of doses for the baseline IgE level and body weight of the patient (refer to the TGA-approved Product Information) to be administered every 2 or 4 weeks.
	Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)
	Treatment Phase: Continuing treatment
	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
	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) or (v) general physician experienced in the management of patients with CRSwNP
	Population criteria:
	Patient must be aged at least 18 years or older. of age

Public Summary Document - May 2025 PBAC Meeting

	<p>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).</p>
--	---

Grandfather treatment phase:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OMALIZUMAB					
omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe	NEW/ Public	1	1	€5	Xolair
omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe	NEW/ Private	1	1	€5	Xolair
omalizumab 150 mg/ mL injection, 1 mL syringe	NEW/ Public	1	1	€5	Xolair
omalizumab 150 mg/ mL injection, 1 mL syringe	NEW/ Private	1	1	€5	Xolair

Restriction Summary / Treatment of Concept:

	<p>Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)</p>
	<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
	<p>Restriction type: <input checked="" type="checkbox"/> Authority Required (FULL assessment) in writing only via post/HPOS upload)</p>
	<p>Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply.</p>
	<p>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.</p>
	<p>Indication: Chronic rhinosinusitis with nasal polyps (CRSwNP)</p>
	<p>Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements</p>
	<p>Clinical criteria:</p>
	<p>Patient must have received non-PBS-subsidised treatment with this biological medicine for this PBS-indication prior to [listing date]</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have 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.</p>
	<p>OR</p>
	<p>Patient must have had a diagnosis of CRSwNP from at least two physicians of the above mentioned prescriber types, prior to initiating non-PBS-subsidised treatment with this drug for this condition.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have undergone surgery for the removal of nasal polyps prior to initiating non-PBS-subsidised treatment with this drug for this condition.</p>

Public Summary Document - May 2025 PBAC Meeting

	OR
	<i>Patient must have the written advice from at least two physicians of the above mentioned prescriber types demonstrating inappropriateness for surgery, prior to initiating non-PBS-subsidised treatment with this drug for this condition.</i>
	AND
	Clinical criteria:
	<i>Patient must have had, prior to initiating non-PBS-subsidised treatment with this drug for this condition, despite optimised nasal polyp therapy, at least two of: (i) 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), (ii) nasal obstruction visual analogue scale (VAS) score greater than 5 (out of a maximum score of 10), (iii) overall symptom VAS score greater than 7 (out of a maximum score of 10),</i>
	AND
	Clinical criteria:
	<i>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,</i>
	AND
	Clinical criteria:
	<i>Patient must have failed to achieve adequate control with optimised nasal polyp therapy which has been documented</i>
	AND
	Clinical criteria:
	<i>Patient must have a total serum immunoglobulin E level greater than or equal to 30 IU/mL in the last 12 months prior to initiating non-PBS-subsidised treatment with this drug for this condition</i>
	Treatment criteria:
	<i>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) or (v) general physician experienced in the management of patients with CRSwNP</i>
	Population criteria:
	<i>Patient must be at least 18 years of age</i>
	Prescribing Instructions: <i>At the time of the authority application, medical practitioners should request the appropriate maximum quantity and number of repeats to provide for an initial course of omalizumab consisting of the recommended number of doses for the baseline IgE level and body weight of the patient (refer to the TGA-approved Product Information) to be administered every 2 or 4 weeks.</i>
	Prescribing Instructions: <i>Optimised nasal polyps therapy includes:</i> <ul style="list-style-type: none"> a) <i>Adherence to intranasal corticosteroid therapy for at least 2 months, unless contraindicated or not tolerated</i> b) <i>If required, nasal irrigation with saline</i> <i>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.</i>

Public Summary Document - May 2025 PBAC Meeting

	<p>Prescribing Instructions: <i>The authority application must be made in writing and must include:</i></p> <ul style="list-style-type: none"> a) <i>A completed authority prescription form,</i> b) <i>A completed authority application form relevant to the indication and treatment phase</i> c) <i>Details (date of commencement and duration of therapy) of prior optimised nasal polyp medicine treatment,</i> d) <i>Details (date and treatment) of nasal polyp surgery; or</i> e) <i>If applicable, details of surgical exception including serious comorbid disease (e.g. cardiovascular, stroke) making the risk of surgery unacceptable,</i> f) <i>The free serum immunoglobulin E level and date,</i> g) <i>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</i>
	<p>Administrative advice: <i>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).</i> <i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</i> <i>Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)</i> <i>Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</i> <i>Or mailed to:</i> <i>Services Australia</i> <i>Complex Drugs</i> <i>Reply Paid 9826</i> <i>HOBART TAS 7001</i></p>
	<p>Administrative Advice: <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i></p>

- 3.2 The submission proposed the published approved ex-manufacturer price (AEMP) for omalizumab for the 75 mg (\$398.59) and 150 mg (\$797.18) pre-filled syringes based on the cost-minimisation approach against mepolizumab. The submission stated that the published price of mepolizumab was used, as the effective price was not known to the sponsor.
- 3.3 The proposed restriction is broadly in line with the PBS restrictions for mepolizumab for the treatment of CRSwNP, except for the proposed removal of the blood eosinophilic count (BEC) threshold (to include patients with <300 cells/ μ L) and the addition of a restriction based on IgE levels (\geq 30 IU/mL). The ESC considered this difference between the mepolizumab and proposed omalizumab restrictions was reasonable, given the different mechanisms of action. The current restrictions for mepolizumab also include: a formalised diagnosis by a medical practitioner experienced in the management of patients with CRSwNP, prior surgery (or two physicians who say surgery is inappropriate), meeting threshold score on one objective (NPS) and two symptom (NO-VAS, overall-VAS) scores.
- 3.4 The submission justified the difference in criteria given differences between the treatments in terms of mechanism of action: omalizumab primarily involves targeting and inhibiting the activity of IgE, while mepolizumab targets IL-5, which is critical for eosinophil activation and survival. This acknowledgement of difference has been

Public Summary Document - May 2025 PBAC Meeting

- previously applied in the restrictions for severe asthma and been accepted by the PBAC (para 7.2, mepolizumab PSD, March 2016 PBAC meeting).
- 3.5 The submission's expanded listing with removal of BEC threshold was also based on post-hoc analyses from the pivotal clinical trials (POLYP 1 and POLYP 2). The PBAC previously recommended mepolizumab for CRSwNP include a BEC threshold of ≥ 300 cells/ μ L (para 7.1, mepolizumab, PSD, November 2021 PBAC meeting; paras 3.9 and 7.4, mepolizumab PSD, November 2022 PBAC meeting). The European Forum for Research and Education in Allergy and Airway Disease (EUROFEA) 2023 treatment guideline recommends, as potential criteria, a BEC threshold of ≥ 150 cells/ μ L or IgE ≥ 100 IU/mL or tissue eos of ≥ 10 hpf) for use of biologics for treatment of CRSwNP. The 2021 Australasian Society of Clinical Immunology and Allergy (ASCIA) Position Paper on CRSwNP does not recommend any specific thresholds.
- 3.6 The submission's proposed restriction for an IgE threshold of ≥ 30 IU/mL was based on the current omalizumab PBS restrictions for asthma. This threshold aligns with the inclusion criteria in the POLYP trials; however, it is lower than the European recommended threshold of IgE ≥ 100 IU/mL (EUROFEA, 2023). The PBS listing for mepolizumab for treatment of CRSwNP does not specify an IgE threshold. The ESC noted that IgE ≥ 100 IU/mL was only one of five criteria in the EUFOREA guidance which included demonstrating evidence of type 2 inflammation. Given the high degree of overlap between CRSwNP and asthma, ESC considered that using the same IgE threshold as currently used for asthma would be appropriate.
- 3.7 As well as an IgE threshold of ≥ 30 IU/mL, eligibility criteria for the pivotal clinical trials (POLYP 1 and POLYP 2) for omalizumab included a Nasal Polyp Score (NPS) of ≥ 5 , Sinonasal Outcome Test (SNOT-22) score ≥ 20 and nasal congestion score (NCS) ≥ 2 . While the PBS clinical criteria for NPS was included, the two trial populations may have included patients with moderate to severe disease based on the SNOT-22 score classification: Mild (8 to 20), Moderate (>20 to 50) and Severe (>50)². The EUROFEA 2023 guidance on biologics for CRSwNP recommends a SNOT-22 score ≥ 40 for biologic treatment eligibility.
- 3.8 The lack of consistency in the definition of disease severity across studies investigating use of biologics to treat CRSwNP was similarly raised in the TGA Delegate's Overview which noted that on the basis of prior surgery and systemic corticosteroid use, populations with more severe disease were investigated in the mepolizumab studies (omalizumab Delegate's Overview for ACM's advice). Despite concerns about the severity criteria, the Delegate concluded that patients enrolled in the POLYP trials should be considered as having "severe" disease based on baseline severity scores.

² Toma Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. *Rhinology*. 2016 Jun 1;54(2):129-33.

Public Summary Document - May 2025 PBAC Meeting

- 3.9 Based on the proposed PBS restriction for omalizumab, some current mepolizumab patients would not meet the proposed omalizumab eligibility criteria (i.e., IgE < 30 IU/mL) and there will be additional patients who will only be able to access omalizumab (i.e., BEC <300 cells/ μ L and IgE \geq 30 IU/mL). Overall, this would result in a larger treatment population than the current PBS population for CRSwNP which would have financial implications and potentially impact the financial caps in place for mepolizumab. The ESC considered the difference in the restrictions was acceptable, however the magnitude of the potential increase in the treatment population was unclear (see paragraph 6.84).
- 3.10 New pre-filled syringe (PFS) and pre-filled pen (PFP) forms and a new 300 mg/2 mL presentation of omalizumab were recommended at the March 2025 PBAC meeting. The pre-sub-committee response (PSCR) requested that the additional forms and strength also be made available for the CRSwNP indication if PBAC recommends PBS listing.
- 3.11 The submission proposed that the requested listing include six repeats which replicates the uncontrolled severe allergic asthma indication for omalizumab. The Secretariat has proposed five repeats may be more reasonable as this aligns with the PBS listing for mepolizumab for CRSwNP.

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

4 Population and disease

- 4.1 Chronic rhinosinusitis (CRS) affects approximately 9.8% of Australians and is defined as chronic inflammation of the paranasal sinuses that persists for more than 12 weeks. There are two types of CRS –CRSwNP or CRS without NP. The prevalence of CRSwNP has been estimated to be 2-4% of the global adult population and increases with age. The average age of disease onset is estimated to be around 40 years of age. CRSwNP also occurs in 0.1% of the general paediatric population.³
- 4.2 CRSwNP is largely driven by type 2 cytokine-mediated inflammation, characterised by eosinophilic airway inflammation associated with high levels of type 2-related cytokines (interleukins 4 [IL-4], 5 [IL-5] and/or 13 [IL-13]) and IgE. Increased local production of IgE in nasal mucosa is considered a hallmark of the pathogenesis of CRSwNP, triggering the release of inflammatory mediators.
- 4.3 The clinical presentation of CRSwNP may include a range of symptoms. As NP tissue obstructs the nasal cavity, symptoms of nasal obstruction or congestion are common, occurring in 95% of patients. CRSwNP has a significant impact on quality of life (QoL), due to the patient experiencing symptoms such as nasal obstruction, loss of smell, facial pain and nasal discharge, and QoL may be further reduced by the presence of

³ Cicco MED, Bizzoco F, Morelli E, et al. Nasal Polyps in Children: the early origins of a challenging adulthood condition. *Children*. 2021;8(11) <https://doi.org/10.3390/children8110997>

Public Summary Document - May 2025 PBAC Meeting

comorbid disease, such as asthma, infection, and aspirin-exacerbated respiratory disease (AERD). Patients diagnosed with CRSwNP have a high prevalence of asthma (reported to be up to 60%).^{4 5}

- 4.4 Nasal saline irrigation and INCS are considered first-line treatments in the management of CRSwNP, however, patients with an inadequate response to these treatments may undergo surgery for removal of NP. Regrowth of NP occurs in approximately 50% of patients⁶. The EUROFEA 2023 guidance recommended consideration of biologics for patients with uncontrolled CRSwNP despite appropriate medical treatment and appropriate sinus surgery, and who fulfil 3 of 5 criteria: presence of type 2 inflammation; regular need for systemic corticosteroids; significant impact on quality of life; loss of smell; and comorbid asthma. Mepolizumab is currently the only biologic PBS-listed for the treatment of CRswNP.
- 4.5 Omalizumab is a recombinant deoxyribonucleic acid (DNA)-derived humanised monoclonal antibody that selectively binds to human IgE. Treatment with omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13 by innate, adaptive and non-immune cells (Ruffin and Busch, 2004). Omalizumab binds to IgE and prevents binding of IgE to FcεRI (high-affinity IgE receptor) expressed on mast cells and basophils, thereby reducing the amount of free IgE available to trigger the type II inflammatory cascade.

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

5 Comparator

- 5.1 The submission nominated mepolizumab as the main comparator as it is the only biologic currently available on the PBS for the treatment of CRSwNP. The ESC considered the choice of comparator was appropriate.
- 5.2 Mepolizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that is PBS-listed as an add-on treatment for adult patients (≥18 years of age) with CRSwNP with an inadequate response to intranasal corticosteroids (INCS) and BEC ≥300 cells/μl.
- 5.3 The submission did not propose a comparison to standard of care for the expanded population not eligible for mepolizumab. In the mepolizumab resubmission, the PBAC accepted standard of care, which included background INCS therapy with intermittent

⁴ Cristobal Langdon & Joaquim Mullol (2016) Nasal polyps in patients with asthma: prevalence, impact, and management challenges, *Journal of Asthma and Allergy*, 45-53

⁵ Stevens et al. "Chronic rhinosinusitis with nasal polyps." *The journal of allergy and clinical immunology: In practice* 4.4 (2016): 565-572.

⁶ https://www.allergy.org.au/images/pc/ASCIA_PC_Nasal_Polyps_FAQ_2024.pdf

Public Summary Document - May 2025 PBAC Meeting

usage of OCS and saline spray or rinses, as the appropriate comparator (para 5.1 and 7.5, mepolizumab, PSD, November 2022 PBAC meeting).

