6.06 DUPILUMAB, Injection 200 mg in 1.14 mL single dose pre-filled syringe, Injection 300 mg in 2 mL single dose pre-filled syringe, Dupixent®, Sanofi-Aventis Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 Highly Specialised Drugs Program listing for dupilumab for the treatment of patients aged 6 to 11 years of age with uncontrolled severe asthma who have:

- Total serum immunoglobulin E (IgE) ≥ 30 IU/mL and evidence of atopy **and/or**
- blood eosinophils ≥ 150 x 10^9/L **and/or**
- fractional exhaled nitric oxide (FeNO) ≥ 20 parts per billion (ppb). [1]

1.2 The submission defined two subgroups of patients: Subgroup A patients were those with uncontrolled severe asthma who meet the PBS requirements for omalizumab treatment, including the requirement for total serum IgE ≥ 30 IU/mL, and Subgroup B patients were those who meet the PBS requirements for use of omalizumab, **except** the requirement to have total serum IgE ≥ 30 IU/mL. The submission proposed that Subgroup B patients could qualify by either of two new requirements: **either** blood eosinophil count ≥ 0.15 x 10^9/L or FeNO ≥ 20 ppb.

1.3 Two clinical claims were made: for patients in Subgroup A, dupilumab was non-inferior in efficacy and safety to omalizumab, and for patients in Subgroup B, dupilumab was superior in efficacy and non-inferior in safety compared to placebo.

1.4 Listing was requested on the basis of a cost-minimisation approach versus omalizumab.

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

Component	Description
Population	Patients 6 to 11 years of age with uncontrolled severe asthma. This includes: • 'Subgroup A' patients with IgE ≥ 30 IU/mL ± EOS ≥ 150 cells/µL ± FeNO ≥ 20 ppb (omalizumab-eligible patients) • 'Subgroup B' patients with IgE < 30 IU/mL with EOS ≥ 150 cells/µL AND/OR FeNO ≥ 20 ppb (non-omalizumab eligible patients)
Intervention	VOYAGE dosing • Patients weighing ≤ 30 kg: 100 mg Q2W • Patients weighing > 30 kg: 200 mg Q2W Requested PBS dosing (as per dupilumab product information) • Patients weighing 15 - <30 kg: 300 mg Q4W • Patients weighing 30 - <60 kg: 200 mg Q2W or 300 mg Q4W • Patients weighing ≥ 60 kg: 200 mg Q2W
Comparator	'Subgroup A': omalizumab 'Subgroup B': Placebo, representing Standard of Care (SoC)
Outcomes	Primary: annualised rate of severe asthma exacerbations Secondary: change from baseline in percent predicted pre BD FEV1, change from baseline in ACQ-7-IA, change from baseline in FeNO, change in percent predicted FEV1 over time, loss of asthma control events, change in lung function measures, change in daily efficacy assessments (systemic corticosteroids, morning symptoms, nocturnal symptoms, reliever medication use), change in patient reported outcomes (ACQ-7-IA, ACQ-5-IA, PAQLA(S)-IA).
Clinical claim	• 'Subgroup A' - dupilumab has non-inferior efficacy and non-inferior safety compared to omalizumab for the treatment of paediatric patients with uncontrolled severe asthma • 'Subgroup B' - dupilumab has superior efficacy and non-inferior safety compared to SoC for the treatment of paediatric patients with uncontrolled severe asthma

Source: Table ES.1 of the submission. Abbreviations: IgE = immunoglobulin E; EOS = eosinophils; FeNO = fractional exhaled nitric oxide; Q2W = every two weeks; Q4W = every four weeks; SoC = standard of care; BD = bronchodilator; FEV1 = forced expiratory volume in 1 second; ACQ-IA = asthma control questionnaire interviewer administered; PAQLA(S)-IA = paediatric asthma quality of life questionnaire with standardised activities interviewer administered; µL = microlitre; ppb = parts per billion

2 Background

Registration status

2.1 Dupilumab was initially TGA registered in January 2018 for the treatment of atopic dermatitis in adults, and is currently registered for prurigo nodularis, asthma and chronic rhinosinusitis with nasal polyposis. The indication was expanded on 29 June 2022 to include "add on maintenance treatment in patients aged 6 years and older with moderate to severe asthma with type 2 inflammation (elevated eosinophils or elevated FeNO) that is inadequately controlled despite therapy with other medicinal products for maintenance treatment". [2]

Previous PBAC consideration

2.2 The PBAC has not previously considered a submission for dupilumab for paediatric asthma.

[2] Dupilumab PI, para 4.1, p2/71.

2.3 In November 2020 the PBAC recommended dupilumab for use in adults and adolescents with uncontrolled severe allergic or eosinophilic asthma on the basis of a cost-minimisation approach compared to the least costly of benralizumab, mepolizumab and omalizumab (listed 1 April 2021).

2.4 Dupilumab was recommended by the PBAC for use in adults and adolescents with atopic dermatitis in March 2020 and recommended for use in paediatric populations for that indication in March 2022. In its consideration in March 2022, the PBAC considered that the clinical evidence suggests the magnitude of benefit in patients aged 6-11 years is similar to that in the adult/adolescent population and the cost-effectiveness was acceptable at the same price per month as for the adult/adolescent population.

2.5 Listing for an autoinjector presentation for severe atopic dermatitis and uncontrolled severe asthma in patients 12 years and over was recommended in November 2022 (listing pending).

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

3 Requested listing

3.1 The submission proposed four sets of restrictions including one for grandfathered patients. An abbreviated version of the proposed restrictions is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty (published*)	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DUPILUMAB					
Tx phase: Initial 1/Initial 2 dupilumab 200 mg/1.14 mL injection, 2 x 1.14 mL syringes	Public: $1609.86 Private: $1658.23	1	2	7	Dupixent
Tx phase: continuing dupilumab 200 mg/1.14 mL injection, 2 x 1.14 mL syringes	Public: $1609.86 Private: $1658.23	1	2	5	Dupixent
Tx phase: GF dupilumab 200 mg/1.14 mL injection, 2 x 1.14 mL syringes	Public: $1609.86 Private: $1658.23	1	2	5	Dupixent
Tx phase: Initial 1/Initial 2 dupilumab 300 mg/2 mL injection, 2 x 2 mL syringes	Public: $3219.72 Private: $3268.09	1	2	3	Dupixent
Tx phase: continuing dupilumab 300 mg/2 mL injection, 2 x 2 mL syringes	Public: $3219.72 Private: $3268.09	1	2	2	Dupixent
Tx phase: GF dupilumab 300 mg/2 mL injection, 2 x 2 mL syringes	Public: $3219.72 Private: $3268.09	1	2	2	Dupixent

*The submission stated that should dupilumab receive a positive recommendation in the paediatric asthma cohort, the sponsor will request a weighted published AEMP across all reimbursed dupilumab indications.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
DUPILUMAB					
dupilumab 200 mg/1.14 mL injection, 2 x 1.14mL	NEW (Public) NEW (Private)	1	2	~~6~~7	Dupixent
dupilumab 300 mg/2 mL injection, 2 x 2mL syringes	NEW (Public) NEW (Private)	1	2	3	Dupixent
Restriction Summary / Treatment of Concept					
Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private)					
Prescriber type: ☒Medical Practitioners					
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)					
Administrative Advice: See overarching administrative note below.					
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Uncontrolled Severe Asthma					
Treatment Phase: Initial treatment 1 – (New patient; or Recommencement *of treatment* in a new treatment cycle following a break in PBS-subsidised biological medicine therapy)					
Clinical criteria:					
Patient must not have received PBS-subsidised treatment with a biological medicine for severe asthma; or					
Patient must have had a break in treatment from the most recently approved PBS-subsidised biological medicine for severe asthma					
AND					
Clinical criteria:					
Patient must have a diagnosis of asthma confirmed and documented by a paediatric respiratory physician, clinical immunologist, or allergist; or paediatrician or general physician experienced in the management of patients with severe asthma in consultation with a respiratory physician, defined by the following standard clinical features: forced expiratory volume (FEV1) reversibility or airway hyperresponsiveness or peak expiratory flow (PEF) variability,					
AND					
Clinical criteria:					
Patient must have a duration of asthma of at least 1 year					
AND					
Clinical criteria:					
Patient must have total serum human immunoglobulin E greater than or equal to 30 IU/mL with past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE in the last 12 months, ~~AND/~~OR					
Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre in the last 12 months; ~~AND/~~OR					
Patient must have a fractional exhaled nitrous oxide greater than 20 ppb in the last 12 months					
AND					
Clinical criteria:					
Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented,					
AND					
Clinical criteria:					
Patient must not receive more than 32 weeks of treatment under this restriction,					
AND					