- 5.4 ESC noted that other drugs are on the horizon such as dupilumab, with a meta-analysis suggesting greater efficacy. A head-to-head trial by Sanofi of dupilumab versus omalizumab is underway (NCT04998604).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no sponsor hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from one individual and one health care professional, as well as, one medical and one consumer organisation via the Consumer Comments facility on the PBS website. The comments described how the symptoms of CRSwNP make those affected feel like they have a flu or acute upper respiratory tract infection every day and leads to impaired sleep, poor concentration and fatigue. The input stated that omalizumab reduces nasal blockage thereby improving sleep, concentration and energy levels enabling fuller contribution to their family, work and society. The input noted the initial inconvenience of administration by a general practitioner and that omalizumab must be refrigerated and is not held in stock at pharmacies. Access through self-administration at home was described as much improved.
- 6.3 The PBAC noted the advice received from The Australasian Society of Clinical Immunology and Allergy (ASCIA) supported PBS listing of omalizumab noting its acceptable safety profile and that it would likely be steroid-sparing and reduce the number of surgical procedures. Further, ASCIA described how omalizumab is already effective for treatment of chronic spontaneous urticaria and uncontrolled severe asthma and use of for CRSwNP would enable patients to change to another biologic therapy if they have a sub-optimal response to other treatments. Allergy & Anaphylaxis Australia (A&AA) and the National Allergy Council provided a joint submission to support the submission noting that patients with CRSwNP have often endured years of different treatments including nasal sprays, oral medication, and even nasal polyp surgery, only to have the polyps regrow and the symptoms recur. The requirement for repeated surgery is associated with the risk of complications, as well as monetary costs and time off work for recovery. The input described how CRSwNP is often associated with allergic conditions and that these patients may be under the care of different specialists including clinical immunologist/allergist, Ear Nose and Throat surgeon, or respiratory physician. The use of omalizumab offers patients and their treating doctors a choice of treatments that best suit the disease

Public Summary Document - May 2025 PBAC Meeting

state. The PBAC noted the statements were supported by the evidence provided in the submission.

Clinical trials

- 6.4 No head-to-head randomised controlled trials (RCTs) comparing omalizumab and mepolizumab were available. The submission was based on two RCTs which compared omalizumab to standard of care (SoC; placebo) (POLYP 1 and POLYP 2), and one RCT comparing mepolizumab to placebo (SYNAPSE), to inform an anchored indirect treatment comparison (ITC) between omalizumab and mepolizumab. An additional mepolizumab trial, MERIT, was not included in the submission's main ITC but was included in sensitivity analyses (explanation below).
- 6.5 POLYP 1 (N=138) and POLYP 2 (N=127) were replicate/identical phase 3, randomised, multicentre, double-blind, placebo-controlled studies evaluating the efficacy and safety of omalizumab versus SoC (placebo) in patients with inadequately controlled CRSwNP despite daily INCS therapy for 24 weeks. There was an open-label extension phase for both trials that consisted of a further 28-week treatment phase whereby all patients received omalizumab irrespective of previous treatment assignment.
- 6.6 SYNAPSE (N=407) was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial comparing mepolizumab versus placebo, in addition to SoC in adult patients with recurrent, refractory, severe, bilateral nasal polyp symptoms for 52 weeks. This trial was previously considered by PBAC for mepolizumab for the same indication (para 6.4, mepolizumab, PSD, November 2022 PBAC meeting).
- 6.7 MERIT (N=169) was a phase 3, randomised, double-blind, placebo-controlled, parallel-group study assessing the efficacy and safety of mepolizumab versus placebo alongside SoC in patients with CRSwNP/eosinophilic chronic rhinosinusitis (ECRS) for 52 weeks. Eligibility criteria specified that patients were not required to be using INCS. This trial has not been previously considered by PBAC.
- 6.8 The main ITC included data from POLYP 1/POLYP 2 and SYNAPSE and was based on the currently PBS-eligible population for mepolizumab (post-surgical with BEC ≥ 300 cells/ μ L) and the proposed PBS population for omalizumab (post-surgical with IgE ≥ 30 IU/mL). To support the comparative efficacy of omalizumab and mepolizumab in these populations, the submission presented ITCs for the following post-hoc subgroups: post-surgical; post-surgical with BEC ≥ 300 cells/ μ L; and proposed PBS restriction.
- 6.9 The main ITC analyses did not include the MERIT trial based on the rationale that this trial was less applicable to the Australian setting (study conducted in China, Japan and Russia; included a proportion of patients (26%) who did not receive background INCS; and no subgroup analysis for patients with BEC ≥ 300 cells/ μ L). However, an additional ITC including MERIT was provided as a sensitivity analysis. The submission stated that no statistically significant improvements in nasal polyp score (NPS) for mepolizumab

Public Summary Document - May 2025 PBAC Meeting

relative to SoC (placebo) were identified in the MERIT trial, so this approach was likely to be conservative.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
POLYP 1 (NCT03280550) and/or POLYP 2 (NCT03280537)	Final CSR GA39688 (POLYP 1), A Phase III, Randomized, Multicenter, Double-Blind, Placebo-Controlled Clinical Trial of Omalizumab in Patients with Chronic Rhinosinusitis With Nasal Polyps. Report No. 1094284.	August 2019
	Final CSR GA39855 (POLYP 2), A Phase III, Randomized, Multicenter, Double-Blind, Placebo-Controlled Clinical Trial of Omalizumab in Patients with Chronic Rhinosinusitis With Nasal Polyps. Report No. 1092977	August 2019
	Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials.	Journal of Allergy and Clinical Immunology. 2020;146(3):595-605.
SYNAPSE NCT03085797	Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial.	The Lancet Respiratory Medicine. 2021;9(10):1141-53.
	Mepolizumab for the treatment of CRSwNP. Public Summary Document.	November 2022 PBAC Meeting
	Mepolizumab for the treatment of CRSwNP. Public Summary Document	November 2021 PBAC Meeting.
MERIT NCT04607005	Fujieda S, Wang C, Yoshikawa M, Asako M, Suzaki I, Bachert C, et al. Mepolizumab in CRSwNP/ECRS and NP: the phase III randomised MERIT trial in Japan, China, and Russia.	Rhinology. 2024

Source: Table 2.5, pp44-48 of the submission.

CRSwNP, chronic rhinosinusitis with nasal polyps; CSR, clinical study report; ECRS, eosinophilic chronic rhinosinusitis; NP, nasal polyps; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document.

Note: Only the main sources of evidence included in the submission were listed in this table. Conference abstracts presented in the submission were excluded given the availability of full-text publications, from which outcomes were extracted and presented in the submission.

6.11 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Omalizumab versus placebo (in addition to INCS)					
POLYP 1 NCT03280550	138	Phase 3, R, MC, DB, PC, 24 weeks OL (extension) 28 weeks	Low ^a	Patients with inadequately controlled CRSwNP despite daily intranasal corticosteroid therapy	Change from baseline in NPS, NCS, SNOT-22, AEs
POLYP 2 NCT03280537	127	Phase 3, R, MC, DB, PC, 24 weeks OL (extension) 28 weeks	Low ^a	Patients with inadequately controlled CRSwNP despite daily intranasal corticosteroid therapy	Change from baseline in NPS, NCS, SNOT-22, AEs
Meta-analysis	265	Included POLYP 1 and POLYP 2; sub-group analysis; assessed outcomes above and multiple secondary and exploratory outcomes			
Mepolizumab versus placebo (in addition to/alongside SoC^b)					

Public Summary Document - May 2025 PBAC Meeting

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
SYNAPSE NCT03085797	407	Phase 3, R, MC, DB, PC, PG 52 weeks	Low	Patients with recurrent, refractory, severe, bilateral NP symptoms (NO-VAS score of >5) and with prior NP surgery	Change from baseline in NPS, SNOT-22, AEs
MERIT NCT04607005 (sensitivity analysis only)	169	Phase 3, R, MC, DB, PC, PG 52 weeks	Some concerns	Patients with CRSwNP/ E CRS	Change from baseline in NPS, SNOT-22, AEs

Source: Table 2.6, p55 of the submission, p49-57 of submission, Table 5.1 and Table 5.2, pp162-165 of the submission.

AE, adverse events; CRSwNP, chronic rhinosinusitis with nasal polyps; DB, double blind; ECRS, eosinophilic chronic rhinosinusitis; INCS, intranasal corticosteroids; MC, multi-centre; NCS, nasal congestion score; NO-VAS, nasal obstruction visual analogue scale; NP, nasal polyp; NPS, nasal polyp score; OL, open label; PC, placebo- controlled; PG, parallel-group; R, randomised; SNOT-22, sino-nasal outcomes test-22; SoC, standard of care.

^a Risk of bias assessment considering results presented at week 24.

^b SoC was included in both treatment arms in addition to the study drug in SYNAPSE and MERIT. In SYNAPSE, SoC included mometasone furoate intranasal spray for at least 8 weeks before screening and during the study, saline nasal irrigations, systemic corticosteroids or antibiotics, or both (as required). In MERIT, SoC treatments was in accordance with local practice, which could have included optional daily intranasal corticosteroids (INCS) and saline nasal douching, occasional short courses of high-dose oral corticosteroids (OCS), and/or antibiotics when required.

Note: While POLYP trials did not specify SoC, patients received INCS and systemic corticosteroids along with the study treatment.

6.12 While the POLYP 1, POLYP 2 and SYNAPSE trials were assessed with an overall low risk of bias, the MERIT trial was considered to have a moderate risk of attrition bias due to discontinuations (7.1% mepolizumab and 18.8% SoC (placebo)) leading to an overall risk of bias of ‘some concerns’. The low overall risk of bias for the SYNAPSE trial is consistent with a prior assessment of mepolizumab (para 6.6, mepolizumab, PSD, November 2022 PBAC meeting).

6.13 The open label extensions of the POLYP trials (week 24 to week 52) are subject to high risk of performance and attrition bias with all patients crossing over to receive omalizumab after Week 24. However, the open label results were excluded from the ITC analyses. Only 24-week results were used for these analyses and to support the clinical claim.

6.14 The eligibility criteria of the four studies were broadly consistent with the proposed PBS listing, however, there were some key differences in study design, inclusion/exclusion criteria and baseline characteristics between studies, which impact the transitivity assumption:

- The SYNAPSE study was limited to patients who had undergone prior surgery for NPs (100%), while the POLYP 1/2 and MERIT trials were not restricted to nasal surgery in the previous 6 months, and included 60% and 64% of patients with previous surgery, respectively. The submission presented an ITC including available data for post-surgical populations from the POLYP 1/2 and MERIT trials.
- Eligibility criteria related to severity of the disease varied across studies. While all studies required an NPS of ≥ 5 , SYNAPSE and MERIT additionally required an obstruction Visual Analog Scale (VAS) symptom score of >5 (and overall VAS symptom score >7 for SYNAPSE only) whereas POLYP 1/2 trials included patients with a SNOT-22 score of ≥ 20 . This variation indicated a range in severity of nasal

Public Summary Document - May 2025 PBAC Meeting

symptoms from moderate to severe. The lack of consistency across the trials in the definition of disease severity in CRSwNP was similarly raised in the TGA Delegate's Overview for omalizumab. The Delegate considered on the basis of prior surgery and systemic corticosteroid use, populations with more severe disease were investigated in the mepolizumab study. However, the mean NPS and SNOT-22 indicated similar disease severity across the studies.

- Mean NPS was highest in the POLYP trials (mean=6.3) followed by MERIT (mean=6.0) and lowest in SYNAPSE (mean=5.5), whereas the mean SNOT-22 score was highest in SYNAPSE (mean=64) followed by POLYP (mean=60) and lowest in MERIT (mean=57). NPS scores ≥ 5 and SNOT-22 score ≥ 50 indicate severe CRSwNP and severe nasal symptoms, respectively.^{7 8}
- POLYP 1/2 and SYNAPSE required prior treatment with INCS. While this was not a requirement for MERIT, a high proportion (74%) of the MERIT population had used INCS previously. It is unclear how this may bias the results. A subgroup analysis of this population was not presented.
- MERIT was conducted in three countries (Russia, China and Japan), while POLYP 1/2 and SYNAPSE were conducted in 20 and 11 countries, respectively, across South America, North America, Europe and Asia. A lower proportion of patients were white/Caucasian in the MERIT trial (28-29%) compared to the other trials (91% to 100%). Differences in study site geographic locations and patient demographics may impact generalisability of results, although the direction and magnitude of the potential impact is unclear.

6.15 There are several patient characteristics and variables that might indicate less complexity in patients enrolled in the POLYP trials compared to MERIT and SYNAPSE as follows:

- Patients in the MERIT trial were required to have a BEC level $>2\%$ while this was not a requirement for POLYP 1/2 and SYNAPSE trials. A minimum threshold of 2% for BEC is approximately equivalent to the minimum threshold of the 150 cells/ μL absolute count recommended in the recent European guidelines.
- A higher proportion of patients (54%) in the MERIT and SYNAPSE (48%) trial used systemic corticosteroids (SCS) prior to the study treatment compared to and POLYP 1/2 trials (20%). SCS use was also permitted during each of the three trials with SYNAPSE reporting a higher SCS use (25% in the mepolizumab arms and 37% in the SoC (placebo) arm) compared to the POLYP trials (2.3% in the omalizumab arms and 6.2% in the SoC (placebo) arm), while SCS use was not reported in the

⁷ Toma S, Hopkins C. (2016), 'Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments'. *Rhinology*. 2016 Jun;54(2):129-33. doi: 10.4193/Rhino15.072.

⁸ Gelardi M, et al. (2022). 'Chronic rhinosinusitis with nasal polyps: how to identify eligible patients for biologics in clinical practice'. *Acta Otorhinolaryngol Ital*. 2022 Feb;42(1):75-81. doi: 10.14639/0392-100X-N1699.

Public Summary Document - May 2025 PBAC Meeting

MERIT trial. The higher use of SCS in the SoC (placebo) arm may have underestimated the treatment effect of mepolizumab considered in the ITC.

- POLYP trials had fewer asthmatic patients (54-60%) compared to SYNAPSE (68-74%) and MERIT (79%). As stated in para 4.3, patients with asthma as a comorbidity are likely to suffer a more detrimental impact from CRSwNP.
- Lower proportion of aspirin sensitive patients in POLYP trials (21-26%) compared to SYNAPSE (22-31%) and MERIT (30-45%). Similarly to asthmatic patients, those with aspirin sensitivity as a comorbidity are more likely to suffer a more detrimental impact on quality of life from CRSwNP (see para 4.3).
- Lower mean BEC levels in patients across treatment arms in the POLYP trials (320-360 cells/ μ L) compared to SYNAPSE (390-400 cells/ μ L) and MERIT (390-450 cells/ μ L). Patients with higher BEC levels are more likely to have increased risk of exacerbations in various pulmonary and extra pulmonary diseases such as allergy.⁹

6.16 The following characteristics suggest more complex patients in the POLYP 1/2 subgroups compared to mepolizumab patients:

- Higher BEC levels for the post-surgical + BEC \geq 300 subgroup of the POLYP 1/2 trials (530-550 cells/ μ L) compared to the ITT population of SYNAPSE (390-400 cells/ μ L) and MERIT (390-450 cells/ μ L).
- Higher proportion of aspirin sensitive patients for the post-surgical (30-37%) and post-surgical + BEC \geq 300 (31-34%) subgroups compared to SYNAPSE (22-31%) but lower compared to MERIT (30-45%).
- Higher proportion of asthmatic patients for the post-surgical + BEC \geq 300 (77-79%) subgroup compared to SYNAPSE (68-74%), but similar to MERIT (79%).

6.17 The submission included adjusted ITC analyses for differences between treatment arms within each trial, but these analyses did not account for the differences between trials. Differences in the eligibility criteria, study design and baseline characteristics described above were identified to be important transitivity concerns that could have confounded the results of the indirect comparisons. As such, these results should be interpreted with caution given the combined impact of the identified differences on observed outcomes are uncertain.

6.18 Overall, the definitions of the outcomes of all included trials were broadly aligned. However, outcomes included in POLYP trials were measured at week 24 while outcomes included in the mepolizumab trials were measured at week 52. The different duration of the trials may have biased the comparability of omalizumab versus mepolizumab in favour of mepolizumab given greater data maturity. Data from

⁹ Lim et al, (2024), 'Type-2 Inflammation in Health and Disease: Prevalence, Risk Factors and Multimorbidity'. J Clin Med. 2024 Nov 6;13(22):6662. doi: 10.3390/jcm13226662.

Public Summary Document - May 2025 PBAC Meeting

SYNAPSE suggested that efficacy outcomes continued to improve between Week 24 and Week 52.

- 6.19 The POLYP and MERIT trials compared change from baseline of NPS and of SNOT-22 across treatment arms as mean differences with 95% confidence interval [CI] while SYNAPSE reported median (95% CI) differences. To account for the variation in measures in the ITC, the submission reported treatment effects as median (95% CI) changes to align with the SYNAPSE trial using quantile regression and accounting for the same covariates as SYNAPSE. Sensitivity analyses for the ITCs were conducted in the submission using the mean change in NPS between the POLYP and MERIT trials where data were available. These analyses were not adjusted for differences between trials and their impact on direction and magnitude of the results was uncertain.
- 6.20 Overall, the trial setting (POLYP 1/2) was reasonably consistent with the proposed Australian setting; however, similar to mepolizumab, there were applicability issues as the requested restriction allowed patients to access omalizumab if they were unsuitable for surgery or contraindicated or intolerant to INCS, but there was no evidence to support the use of omalizumab in these populations. The PBAC previously 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). An RSA is in place for mepolizumab for CRSwNP and is discussed in Financial Management – Risk Sharing Arrangements below.
- 6.21 The submission proposed the following MCID for NPS and SNOT-22 based on the proposed MCID for mepolizumab in the November 2022 submission:
- Change from baseline in total NPS: An NPS score responder was defined as a participant who had an improvement (decrease) of ≥ 1.0 point (based on Bachert 2021). The submission proposed a non-inferiority margin based on this MCID for NPS, claiming consistency with the published literature on CRSwNP (Sedaghat et al., 2024). This MCID is not validated.
 - Change from baseline in SNOT-22 total score: The MCID for was defined as a ≥ 8.9 change in SNOT-22 score (Hopkins 2009).
- 6.22 As documented in the mepolizumab PSD, the proposed MCIDs for NPS were not explicitly stated in Bachert 2021 (the proportion of patients who achieved a reduction of the endoscopic nasal polyp (ENP) score by at least 1 point was reported but it was not stated whether this was clinically meaningful) (para 6.10, mepolizumab, PSD, November 2022 PBAC meeting). However, the PBAC considered that mepolizumab treatment was expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of change from baseline in endoscopic NPS and nasal obstruction VAS (NO-VAS) score along with the impact seen on time to first nasal surgery and improvements in QoL (para 7.13, mepolizumab, PSD, November 2022 PBAC meeting).

Public Summary Document - May 2025 PBAC Meeting

- 6.23 The submission included post hoc analyses for NPS \geq 1-point improvement from baseline, NPS \geq 2-point improvement from baseline, SNOT-22 \geq 8.9-point improvement from baseline and change from baseline in EuroQol 5-Dimension 5-level Questionnaire (EQ-5D-5L). Post hoc analyses are less rigorous and have additional potential for bias than analyses pre-specified in trial protocols.
- 6.24 A systematic review (Papacharalampous et al. 2024)¹⁰ comparing (indirectly) the efficacy of omalizumab, mepolizumab, and dupilumab in CRS treatment was identified during the evaluation. This review considered results from the POLYP 1, POLYP 2, SYNAPSE (included in the citation list of this submission), and dupilumab trials (SINUS-24 and SINUS 52) as well as published systematic reviews, meta-analyses and ITCs of omalizumab, dupilumab, and mepolizumab. The study comparisons were based on the literature for their impact on selected endpoints of interest including change from baseline in NPS, NCS, sense of smell/loss of smell (LoS), SNOT-22, radiologic severity and the need for rescue sinonasal surgery in CRS patients. The ESC noted a head-to-head trial by Sanofi of dupilumab versus omalizumab was underway (NCT04998604).

Comparative effectiveness

Direct comparison of omalizumab versus SoC (placebo)

- 6.25 Table 4 presents a summary of the results of the primary efficacy outcomes (mean change from NPS and NCS at Week 24) and key secondary outcome (mean change from baseline in SNOT-22 at Week 24) along with the meta-analyses results for the POLYP 1/2 trials.

Table 4: Results of change from baseline in NPS, NCS and SNOT-22 across the POLYP trials

Trial ID	Omalizumab			SoC (Placebo)			MD [95% CI]; p-value
	Mean	SD	N	Mean	SD	N	
Change from baseline in NPS at Week 24							
POLYP 1	-1.08	1.36	72	0.06	1.30	66	-1.14 [-1.58, -0.70]; p<0.00001
POLYP 2	-0.9	1.34	62	-0.31	1.29	65	-0.59 [-1.05, -0.13]; p=0.01
Meta-analysis:							-0.87 [-1.41, -0.33]; p=0.002
Heterogeneity of meta-analysed studies							$I^2=65\%$; p=0.09
Change from baseline in NCS at Week 24							
POLYP 1	-0.89	0.85	72	-0.35	0.89	66	-0.54 [-0.83, -0.25]; p=0.0003
POLYP 2	-0.70	0.87	62	-0.20	0.89	65	-0.50 [-0.80, -0.20]; p=0.001
Meta-analysis:							-0.52 [-0.73, -0.31]; p<0.00001
Heterogeneity of meta-analysed studies							$I^2=0\%$; p=0.85
Change from baseline in SNOT-22 at Week 24							
POLYP 1	-24.70	17.06	72	-8.58	16.90	66	-16.12 [-21.79, -10.45]; p<0.00001
POLYP 2	-21.59	17.72	62	-6.55	17.66	65	-15.04 [-21.19, -8.89]; p<0.00001
Meta-analysis:							-15.62 [-19.79, -11.45]; p<0.00001
Heterogeneity of meta-analysed studies							$I^2=0\%$; p=0.80

¹⁰ Papacharalampous GX, Constantinidis J, Fotiadis G, Zhang N, Bachert C, Katotomichelakis M. (2024), ‘Chronic rhinosinusitis with nasal polyps (CRSwNP) treated with omalizumab, dupilumab, or mepolizumab: A systematic review of the current knowledge towards an attempt to compare agents’ efficacy’. Int Forum Allergy Rhinol. 2024; 14: 96–109. <https://doi.org/10.1002/alr.23234>

Public Summary Document - May 2025 PBAC Meeting

Source: Table 2.17, Table 2.18 and Table 2.19, pp-79-83 of the submission.

CI, confidence interval; MD, mean difference; N, total participants in group; NCS, nasal congestion score; NPS, nasal polyp score; SD, standard deviation; SoC, standard of care; SNOT-22, Sino-Nasal Outcome Test-22.

Note: Results in **bold** indicate statistically significant difference (p<0.05)

- 6.26 Based on the meta-analysis results of POLYP 1/2, omalizumab showed statistically significant reduction in NPS (mean difference (MD)=-0.87 [95% CI: -1.41, -0.33]; p=0.002), in NCS (MD=-0.52 [-0.73, -0.31]; p<0.00001) and SNOT-22 (MD=-15.62 [-19.79, -11.45]; p<0.00001) at Week 24 compared to SoC (placebo). For NPS, there was substantial heterogeneity across the two POLYP studies (I²=65%; p=0.09), with a greater reduction in NPS in POLYP 1 (MD -1.14 [95% CI: -1.58, -0.70]) than in POLYP 2 (MD -0.59 [95% CI: -1.05, -0.13]) and the meta-analysis results did not meet the specified MCID. However, ESC was reassured that CRSwNP patients treated with omalizumab were significantly more likely to experience ≥1 point improvement in NPS compared with those who received placebo (see Table 5) and this was similar to the results for mepolizumab (see Table 7 and Table 8). The meta-analysis results for SNOT-22 met the specified MCID.
- 6.27 The open label extension results reflecting omalizumab use from week 24 to 52 showed greater reductions from baseline in NPS and NCS in both omalizumab (Mean=-1.31 and mean=-1.12, respectively) and SoC (placebo) (Mean=-0.97 and mean=-0.99, respectively) arms.
- 6.28 Table 5 summarises the responder outcomes based on a ≥ 1-point improvement in NPS, ≥ 2-point improvement in NPS, and ≥ 8.9-point improvement in SNOT-22 from baseline to Week 24 in the POLYP trials.

Table 5: Results of the responder outcomes in the POLYP trials

Trial ID	Omalizumab n/N (%)	SoC (placebo) n/N (%)	OR [95% CI]; p-value
≥1 point improvement in NPS^a			
POLYP 1	39/60 (56.5)	17/65 (26.2)	4.0 [1.91, 8.66]; p=0.0003
POLYP 2	33/59 (55.9)	20/64 (31.3)	2.84 [1.32, 6.14]; p=0.0077
Meta-analysis:			3.79 [95% CI: 2.05, 7.03]; p<0.0001
Heterogeneity of meta-analysed studies			I ² =26%; p=0.25
≥2 point improvement in NPS^a			
POLYP 1	22/69 (31.9)	6/65 (9.2)	5.44 [1.97, 15.03]; p=0.0011
POLYP 2	18/59 (30.5)	9/64 (14.1)	2.39 [0.95, 6.05]; p=0.0649
Meta-analysis:			3.43 [95% CI: 1.77, 6.65]; p=0.0003
Heterogeneity of meta-analysed studies			I ² =0%; p=0.43
≥ 8.9-point improvement in SNOT-22^b			
POLYP 1	53/69 (76.8)	30/65 (46.2)	4.55 [2.07, 9.97]; p=0.0002
POLYP 2	39/59 (66.1)	23/63 (36.5)	3.71 [1.72, 8.04]; p=0.0009
Meta-analysis:			3.62 [95% CI: 2.14, 6.12]; p<0.00001
Heterogeneity of meta-analysed studies			I ² =0%; p=0.81

Source: Table 2.22, Figure 2.12, Figure 2.13, Figure 2.14, pp85-87 of the submission

CI, confidence interval; n, number of participants; N, total participants in group; NPS, nasal polyp score; OR, odds ratio; SoC, standard of care; SNOT-22, Sino-Nasal Outcome Test-22.

Note: Results in **bold** indicate statistically significant difference (p<0.05)

Public Summary Document - May 2025 PBAC Meeting

^a Unadjusted p values for comparison between omalizumab and SoC (placebo) groups are presented. The worst observed post-baseline and pre-intercurrent event NPS for a given patient is used to impute values post rescue treatment or discontinuation of study drug due to PD, AE, or LOE (whichever is earlier). Response variables defined as improvement at Week 24 in NPS ≥ 1 are analysed separately and adjusted for baseline NPS, asthma/asthma sensitivity comorbidity status and geographic region.

^b Logistic regression models are adjusted for baseline SNOT-22, geographic region and asthma/asthma sensitivity comorbidity status.

6.29 The meta-analysed results demonstrated that patients treated with omalizumab are statistically significantly more likely to experience a ≥ 1 -point improvement in NPS (odds ratio [OR]=3.79 [95% CI: 2.05, 7.03]; $p < 0.0001$), a ≥ 2 -point improvement in NPS (OR=3.43 [95% CI: 1.77, 6.65]; $p = 0.0003$) and a ≥ 8.9 -point improvement in SNOT-22 (OR=3.62 [95% CI: 2.14, 6.12]; $p < 0.00001$), noting the results in ≥ 2 -point improvement in NPS were not statistically significant for the POLYP 2 trial. These analyses have additional potential for bias due to being post-hoc.

6.30 Table 6 presents the QoL outcome of change from baseline in EQ-5D-5L VAS score at Week 24 in the POLYP trials.

Table 6: Change from baseline in EQ-5D-5L VAS score at Week 24 in the POLYP trials

Trial ID	Omalizumab			SoC (placebo)			MD [95% CI]; p-value
	Mean	SD	N	Mean	SD	N	
POLYP 1	9.8	16.9	72	4.2	21.2	66	5.60 [-0.83, 12.03]; $p = 0.09$
POLYP 2	4.9	16.7	62	0.4	17.5	65	4.50 [-1.45, 10.45]; $p = 0.14$
Meta-analysis:							5.01 [0.64, 9.37]; $p = 0.02$
Heterogeneity of meta-analysed studies							$I^2 = 0\%$; $p = 0.81$

Source: Table 2.23, p87 of the submission

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-Dimension 5-level; MD, mean difference; N, total participants in group; SD, standard deviation; SoC, standard of care; VAS, visual analogue score.

Note: Results in **bold** indicate statistically significant difference ($p < 0.05$)

6.31 The meta-analysis of the POLYP trials showed that patients treated with omalizumab experienced a statistically significant greater improvement in EQ-5D-5L VAS score compared to patients treated with SoC (placebo) (MD=5.01 [95% CI: 0.64, 9.37]; $p = 0.02$). However, the individual POLYP 1 and POLYP 2 results showed no significant differences in EQ-5D-5L VAS score, noting these analyses have additional potential for bias due to being post-hoc.

6.32 The submission also presented additional secondary outcomes results from POLYP trials. These outcomes were not used to support the clinical claim, economic analysis or financial estimates. In summary, these results showed that omalizumab provided statistically significant improvements ($p < 0.05$) in Total Nasal Symptom Score (TNSS), Sense of Smell Score (SSS), Posterior Rhinorrhoea Score (PRS), Anterior Rhinorrhoea Score (ARS), the University of Pennsylvania Smell Identification Test (UPSIT), Asthma Quality of Life Questionnaire (AQLQ) and the reduction in the need for nasal surgery compared to SoC (placebo) (OR=6.76 [95% CI: 2.26, 20.19]; $p = 0.0006$). Time to first nasal surgery was an important factor in the mepolizumab consideration (para 7.13, mepolizumab, PSD, November 2022 PBAC meeting), however this outcome was not included in the ITC presented in the submission.

Indirect comparison of omalizumab versus mepolizumab

6.33 Table 7 presents the ITC results of the median and mean change from baseline in NPS for the ITT population and the post-surgical, post-surgical with BEC ≥ 300 cells/ μ L and restriction-based subgroups. The ITCs used pooled data rather than meta-analysed results from the POLYP trials. The submission stated that given that POLYP 1/2 were replicate trials, pooled data was considered appropriate. The approach applied was inconsistent with ITC presented for safety which included meta-analysis results from the POLYP trials and mepolizumab trials.

6.34 The pooled results for NPS (MD=-0.80 [95% CI: -1.12, -0.48]; $p < 0.00001$) reported a lower MD compared with the meta-analysed results (MD=-0.87 [95% CI: -1.41, -0.33]; $p = 0.002$) but trended in the same direction. Given the availability of meta-analysed results which have the advantage of increasing statistical power and account for heterogeneity, it may have provided a more precise estimate of treatment effect.