Clinical criteria:
Patient must be under the care of the same physician for at least 6 months.
AND
Clinical criteria:
The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma
Treatment criteria:
Must be treated by a paediatric respiratory physician, clinical immunologist, allergist; or paediatrician or general physician experienced in the management of patients with severe asthma, in consultation with a respiratory physician.
Population criteria:
Patient must be aged 6 to less than 12 years.
Prescribing Instructions: Optimised asthma therapy includes: (i) Adherence to optimal inhaled therapy, including high dose inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) therapy for at least six months. If LABA therapy is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative; AND (ii) treatment with at least 2 courses of oral or IV corticosteroids (daily or alternate day maintenance treatment courses, or 3-5 day exacerbation treatment courses), in the previous 12 months unless contraindicated or not tolerated. If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications (including those specified in the relevant TGA-approved Product Information) and/or intolerances of a severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance must be provided in the Authority application.
Prescribing Instructions: The initial IgE assessment*, blood eosinophil count or fractional exhaled nitrous oxide measurement* must be no more than 12 months old at the time of application.
Prescribing Instructions: The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) An Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month (for children aged 6 to 10 years it is recommended that the Interviewer Administered version – the ACQ-IA be used), AND (b) while receiving optimised asthma therapy in the previous 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. The Asthma Control Questionnaire (5 item version) or ACQ-IA assessment of the patient's response to this initial course of treatment, the assessment of oral corticosteroid dose, and the assessment of exacerbation rate should be made at around ~~24~~ *28* weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. This assessment, which will be used to determine eligibility for continuing treatment, should be submitted within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a response assessment is not undertaken and submitted, the patient will be deemed to have failed to respond to treatment with ~~dupilumab~~ *this drug for this condition*. A patient who fails to *demonstrate a response* ~~respond~~ to ~~a course of PBS-subsidised treatment dupilumab for the treatment of uncontrolled severe asthma~~ *treatment with this drug* will not be eligible to receive further PBS-subsidised treatment with *this drug* ~~dupilumab~~ for this condition within *the same treatment cycle* ~~6 months of the date on which treatment was ceased~~. *A treatment break in PBS-subsidised biological medicine therapy of at least 6 months must be observed in a patient who has either failed to achieve or sustain a response to treatment with 2 biological medicines within the same treatment cycle.*

The length of the break in therapy is measured from the date of the most recent treatment with a PBS-subsidised biological medicine was administered until the date of the first application for recommencement of treatment with a biological medicine under the new treatment cycle. 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 dupilumab of up to 32 weeks. The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed ~~Paediatric Severe Allergic Asthma Initial PBS Authority Application – Supporting Information form, which includes the following:~~ *authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice), which includes:* (i) details of prior optimised asthma drug therapy (dosage, date of commencement and duration of therapy); and (ii) details of severe exacerbation/s experienced in the past 12 months while receiving optimised asthma therapy (date and treatment); and (iii) the IgE, *blood eosinophil or the fractional exhaled nitrous oxide* result *and date*; and (iv) Asthma Control Questionnaire (ACQ-5) score; or (v) Asthma Control Questionnaire interviewer administered version (ACQ-IA) score.
Administrative Advice: *The Services Australia website (www.servicesaustralia.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.*
Administrative Advice: For copies of the ACQ~~-5, ACQ-5-IA~~ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
Administrative Advice: *It is recommended that an application for continuing treatment is submitted at the 28-week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug for this condition.*
Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.servicesaustralia.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
Administrative Advice: 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. ~~EST~~ Monday to Friday). ~~The Services Australia website (www.servicesaustralia.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.~~ 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 authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

OVERARCHING ADMINISTRATIVE NOTE

Administrative Advice: TREATMENT OF PAEDIATRIC PATIENTS WITH UNCONTROLLED SEVERE ASTHMA

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of *the biological medicines* dupilumab and omalizumab for uncontrolled severe asthma. Therefore, where the term 'biological medicine' appears in notes and restrictions, it refers to dupilumab and omalizumab only.

A patient is eligible for PBS-subsidised treatment with only 1 of the above biological medicine at any *one* ~~1~~ time.

A patient receiving PBS-subsidised treatment for uncontrolled severe asthma is able to commence a treatment cycle where they may trial a biological medicine without having to experience a disease flare when swapping to an alternate biological medicine within the same treatment cycle.

Under these arrangements, within a treatment cycle, a patient may receive long-term treatment with a biological medicine as long as they sustain a response to therapy.

A patient currently receiving PBS-subsidised treatment as of [dupilumab list date] is considered to have started a cycle of treatment.

Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to the same PBS-subsidised biological more than once.

Therefore, once a patient fails to meet the response criteria for a PBS-subsidised biological medicine, they must change to an alternate biological medicine if they wish to continue PBS-subsidised biological treatment.

Once a patient has either failed to achieve or sustain a response to treatment 2 times, they are deemed to have completed a single treatment cycle. They must have at least a 6-month break in PBS-subsidised biological medicine therapy before they are eligible to recommence another new treatment cycle [further details are under 'Recommencement of treatment after a break in PBS-subsidised therapy' below].

The length of the break in therapy is measured from the date the most recent treatment with a PBS-subsidised biological medicine is ceased until the date of the first application for recommencement of treatment with a biological medicine under the new treatment cycle.

There is no limit to the number of treatment cycles that a patient may undertake in their lifetime.~~, provided they meet the population criteria.~~

How to prescribe PBS-subsidised biological medicine treatment for uncontrolled severe asthma.

(1) Initial treatment:
Applications for initial treatment should be made where:
(i) a patient has not received prior PBS-subsidised biological medicine treatment and wishes to commence such therapy (Initial 1 restriction); or
(ii) a patient has received prior PBS-subsidised treatment with a biological medicine and wishes to recommence a new treatment cycle with this biological medicine following a treatment break in PBS-subsidised therapy (Initial 1 restriction); or
(iii) a patient has received prior PBS-subsidised biological medicine therapy and wishes to trial an alternate biological medicine within the same treatment cycle (Initial 2 restriction) – [further details are under 'Swapping therapy' below].

All applications for initial treatment will be limited to provide for a maximum of up to 32 weeks of therapy of a biological medicine. It is recommended that a patient be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological medicine supply.

(2) Continuing treatment:
Following the completion of an initial treatment course with a specific biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that biological medicine providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing biological medicine treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. It is recommended that a patient be reviewed the month prior to completing their current course of treatment to ensure uninterrupted biological medicine supply.

(3) Baseline measurements to determine response:
Baseline measurements of the Asthma Control Questionnaire (ACQ, ACQ-IA; 5 item version), *systemic corticosteroid dose* and time adjusted exacerbation rate, submitted with the Initial authority application for a biological medicine must be used to determine whether an adequate response to treatment has been achieved or sustained.
However, prescribers may provide new baseline measurements when a new Initial treatment authority application is submitted and these new baseline measurements may be used to assess response.

(4) Swapping therapy within the same treatment cycle.
Once initial treatment with the first PBS-subsided biological medicine is approved, a patient may swap to an alternate biological medicine at any time by qualifying under an Initial 2 restriction.

However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug with the same treatment cycle.

Within the same treatment cycle a patient may alternate between therapy with either biological medicine of their choice (1 at a time) providing:
(i) they have not received PBS-subsided treatment with that particular biological medicine previously; or
(ii) they have demonstrated an adequate response to that particular biological medicine if they have previously trialled it on the PBS; and
(iii) they have not previously failed to respond to treatment with either 4 *2* biological medicines in this treatment cycle.

(5) Re-commencement of a new treatment cycle after a treatment break in PBS-subsidised therapy:
A patient who wishes to trial a second or subsequent new treatment cycle, following a break in PBS-subsidised therapy of at least 6 months (in patients who have failed to achieve or ceased to sustain a response to treatment 2 times within a treatment cycle), must re-qualify through an Initial 1 restriction.

(6) Monitoring of patients (Omalizumab only):
Anaphylaxis and anaphylactoid reactions have been reported following first or subsequent administration of omalizumab (see Product Information). Patients should be monitored post-injection, and medication for the treatment of anaphylactic reactions should be available for immediate use following administration of omalizumab. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

Source: Submission Table 1.16

3.2 The submission stated that the restriction used the same wording as the omalizumab restriction, but the submission appeared to have intended that patients in Subgroup A and Subgroup B should be combined into one restriction.

3.3 The ESC noted the proposed restriction was broader than the approved TGA indication (which requires either elevated eosinophils or elevated FeNO) in that it allows for treatment of patients with high serum IgE who do not have elevated eosinophils or FeNO.

3.4 The submission also suggested an alternative listing which would "[b]ase the wording of the dupilumab restriction on the patients enrolled into VOYAGE, resulting in slightly different restrictions for omalizumab and dupilumab". For patients who continue therapy, the alternative listing removed reference to an adequate response to dupilumab needing to include reduction in the maintenance dose of corticosteroids by at least 25% from baseline, and no deterioration in the Asthma Control Questionnaire (ACQ) or ACQ-IA score from baseline.

3.5 For adolescents and adults to be treated with dupilumab on the PBS, they must have IgE greater than or equal to 30 IU/mL OR eosinophils of greater than or equal to

150 cells per microlitre. No criteria based on FeNO are included in the listing for adolescents and adults.

3.6 The submission stated that the sponsor proposed "to initiate a Patient Familiarisation Programme (PFP) for dupilumab prior to its listing on the PBS, with a target of enrolling approximately < 500 patients". A "grandfathering restriction is required to allow transition of patients from the PFP to PBS-subsidised drug following PBS listing".

3.7 The ESC noted that for the grandfathering restriction, no criteria for severity of asthma or adequacy of maintenance treatment were included and measurements of IgE or eosinophils or FeNO were not required, so these patients would become PBS-eligible without needing to meet PBS criteria. The ESC agreed with the Secretariat comments on the restriction in relation to grandfathering provisions, considering that only patients meeting the eligibility criteria for dupilumab prior to commencing the PFP should be eligible for dupilumab under the grandfathering restriction.

3.8 The restriction for dupilumab most consistent with the submitted evidence (VOYAGE trial) is severe uncontrolled asthma, defined as in the current restrictions, with:

- total serum IgE $\geq$ 30 IU/mL, **and** (not "and/or")
- eosinophils $\geq$ 0.15 x 10^9/L **or** FeNO $\geq$ 20 ppb.