Table 7: Efficacy results of the ITC: Median and mean change from baseline in NPS across trials

Analysis	Trial ID	N	Intervention, change from baseline	N	SoC (placebo), change from baseline	Treatment effect [95% CI]; p-value <0 favour Intervention
ITT POPULATION						
OMA vs. PBO ^a	POLYP 1/2	134	-1.00	131	0.00	-1.00 [-1.53, -0.47]
MEPO vs. PBO ^a	SYNAPSE	206	-1.00	201	0.00	-0.73 [-1.11, -0.34]
ITC OMA vs. MEPO ^a	POLYP 1/2 (N=134) vs. SYNAPSE (N=206)					-0.27 [-0.92, 0.38]; $p=0.4171$
OMA vs. PBO ^b	POLYP 1/2	134	-0.99	131	-0.19	-0.73 [-1.06, -0.41]
MEPO vs. PBO ^b	MERIT	84	-0.65	85	-0.19	-0.47 [-0.92, -0.02]; $p=0.043$
ITC OMA vs MEPO ^b (SENSITIVITY)	POLYP 1/2 (N=134) vs. MERIT (N=84)					-0.26 [-0.82, 0.30]; $p=0.3581$
POST-SURGICAL SUBGROUP						
OMA vs. PBO ^a	POLYP 1/2	78	-1.00	80	0.00	-1.00 [-1.75, -0.25]
MEPO vs. PBO ^a	SYNAPSE	206	-1.00	201	0.00	-0.73 [-1.11, -0.34]
ITC OMA vs. MEPO ^a	POLYP 1/2 (N=78) vs. SYNAPSE (N=206)					-0.27 [-1.12, 0.58]; $p=0.5313$
OMA vs. PBO ^b	POLYP 1/2	78	-1.04	80	-0.15	-0.76 [-1.46, -0.06]
MEPO vs. PBO ^b	MERIT	55	NR	53	NR	-0.56 [-1.22, 0.10]
ITC OMA vs MEPO ^b (SENSITIVITY)	POLYP 1/2 (N=78) vs. MERIT (N=55)					-0.20 [-1.16, 0.76]; $p=0.6787$
POST-SURGICAL WITH BEC ≥ 300 CELLS/μL SUBGROUP						
OMA vs. PBO ^a	POLYP 1/2	35	-0.5	47	0.0	-1.33 [-2.60, -0.07]
MEPO vs. PBO ^a	SYNAPSE	139	-1.0	139	0.0	-1.00 [-1.50, -0.50]
ITC OMA vs. MEPO ^a	POLYP 1/2 (N=35) vs. SYNAPSE (N=139)					-0.33 [-1.69, 1.03]; $p=0.6329$
RESTRICTION-BASED SUBGROUP						
OMA vs. PBO ^a	POLYP 1/2	78	-1.0	80	0.0	-1.00 [-1.75, -0.25]
MEPO vs. PBO ^a	SYNAPSE	139	-1.0	139	0.0	-1.00 [-1.50, -0.50]
ITC OMA vs. MEPO ^a	POLYP 1/2 (N=78) vs. SYNAPSE (N=139)					0 [-0.904, 0.904]; $p=1.0$

Source: Table 2.38, Table 2.40, Table 2.42, Table 2.44, pp119-123 of the submission.

BEC, blood eosinophil count; CI, confidence interval; ITC, indirect treatment comparison; ITT, intention-to-treat; MEPO, mepolizumab; N, total participants in group; NPS, nasal polyp score; OMA, omalizumab; PBO, placebo; SoC, standard of care.

^a Reported as median difference.

^b Reported as mean difference

Note: the pooled analyses derived from the IPD may differ to the meta-analysed results of the POLYP studies presented in Section 2.5, which reflect adjusted analyses derived from the POLYP CSRs.

Public Summary Document - May 2025 PBAC Meeting

POLYP: As per the analyses of SYNAPSE, quantile regression was run using R software to account for the following covariates: treatment group, age, sex, race, ethnicity, baseline NPS, asthma, and BEC ≥ 300 cells/ μ L.

SYNAPSE: Adjusted difference in medians; quantile regression with covariates of treatment group, geographic region, baseline score, and loge baseline blood eosinophil count.

MERIT: The differences in change from baseline scores between treatment groups were assessed using the mixed model repeated model, adjusting for covariates of baseline value, log baseline blood eosinophil count, background INCS use, country, and timepoint, presented as a difference in means between treatment groups.

- 6.35 The ITC of median change from baseline in NPS for POLYP 1/2 and SYNAPSE showed no statistically significant difference between omalizumab and mepolizumab for the ITT population nor for any of the subgroups: (MD=-0.27 [95% CI: -0.92, 0.38]; p=0.4171), post-surgical subgroup (MD=-0.27 [95% CI: -1.12, 0.58]; p=0.5313), post-surgical + BEC ≥ 300 cells/ μ L subgroup (MD=-0.33 [95% CI: -1.69, 1.03]; p=0.6329) and restriction based subgroup (MD=0 [95% CI: [-0.904, 0.904]; p=1.0).
- 6.36 In addition, the sensitivity analyses of the ITC for POLYP 1/2 and the MERIT trial for mean change from baseline in NPS also demonstrated no statistically significant difference between omalizumab and mepolizumab for the ITT populations (MD= -0.26% [95% CI: -0.82, 0.30]) and post-surgical subgroup (MD=-0.20% [95% CI: -1.16, 0.76]; p=0.6787).
- 6.37 The submission indicated that the upper 95% CIs of the indirect treatment difference for median and mean change from baseline in NPS is less than the non-inferiority margin of 1, supporting the non-inferiority of omalizumab against mepolizumab in the ITT populations. This was uncertain given the transitivity issues identified across trials as described above (para 6.17, 6.18 and 6.19); the MCID for the non-inferiority margin was not strongly justified, and the use of post-hoc analyses with the potential for additional bias.
- 6.38 Table 8 presents the results of the responder outcomes based on ≥ 1 -point improvement in NPS, ≥ 2 -point improvement in NPS, and ≥ 8.9 -point improvement in SNOT-22 from baseline across all trials for the ITC population and subgroups, including meta-analyses and ITC results.

Public Summary Document - May 2025 PBAC Meeting

Table 8: Efficacy results of ITC: Responder outcomes across trials

Analysis	Trial ID	Intervention, n/N (%)	SoC (placebo), n/N (%)	OR [95% CI]; p-value >1 favour Intervention
ITT POPULATION				
≥1-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^a	72/128 (56.3%)	37/129 (28.7%)	3.20 [1.91, 5.36]
MEPO vs. PBO	SYNAPSE	104/206 (50.5%)	57/201 (28.4%)	2.58 [1.71, 3.88]
	MERIT	43/84 (51.2%)	32/85 (37.6%)	1.74 [0.94, 3.21]
	SYNAPSE/MERIT meta-analysis k=2			2.26 [1.58, 3.25]
ITC OMA vs. MEPO	POLYP 1/2 (N=128) vs. SYNAPSE (N=206)			1.24 [0.64, 2.40]; p=0.5217
ITC OMA vs MEPO (SENSITIVITY)	POLYP 1/2 (N=128) vs. SYNAPSE/MERIT (N=290) meta-analysis k=2			1.42 [0.76, 2.66]; p=0.2789
≥2-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^a	40/128 (31.25%)	15/129 (11.63%)	3.45 [1.79, 6.65]
MEPO vs. PBO	SYNAPSE	74/206 (35.9%)	26/201 (12.9%)	3.77 [2.29, 6.23]
ITC OMA vs. MEPO	POLYP 1/2 (N=128) vs. SYNAPSE (N=206)			0.92 [0.40, 2.09]; p=0.8331
≥8.9 improvement from baseline in SNOT-22				
OMA vs. PBO	POLYP 1/2 ^b	92/128 (71.88%)	53/128 (41.41%)	3.62 [2.15, 6.09]
MEPO vs. PBO	SYNAPSE ^c	150/205 (73.2%)	106/198 (53.5%)	2.37 [1.56, 3.59]
ITC OMA vs. MEPO	POLYP 1/2 (N=128) vs. SYNAPSE (N=205)			1.53 [0.78, 2.98]; p=0.2131
POST-SURGICAL SUBGROUP				
≥1-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^d	43/73 (58.9%)	20/79 (25.3%)	4.23 [2.12, 8.42]
MEPO vs. PBO	SYNAPSE	104/206 (50.5%)	57/201 (28.4%)	2.58 [1.71, 3.88]
ITC OMA vs. MEPO	POLYP 1/2 (N=73) vs. SYNAPSE (N=206)			1.64 [0.74, 3.66]; p=0.227
≥2-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^d	27/73 (36.99%)	10/79 (12.66%)	4.05 [1.79, 9.16]
MEPO vs. PBO	SYNAPSE	74/206 (35.92%)	26/201 (12.94%)	3.77 [2.29, 6.23]
ITC OMA vs. MEPO	POLYP 1/2 (N=73) vs. SYNAPSE (N=206)			1.07 [0.41, 2.8]; p=0.8834
≥8.9 improvement from baseline in SNOT-22				
OMA vs. PBO	POLYP 1/2 ^e	51/73 (69.86%)	32/78 (41.03%)	3.33 [1.70, 6.53]
MEPO vs. PBO	SYNAPSE ^c	150/205 (73.17%)	106/198 (53.54%)	2.37 [1.56, 3.59]
ITC OMA vs. MEPO	POLYP 1/2 (N=73) vs. SYNAPSE (N=205)			1.41 [0.64, 3.1]; p=0.3997
POST-SURGICAL WITH BEC ≥300 CELLS/μL SUBGROUP				
≥1-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^f	17/34 (50.0%)	12/46 (26.1%)	2.83 [1.11, 7.26]
MEPO vs. PBO	SYNAPSE	70/139 (50.4%)	39/139 (28.1%)	2.60 [1.58, 4.28]
ITC OMA vs. MEPO	POLYP 1/2 (N=34) vs. SYNAPSE (N=139)			1.09 [0.38, 3.15]; p=0.8758
≥2-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^f	14/34 (41.18%)	5/46 (10.87%)	5.74 [1.81, 18.18]
MEPO vs. PBO	SYNAPSE	50/139 (35.97%)	17/139 (12.23%)	4.03 [2.18, 7.45]
ITC OMA vs. MEPO	POLYP 1/2 (N=34) vs. SYNAPSE (N=139)			1.42 [0.39, 5.26]; p=0.5958
RESTRICTION-BASED SUBGROUP				
≥1-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^g	43/73 (58.9%)	20/79 (25.3%)	4.23 [2.12, 8.42]
MEPO vs. PBO	SYNAPSE	70/139 (50.4%)	39/139 (28.1%)	2.60 [1.58, 4.28]
ITC OMA vs. MEPO	POLYP 1/2 (N=73) vs. SYNAPSE (N=139)			1.63 [0.69, 3.81]; p=0.2622
≥2-point improvement from baseline in NPS				
OMA vs. PBO	POLYP 1/2 ^g	27/73 (36.99%)	10/79 (12.66%)	4.05 [1.79, 9.16]
MEPO vs. PBO	SYNAPSE	50/139 (35.97%)	17/139 (12.23%)	4.03 [2.18, 7.45]
ITC OMA vs. MEPO	POLYP 1/2 (N=73) vs. SYNAPSE (N=139)			1.01 [0.36, 2.79]; p=0.9924

Source: Table 2.37, Table 2.39, Table 2.41, Table 2.43, pp118-123 of the submission.

Public Summary Document - May 2025 PBAC Meeting

BEC, blood eosinophil count; CI, confidence interval; ITC, indirect treatment comparison; ITT, intention-to-treat; MEPO, mepolizumab; n, number of participants; N, total participants in group; NPS, nasal polyp score; OMA, omalizumab; OR, odds ratio; PBO, placebo; SNOT-22, sino-nasal outcomes test-22; SoC, standard of care.

^a n=6 omalizumab-treated patients and n=2 placebo-treated patients with missing values were not included in the analyses.

^b n=6 omalizumab-treated patients and n=3 placebo-treated patients with missing values were not included in the analyses.

^c n=1 mepolizumab-treated patients and n=3 placebo-treated patients with missing values were not included in the analyses.

^d n=5 omalizumab-treated patients and n=1 placebo-treated patients with missing values were not included in the analyses.

^e n=5 omalizumab-treated patients and n=2 placebo-treated patients with missing values were not included in the analyses.

^f n=1 omalizumab-treated patient and n=1 placebo-treated patients with missing values were not included in the analyses.

^g n=5 omalizumab-treated patients and n=1 placebo-treated patients with missing values were not included in the analyses.

Note: the pooled analyses derived from the IPD may differ to the meta-analysed results of the POLYP studies presented in Section 2.5, which reflect adjusted analyses derived from the POLYP CSRs.

No additional analyses were performed to control for covariates on these outcomes (i.e., unadjusted).

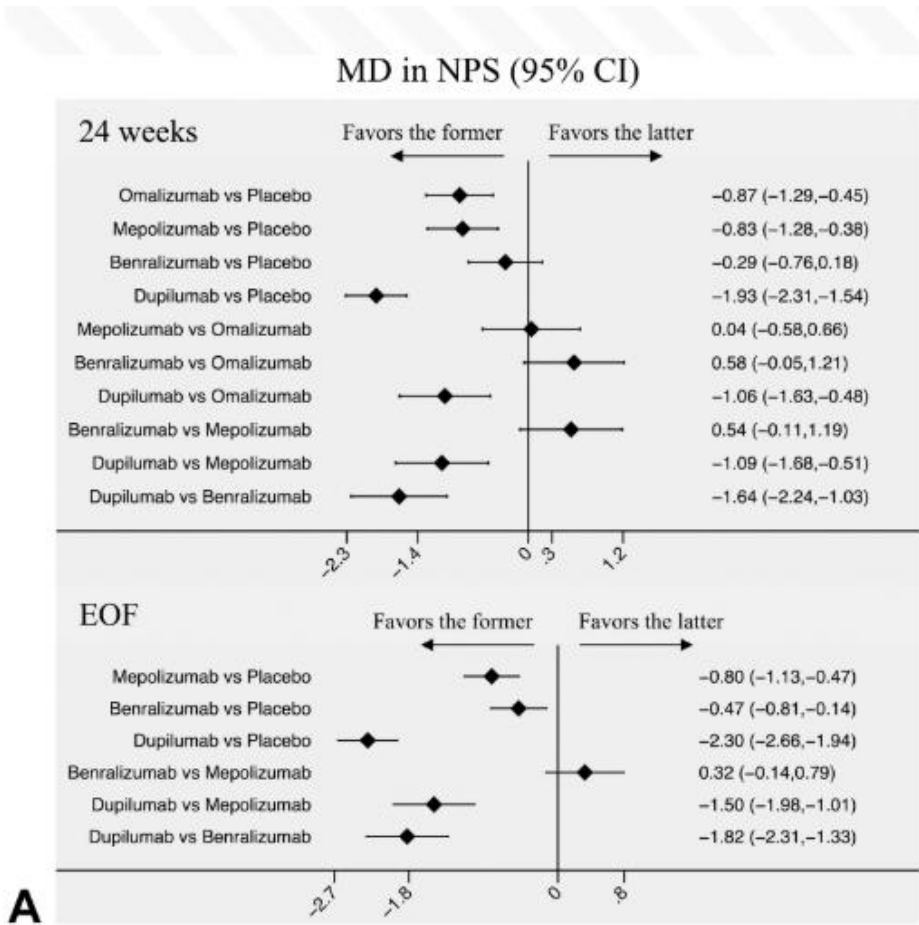
Meta-analyses were conducted online using Review manager.

- 6.39 The ITC of POLYP 1/2 and SYNAPSE based on the ITT populations and post-surgical subgroups reported no statistically significant differences between omalizumab and mepolizumab for all three responder outcomes: ≥ 1 -point improvement from baseline in NPS, ≥ 2 -point improvement from baseline in NPS, and ≥ 8.9 -point improvement from baseline in SNOT-22.
- 6.40 There were also no statistically significant differences observed for the post-surgical + BEC ≥ 300 cells/ μ L subgroup and restriction-based subgroup for the ≥ 1 -point improvement from baseline in NPS and ≥ 2 -point improvement from baseline in NPS.
- 6.41 The sensitivity analyses of the ITC of POLYP 1/2 and meta-analysed results of the SYNAPSE/MERIT trials based on the ITT populations also demonstrated no statistically significant difference between omalizumab and mepolizumab in ≥ 1 -point improvement from baseline in NPS.
- 6.42 The rates of responders in the SoC (placebo) arms were approximately 28% but were comparable between the POLYP and SYNAPSE trials for ≥ 1 -point improvement and ≥ 2 -point improvement from baseline in NPS, however there was a higher event rate in the SYNAPSE SoC (placebo) arm for the ≥ 8.9 -point improvement from baseline in SNOT-22 compared to POLYP trials (53% vs 41%). Meanwhile, the event rate in the MERIT SoC (placebo) arm for ≥ 1 point improvement from baseline in NPS was higher compared with the other trials (37.8% vs 28.4-28.7%). This is likely due to the differences in patient baseline characteristics.
- 6.43 The systematic review (Papacharalampous et al. 2024)¹¹ highlighted that across the included trials and most recent systematic reviews, meta-analyses and ITCs, dupilumab showed greater improvements in all clinical and self-reported endpoints of interest, followed by omalizumab and mepolizumab.

¹¹ Papacharalampous GX, Constantinidis J, Fotiadis G, Zhang N, Bachert C, Katotomichelakis M. (2024), 'Chronic rhinosinusitis with nasal polyps (CRSwNP) treated with omalizumab, dupilumab, or mepolizumab: A systematic review of the current knowledge towards an attempt to compare agents' efficacy'. *Int Forum Allergy Rhinol.* 2024; 14: 96–109. <https://doi.org/10.1002/alr.23234>

6.44 The systematic review (Papacharalampous et al. 2024) results were illustrated through an example of one of the review’s largest recent network meta-analysis for treatment of CRSwNP with biologics (Cai et al, 2022).¹² Results of the indirect comparison using Bucher method for analysis of mean difference in NPS favoured omalizumab over SoC (placebo) and showed no difference between mepolizumab and omalizumab at 24 weeks (Figure 1). Results are shown for comparison rather than as endorsement of rigor or approach used.

Figure 1: Results of the ITC (Cai et al, 2022) of mean difference in NPS at 24 weeks for treatment of CRSwNP with biologics



Source: Cai et al, 2022 Figure 3A.
 CI, confidence interval; EOF, end of follow up; MD, mean difference; NPS nasal polyp score.

6.45 However, several important methodological limitations were noted in the systematic review (Papacharalampous et al. 2024) particularly in relation to heterogeneity across trial populations in terms of inclusion criteria, endpoints selection, methodology, and

¹² Cai S, Xu, S, Lou H, Zhang L (2022), ‘Comparison of Different Biologics for Treating Chronic Rhinosinusitis with Nasal Polyps: A Network Analysis’. *Journal of Allergy and Clinical Immunology: In Practice*, 2022, 10(7):1876-1886.

Public Summary Document - May 2025 PBAC Meeting

data extraction, which made indirect comparative assessment of biologics challenging and problematic. The publication noted that this along with the associated inherent lack of external validity and lack of causality of existing comparison analyses were the main reasons for the relatively low level of evidence. The authors suggested that techniques such as the matching adjusted indirect comparison (MAIC) and Bayesian method provides a more rigorous assessment compared to standard ITCs such as the Bucher's indirect comparison formula.

Comparative harms

Direct comparison of omalizumab versus SoC (placebo)

6.46 The key safety outcomes occurring in patients treated with omalizumab versus SoC (placebo) in the POLYP trials, including meta-analyses results, are summarised in Table 9.

Table 9: Key safety outcomes of the POLYP trials

Trial ID	Omalizumab	SoC (placebo)	Omalizumab vs SoC (placebo)		
			OR [95% CI]	RR [95% CI]	RD [95% CI]
Overall safety profile					
≥1 treatment emergent AE, n/N (%)					
POLYP 1	36/72 (50.0)	41/66 (62.1)	0.61 [0.31, 1.20]	0.80 [0.60, 1.08]	-0.12 [-0.29, 0.04]
POLYP 2	32/63 (50.8)	35/64 (54.7)	0.86 [0.43, 1.72]	0.93 [0.67, 1.29]	-0.04 [-0.21, 0.13]
Meta-analysis	68/135 (50.4)	76/130 (58.5)	0.72 [0.44, 1.17]; p=0.18	0.86 [0.69, 1.07]; p=0.18	-0.08 [-0.20, 0.04]; p=0.18
Heterogeneity (I ²); p-value			I ² =0%; p=0.50	I ² =0%; p=0.53	I ² =0%; p=0.50
≥1 SAE, n/N (%)					
POLYP 1	0/72 (0.0)	1/66 (1.5)	0.30 [0.01, 7.52]	0.31 [0.01, 7.38]	-0.02 [-0.06, 0.03]
POLYP 2	3/63 (4.8)	1/64 (1.6)	3.15 [0.32, 31.13]	3.05 [0.33, 28.52]	0.03 [-0.03, 0.09]
Meta-analysis	3/135 (2.2)	2/130 (1.5)	1.29 [0.14, 12.07]; p=0.82	1.29 [0.15, 11.43]; p=0.82	0.00 [-0.04, 0.05]; p=0.89
Heterogeneity (I ²); p-value			I ² =26%; p=0.24	I ² =26%; p=0.25	I ² =46%; p=0.17
Treatment-related AE, n/N (%)					
POLYP 1	3/72 (4.2)	1/66 (1.5)	2.83 [0.29, 27.86]	2.75 [0.29, 25.79]	0.03 [-0.03, 0.08]
POLYP 2	6/63 (9.5)	4/64 (6.3)	1.58 [0.42, 5.89]	1.52 [0.45, 5.14]	0.03 [-0.06, 0.13]
Meta-analysis	9/135 (6.7)	5/130 (3.8)	1.82 [0.58, 5.71]; p=0.30	1.74 [0.60, 5.08]; p=0.31	0.03 [-0.02, 0.08]; p=0.24
Heterogeneity (I ²); p-value			I ² =0%; p=0.67	I ² =0%; p=0.65	I ² =0%; p=0.90
≥1 AE leading to discontinuation of study drug, n/N (%)					
POLYP 1	0/72 (0.0)	1/66 (1.5)	0.30 [0.01, 7.52]	0.31 [0.01, 7.38]	-0.02 [-0.06, 0.03]
POLYP 2	0/63 (0.0)	0/64 (0.0)	NE	NE	0.00 [-0.03, 0.03]
Meta-analysis	0/135 (0.0)	1/130 (0.8)	0.30 [0.01, 7.52]; p=0.46	0.31 [0.01, 7.38]; p=0.47	-0.01 [-0.03, 0.02]; p=0.66
Heterogeneity (I ²); p-value			NA	NA	NA
AEs occurring in ≥5% of patients					
Headache, n/N (%)					
POLYP 1	4/72 (5.6)	4/66 (6.1)	0.91 [0.22, 3.80]	0.92 [0.24, 3.52]	-0.01 [-0.08, 0.07]
POLYP 2	7/63 (11.1)	3/64 (4.7)	2.54 [0.63, 10.31]	2.37 [0.64, 8.76]	0.06 [-0.03, 0.16]
Meta-analysis	11/135 (8.1)	7/130 (5.4)	1.54 [0.56, 4.20]; p=0.40	1.49 [0.59, 3.82]; p=0.40	0.02 [-0.04, 0.09]; p=0.47
Heterogeneity (I ²); p-value			I ² =1%; p=0.31	I ² =0%; p=0.32	I ² =21%; p=0.26
Nasopharyngitis, n/N (%)					

Public Summary Document - May 2025 PBAC Meeting

Trial ID	Omalizumab	SoC (placebo)	Omalizumab vs SoC (placebo)		
			OR [95% CI]	RR [95% CI]	RD [95% CI]
POLYP 1	3/72 (4.2)	2/66 (3.0)	1.39 [0.23, 8.60]	1.38 [0.24, 7.97]	0.01 [-0.05, 0.07]
POLYP 2	5/63 (7.9)	9/64 (14.1)	0.53 [0.17, 1.67]	0.56 [0.20, 1.59]	-0.06 [-0.17, 0.05]
Meta-analysis	8/135 (5.9)	11/130 (8.5)	0.70 [0.26, 1.84]; p=0.47	0.71 [0.29, 1.73]; p=0.45	-0.01 [-0.09, 0.06]; p=0.72
Heterogeneity (I ²); p-value			I ² =0%; p=0.38	I ² =0%; p=0.39	I ² =41%; p=0.19
Injection site terms^a, n/N (%)					
POLYP 1	2/72 (2.8)	0/66 (0.0)	4.72 [0.22, 100.06]	4.59 [0.22, 93.87]	0.03 [-0.02, 0.07]
POLYP 2	5/63 (7.9)	2/64 (3.1)	2.67 [0.50, 14.32]	2.54 [0.51, 12.61]	0.05 [-0.03, 0.13]
Meta-analysis	7/135 (5.2)	2/130 (1.5)	3.05 [0.70, 13.27]; p=0.14	2.89 [0.70, 11.91]; p=0.14	0.03 [-0.01, 0.07]; p=0.11
Heterogeneity (I ²); p-value			I ² =0%; p=0.75	I ² =0%; p=0.73	I ² =0%; p=0.63
Asthma exacerbation/worsening, n/N (%)					
POLYP 1	3/72 (4.2)	10/66 (15.2)	0.24 [0.06, 0.93]	0.28 [0.08, 0.96]	-0.11 [-0.21, -0.01]
POLYP 2	2/63 (3.2)	5/64 (7.8)	0.39 [0.07, 2.07]	0.41 [0.08, 2.02]	-0.05 [-0.13, 0.03]
Meta-analysis	5/135 (3.7)	15/130 (11.5)	0.29 [0.10, 0.83]; p=0.02	0.32 [0.12, 0.85]; p=0.02	-0.07 [-0.13, -0.01]; p=0.03
Heterogeneity (I ²); p-value			I ² =0%; p=0.67	I ² =0%; p=0.71	I ² =4%; p=0.31
AEs identified as risks associated with omalizumab					
Arterial thrombotic events, n/N (%)					
POLYP 1	0/72 (0.0)	1/66 (1.5)	0.30 [0.01, 7.52]	-0.02 [-0.06, 0.03]	0.31 [0.01, 7.38]
POLYP 2	0/63 (0.0)	0/64 (0.0)	NE	0.00 [-0.03, 0.03]	NE
Meta-analysis	0/135 (0.0)	1/130 (0.8)	0.30 [0.01, 7.52]; p=0.46	-0.01 [-0.03, 0.02]; p=0.66	0.31 [0.01, 7.38]; p=0.47
Heterogeneity (I ²); p-value			NA	I ² =0%; p=0.53	NA
Malignant neoplasms, n/N (%)					
POLYP 1	0/72 (0.0)	1/66 (1.5)	0.30 [0.01, 7.52]	-0.02 [-0.06, 0.03]	0.31 [0.01, 7.38]
POLYP 2	0/63 (0.0)	0/64 (0.0)	NE	0.00 [-0.03, 0.03]	NE
Meta-analysis	0/135 (0.0)	1/130 (0.8)	0.30 [0.01, 7.52]; p=0.46	-0.01 [-0.03, 0.02]; p=0.66	0.31 [0.01, 7.38]; p=0.47
Heterogeneity (I ²); p-value			NA	I ² =0%; p=0.53	NA

Source: Table 2.28, pp96-97 of the submission.

AE, adverse events; CI, confidence interval; NA, not applicable; NE, not estimable; OR, odds ratio; RD, risk difference; RR, relative risk; SAE, serious adverse event; SoC, standard of care.

a Includes injection site reaction, injection-related reaction, and injection site pain.

Note: Results in **bold** indicate statistically significant difference (p<0.05)

- 6.47 The meta-analysis of the POLYP trials showed there were no significant differences between treatment with omalizumab versus SoC (placebo) with regards to the incidence of treatment emergent adverse events (TEAEs) (RR=0.86 [0.69, 1.07]; p=0.18) SAEs (RR=1.29 [0.15, 11.43]; p=0.82) treatment-related AEs (RR=1.74 [0.60, 5.08]; p=0.31) or AEs leading to discontinuation (RR=0.31 [0.01, 7.38]; p=0.47), noting the POLYP trials were not powered to detect differences in adverse events. However, there were also no important differences observed in the event rates.
- 6.48 There were no significant differences in frequently occurring AEs such as headache, nasopharyngitis or injection site events, and in AEs identified as omalizumab-associated risks such as arterial thrombotic events or malignant neoplasms (no omalizumab-associated AEs such as anaphylactic reactions were reported in the omalizumab arm in the POLYP trials). There was a significantly higher incidence of

Public Summary Document - May 2025 PBAC Meeting

asthma occurring in the SoC (placebo) group (11.5%) than the omalizumab group (3.7%) (RR=0.32 [0.12, 0.85]; p=0.02). No deaths were reported in POLYP 1 and POLYP 2 trials. Overall, these results suggest no significant safety concerns for omalizumab apart from those already reported in the PI such as anaphylaxis which requires patients to be monitored post-injection, and medications for the treatment of anaphylactic reactions should be available for immediate use following administration of omalizumab.

- 6.49 During the open label extension phase at week 52, no significant differences were observed between omalizumab versus SoC (placebo) in the frequency of any AEs (43.5% vs 49.6%), SAEs (2.4% vs 4.8%) and AEs of interest (0.8% vs 0) with no new safety concerns identified.

Indirect comparison of omalizumab versus mepolizumab

- 6.50 The submission conducted an ITC for key safety outcomes in the ITT population, since the safety outcomes for the subgroup population of relevance in the POLYP trials were not available. The submission stated that it was unlikely that the safety outcomes would differ between the subgroup of interest and ITT population in the POLYP trials, thus the ITT results for safety outcomes could be considered applicable to the subgroup. The evaluation considered this approach was not appropriate considering that individual participant data (IPD) was available for the POLYP trials and used for the efficacy results and that subgroup safety data based on BEC levels was available and presented in the previous evaluation of mepolizumab (Table 10, mepolizumab, PSD, November 2022 PBAC meeting).
- 6.51 The submission also assumed that the exchangeability issues associated with the MERIT trial were more relevant to the comparative assessment of efficacy than safety, therefore, the safety ITC presented in the submission is based on the comparison between the meta-analysed results as presented below. The evaluation noted it was unlikely that underlying assumptions necessary to conduct an ITC using the Bucher method were fulfilled.
- 6.52 A summary of the key adverse events results for the ITC populations across all trials, including meta-analyses and ITC results, is presented in Table 10.