3.9 This is also consistent with the trial evidence on which the restriction for adults and adolescents was based. The submission stated that in the QUEST trial of dupilumab for asthma in adults and adolescents, there were sufficient patients who did not have raised IgE to establish that patients who had raised eosinophils or raised FeNO responded to dupilumab whether they had raised IgE or not. The submission's argument was, essentially, that the PBAC should extrapolate those results in adolescents and adults to children, noting that the VOYAGE trial had only 7 children who did not have raised IgE.

3.10 The Pre-Sub-Committee Response (PSCR) stated that the proposed restriction should not be limited to patients who have total serum IgE $\geq$ 30 IU/mL given that the VOYAGE trial "study population did include a small number of patients with increased [eosinophils] EOS and/or FeNO with baseline IgE levels <30 IU/mL". The PSCR added that "restricting the reimbursement of dupilumab only to patients with increased EOS or FeNO in combination with increased IgE would deny treatment to a small but important group of patients for whom no alternative therapies are currently available".

3.11 The ESC noted that measurement of FeNO is an MBS item (11507), but availability in remote and some regional areas would be limited.

3.12 The ESC noted the proposed restriction would require patients to be under the care of the same physician for 6 months prior to treatment. The ESC considered this may unduly limit use to patients in private clinics. The ESC considered it would be appropriate to add the following statement to the clinical criteria, noting that this

criterion was included in the PBS restriction for omalizumab: "Patient must have been diagnosed by a multidisciplinary severe asthma clinic team (respiratory physician plus at least one of a pharmacist, nurse or asthma educator)".

3.13 The submission proposed a Special Pricing Arrangement (SPA) for dupilumab for paediatric asthma.

3.14 The current effective price for dupilumab in asthma is: $[redacted], 300 mg/2 mL single dose pre-filled syringe, pack quantity 2; $[redacted], 200 mg/1.14 mL, single dose pre-filled syringe, pack quantity 2.

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

4 Population and disease

4.1 Asthma, characterised by symptoms of "wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation", usually associated with chronic airway inflammation[3] , is common in Australia. In the 2020-1 ABS survey, asthma was reported by 9.5% of boys and 7.9% of girls aged 0-14 years.

4.2 "Uncontrolled asthma" is asthma with frequent symptoms, or two or more exacerbations requiring oral corticosteroids (OCS) in the past year, or any exacerbation(s) in the past year requiring hospitalisation.

4.3 Severe asthma is asthma that can only be controlled with high dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA), or oral corticosteroid (OCS), or is uncontrolled despite this treatment, in the absence of factors such as poor inhaler technique and non-adherence. By this definition a small percentage of asthmatics have severe asthma. Patients with uncontrolled asthma despite prescription of high dose ICS and LABA in whom poor inhaler technique and non-adherence have not been excluded are several times more common.[4]

4.4 Most children with severe asthma have allergic asthma, with high circulating IgE and positive skin tests to common allergens. Allergy is less common in adults with severe asthma.

4.5 Allergy is associated with atopy, an inherited proclivity to produce IgE antibodies after exposure to antigens. Many atopic children have atopic dermatitis and allergic rhinitis as well as asthma. These conditions often occur in sequence: atopic dermatitis in infancy and allergic rhinitis and asthma in later childhood – a phenomenon referred to as the "allergic march". This means that a significant degree of overlap between the

[3] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated July 2023, p22.

[4] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated July 2023, p42, p121.

populations of children eligible for PBS-subsidised use of biological treatments for atopic dermatitis and for asthma may be expected.

4.6 Eosinophilia in sputum or peripheral blood and elevated fractional exhaled nitric oxide (FeNO) characterise Type 2 inflammation. Type 2 inflammation is common but not universal in children with allergic asthma, in adults with allergic asthma, and in adults with non-allergic asthma. Cytokines IL-4 and IL-13, produced by Th2 cells, are key drivers of Type 2 inflammation. IL-4 and IL-13 act on cells which express the Il-4 receptor.

4.7 The current asthma treatment guidelines for the management of severe asthma in children in Australia suggest that there should be referral to a specialist for 'optimised asthma treatment' (OAT) i.e., monitored adherence for 6 months, use of montelukast, cromoglycate or nedocromil, or IV or oral corticosteroids. Biological treatments are recommended for use in patients who fail OAT. Tiotropium is also PBS listed for use in this group of patients.

4.8 The only biological treatment currently PBS listed for use in paediatric patients who fail OAT is omalizumab (although dupilumab, benralizumab and mepolizumab are listed for use in patients 12 years and older.) For PBS use of omalizumab, in addition to failed treatment with OAT, the patients must have Total serum Ig E $\geq$ 30 IU/mL and atopy, documented by skin prick test or an in vitro measure of specific IgE. Notably, the current restriction for omalizumab does not include any requirement to document eosinophilia or elevated FeNO.

4.9 Omalizumab is a monoclonal antibody to IgE that blocks binding to the mast cell receptor. Omalizumab does not prevent allergic reactions caused by IgE already bound to mast cells. Only a small number of IgE molecules have to interact with their specific antigen to cause release of mediators from mast cells, so free IgE has to be reduced to low levels to block allergic asthma. For this reason, and because of the lack of effect on IgE already bound to mast cells, the onset of the omalizumab treatment effect may be relatively slow.

4.10 Dupilumab is a monoclonal antibody to the alpha subunit of the IL-4 receptor, so that it inhibits the action of both IL-4 and IL-13.

4.11 Prolonged treatment with omalizumab may result in persistent benefit after discontinuation of treatment.[5] Similar effects have not been established for dupilumab.

4.12 The omalizumab dose is determined mainly by baseline total serum IgE but also by body weight, and the bands of IgE level and of weight are narrow. Patients with higher baseline IgE require 2nd weekly administration because the higher dose cannot be

[5] Humbert M, Bourdin A, Taille C, et al. Real-life omalizumab exposure and discontinuation in a large nationwide population-based study of pediatric and adult asthma patients. *Eur Respir J* 2022; 60:2103130; DOI 10.1183/13993003.03130-2021.

given in a single 4th weekly injection.[6] The dupilumab dose is determined based on body weight only with three weight bands (15-30 kg, 30-60 kg, and > 60 kg).

4.13 The first three doses of omalizumab must be given under medical supervision, including a period of observation after the dose is given, because of the risk of anaphylaxis.[7] This is not required for dupilumab.

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

5 Comparator

5.1 The submission nominated omalizumab as the comparator for Subgroup A patients, and placebo as the comparator for Subgroup B patients.

5.2 The Global Initiative for Asthma (GINA) guidelines (though not the overview of the GINA guidelines presented in the submission) suggest that, in children aged 6 years or over, tiotropium, a long-acting muscarinic antagonist (LAMA) is an alternative to biological treatments at Step 5.[8] Tiotropium is PBS-listed for treatment of poorly-controlled severe asthma despite use of ICS-LABA in patients aged 6 years and over, and therefore may be an appropriate comparator.

5.3 The PSCR stated that tiotropium is not an appropriate comparator given that it can be used at Step 4 of the GINA guidelines in patients who have only received medium-dose ICS and not high-dose ICS, and given that omalizumab was not considered an appropriate comparator when tiotropium was considered for paediatric patients with severe uncontrolled asthma in March 2018. The ESC considered tiotropium could be considered an appropriate additional comparator, noting potential use of tiotropium at Step 4 of the GINA guidelines does not preclude its use at Step 5.

5.4 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: omalizumab and tiotropium.

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

[6] Table 1, p4, Omalizumab PI.
[7] 4.2, p5, Omalizumab PI.
[8] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated July 2023, p78.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the overlapping endotypes and phenotypes of Type 2 asthma that are identified by clinical differences and combinations of biomarkers, noting that whilst IgE is a marker of allergic asthma, it may be low in other forms of Type 2 asthma characterised by the presence of other biomarkers such as eosinophils and FeNO. The clinician stated that there exists a small number of patients with uncontrolled asthma with low IgE in the presence of other elevated biomarkers for Type 2 asthma who would benefit from IL-4/IL-13 blockade with dupilumab. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dupilumab including the potential for: efficacy in patients with either IgE-mediated asthma or eosinophilic asthma, a lower risk of anaphylaxis, additional benefit for patients who also have atopic dermatitis, a decreased risk of anaphylaxis and allergy allowing for home initiation instead of hospital for the first three treatments, a lower injection frequency, the potential for a reduction in oral corticosteroid use, and improved quality of life.

6.3 The PBAC noted the advice received from Asthma Australia, the Australasian Society of Clinical Immunology and Allergy, and the joint submission from The National Allergy Council and Allergy & Anaphylaxis Australia clarifying the likely use of dupilumab in clinical practice and supporting the requested listing.

Clinical trials

6.4 The submission was based on one randomised controlled trial comparing dupilumab to placebo (VOYAGE).

6.5 To support the claim of non-inferiority to omalizumab in Subgroup A patients, an indirect treatment comparison comparing data from a sub-group of VOYAGE patients with data from a single randomised controlled trial comparing omalizumab to placebo (IA-05) was presented, with placebo as the common arm. IA-05 was the evidence considered by PBAC when omalizumab was recommended for listing in July 2016.

6.6 Three trials of omalizumab, all described as “Key Paper, Phase III trial” in Attachment 5 of the submission, were excluded (Busse, 2011; Milgrom, 2001, and Odajima, 2015). Odajima 2015 was an uncontrolled study and appropriately excluded. Busse, 2011 was excluded because it had “Incomparable study design population”. Patients were aged 6-20 years (but data for age groups were reported separately) and had poorly controlled asthma; optimised treatment was required only for the 4 weeks before randomisation and reductions of ICS dose were allowed during the trial.