Public Summary Document - May 2025 PBAC Meeting

Table 10: Summary of key adverse outcomes across all trials

Analysis	Trial ID	Intervention, n/N (%)	SoC (placebo), n/N (%)	OR [95% CI]; p-value <1 favour Intervention
Any AE				
OMA vs. PBO	POLYP 1	36/72 (50.0)	41/66 (62.1)	0.61 [0.31, 1.20]
	POLYP 2	32/63 (50.8)	35/64 (54.7)	0.86 [0.43, 1.72]
	POLYP 1/POLYP 2 MA k=2			0.72 [0.44, 1.17]
MEPO vs. PBO	SYNAPSE	169/206 (82.0)	168/201 (83.6)	1.31 [0.62, 2.74]
	MERIT	68/84 (81.0)	65/85 (76.5)	0.90 [0.54, 1.50]
	SYNAPSE/MERIT MA k=2			1.01 [0.66, 1.55]
ITC OMA vs. MEPO	POLYP 1/2 (N=135) vs. SYNAPSE/MERIT (N=290) MA			0.71 [0.37, 1.36]; p=0.3068
Any treatment-related AE				
OMA vs. PBO	POLYP 1	3/72 (4.2)	1/66 (1.5)	2.83 [0.29, 27.86]
	POLYP 2	6/63 (9.5)	4/64 (6.3)	1.58 [0.42, 5.89]
	POLYP 1/POLYP 2 MA k=2			1.82 [0.58, 5.71]
MEPO vs. PBO	SYNAPSE	30/206 (14.6)	19/201 (9.5)	0.39 [0.07, 2.07]
	MERIT	2/84 (2.4)	5/85 (5.9)	1.63 [0.89, 3.01]
	SYNAPSE/MERIT MA k=2			0.99 [0.26, 3.78]
ITC OMA vs. MEPO	POLYP 1/2 (N=135) vs. SYNAPSE/MERIT (N=290) MA			1.84 [0.32, 10.69]; p=0.4978
Any AE leading to discontinuation				
OMA vs. PBO	POLYP 1	0/72 (0.0)	1/66 (1.5)	0.30 [0.01, 7.52]
	POLYP 2	0/63 (0.0)	0/64 (0.0)	NE
	POLYP 1/POLYP 2 MA k=2			0.30 [0.01, 7.52]
MEPO vs. PBO	SYNAPSE	4/206 (1.9)	4/201 (2.0)	0.98 [0.24, 3.95]
	MERIT	0/84 (0)	2/85 (2.4)	0.20 [0.01, 4.18]
	SYNAPSE/MERIT MA k=2			0.74 [0.21, 2.64]
ITC OMA vs. MEPO	POLYP 1/2 (N=135) vs. SYNAPSE/MERIT (N=290) MA			0.41 [0.01, 14.04]; p=0.6177
Any SAE				
OMA vs. PBO	POLYP 1	0/72 (0.0)	1/66 (1.5)	0.30 [0.01, 7.52]
	POLYP 2	3/63 (4.8)	1/64 (1.6)	3.15 [0.32, 31.13]
	POLYP 1/POLYP 2 MA k=2			1.29 [0.14, 12.07]
MEPO vs. PBO	SYNAPSE	12/206 (5.8)	13/201 (6.5)	0.89 [0.40, 2.01]
	MERIT	0/84 (0)	4/85 (4.7)	0.11 [0.01, 2.02]
	SYNAPSE/MERIT MA k=2			0.49 [0.07, 3.33]
ITC OMA vs. MEPO	POLYP 1/2 (N=135) vs. SYNAPSE/MERIT (N=290) MA			2.63 [0.14, 50.24]; p=0.52

Source: Table 2.45, pp123-124 of the submission.

AE, adverse event; CI, confidence interval; ITC, indirect treatment comparison; k, number of studies; MA, meta-analysis; MEPO, mepolizumab; n, number of participants; N, total participants in group; OMA, omalizumab; OR, odds ratio; PBO, placebo; SAE, serious adverse events; SoC, standard of care.

6.53 The ITC between the meta-analysed results of the POLYP 1/2 trials and meta-analysed results of the SYNAPSE/MERIT trials showed no statistically significant differences between omalizumab and mepolizumab in any AE (OR=0.71 [95% CI: 0.37, 1.36]), any treatment-related AE (OR=1.84 [95% CI: 0.32, 10.69]), any AE leading to discontinuation (OR=0.41 [95% CI: 0.01, 14.04]) and any SAE (OR=2.63 [95% CI: 0.14, 50.24]). Results from MERIT were inconsistent and different from SYNAPSE (for example OR 1.63 (0.89, 3.01) versus OR 0.39 (0.07, 2.07) for any treatment-related AE). SYNAPSE was considered more similar to Australian patients and setting.

Benefits/harms

6.54 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

6.55 The submission described omalizumab as non-inferior in terms of effectiveness and safety compared to mepolizumab. The ESC considered the claims reasonable, noting the following issues raised in the evaluation:

- There were limitations in the methodology in the ITC between omalizumab versus mepolizumab.
 - The transitivity assumption was unlikely to hold because there were key differences in the eligibility criteria, study design, baseline characteristics and duration of treatment between the ITT populations and post-hoc subgroups of omalizumab (POLYP 1/2) and mepolizumab (SYNAPSE and MERIT) trials. There was no adjustment for differences between trials and the direction and magnitude of the impact of these combined differences on results was uncertain. Given the availability of IPD of the POLYP trials, a matched adjusted ITC could have been a more appropriate methodology to account for differences between trials and support the clinical claim. The PSCR argued that a MAIC was not appropriate because of the limited number of treatment effect modifier variables available for matching and the small effective sample size after matching, and this was consistent with recent PBAC decisions (paragraph 7.7, Ibrutinib PSD, March 2024). The ESC advised that the PSCR argument was reasonable and that it was unlikely that a MAIC would have produced a different result.
- All post hoc subgroup analyses of pooled data from these trials (including different BEC levels) showed no notable differences in efficacy outcomes. These results were used to support the removal of the clinical criterion of BEC level but should be interpreted with caution due to risk of bias associated with post hoc analyses.
- The systematic review (Papacharalampous et al. 2024) identified during the evaluation highlighted similar limitations with the included ITC studies, in which there was heterogeneity in terms of inclusion criteria, endpoints selection, methodology, and data extraction, making indirect comparative assessment of biologics challenging and problematic, providing a low level of evidence.
- There was no evidence available to support assessments of non-inferiority between omalizumab and mepolizumab in patients who were unsuitable for surgery or contraindicated or intolerant to INCS, however the proposed PBS restriction would allow use of omalizumab in these patients. The PSCR acknowledged there was a lack of data supporting the efficacy of omalizumab in

Public Summary Document - May 2025 PBAC Meeting

this population. PSCR noted that during PBAC's consideration of mepolizumab, despite the absence of this evidence, PBAC agreed to reimburse this population with a risk sharing arrangement (RSA) (para. 7.2, mepolizumab PSD, November 2022). PSCR acknowledged that any uncertainty in the clinical claim for omalizumab in this patient population would also be managed through same RSA arrangements.

- 6.56 The ESC noted that the results of the POLYP trials suggest omalizumab is more effective than SoC.
- 6.57 The ESC considered, despite the identified limitations with the ITCs, there were no significant differences between omalizumab and mepolizumab and although the confidence intervals were wide the point estimates were near zero, and the conclusion of non-inferior comparative efficacy was reasonable.
- 6.58 The ESC noted both medicines were well established in clinical practice for other allergic disorders and no new safety concerns were signalled.
- 6.59 The PBAC considered that the claim of non-inferior comparative effectiveness of omalizumab versus mepolizumab in the overlap population and superior comparative effectiveness of omalizumab versus SOC in the incremental population was reasonable and adequately supported by the data.
- 6.60 The PBAC considered that the claim of non-inferior comparative safety was reasonable and adequately supported by the data.

Economic analysis

- 6.61 The submission presented a CMA of omalizumab versus mepolizumab based on the claim of non-inferiority efficacy and safety.
- 6.62 The CMA presented in the submission was based on the published price for mepolizumab.
- 6.63 The submission claimed there was no statistically significant difference in terms of efficacy and safety between the BEC <300 cells/ μ L subgroup and the BEC \geq 300 cells/ μ L subgroup among omalizumab-treated patients. The subgroup analyses have additional potential for bias due to being post-hoc. Hence, the proposed price for omalizumab, as determined in the CMA based on the equi-effective dose to mepolizumab for the BEC \geq 300 cells/ μ L subgroup, would also represent a cost-effective price for omalizumab in the BEC <300 cells/ μ L subgroup. The ESC advised that it was reasonable to apply the same price in the BEC <300 cells/ μ L and the BEC \geq 300 cells/ μ L subgroups. The ESC noted that both the BEC and IgE thresholds aim to identify patients with the same underlying biological process but account for the different modes of action between the two treatments. The ESC noted that this difference has been previously acknowledged by the PBAC (para 7.2, mepolizumab, PSD).

Public Summary Document - May 2025 PBAC Meeting

- 6.64 The submission estimated a [REDACTED] % increase in the current expenditure cap for CRSwNP based on the expanded population proposed in the submission (patients with BEC <300 cells/ μ L and IgE \geq 30 IU/mL) (see paragraph 6.84).
- 6.65 The submission stated that the proposed PBS restriction subgroup analysis (ITC including post-surgical population for omalizumab and post-surgical+BEC \geq 300 cells/ μ L population for mepolizumab) supports the 'frame-of-reference' approach to pricing, whereby it is assumed that similar treatment benefits in the currently reimbursed population and the population proposed for reimbursement should translate to similar cost-effectiveness in both groups. The ESC considered this approach to pricing was reasonable given that results were similar between subgroups.
- 6.66 The submission equi-effective doses were estimated as omalizumab 292.8 mg every 4 weeks is equivalent to mepolizumab 100 mg every 4 weeks.
- 6.67 The proposed dose for mepolizumab was based on the recommended fixed dose in the approved TGA product information (PI) of 100 mg every 4 weeks, which also reflects the dose in the SYNAPSE trial. For omalizumab, the average 4-weekly dose from the POLYP 1/2 trial populations was used, after excluding patients who were administered doses outside of the recommended dose (> 750 mg per 4-weekly cycle) as described in the TGA approved PI (n=10, 7.4%). The exclusion of patients with doses > 750 mg does not reflect the data used to support the non-inferiority claim and does not align with the PBAC guidelines (2016 v5.0) which suggests the 'steady state' dose comparison is generally most relevant. However, the submission argued, the exclusion of this small number of patients exposed to the higher doses is not expected to compromise the clinical trial evidence and associated non-inferiority claims upon which the current CMA is based. The subgroup analysis described in the submission for this claim could not be verified during the evaluation. The mean average dose when all patients in the POLYP trials were considered was 346.67 mg. The impact of this is tested in sensitivity analysis during the evaluation and presented in para 6.71.
- 6.68 The results of the CMA based on the published AEMP of mepolizumab are presented in Table 11.

Table 11: Results of the cost-minimisation

Component	Omalizumab	Mepolizumab
Cost per dose	\$1,556.10	\$1,556.10
Equi-effective dose (mg)	292.8	100
Cost per mg	\$5.31	\$15.56
Dose frequency	Every 4 weeks	Every 4 weeks
Administrations per year	13	13
Total medicine cost per year	\$20,229.30	\$20,229.30
Difference in cost per year	\$0	\$0
Estimated cost minimised price for omalizumab		
75 mg pre-filled syringe		\$398.59
150 mg pre-filled syringe		\$797.18

Source: Table 3.3, p142 of the submission and completed during the evaluation based on data provided in the submission

Public Summary Document - May 2025 PBAC Meeting

- 6.69 The resulting cost-minimised price for the 75 mg and 150 mg presentations were calculated to be \$398.59 and \$797.18, respectively, based on published mepolizumab prices.
- 6.70 Based on the approach applied, the submission assumed a 100% treatment compliance (resulting in 13 scripts per year). Patients in the POLYP 1/2 trials reported a mean treatment duration with omalizumab of approximately 20 weeks (out of 24 weeks). Further, this did not align with the 9.6 scripts applied in the financial estimates which was based on a (assumed) compliance rate of 94.6% and response rate of 72.6% from PBAC’s consideration of mepolizumab in November 2022 (para 6.61, mepolizumab PSD, July 2016 PBAC meeting).
- 6.71 Table 12 shows the cost-minimisation approach results when applying a mean treatment dose of 346.67 mg which was the average for all patients in POLYP trials (compared to 292.8 mg in base case). This resulted in lower cost-minimised prices of \$336.66 and \$673.31 for 75 mg and 150 mg presentations (pre-filled syringe), respectively. This represents a 16% difference.

Table 12: Sensitivity analysis conducted during the evaluation using mean treatment dose of all POLYP patients

Component	Omalizumab	Mepolizumab
Cost per dose	\$1,556.10	\$1,556.10
Equi-effective dose (mg)	346.7	100
Cost per mg	\$4.49	\$15.56
Dose frequency	Every 4 weeks	Every 4 weeks
Administrations per year	13	13
Total medicine cost per year	\$20,229.30	\$20,229.30
Difference in cost per year	\$0	\$0
Estimated cost minimised price for omalizumab		
75 mg pre-filled syringe		\$336.66
150 mg pre-filled syringe		\$673.31

Source: Calculated during the evaluation based on data provided in the submission

- 6.72 Anaphylaxis reactions following administration of omalizumab have been reported, with the majority occurring within the first three doses of omalizumab (p6 of omalizumab PI). Given this, it may be reasonable to expect the first three administrations to be supervised and associated costs be included, consistent with the approach taken in the PBAC’s prior consideration of mepolizumab, and to align with the TGA PI (para 6.21, 6.22, mepolizumab PSD, July 2016 PBAC meeting). This includes specialist fees for administration (MBS item 116; \$87.30) and nurse supervision post dose (MBS item 82210; \$58.85). Sensitivity analysis conducted during the evaluation including these costs are presented in Table 13.

Public Summary Document - May 2025 PBAC Meeting

Table 13: Additional administration costs incorporated into the submission cost-minimisation analysis

Component	Omalizumab	Mepolizumab
Cost per dose	\$1,539.24	\$1,556.10
Equi-effective dose (mg)	292.8	100
Cost per mg	\$5.26	\$15.56
Dose frequency	Every 4 weeks	Every 4 weeks
Administrations over 2 years	26	26
Total medicine cost over 2 years	\$40,020.15	\$40,458.60
Total supervised administration cost ^a	\$438.45	\$0
Specialist ^b	\$261.90	\$0
Nurse supervision post-dose ^c	\$176.55	\$0
Difference in cost per year	\$0	\$0
Estimated cost minimised price for omalizumab		
75 mg pre-filled syringe		\$394.27
150 mg pre-filled syringe		\$788.15

Source: Calculated during the evaluation based on data provided in the submission

^a For the first three initiating doses to monitor for anaphylaxis and anaphylactoid reactions

^b MBS item 116

^c MBS item 82210

6.73 Sensitivity analysis conducted during the evaluation applying the mean treatment dose (346.67 mg) based on all patients in POLYP trials and supervised administration costs is presented in Table 14 below. The resulting cost-minimised price for the 75 mg and 150 mg presentations (pre-filled syringe) were calculated to be \$333.01 and \$666.02, respectively, which is 16% lower than the base case prices.

Table 14: Sensitivity analysis using mean treatment dose of all POLYP patients and supervised administration costs

Component	Omalizumab	Mepolizumab
Cost per dose	\$1,539.24	\$1,556.10
Equi-effective dose (mg)	346.7	100
Cost per mg	\$4.44	\$15.56
Dose frequency	Every 4 weeks	Every 4 weeks
Administrations over 2 years	26	26
Total medicine cost over 2 years	\$40,020.15	\$40,458.60
Total supervised administration cost ^a	\$438.45	\$0
Specialist ^b	\$261.90	\$0
Nurse supervision post-dose ^c	\$176.55	\$0
Difference in cost per year	\$0	\$0
Estimated cost minimised price for omalizumab		
75 mg pre-filled syringe		\$333.01
150 mg pre-filled syringe		\$666.02

Source: Calculated during the evaluation based on data provided in the submission

^a For the first three initiating doses to monitor for anaphylaxis and anaphylactoid reactions

^b MBS item 116

^c MBS item 82210

6.74 Should the PBAC accept the clinical claim of overall non-inferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with omalizumab would be no more than the cost per patient of mepolizumab. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Public Summary Document - May 2025 PBAC Meeting

6.75 The ESC advised that the data used in the clinical and economic sections should be consistent. Consequently, ESC argued that it was more appropriate to apply the mean treatment dose of 346.67 mg which includes all patients in the trials, and which resulted in lower cost-minimised prices. The ESC also considered it appropriate to include the additional supervision costs required for initial monitoring for anaphylaxis and anaphylactoid reactions for omalizumab (see Table 14 for the sensitivity analysis using mean treatment dose of all POLYP patients and including supervised administration costs).

Drug cost/patient/year

Table 15: Drug cost per patient for omalizumab and mepolizumab

	Omalizumab Trial dose and duration	Omalizumab CMA	Omalizumab Financial estimates	Mepolizumab Trial dose and duration	Mepolizumab CMA	Mepolizumab Financial estimates
Mean dose	346.7 mg Q4W ^a	292.8 mg Q4W ^d	NA	100 mg Q4W ^h	100 mg Q4W	100 mg Q4W
Treatment duration	20 weeks ^b	NA	NA	11.3 months ^h	NR	NR
Number of scripts per year	5	13	9.6 ^f	12.3	13	9.6 ^f
Cost/patient/year	\$10,236.35 ^c	\$21,268.52 ^e	\$15,170 ^g	\$19,353 ⁱ	\$20,552 ⁱ	\$15,177 ⁱ

Source: Compiled during the evaluation based on data presented in the submission

CMA, cost minimisation analysis; NA, not applicable; NR, not reported; Q4W, every 4 weeks.

^a Estimated based on POLYP and POLYP 2 trial populations

^b Mean treatment duration of POLYP trials over 24-week treatment duration

^c Calculated using weighted DPMQ (75 mg \$411.23; 150 mg \$818.02) and number of scripts ((2 x \$818.02 + \$411.23) x 5)

^d Estimated based on POLYP 1 and POLYP 2 trial populations excluding those with >750 mg per 4-weekly cycle (as per PI recommendation)

^e Calculated using weighted DPMQ (75 mg \$411.23; 150 mg \$818.02) and number of scripts ((2 x \$818.02) x 13)

^f Number of scripts considered to be appropriate by the PBAC for mepolizumab November 2022 PSD based on compliance rate of 94.6% and a response rate of 72.6%.

^g Calculated based using weighted DPMQ multiply by 9.6 mepolizumab equivalent scripts (i.e. 0.024 of 75 mg and 1 of 150 mg omalizumab script is equivalent to 1 mepolizumab script)

^h Derived from Table 16, para 6.54, mepolizumab, PSD, November 2022 PBAC meeting

ⁱ Calculated using weighted (public/private split of 48.63/51.37%) published DPMQ for mepolizumab

Estimated PBS usage & financial implications

6.76 This submission was not considered by DUSC.

6.77 The submission used an epidemiological approach to estimate the predicted use and cost of requested listing of omalizumab for CRSwNP. The submission noted that limited utilisation data is available for mepolizumab as it was only listed on the PBS in April 2023, which made a market share approach based on utilisation data unreliable. The approach therefore included reproduction of the financial estimates based on PBAC’s consideration of mepolizumab in the November 2022 meeting and an additional analysis to account for patients that would not meet mepolizumab’s PBS criteria but would be eligible for omalizumab based on the proposed PBS restriction.

6.78 In order to account for the expanded population (patients with BEC <300 cells/μL and IgE ≥30 IU/mL), the submission requested upward adjustments to the current RSA cap amounts for mepolizumab if omalizumab were to enter the same RSA.

Public Summary Document - May 2025 PBAC Meeting

6.79 The key inputs used in the financial analysis are summarised in Table 16.

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

Data	Value	Source	Comment
Eligible population			
Prevalence rate of CRSwNP	0.51%	Prevalence rate used in the financial estimates of the mepolizumab November 2022 PSD, which were based on the UK CPRD Starry et al., 2022.	This was considered reasonable by the PBAC in the mepolizumab November 2022 PSD (Table 17, para 6.57, mepolizumab, PSD, November 2022 PBAC meeting). A higher global prevalence rate was noted by ASCIA 2021 and was referenced in Section 1 of the submission (2-4%).
Proportion with BEC \geq 300 cells/ μ L	68.3%	Proportion used in the financial estimates of the mepolizumab November 2022 PSD, which were based on the subgroup in the SYNAPSE trial.	This was considered reasonable by the PBAC in the mepolizumab November 2022 PSD (Table 17, para 6.57, mepolizumab, PSD, November 2022 PBAC meeting). However, the POLYP trials reported that 50.4% of the participants had BEC >300 cells/ μ L.
Proportion with BEC <300 cells/ μ L	31.7%	Calculated using the proportion of patients not included in the "proportion with BEC \geq 300 cells/ μ L" rate (i.e. 100% - 68.3%).	This may be underestimated if based on data from the POLYP trials as per above.
Proportion with IgE \geq 30 IU/mL	83%	Calculated using the weighted average of the proportion of patients who failed to meet the inclusion criterion of 'serum IgE \geq 30 IU/mL to \leq 1500 IU/mL and body weight \geq 30 to \leq 150 kg' in POLYP 1 (19.4%) and POLYP 2 (14.3%), which was 17% and subtracting this from 100%.	This may be underestimated because the patients excluded from the POLYP trials based on this criterion were not limited to those with IgE <30 IU/mL and included patients with body weight outside the criterion (\geq 30 to \leq 150 kg) or IgE \geq 1500 IU/mL.
Proportion requiring (first) NP surgery	47%	Proportion used in the financial estimates of the mepolizumab November 2022 PSD, which was based on Chen et al., 2020.	The PBAC noted that this may be underestimated due to the potentially unjustified removal of one outlier study from the systematic literature review (Table 17, para 6.57, mepolizumab, PSD, November 2022 PBAC meeting). The POLYP trials reported higher proportions, with 57.2% of all participants in POLYP 1 and 62.2% of all participants in POLYP 2 with prior sinonasal surgery.
Treatment utilisation			
Uptake rate	█%	Uptake rate considered by the PBAC to be appropriate across all six years in the mepolizumab November 2022 PSD.	The PBAC considered that the percentage of enrolled versus randomised patients from the SYNAPSE, POLYP 1 and POLYP 2 trials indicated an overall uptake rate of █% was appropriate (para 6.60, mepolizumab, PSD, November 2022 meeting). Given the initial monitoring requirements for anaphylaxis reactions (para 6.72), uptake of omalizumab may be less than mepolizumab.

Public Summary Document - May 2025 PBAC Meeting

Data	Value	Source	Comment
Scripts per year	9.6	The number of scripts considered to be appropriate by PBAC in the mepolizumab November 2022 PSD based on total treatment duration of 116.46 weeks, a compliance rate of 94.6% and a response rate of 72.6%.	This was based on the treatment duration, compliance rate and response rate from the SYNAPSE trial for mepolizumab. It is uncertain whether this script number is appropriate for omalizumab, given the difference in dosing regimen, treatment duration and clinical data from the POLYP trials
Costs			
Proposed medicine	75 mg vial: \$398.59 (public) \$423.20 (private) 150 mg vial: \$797.18 (public) \$837.74 (private)	Published derived DPMQ	
MBS costs	\$87.30 \$58.85	MBS item 116 MBS item 82210	Additional costs associated with supervised administration and monitoring for anaphylaxis reactions for omalizumab are also relevant.
Market share in the BEC ≥300 cell/μL segment	Yr 1: █%:█% Yr 2: █%:█% Yr 3: █%:█% Yr 4: █%:█% Yr 5: █%:█% Yr 6: █%:█%	Assumption of omalizumab:mepolizumab market share.	This is uncertain. It was assumed that mepolizumab has the first market advantage over omalizumab, however clinical guidelines and processes for patient selection for CRSwNP appears to be evolving and may change.

Source: Compiled during the evaluation using Table 4.2, p146 of the submission; Table 9, p65-67 of the POLYP 1 CSR; Table 9, p65-67 of the POLYP 2 CSR; mepolizumab, PSD, November 2022 PBAC meeting.

ASCIA, Australasian Society of Clinical Immunology and Allergy; BEC, blood eosinophilic count; CPRD, Clinical Practice Research Datalink; CRSwNP, chronic rhinosinusitis with nasal polyps; CSR, clinical study report; DPMQ, dispensed price for maximum quantity; IgE, immunoglobulin E; NP, nasal polyps; MBS, Medicare Benefits Schedule; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document.

6.80 The estimated use and financial impact of listing omalizumab on the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) is shown in Table 17.

Public Summary Document - May 2025 PBAC Meeting

Table 17: Estimated use and financial implications (published price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	1	1	1	1	1
BEC ≥300 cell/μl segment	2	2	2	2	2	2
BEC <300 cells/μl segment	2	2	2	2	2	2
Number of scripts dispensed^a	3	4	4	4	5	5
BEC ≥300 cell/μl segment	2	1	1	3	3	3
BEC <300 cells/μl segment	3	3	3	3	3	3
Estimated financial implications of omalizumab						
Cost to PBS/RPBS less copayments	\$ 6	\$ 7	\$ 7	\$ 8	\$ 8	\$ 9
BEC ≥300 cell/μl segment	\$ 10	\$ 10	\$ 11	\$ 11	\$ 6	\$ 6
BEC <300 cells/μl segment	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6
Estimated financial implications for mepolizumab						
Total cost offsets to the PBS/RPBS	-\$ 12	-\$ 12	-\$ 12	-\$ 12	-\$ 12	-\$ 12
Net financial implications						
Net cost to PBS/RPBS	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6
Net cost to MBS	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
Net health budget	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6	\$ 6

Source: Compiled during the evaluation from Table 4.13, p155 of the submission and Table 4.15, p157 of the submission. BEC, blood eosinophilic count; MBS, Medicare Benefits Scheme; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

a Assuming 9.6 scripts per year as estimated by the submission and script equivalence adjusted (0.024 x omalizumab 75 mg vial script & 1 x omalizumab 150 mg vial script = 1 mepolizumab script).

The redacted values correspond to the following ranges:

- ¹ 5,000 to < 10,000
- ² 500 to < 5,000
- ³ 10,000 to < 20,000
- ⁴ 20,000 to < 30,000
- ⁵ 30,000 to < 40,000
- ⁶ \$20 million to < \$30 million
- ⁷ \$30 million to < \$40 million
- ⁸ \$40 million to < \$50 million
- ⁹ \$50 million to < \$60 million
- ¹⁰ \$0 to < \$10 million
- ¹¹ \$10 million to < \$20 million
- ¹² net cost saving

- 6.81 The total cost to the PBS/RPBS of listing omalizumab (based on the published price) was estimated to be \$20 million to < \$30 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing.
- 6.82 The price applied for the financial estimates was the proposed published AEMP for omalizumab based on the cost-minimisation approach against mepolizumab (see para 3.2)
- 6.83 The approach taken to estimate the number of treated patients and prescriptions in patients with BEC ≥300 cells/μL closely aligned with the approach taken from the mepolizumab November 2022 PSD, employing a number of the same inputs in the financial analysis. While the approach may be reasonable to align with calculations for mepolizumab’s RSA cap, it assumes that the proposed omalizumab population would

Public Summary Document - May 2025 PBAC Meeting

be similar to mepolizumab. There are a number of differences that could affect the financial estimates. This includes:

- The proportion of patients with BEC ≥ 300 cells/ μL of 68.3% based on the SYNAPSE trial is higher than the proportion reported in the POLYP 1 (42.3%) and POLYP 2 trial (50.4%), which would result in more patients being eligible for omalizumab based on BEC < 300 cells/ μL .
- The proportion of patients requiring (first) NP surgery (47%) was considered to be underestimated in the mepolizumab consideration (Table 17, para 6.57, mepolizumab, PSD, November 2022 PBAC meeting). The POLYP trials reported higher proportions for participants who had undergone prior sinonasal surgery (57.2% in POLYP 1 and 62.2% in POLYP 2). Increasing the rate to align with the POLYP trials increases the number of treated patients by 20-28% patients in the first year of treatment.
- The proportion of patients who experienced post-surgical NP regrowth (21%) was lower than the proportion noted by Australasian Society of Clinical Immunology and Allergy (ASCIA) (50%). Applying the increased proportion of 50% would increase the estimated number of eligible patients.
- The submission applied 9.6 scripts per year to estimate the number of omalizumab scripts. This was based on the number of scripts used in the mepolizumab November 2022 PSD, which the PBAC considered to be appropriate based on SYNAPSE trial data (treatment duration of 116.46 weeks, compliance rate of 94.6% and response rate of 72.6%) (para 6.61, mepolizumab, PSD, November 2022 PBAC meeting). This may not be applicable for omalizumab given the difference in dosing regimen and treatment duration (6.3 doses per patient over 20 weeks in POLYP 1 and 6.6 doses per patient over 19.8 weeks in POLYP 2) in the POLYP trials.
- The estimate for the proportion of patients with IgE ≥ 30 IU/mL was based on the POLYP trials' inclusion criterion of 'IgE level ≥ 30 to ≤ 1500 IU/mL and body weight ≥ 30 to ≤ 150 kg'. A proportion of 83% was calculated in the submission when accounting for the 17% of patients who were excluded from the trials based on this criterion. The ESC advised that IgE ≥ 30 was not a high threshold to fulfill and thus 83% was likely an underestimate of the proportion of CRSwNP patients meeting the other existing restrictions that would also meet the proposed IgE threshold.