Exacerbations, defined similarly to VOYAGE, were not the primary outcome but were reported. The evaluation considered that the trial should have been included. The PSCR argued that the Busse, 2011 (ICATA) trial was unsuitable for providing a meaningful comparison between dupilumab and omalizumab for the following reasons:

- the trial "failed to report baseline characteristics for most key effect modifiers, thereby constraining comparability with VOYAGE", and
- at "study entry, patients enrolled into the ICATA study underwent a 4-week run in period during which (non-biologic) treatments for asthma were optimised. Over this run-in period, the average daily ICS dose was increased by a mean of 204 µg and the proportion of patients of patients receiving a LABA in combination with ICS increased to 42%. As a result of this treatment optimization, asthma symptoms improved such that, at the time of randomisation to omalizumab or placebo, only 73% of the study participants were considered to have moderate-to-severe asthma. In contrast, the VOYAGE study required all patients to have received a stable dose of medium or high-dose ICS plus a second controller for at least 3 months, with a stable dose for at least 1 month prior to study entry. In addition, during the 60 day treatment period in the ICATA trial, patients were assessed every three months, at which time adjustments to background ICS-LABA treatments could be made depending on asthma symptoms experienced in the previous two weeks, whist in the VOYAGE trial baseline ICS and LABA doses were maintained throughout the entire study period except where two or more severe exacerbations had occurred, at which time a step up in the controlled medication was allowed".

6.7 The submission stated that Milgrom, 2001, was excluded because it had an "ICS dose-reduction phase [and] reported outcomes at 16 weeks" – the end of the stable-dose phase. This was misleading: exacerbations (defined as worsening requiring any additional treatment) were reported both for the stable-dose phase ending at 16 weeks and the steroid-reduction phase (17-28 weeks). The evaluation considered this trial should have been included. The PSCR stated "no changes in background medication (including ICS dose) were allowed during the VOYAGE trial" and that while baseline characteristics were not reported for most key effect modifiers that the characteristics which were reported indicated that the study included an older cohort of patients who had a lower baseline mean ICS dose (284 µg/day) relative to VOYAGE (496.22 µg/day) and IA-05 (515.1 µg/day). As such, the PSCR stated that due to differences in both study design and included participants, the study was not considered comparable to the VOYAGE study and therefore its exclusion from the [indirect treatment comparisons] ITCs presented in the submission was appropriate. The PSCR also stated that the study was not assessed by the PBAC during their consideration of the reimbursement of omalizumab for the treatment of uncontrolled severe paediatric asthma in July 2016. The ESC considered the additional trials

identified during the evaluation (Busse 2011, and Milgrom 2001) should have been included.

6.8 The ESC noted that no data to support the claim of superior efficacy to placebo in Subgroup B patients was presented. As only seven patients enrolled in VOYAGE had IgE < 30 IU/mL the ESC considered that no conclusions about efficacy in this group could be made.

6.9 Evaluation of the data submitted was hampered by the data for IA-05 being confined to that provided in published papers, and by the method of presentation of data from the VOYAGE trial.

6.10 VOYAGE defined three pre-specified populations for analysis:

- the ITT population;
- patients with a "Type 2 inflammatory phenotype", defined as baseline eosinophil count $\geq$ 0.15 x 109/L or FeNO $\geq$ 20 ppb;
- patients with baseline eosinophils $\geq 0.3 \times 10^9$/L.

6.11 The submission and the VOYAGE Clinical Study Report (CSR) presented only limited data for the intention to treat (ITT) population of VOYAGE; most data presented was for the Type 2 inflammatory phenotype population (eosinophils $\geq 0.15 \times 10^9$/L or FeNO $\geq$ 20 ppb) and the population with eosinophils $\geq 0.3 \times 10^9$/L. Because these populations overlap, but exclude some randomised patients, the data from these populations were difficult to interpret. The justification for presenting only data for these populations was weak because they were not the Subgroups A and B defined in the submission. For these reasons, the evaluation presented data for the ITT population, but this was incomplete for some parameters.

6.12 Details of the trials presented in the submission are provided in Table 2, and key features of the trials are shown in Table 3.

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
VOYAGE NCT02948959	Evaluation of Dupilumab in Children With Uncontrolled Asthma Bacharier L.B., Maspero J.F., Katelaris C.H., et al, Dupilumab in children with uncontrolled moderate-to-severe asthma Jackson, J.D., Bacharier, L.B., Phipatanakul W., et al, Dupilumab pharmacokinetics and effect on type 2 biomarkers in children with moderate-to-severe asthma	7 December 2020 NEJM 2021; 385:2230-2240. Ann Allergy Asthma and Immunology 2023; 131:44-51.e4.
IA05 NCT00079937	Efficacy and Safety of Omalizumab in Children (6 - < 12 Years) With Moderate-severe, Inadequately Controlled Allergic Asthma Kulus M., Hébert J., Garcia E., et al, Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma, Lanier B., Bridges T., Kulus M., Taylor A.F., et al, Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma.	Not provided Current Medical Research and Opinion 2010 26:1285-1293. Journal of Allergy and Clinical Immunology 2009; 124: 1210-1216.

Source: Table 2.5 of the submission.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Primary Outcome	Use in economic evaluation
Dupilumab vs placebo						
VOYAGE	408	R, DB, MC, 52 weeks	Low	Uncontrolled asthma despite medium or high-dose ICS and recent severe exacerbations	Rate of exacerbations over 52 weeks requiring systemic steroids ≥3 days, or which resulted in hospitalisation or emergency room visit and use of systemic steroids	Used
Omalizumab vs placebo						
IA05	627	R, DB, MC, 52 weeks	Low	Uncontrolled asthma despite medium or high-dose ICS and recent severe exacerbations, and total serum IgE ≥ 30 IU/mL and < 1300 IU/mL	Rate of exacerbations over 24 weeks requiring doubling of ICS dose or systemic steroids ≥ 3 days	Used

Source: Constructed during the evaluation from VOYAGE CSR and Lanier et al, 2009, Attachment 12.
DB = double blind; ICS = inhaled corticosteroids; MC = multi-centre; R = randomised.

6.13 Both trials enrolled children aged 6 to <12 years, with severe asthma as defined by significant symptoms on medium or high dose ICS, and a recent history of exacerbations.

6.14 The ESC noted the eligibility criteria for VOYAGE and for IA-05 were different than that proposed for PBS use of dupilumab and the existing PBS restriction for omalizumab.

6.15 Differences in the VOYAGE and PBS populations included:

- Patients in VOYAGE had received treatment for at least 3 months (not 6 months as required for the PBS criteria), with stable dose for at least one month, with medium dose ICS + a second controller (LABA, LTRA, LAMA, or methylxanthine) or high-dose ICS alone or with a second controller,[9] and were symptomatic during the month before randomisation, but the ESC noted there was no requirement to check inhaler technique or to correct it if it was inadequate, as in the PBS criteria;
- Patients in VOYAGE had, within the previous 12 months, taken oral or injected corticosteroids prescribed by a health professional for worsening asthma, or been hospitalised or made an "emergency medical care visit" for worsening asthma, but the ESC noted there was no requirement that these events must have occurred while receiving medium- or high-dose ICS, as in the PBS criteria.

6.16 Differences in the IA-05 and PBS populations included:

- Patients in IA-05 had to be symptomatic while receiving medium- or high-dose ICS, but the ESC noted that the minimum duration of use was not specified, and it was not clear from the published reports whether satisfactory inhaler technique was required;
- Patients in IA-05 had to have experienced ≥2 "exacerbations" (not defined in the published reports) in the previous year, or ≥3 exacerbations in the previous 2 years, or ≥1 exacerbation in the previous year that required hospitalisation, but the ESC noted it was not clear from the published reports whether the exacerbations had to have occurred while the patients were receiving medium- or high-dose ICS.

6.17 There were minor differences in the primary outcomes. The primary outcome in VOYAGE was the rate of severe exacerbations during the 52-week placebo-controlled treatment period. A severe exacerbation was defined as worsening asthma for which systemic corticosteroids were used for ≥3 days, or which resulted in hospitalisation or emergency room visit and use of systemic corticosteroids.

6.18 In IA05 the primary outcome was the rate of clinically significant exacerbations over the first 24 weeks of treatment. A clinically significant exacerbation was defined as requiring either use of systemic steroids for ≥3 days or doubling of the ICS dose. Increasing the dose of ICS is no longer recommended as treatment of worsening asthma, and only 10% of exacerbations were treated with increased doses of ICS, so in practice the definition of exacerbation was similar to that in VOYAGE. In IA05 the primary outcome was taken over the first 24 weeks of treatment, because after this

[9] No patients taking LAMA or methylxanthines as second controller were enrolled. Only a few patients enrolled were taking ICS only. ICS = inhaled corticosteroid; LABA = long-acting beta-agonist, LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist.

time well-controlled patients were eligible for reduction of ICS dose.[10] However, reductions in ICS dose were either small or affected few patients: ICS dose was reduced by 4% in omalizumab-treated patients and increased by 2% in placebo-treated patients (P = 0.053). IA05 also reported the rate of exacerbations over 52 weeks, and the rate of severe exacerbations, defined as exacerbations that required treatment with systemic corticosteroids and where peak expiratory flow or FEV_1 was <60% of personal best, over 24 and 52 weeks.

6.19 In relation to baseline characteristics of patients enrolled in the trials, one notable difference was in baseline IgE levels. Although raised serum IgE was not a requirement for enrolment in VOYAGE, mean IgE levels were higher than in IA-05, 401/408 (98.3%) had total serum IgE ≥ 30 IU/mL, and 309/408 (75.7%) had total IgE ≥ 100 IU/mL (VOYAGE CSR, Figure 12, p141). Higher mean levels may be contributed to by IA-05 but not VOYAGE having an upper limit of total serum IgE of 1300 IU/mL, and some patients in VOYAGE having very high levels, but the available data are not sufficient to confirm this.