6.84 The submission estimated that approximately an additional 500 to $< 5,000$ patients per year would meet proposed PBS eligibility for omalizumab (5,000 to $< 10,000$ patients over six years), resulting in a [REDACTED] % increase in the current expenditure cap for CRSwNP. This increase is attributed to the expanded population proposed in the submission (patients with BEC < 300 cells/ μL and IgE ≥ 30 IU/mL). The number of additional patients was based on the proportion of patients with IgE ≥ 30 IU/mL (83%

Public Summary Document - May 2025 PBAC Meeting

in POLYP trials) and BEC <300 cells/ μ L (31.7% in SYNAPSE trial) (26.3%); the evaluation noted this was lower than that reported in the POLYP trials (41.2%). Increasing this proportion to match the POLYP trials (41.2%) would increase the caps by [REDACTED]%. While the ESC agreed that the size of treatment eligible population would increase by inclusion of patients with IgE \geq 30 IU/mL and BEC <300 cells/ μ L, it advised that the magnitude of this increase was uncertain and likely overestimated. The ESC noted that it was unclear if the POLYP trials were a more suitable source of data for this estimate. It was noted the PSCR argued that the POLYP trials were an inappropriate basis for determining the size of the proposed incremental population for omalizumab (those with IgE \geq 30 IU/mL and BEC <300 cells/ μ L) relative to the existing population of mepolizumab (those with BEC \geq 300 cells/ μ L) because the POLYP trials excluded patients who would be currently eligible for mepolizumab on the basis of high BEC but with “normal” IgE (<30 IU/mL). The ESC also noted that patients with comorbid asthma may already be treated with a monoclonal antibody in clinical practice and that this was not taken into account.

- 6.85 The submission assumed a market share of [REDACTED]%. [REDACTED]% to [REDACTED]%. [REDACTED]% for omalizumab:mepolizumab in the BEC \geq 300 cell/ μ L segment from Years 1 to 6. In addition, it was assumed that 17% of patients would not meet the proposed PBS restriction criteria (i.e., IgE \geq 30 IU/mL) for omalizumab, and that mepolizumab has the first to market advantage over omalizumab. The market share assumptions for the BEC \geq 300 cells/ μ L segment are uncertain.
- 6.86 The submission estimated no net changes to the MBS. MBS items for specialist fees (MBS item 116; \$87.30) and nurse supervisions post dose (MBS item 82210; \$58.85) to monitor anaphylaxis reactions following administration of omalizumab were included during the evaluation. The ESC agreed with inclusion of additional costs associated with medical supervision for first three doses of omalizumab due to risk of anaphylaxis.
- 6.87 The submission did not include sensitivity analyses. Table 18 presents the sensitivity analyses conducted during the evaluation to test the impact of the assumptions made in estimating the proportion of patients with BEC <300 cell/ μ L and IgE level \geq 30. Removing the BEC <300 cell/ μ L patients to maintain consistency with the mepolizumab restriction would lower the financial impact to slightly below the current cost (approx. -100%) due to the expected reduction in mepolizumab scripts based on the market share assumptions presented in the submission.

Public Summary Document - May 2025 PBAC Meeting

Table 18: Sensitivity analyses (net cost to R/PBS) for the expanded population (BEC <300 cells/µL segment) (published price)

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)	Year 6 (2030)	Sum across 6 years	% change
Base case (Proportion of patients with BEC <300 cells/µL and IgE ≥30 IU/mL: 26.3%^a)								
Net cost	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ¹	\$█ ²	-
Proportion of patients with BEC <300 cells/µL and IgE ≥30 IU/mL: 41.2%^b								
Net cost	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ⁴	█%
Proportion of patients with BEC <300 cells/µL and IgE ≥30 IU/mL: 0%								
Net cost ^c	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	Approx -100%

Source: Conducted during the evaluation.

BEC, blood eosinophilic count.

^a Submission estimated this based on 31.7% (BEC <300 cells/µL from SYNAPSE trial) and 83% (IgE ≥30 IU/mL from POLYP trials)

^b Revised to match the BEC <300 cells/µL to match the POLYP trials

^c A net cost below zero is due to the expected reduction in mepolizumab scripts as a result of the market share assumptions presented in the submission.

The redacted values correspond to the following ranges:

¹ \$20 million to < \$30 million

² \$100 million to < \$200 million

³ \$30 million to < \$40 million

⁴ \$200 million to < \$300 million

⁵ net cost saving

Quality Use of Medicines

6.88 The submission noted that omalizumab is approved for subcutaneous administration in this indication, and that patients with CRSwNP would self-administer omalizumab in the home. The cost minimisation approach was, therefore, based on drug acquisition costs only. Administration costs for initial administration and monitoring for anaphylaxis were not considered relevant by the submission. The ESC did not consider this was reasonable for reasons discussed in para 6.72.

6.89 Although treatment with omalizumab may be familiar to healthcare professionals as it was currently listed on the PBS for other indications (chronic spontaneous urticaria and allergic asthma), there may be a need for training of clinical teams on the optimal choice of treatment and use of omalizumab for CRSwNP given the proposed change in clinical criteria and the recent updates to clinical guidelines. It was noted that the sponsor of mepolizumab planned to offer an educational program (meetings, nurse support programs and patient resources) on CRSwNP on how to use the pre-filled pen and who is an appropriate candidate for treatment (para 6.64, mepolizumab, PSD, November 2022 PBAC meeting).

Financial Management – Risk Sharing Arrangements

6.90 The PBAC’s recommendation for listing of mepolizumab 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 RSA to address the uncertainty associated with including patients unsuitable for surgery in the proposed PBS population (para 7.2, mepolizumab, PSD, November 2022 PBAC

Public Summary Document - May 2025 PBAC Meeting

meeting). The PBAC considered financial caps set at the level of the revised financial estimates and a [REDACTED] % rebate for any use above the caps would be appropriate (para 7.10, mepolizumab, PSD, November 2022 PBAC meeting).

- 6.91 The submission requested upward adjustments to the cap amounts if omalizumab were to enter the same RSA, to account for the expanded access for the BEC <300 cells/ μ L and IgE \geq 30 IU/mL population.
- 6.92 The PBAC noted that the recommendation at the March 2025 meeting to list a biosimilar brand of omalizumab may result in multiple brands/sponsors for the same drug on the PBS, which could impact the feasibility of omalizumab joining the mepolizumab 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 omalizumab 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 Drug Program (HSD). The PBAC considered that access to omalizumab should be broadly in line with mepolizumab for the treatment of CRSwNP, except for the removal of the blood eosinophilic count (BEC) threshold and the addition of immunoglobulin E (IgE) levels \geq 30 IU/mL, to reflect omalizumab's different mechanism of action. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of omalizumab would be acceptable if it were cost minimised to mepolizumab.
- 7.2 The PBAC considered the equi-effective doses were:
- omalizumab 346.67 mg every 4 weeks is equivalent to mepolizumab 100 mg every 4 weeks.
- 7.3 The PBAC noted support from individuals, health professionals and organisations for additional treatment options for CRSwNP, with descriptions of how patients with the condition feel like they have a flu or acute upper respiratory tract infection every day, leading to impaired sleep, poor concentration and fatigue and that after years of different treatments, nasal polyps can regrow, and symptoms recur. The PBAC noted Allergy & Anaphylaxis Australia and the National Allergy Council described how CRSwNP was associated with allergic conditions and patients are being treated by a range of specialist physicians, including Ear, Nose and Throat surgeons; access to omalizumab would provide patients and these care providers with more opportunity to choose the treatment that best suits the disease state and the clinical needs of the individual patient. The PBAC acknowledged that CRSwNP has a significant impact on quality of life and considered there remained a clinical need for additional effective therapies. The PBAC considered that omalizumab may provide a more suitable

Public Summary Document - May 2025 PBAC Meeting

treatment for CRSwNP patients who present with high serum IgE and less eosinophilic disease.

- 7.4 With regard to the requested listing and restriction the PBAC advised that:
- a Section 100 Highly Specialised Drugs Program listing is appropriate and consistent with the current restriction for mepolizumab for CRSwNP.
 - the proposed IgE threshold of ≥ 30 IU/mL and the removal of the BEC threshold was reasonable given this was consistent with the current PBS restriction of omalizumab for uncontrolled severe asthma and uncontrolled severe allergic asthma and the high degree of overlap between presence of CRSwNP and asthma.
 - the number of repeats should align with the allergic asthma listing for omalizumab given it has the same dosing schedule as CRSwNP.
 - no additional limits on maximum quantity or repeats were required, to align with asthma indications.
 - the new pre-filled syringe (PFS) and pre-filled pen (PFP) forms and a new 300 mg/2 mL presentation of omalizumab recommended at the March 2025 PBAC meeting be made available for the CRSwNP indication.
 - the grandfather restriction was appropriate noting that the patient must have received omalizumab treatment prior to PBS listing date and must have achieved and maintained an adequate response (defined above) in order to be eligible for subsequent and continuing PBS-subsidised treatment.
- 7.5 The PBAC accepted that mepolizumab was the appropriate comparator for the patient population which overlaps with the mepolizumab PBS listing. The PBAC accepted standard of care as the appropriate comparator for the for the expanded population not eligible for mepolizumab which included background INCS therapy with intermittent usage of OCS and saline spray or rinses aligning with the PBAC acceptance of standard of care as the appropriate comparator in the mepolizumab resubmission (para 5.1 and 7.5, mepolizumab, PSD, November 2022 PBAC meeting).
- 7.6 The PBAC noted that there were no head-to-head randomised clinical trials of omalizumab compared to mepolizumab and the submission was based on two RCTs which compared omalizumab to standard of care (SoC; placebo) (POLYP 1 and POLYP 2), and one RCT comparing mepolizumab to placebo (SYNAPSE), to inform an anchored indirect treatment comparison (ITC) between omalizumab and mepolizumab. An additional mepolizumab trial, MERIT, was not included in the submission's main ITC but was included in sensitivity analyses. The main ITC was based on the currently PBS-eligible population for mepolizumab (post-surgical with BEC ≥ 300 cells/ μ L) and the proposed PBS population for omalizumab (post-surgical with IgE ≥ 30 IU/mL).
- 7.7 The PBAC noted the ITC of median change from baseline in NPS for POLYP 1/2 and SYNAPSE showed no statistically significant difference between omalizumab and

Public Summary Document - May 2025 PBAC Meeting

- mepolizumab for the ITT population nor for any of the subgroups: (MD=-0.27 [95% CI: -0.92, 0.38]; p=0.4171), post-surgical subgroup (MD=-0.27 [95% CI: -1.12, 0.58]; p=0.5313), post-surgical + BEC \geq 300 cells/ μ L subgroup (MD=-0.33 [95% CI: -1.69, 1.03]; p=0.6329) and restriction based subgroup (MD=0 [95% CI: [-0.904, 0.904]; p=1.0).
- 7.8 The PBAC noted the evaluator and ESC's concerns that there were limitations in the methodology of the ITC related to transitivity assumptions due to differences in the eligibility criteria, study design, baseline characteristics and duration of treatment between the ITT populations and the risk of bias with the post hoc subgroup analyses. However, overall, the PBAC agreed with the ESC that despite the identified limitations with the ITCs, there were no significant differences between omalizumab and mepolizumab and the conclusion of non-inferior comparative effectiveness was reasonable.
- 7.9 In regard to comparative safety, the PBAC considered that the meta-analysis of the POLYP trials showed no difference between treatment with omalizumab and SOC in treatment emergent adverse events; serious adverse events, treatment related adverse events or adverse events leading to treatment discontinuation (see Table 9). Further, no differences between omalizumab and mepolizumab were observed in the ITC between POLYP1/1 and SYNAPSE/MERIT (see Table 10). Overall, the PBAC was satisfied that the claim of non-inferior comparative safety was reasonable.
- 7.10 The PBAC considered the cost minimisation approach (CMA) of omalizumab versus mepolizumab based on the claim of non-inferior efficacy and safety was reasonable. The PBAC agreed with the ESC that it was reasonable to accept the same price for patient subgroups with BEC $<$ 300 cells/ μ L and the BEC \geq 300 cells/ μ L subgroups given that both the BEC and IgE thresholds aim to identify patients with the same underlying biological process but account for the different modes of action between the two treatments. PBAC considered that extrapolating from the ITC with mepolizumab to establish cost effectiveness in the expanded patient population was uncertain but likely acceptable in clinical terms.
- 7.11 The PBAC noted that equi-effective doses for omalizumab in the submission were estimated after excluding patients in the POLYP 1//2 trials who were administered doses outside of the recommended dose ($>$ 750 mg per 4-weekly cycle) as described in the TGA approved PI (n=10, 7.4%). The PBAC agreed with the ESC (paragraph 6.75) that it was more appropriate to include these patients and use the mean treatment dose in the POLYP trials resulting in a higher mean omalizumab dose of 346.67 mg every 4 weeks.
- 7.12 The PBAC agreed with the ESC that given anaphylaxis reactions following administration of omalizumab have been reported, it was reasonable for the cost of supervision for the first three administrations to be included, consistent with the TGA Product Information and the approach taken in the PBAC's prior consideration of mepolizumab (para 6.21, 6.22, mepolizumab PSD, July 2016 PBAC meeting). This

Public Summary Document - May 2025 PBAC Meeting

includes specialist fees for administration, and nurse supervision for monitoring post dose (see sensitivity analysis in Table 14).

- 7.13 The PBAC noted the submission included a reproduction of the financial estimates based on PBAC's consideration of mepolizumab in the November 2022 meeting and an additional analysis to account for patients that would not meet mepolizumab's PBS criteria but would be eligible for omalizumab based on the proposed PBS restriction. The PBAC noted that mepolizumab was subject to a risk sharing arrangement for CRSwNP. The PBAC noted the submission suggested the increase in Government expenditure due to the expanded eligibility under the omalizumab listing was estimated to be up to 500 to < 5,000 patients per year, resulting in a [REDACTED] % increase to current CRSwNP expenditure caps (see paragraph 6.84). The PBAC agreed with the ESC that the magnitude of the potential increase in the treatment population was uncertain and likely overestimated given a substantial proportion of patients would already be eligible for omalizumab for co-morbid severe/allergic asthma and that this overlap was not accounted for in financial estimates. The PBAC considered any amendment to the current RSA should take into account actual expenditure against the caps.
- 7.14 While a matter for the Department, the PBAC noted the introduction of biosimilar brands on the PBS may affect the feasibility of establishing an RSA for omalizumab.
- 7.15 The PBAC advised that omalizumab is not suitable for prescribing by nurse practitioners.
- 7.16 The PBAC recommended that the Early Supply Rule should not apply.
- 7.17 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because omalizumab is not expected to address a high and urgent unmet clinical need, given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.18 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

This restriction is in the process of being finalised, due to the complex nature of the listings and the flow on impacts that exist to mepolizumab for CRSwNP. The sponsor will be notified of the final restriction.

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.