6.20 In relation to flow of patients through the trials, more patients withdrew from the trial or discontinued treatment in IA-05 than in VOYAGE. In VOYAGE more patients randomised to dupilumab than to placebo withdrew from the trial or discontinued treatment. In neither case was this accounted for by a difference in withdrawals due to adverse events.

Comparative effectiveness

6.21 The results of the trials are shown in Table 4.

6.22 IA-05-EU was a pre-specified sub-group of the IA05 population including patients treated with ≥ 500 μg/day of fluticasone or equivalent + LABA. This was called IA05-EU, because it corresponded to the EU indication in adults and adolescents. When PBAC considered omalizumab for use in children, it noted that this sub-group matched the proposed omalizumab restriction well.

[10] No reductions in maintenance treatment were allowed in VOYAGE (CSR, p36).

Table 4: Results of primary efficacy outcomes in VOYAGE, IA-05 and IA-05-EU, ITT population

	VOYAGE[1]		IA-05[2]		IA-05-EU[2]	
	Dupilumab N = 273	Placebo N = 135	Omalizumab N = 421	Placebo N = 206	Omalizumab N = 159	Placebo N = 76
Exacerbation rate at 24 wk by trial definition[3]	NR	NR	0.45	0.64	0.42	0.63
RR (95% CI) vs placebo	NR		**0.69 (0.53, 0.90)**		**0.66 (0.44, 0.995)**	
Exacerbation rate at 52 wk by trial definition[3]	0.28	0.61	0.78	1.36	0.73	1.44
RR (95% CI) vs placebo	**0.46 (0.31, 0.67)**		**0.57 (0.45, 0.73)**		**0.50 (0.35, 0.72)**	
Severe exacerbation rate at 24 wk by IA05 definition[3,4]	NR	NR	0.10	0.18	NR	NR
RR (95% CI) vs placebo	NR		**0.55 (0.32, 0.95)**		NR	
Severe exacerbation rate at 52 wk by IA05 definition[3,4]	NR	NR	0.12	0.24	NR	NR
RR (95% CI) vs placebo	NR		**0.49 (0.30, 0.80)**		NR	

Source: Table 2.27 of the submission; Lanier, et al, 2009, Attachment 12, Kulus, et al, 2010, Attachment 12.
NR = not reported; RD = risk difference; RR = relative risk; wk = week. Statistically significant results are in **bold**.
[1] Rates adjusted for treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study.
[2] Rates adjusted for treatment, dosing schedule, country, and exacerbation history.
[3] See paragraphs 6.16 and 6.17.
[4] Results for severe exacerbations by the IA05 definition are not reported in Kulus et al, 2010, but when the PBAC reviewed the data, it noted that there were "no differences between omalizumab and placebo for the severe exacerbation rate" in the IA-05-EU sub-group (para 6.16, omalizumab public summary document (PSD), July 2016 PBAC Meeting).

6.23 Both omalizumab and dupilumab were effective in reducing exacerbations, and in the ITT populations the differences in the point estimates were small relative to the confidence intervals.

6.24 It appeared from the IA-05 results that efficacy of omalizumab at 52 weeks may be better than at 24 weeks. This is consistent with the mechanism of action of omalizumab, and was supported by the finding in the IA-05-EU sub-group that the relative risk (95% CI) for exacerbations in the first 24 weeks was 0.66 (0.44, 0.995) but from weeks 25 to 52 the relative risk (95% CI) was 0.37 (0.24, 0.57). The ITC reported in the submission used the 24-week data from IA-05, and although rapid onset of action is a beneficial effect in patients with poorly controlled asthma, in the context of a clinical claim of non-inferiority the ESC considered it may be more appropriate to consider the efficacy of dupilumab compared to omalizumab at the same timepoint of 52 weeks, rather than omalizumab at 24 weeks compared to dupilumab at 52 weeks.

6.25 Because additional markers of airway inflammation were measured in VOYAGE, it was possible to assess the efficacy of dupilumab in subgroups defined by these markers. Table 5 shows exacerbations according to baseline categories of eosinophil count and FeNO. Results for the four combinations of eosinophil and FeNO threshold results proposed in the definition of Subgroup B are shown in Figure 1.

6.26 The submission contended that the data in Figure 1 "support the independent role of either baseline blood eosinophils or FeNO to select patients with type 2 inflammation that respond to dupilumab with respect to exacerbation reduction". However, no confidence intervals or significance testing were provided for these data, and the result for patients with eosinophils < 0.15 x 10^9/L and FeNO ≥ 20 ppb was based on 20 patients (= 0.048 x 408), so it must have been based on very small numbers of events and therefore be highly uncertain.

6.27 Greater responses to omalizumab in patients with higher eosinophil counts have been reported in some trials.[11] However, although it is likely that IA-05 included patients with higher and lower eosinophils and higher and lower FeNO, it cannot be confirmed whether omalizumab was effective in patients with allergic asthma but neither elevated eosinophils or elevated FeNO.

6.28 The evidence did not support the conclusion that raised eosinophil counts or raised FeNO identify patients with total serum IgE < 30 IU/mL (i.e., Subgroup B) who will benefit from dupilumab, because there were only seven patients in VOYAGE with IgE < 30 IU/mL.

6.29 Data from these patients were presented in Appendix B of the submission. Of seven patients with IgE < 30 IU/mL, complete data were presented for the five who were also taking high-dose ICS. Their baseline clinical features were broadly similar to those of the ITT population, except that only 3/5 had an ongoing atopic condition other than asthma, compared to over 80% of the ITT population. Four of the five had a baseline eosinophil count ≥ 0.15 x 10^9/L and one had baseline FeNO ≥ 20 ppb, but whether this patient also had an elevated eosinophil count is not clear, so the number of Subgroup B patients may have been four or five. No protocol-defined severe exacerbation events were recorded over 52 weeks, so efficacy could not be defined.

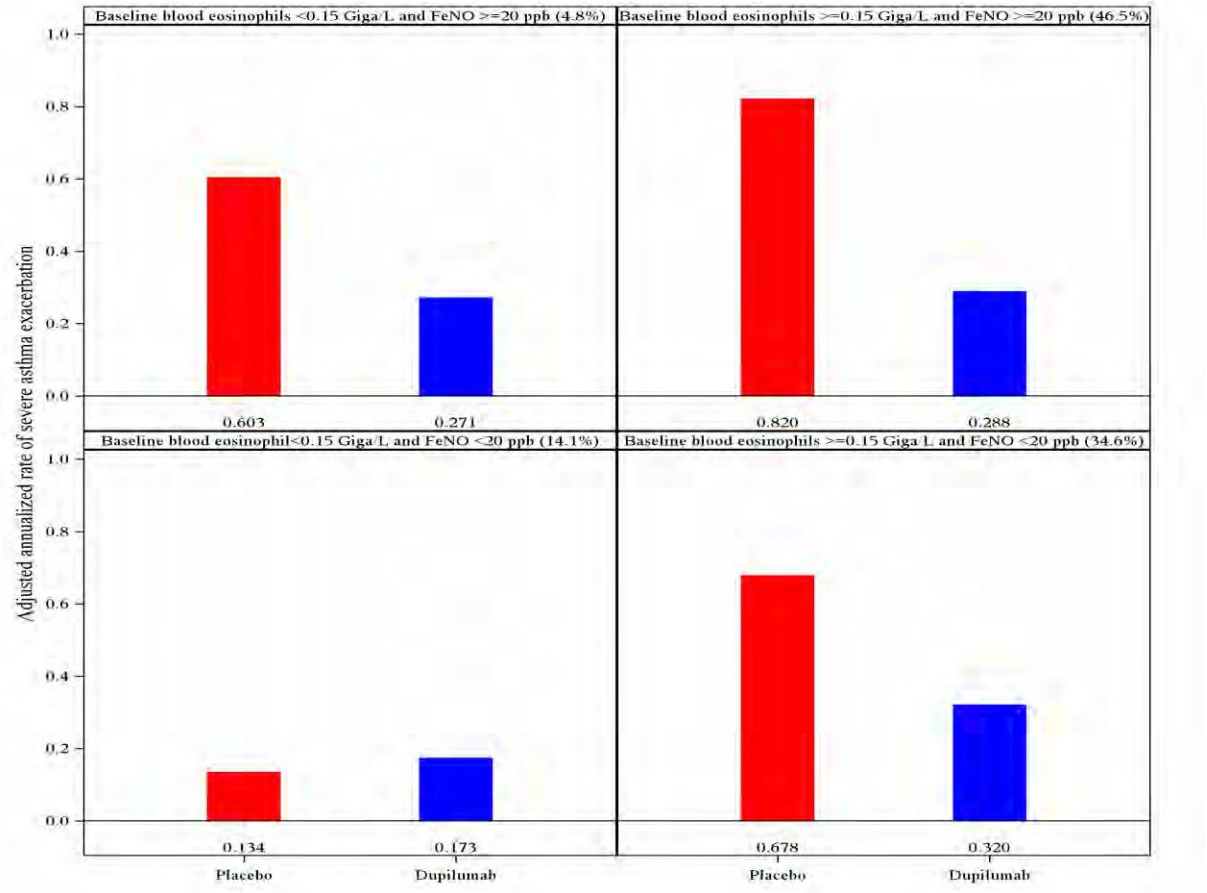
[11] Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *J Allergy Clin Immunol* 2013;132:485. Epub 2013 Apr 13.

Table 5: Exacerbations according to inflammatory markers in VOYAGE

	Dupilumab	Placebo	RR (95% CI) vs placebo
Eosinophils < 0.15 x 10^9/L			
N	50	27	
Number of exacerbations	16	7	
Rate[1]	0.18 (0.07, 0.44)	0.11 (0.03, 0.38)	1.57 (0.51, 4.9)
Eosinophils ≥ 0.15 but < 0.3 x 10^9/L			
N	48	24	
Number of exacerbations	23	18	
Rate[1]	0.30 (0.16, 0.57)	0.70 (0.36, 1.38)	**0.42 (0.20, 0.87)**
Eosinophils ≥ 0.3 x 10^9/L			
N	175	84	
Number of exacerbations	53	61	
Rate[1]	0.24 (0.16, 0.34)	0.66 (0.47, 0.95)	**0.35 (0.22, 0.56)**
FeNO < 20 ppb			
N	124	69	
Number of exacerbations	37	35	
Rate[1]	0.27 (0.18, 0.42)	0.46 (0.30, 0.72)	0.59 (0.34, 1.03)
FeNO ≥ 20 ppb			
N	141	62	
Number of exacerbations	51	49	
Rate[1]	0.27 (0.17, 0.43)	0.70 (0.42, 1.18)	**0.38 (0.23, 0.65)**

Source: Table 1, 15.2 Efficacy Data, VOYAGE CSR.
FeNO = fractional exhaled nitric oxide; RR = risk ratio.
[1] Adjusted for treatment group, age, baseline weight group, region, baseline eosinophil level, baseline FeNO level, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study.

Figure 1: Bar plot of annualized event rate of severe exacerbation by quadrant subgroups defined by baseline blood eosinophils and FeNO



Source: VOYAGE CSR, Figure 9, p136. The percentage shown in parentheses is the proportion of patients in each of the 4 subgroups out of all patients in the ITT population who had both a blood eosinophil count and FeNO value at baseline.

6.30 Two ITCs were presented in the submission, one for IA-05 vs VOYAGE patients with elevated eosinophils or FeNO, and one for the IA-05-EU (high-dose ICS+LABA) population vs VOYAGE patients with elevated eosinophils or FeNO and high-dose ICS+LABA. The results for exacerbations (as defined in each trial) are shown in Table 6.

Table 6: Indirect treatment comparisons of annualised rates of severe exacerbations[1] in trials of dupilumab (VOYAGE) vs omalizumab (trial IA-05 and IA-05-EU)

	Rate Ratio (95% CI)
VOYAGE subgroup[2] vs IA-05	
Omalizumab vs placebo	**0.69 (0.53, 0.90)**
Dupilumab vs placebo	**0.41 (0.22, 0.75)**
Dupilumab vs omalizumab	0.59 (0.31, 1.15)
VOYAGE subgroup vs IA-05-EU[3]	
Omalizumab vs placebo	**0.66 (0.44, 0.0995)**
Dupilumab vs placebo	**0.37 (0.15, 0.81)**
Dupilumab vs omalizumab	0.52 (0.20, 1.35)

Source: Tables 2.51 of the submission.

[1] See paras 6.16 and 6.17 for definitions of exacerbations.

[2] Patients with elevated eosinophils or FeNO.

[3] IA-05-EU was patients treated with high-dose ICS+LABA regardless of eosinophils or FeNO; the VOYAGE subgroup compared in the ITC was patients with elevated eosinophils or FeNO and treated with high-dose ICS+ LABA.

6.31 The submission stated that "the transitivity assumption would be unlikely to hold due to differences in participant baseline characteristics". The most salient difference in baseline characteristics may be that the number of prior severe exacerbations seems to have been higher in IA-05. There were also differences in the definitions of exacerbations, and in the time period for outcome evaluation. The ESC noted that the time period is relevant because of the slower onset of action of omalizumab when IgE levels are high. The ESC also noted that there was only one outcome reported for both trials, exacerbations at 52 weeks, and for this outcome the rate of response in the placebo-treated patients was more than twice as high in IA-05 (Table 4 above).

6.32 The nominated non-inferiority margin was an upper bound of the 95% CI for the risk ratio for exacerbations of 1.28. This margin was used in the submission for benralizumab in severe asthma considered by PBAC in March 2018, in which a claim of non-inferiority to omalizumab was made. The basis for this non-inferiority margin was that the EXTRA trial, in which the efficacy of omalizumab in adolescent and adult patients was studied, was powered to detect a 28% reduction in exacerbations. The PBAC noted that "the non-inferiority margin chosen by the submission was poorly justified […]. The PBAC Guidelines (Version 5.0) state that a submission should 'justify the approach taken to establish the non-inferiority margin, noting that a statistical approach by itself is inadequate' (page 39) […] it was unclear whether a 28% difference in clinically significant exacerbations represents the smallest clinically meaningful difference given the seriousness of exacerbations" (para 6.14, benralizumab PSD, March 2018 PBAC Meeting).

6.33 However, benralizumab did not meet the specified non-inferiority margin of 1.28, so the PBAC was not required to answer the question of whether a narrower margin would have been more appropriate. The claim in the submission that adopting the 1.28 non-inferiority margin was appropriate "to permit consistency of decision making across the asthma biologics" is, therefore, invalid.

6.34 In the VOYAGE trial, about 30% of patients treated with dupilumab had a severe exacerbation over one year. A 28% difference in efficacy would correspond to about

8 extra exacerbations per 100 patients treated for one year. The view expressed by the PBAC in its consideration of benralizumab, that a difference of this order may reasonably be considered clinically significant, could equally well apply to dupilumab.

6.35 The ITCs were not directly relevant to the clinical claims made in the submission. ITC1 considered IA-05 patients versus the "omalizumab-like with Type 2 inflammation population" from VOYAGE (i.e., eosinophils $\geq$ 0.15 x 10^9/L or FeNO $\geq$ 20 ppb; patients with total serum IgE < 30 IU/mL do not seem to have been excluded, although they would be ineligible for omalizumab, but since there were only seven such patients the effect on the results would probably be minor). ITC2 considered the IA-05-EU population versus "omalizumab-like with Type 2 inflammation population taking high-dose ICS" (although, again, patients with IgE < 30 IU/mL do not seem to have been excluded). This limitation of the VOYAGE population markedly reduced the number of patients included in the ITCs: of 408 patients randomised in VOYAGE, ITC1 included 182 (44.6%) and ITC2 included 80 patients (19.6%).

6.36 PBS restrictions for omalizumab do not require elevated eosinophils or FeNO, and it was not proposed by the sponsor that elevated eosinophils or elevated FeNO should be additional PBS-eligibility requirements in patients with total serum IgE $\geq$ 30 IU/mL. For this reason, excluding patients who did not have elevated eosinophils or elevated FeNO from the ITC was unjustified.

6.37 The results shown in Table 5 above suggest that the benefit of dupilumab was less in patients who did not have elevated eosinophils, and that dupilumab was ineffective in patients with neither elevated eosinophils nor elevated FeNO. Excluding these patients from the ITC increased the estimated effect size for dupilumab.

6.38 It is unknown whether there were patients with neither elevated eosinophils nor elevated FeNO in IA-05, although it is likely that there were, and the efficacy of omalizumab in these patients is unknown. Comparing the ITT population from IA-05 with the Type 2 inflammatory population from VOYAGE was not appropriate.

6.39 The ITCs presented would not be relevant to a restriction based on the VOYAGE results (total serum IgE $\geq$ 30 IU/mL and either eosinophils $\geq$ 0.15 x 10^9/L or FeNO $\geq$ 20 ppb) because patients meeting that criteria were not identified in in IA-05.

Comparative harms

6.40 Adverse events were common in both trials, but serious adverse events and adverse events requiring discontinuation of study treatment were infrequent. A summary of adverse events is shown in Table 7.

Table 7: Summary of adverse events in the trials

	VOYAGE		IA-05	
	Dupilumab N = 271	**Placebo N = 135**	**Omalizumab N = 421**	**Placebo N = 207**
AE, n (%)	225 (83.0%)	107 (79.9%)	380 (90.3%)	194 (93.7%)
Nasopharyngitis or pharyngitis, n (%)	74 (27.3%)	44 (32.6%)	117 (27.8%)	56 (27.1%)
URTI *or* Viral URTI, n (%)	68 (25.1%)	31 (23.0%)	69 (16.4%)	46 (22.0%)
Eosinophilia > 3.0 x 10^9/L, n (%)	16 (5.9%)	1 (0.7%)	NR	NR
Injection site reactions, n (%)	80 (29.5%)	23 (17.0%)	NR	NR
SAE, n (%)	13 (4.8%)	6 (4.5%)	17 (4.0%)	17 (8.2%)
AE leading to treatment discontinuation, n (%)	5 (1.8%)	2 (1.5%)	2 (0.5%)	1 (0.5%)
Anaphylactic reaction, n (%)	0	2 (1.5%)	1 (0.2%)	1 (0.5%)
Anti-drug antibodies, n (%)	17 (6.3%)	4 (3.0%)	NR	NR

Source: Submission.
AE = adverse event; n = number of participants reporting data; N = total participants in group; SAE = serious adverse event; URTI = upper respiratory tract infection

6.41 Eosinophilia > 3.0 x 10^9/L, a pre-specified adverse event of special interest (AESI), was seen in 5.9% of patients treated with dupilumab. A similar increase in marked eosinophilia associated with dupilumab has been reported in older patients.[12]

6.42 The significance of marked eosinophilia as an adverse event of dupilumab is unclear. Most patients with marked eosinophilia in VOYAGE were asymptomatic, but one patient was withdrawn from the study because of eosinophilia associated with headache and blurred vision. Cases of eosinophilic pneumonia and of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) have been reported in adults receiving dupilumab, but causation has not been established.[13]

6.43 Injection site reactions were more frequent in dupilumab-treated patients than in placebo-treated patients in VOYAGE, but injection site reactions were not included in the published data for IA-05.

6.44 Anti-drug antibodies were commoner in dupilumab-treated patients, but the significance of this finding is not clear.

Clinical claim

6.45 The submission described dupilumab as non-inferior in efficacy and safety to omalizumab in patients meeting the current criteria for omalizumab (i.e., those with total serum IgE ≥ 30 IU/mL) (Subgroup A). The ESC considered that this claim was not adequately supported.

6.46 The submission described dupilumab as superior in terms of efficacy and non-inferior in terms of safety compared to placebo in patients with total serum IgE < 30 IU/mL but with evidence of airway inflammation (Subgroup B). The ESC considered this claim

[12] Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378:2486-2496.
[13] Dupilumab PI, 4.4, p8.

was not adequately supported. The ESC noted that limited data was presented for this patient population.

6.47 For patients meeting the current criteria for omalizumab (i.e., those with serum IgE of ≥ 30 IU/mL), the PBAC noted that there were transitivity issues associated with the trials but considered that on balance the claim of non-inferior comparative effectiveness and safety for dupilumab compared to omalizumab was likely to be reasonable.

6.48 For patients with total serum IgE of < 30 IU/mL the PBAC considered that there was insufficient evidence presented to determine whether the claim of superior comparative effectiveness and non-inferior safety for dupilumab compared to standard of care was reasonable.

Benefits/harms

6.49 A benefits and harms table was not presented as the submission made a claim of non-inferiority for patients in Subgroup A, and limited data was presented for patients in Subgroup B.

Economic analysis

6.50 The submission presented a cost-minimisation approach. The key components of the approach are presented in Table 8.

Table 8: Key components and assumptions of the cost-minimisation approach

Component	Claim or assumption
Therapeutic claim: effectiveness	Subgroup A) dupilumab has non-inferior efficacy compared to omalizumab for the treatment of paediatric patients with uncontrolled severe asthma; Subgroup B) dupilumab has superior efficacy compared to standard of care for the treatment of paediatric patients with uncontrolled severe asthma
Therapeutic claim: safety	Subgroup A) dupilumab has non-inferior safety compared to omalizumab for the treatment of paediatric patients with uncontrolled severe asthma; Subgroup B) dupilumab has non-inferior safety compared to standard of care for the treatment of paediatric patients with uncontrolled severe asthma
Evidence base	Indirect comparison of dupilumab and omalizumab
Equi-effective doses	Dupilumab 300 mg every four weeks as a subcutaneous injection for patients weighing 15 - <30 kg, 200 mg every 2 weeks as a subcutaneous injection or 300 mg every four weeks as a subcutaneous injection for patients weighing 30 - <60 kg, and 200 mg every two weeks as a subcutaneous injection for patients weighing ≥ 60 kg, is therapeutically equivalent to; Omalizumab 375 mg every four weeks subcutaneous injection, either as one dose (i.e., once every 4 weeks) or split into two equal doses (i.e., once every 2 weeks) depending on patient weight and IgE level.
Direct medicine costs	Drug costs were considered.
Other costs or cost offsets	None.

Source: Table 3.1, p 196 of the submission.

6.51 The ESC noted an economic analysis was not presented for Subgroup B and the submission proposed that the cost-effective price would be the same as for Subgroup A. The ESC considered this assumption uncertain.

6.52 Calculation of the equi-effective doses was complex and not derived directly from the clinical trials. The submission proposed:

- Dupilumab 300 mg every four weeks as a subcutaneous injection for patients weighing 15 - <30 kg, 200 mg every 2 weeks by subcutaneous injection or 300 mg every four weeks by subcutaneous injection for patients weighing 30 - <60 kg, and 200 mg every two weeks by subcutaneous injection for patients weighing ≥ 60 kg, is therapeutically equivalent to
- Omalizumab 375 mg every four weeks by subcutaneous injection, either as one dose (i.e., once every 4 weeks) or split into two equal doses (i.e., once every 2 weeks).

6.53 Given that the dose of and frequency of dupilumab injections is based on weight, the submission used the US Centres for Disease Control (CDC) age-weight charts to calculate a weighted mean dose of dupilumab. It was assumed for the economic analysis that 90% of patients weighing 30 to < 60 kg would be treated using the 4-weekly regimen, and 10% will be treated using the 2-weekly regimen. The submission has proposed effective prices such that the monthly treatment cost for a patient receiving Q2W or Q4W dosing would be the same, and stated this assumption has no impact on the overall estimated cost of dupilumab to the PBS. The ESC noted the same monthly cost requires the cost per syringe for the 2 weekly regimen to be half that for the 4 weekly regimen. The submission stated the impact of the different per pack prices for Q2W and Q4W regimens will be reconciled via the derivation of a weighted AEMP at the published price level.

6.54 The proportion of patients in each weight band is shown in Table 9. Based on this it was estimated 94.1.% (i.e., 47.0% + [90%*52.3%]) of patients are expected to be treated with dupilumab every four weeks and 5.9% (i.e., 0.7% + [10%*52.3%]) of patients are expected to be treated with dupilumab every two weeks.

Table 9: Proportion of patients in each dupilumab weight band

Age (years)	Weight: 15 - <30 kg Dose: 300 mg Q4W	Weight: 30 - <60 kg Dose: 200 mg Q2W (10%) 300 mg Q4W (90%)	Weight: ≥ 60 kg Dose: 200 mg Q2W
6	98%	2%	0%
7	83%	17%	0%
8	55%	45%	0%
9	28%	72%	0%
10	11%	89%	0%
11	5%	91%	4%
Weighted 6-11	47%	52%	0.7%

Source: Table 3.2, p 197-198 of the submission.

6.55 The mean dose of dupilumab in VOYAGE was not provided in the submission or in the VOYAGE Clinical Study Report. The evaluation considered that it would be valuable to compare the mean doses in the trial, stratified by age and weight bands as shown in Table 9 with the equi-effective dose calculated in the submission. The PSCR stated "as the proposed PBS dosing is different to that used in the VOYAGE trial and the average

doses used in the VOYAGE trial would be reflective of the dosing used in the trial (100 mg Q2W for patients weighing ≤30 kg and 200 mg Q2W for patients weighing > 30 kg), any analysis of the average doses from the trial would not be reflective of the expected dosing in the proposed PBS population and would not add any useful additional information".

6.56 The mean dose of omalizumab given to patients in the IA-05 trial was not reported in the published papers. During the PBAC's consideration of omalizumab in July 2016 it was reported that, based on the IA05-EU dosing schedule, "on average 0.6 x 75 mg syringes and 2.2 x 150 mg syringes were used every four weeks". Although (0.6 x 75) + (2.2 x 150) = 375, the PBAC did not convert the average syringe use to an average dose of 375 mg. Rather, it multiplied the cost of a 75 mg syringe by 0.6 and the cost of a 150 mg syringe by 2.2, added the results and multiplied the sum by 13 to obtain the yearly cost per patient.

6.57 The submission did not do this. On the grounds that partial syringes cannot be dispensed, the submission rounded up the dispensed dose to 1 x 75 mg and 3 x 150 mg syringes every 4 weeks. This is incorrect, because anyone requiring 375 mg would have been dispensed 1 x 75 mg and 2 x 150 mg syringe. The ESC noted that the recommended doses for omalizumab can be administered with the 75 mg and 150 mg syringes and as such there would be no wastage.

6.58 If the cost of omalizumab is calculated using 1 x 75 mg and 2 x 150 mg syringes, at published prices ($205 per 75 mg syringe and $410 per 150 mg syringe) the cost of an average dose of 375 mg 4 weekly is $1,025, not $1,435 and the annual cost is $13,370.76, not $18,796. The results of the corrected cost minimisation approach are shown in Table 10.

6.59 The PSCR stated that "partial syringes cannot be dispensed, therefore, in cases where partial vials are used, the cost to the PBS is dependent on the total number of vials dispensed rather than the actual dose administered. To achieve an average dose of 0.6 x 75mg plus 2.2 x 150mg, a total of 1 x 75mg plus 3 x 150mg vials are required". The PSCR claimed that the cost per dose per patient per month should be "the sum of the cost of these vials ($1,435 published), resulting in an average cost per patient per year to the PBS of $18,719.06 (published). Dividing this by the number of syringes required per year, the published cost per syringe for dupilumab is $1,435 for patients receiving Q4W dosing ($2,870 per pack of two syringes), or $717.50 per syringe for patients receiving Q2W dosing ($1,435 per pack)." The ESC disagreed with the PSCR. The ESC considered the cost should be calculated in the same way as was calculated for omalizumab in July 2016 i.e., 0.6 x $205 + 2.2 x $410 which is $1,025. This the same as calculated in the evaluation as cost per mg for omalizumab is the same for both strengths.

6.60 The ESC noted that the dose of dupilumab was not derived from the trials, and that as the dose of omalizumab was based on the estimated average dose and inappropriately included wastage that the submission had overestimated the cost-minimised price for

dupilumab. In their pre-PBAC response the sponsor agreed to calculate the cost-minimised price in the same way that it was calculated for omalizumab in July 2016, noting that this would equate to $1,025 every 4 weeks.

6.61 The evaluation did not include the costs of medical supervision for the first 3 doses of omalizumab based on the PBAC advice in its assessment of dupilumab in 2020.

Table 10: Results of the cost-minimisation approach based on published prices (AEMP)

Component	Dupilumab		Omalizumab
Estimated dose per 4 weeks	300 mg Q4W	200 mg Q2W	375 mg (= 2.2*150 mg +0,6*75 mg)
Cost per dose	$1,025 per syringe	$512.50 per syringe	=2.2*$410+0.6*$205 = $1,025
Estimated use	94.1%	5.9%	
Weighted average cost per syringe	$994.61	$994.61	
Dose duration	1 year	1 year	1 year
Administrations per year	13.04	26.09	13.04
Total medicine cost per year	$13,370.76	$13,370.76	$13,370.76
Difference in cost per week	$0	$0	$0

Source: constructed during the evaluation and corrected based on values from Tables 3.3 and 3.4 of the submission.

6.62 The ESC noted if the use of the Q2W regimen increased to 10% the weighted average cost per syringe would reduce to $973.75. The pre-PBAC response stated that should dupilumab receive a positive recommended for this indication, the sponsor is committed to collaborating with the Department to ensure the final utilisation estimates are based on the best available assumptions regarding regimen split.

6.63 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 dupilumab would be no more than the cost per patient of omalizumab. 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. In this case, the PBAC should consider the following parameters: weight and total serum IgE distribution in Australian children receiving omalizumab, since the average dose in Australian children may be less than that in IA-05, but the dose of dupilumab would be the same.

Drug cost/patient /year

6.64 Based on the published price of omalizumab, using the corrected equivalence calculations, and using the 300 mg/4-week dose of dupilumab as the likely average dose, the estimated cost per patient per year is $13,370.76 (see also Table 10).

Estimated PBS usage & financial implications

6.65 This submission was not considered by DUSC.

6.66 The submission presented a mixed market share and epidemiological approach to estimate the use and financial impact of listing dupilumab for paediatric asthma for

the period 2024-2029. The market share approach applied to the Subgroup A patients and the epidemiological approach was applied to Subgroup B patients.

6.67 The estimates of use and financial impact presented below are for Subgroup A and are based on the market share assessment. Estimates of use for Subgroup B are presented in Table 16.

6.68 The key inputs used for the financial estimates are shown in Table 11.

Table 11: Key inputs for financial estimates – market share 2024 (year 1)-2029 (year 6)

Parameter	Value	Data source	Comment
Predicted market growth of the omalizumab market [scripts (growth %)]	Y1: [redacted][1] (27%) Y2: [redacted][1] (16%) Y3: [redacted][2] (14%) Y4: [redacted][2] (12%) Y5: [redacted][2] (11%) Y6: [redacted][2] (10%)	Services Australia utilisation database	Based on regression model from omalizumab services; does not truly represent paediatric population so therefore a substantial overestimate.
Segment of 'existing market' that is expected to be captured by dupilumab	Y1: 50% Y6: 50%	Sponsor assumption	May be reasonable or an underestimate.
Predicted expansion of the biologic market post arrival of a dupilumab [scripts (growth %)]	Y1: [redacted][2] (128%) Y2: [redacted][2] (16%) Y3: [redacted][2] (14%) Y4: [redacted][3] (12%) Y5: [redacted][3] (10%) Y6: [redacted][3] (10%)	Commissioned research, Attachment 15, assuming the current omalizumab utilisation reflects 56% of total biologic market.	Based on survey of 17 physicians. Likely overestimate year 1, uncertain for years 2-6.
Segment of expanded services captured by dupilumab [scripts (%)]	Y1: [redacted][1] (76%) Y2: [redacted][1] (76%) Y3: [redacted][1] (76%) Y4: [redacted][1] (76%) Y5: [redacted][1] (76%) Y6: [redacted][1] (76%)	Commissioned research, Attachment 15 of the submission.	As above and is not consistent with the estimate for the segment of the existing market.
Grandfathered patients	Y1: [redacted][4] Y2: [redacted][4] Y3: [redacted][4] Y4: [redacted][4] Y5: [redacted][4] Y6: [redacted][4]	Sponsor assumption, applying 80% continuation per year	Likely overestimate based on total market size
Script equivalence	0.28	Derived from omalizumab item codes, predicted use of omalizumab in 2016 PSD, and predicted use of dupilumab by weight of patients.	Depends on accuracy of predicted use of different strengths of omalizumab from 2016- and actual eventual use of dupilumab strengths, which may or may not be correct.
Treatment regimen	Q2W: 5.9% Q4W: 94.1%	Based on US CDC Data Table of Weight-for-age Charts	Weight is based on US CDC data table, but the split of doses is considered uncertain.
Dupilumab services	Y1: [redacted][1] Y2: [redacted][1] Y3: [redacted][1] Y4: [redacted][1] Y5: [redacted][1] Y6: [redacted][1]	Derived from script equivalence, estimate of projected services and estimate of reduction in omalizumab services.	Uncertain given sources used in derivation as noted above.

Source: Tables 4.2.1, 4.3, 4.4, 4.7 of the submission.
The redacted values correspond to the following ranges:
[1] *500 to < 5,000*
[2] *5,000 to < 10,000*
[3] *10,000 to < 20,000*
[4] *< 500*

6.69 To estimate the size of the market the submission estimated omalizumab scripts for 2024, based on 2023, using the item codes for paediatric scripts. The total was

estimated to be 500 to < 5,000, of which 500 to < 5,000 were initiating scripts and 500 to < 5,000 continuing scripts (item codes 10967F, 11946R, 10956P, 11952C, 10973M, 11945Q, 10968G, 11935D). The largest numbers of scripts were for items 11945Q, 150 mg/mL for continuing treatment (predicted total number of services for 2024 of 500 to < 5,000) and item 10968G, 150 mg/mL for initiating treatment (predicted total for 2024 of 500 to < 5,000 services), accounting for the majority of the estimate of market size.

6.70 DUSC last reviewed the use of biologicals for uncontrolled and severe allergic asthma in October 2019, but did not present data for paediatric use separately in that review. During the evaluation, the DUSC Secretariat provided data extracted from the PBS claims database maintained by the Department of Health and Aged Care and processed by Services Australia. Prescription data were extracted from 1 January 2017 up to and including 30 September 2023, using all PBS item codes that contain the word "asthma" (i.e., not just item codes specific to patients younger than 12 years of age). The number of prescriptions of omalizumab, mepolizumab, benralizumab and dupilumab supplied to patients younger than 12 was summarised by year and are shown in Table 12.

Table 12: Utilisation of omalizumab, mepolizumab, benralizumab and dupilumab in patients under the age of 12 years

Year	Prescription count	Treated patient count	Initiating patient count
2017	[1]	[1]	[1]
2018	[1]	[1]	[1]
2019	[1]	[1]	[1]
2020	[1]	[1]	[1]
2021	[2]	[1]	[1]
2022	[1]	[1]	[1]
2023	[1]	[1]	[1]

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

6.71 The ESC noted that the estimate in the submission of the total market size (for omalizumab alone) appears to be a substantial overestimate (i.e., < 500 scripts dispensed in 2023 vs estimated 500 to < 5,000 in Year 1) and may be due to patients 12 years and over receiving prescriptions that are coded incorrectly.

6.72 The ESC noted that the proportion of the existing market share (50%) estimated to be taken by dupilumab may be reasonable, but if the restriction is based on the dupilumab trial population i.e., high IgE and Type 2 inflammation, the total market would be approximately 85% of the existing population) as approximately 15% of patients in the trial did not have this asthma phenotype. However, the ESC considered the ease of use of dupilumab compared to omalizumab could result in an expansion of the total existing market as well a larger market share.

6.73 The ESC considered that there may be treatment overlap with children who are eligible to receive dupilumab for atopic dermatitis, once the recommendation for patients aged 6 to 11 years from the March 2022 PBAC meeting is implemented.

6.74 Given the uncertainty about the market size, and noting that tiotropium is a potential alternative comparator, the DUSC Secretariat also extracted data for patient numbers and prescriptions for tiotropium supplied to patients aged 0-11 years for the period 2018-2023. The item codes used were 11892X, 11629C, 11043F, 10509D, 08626B. Data were extracted on 18 January 2024 and are shown in Table 13.

Table 13: Utilisation of tiotropium in patients aged 0-11 years

Year	Age range (years)	Patient count	Prescription count
2018	0-11	[redacted][1]	[redacted][1]
2019	0-11	[redacted][1]	[redacted][1]
2020	0-11	[redacted][1]	[redacted][1]
2021	0-11	[redacted][1]	[redacted][1]
2022	0-11	[redacted][1]	[redacted][1]
2023	0-11	[redacted][1]	[redacted][2]

The redacted values correspond to the following ranges:
[1] < 500
[2] 500 to < 5,000

6.75 Although it is not possible to estimate exactly how many patients would switch from tiotropium to dupilumab, it is reasonable to assume that some might, given the relative ease of use of dupilumab compared to omalizumab. The tiotropium utilisation data also confirm that the total market size is likely to be smaller than that estimated in the submission.

6.76 The market research used as the basis for some of the assumptions was based on a survey of physicians (immunologists, respiratory physicians, and paediatricians) with experience in managing patients failing optimisation of asthma therapy and accredited S100 prescribers. Of 670 physicians approached, 17 completed the survey, of whom 2 were paediatricians. Given the very low response rate to this survey, the ESC considered that assumptions based on the results may not be representative or accurate.

6.77 The calculation of script equivalence was complex. The submission stated that it attempted to align the omalizumab item codes with the proposed dupilumab restrictions, take account of the different strengths of omalizumab compared to the 2 proposed strengths of dupilumab as well as the 2 weekly and 4 weekly dosing regimen options. The submission used the 2016 PSD for omalizumab as the basis for determining the usage of 75 mg and 150 mg syringes and calculated the weighted average existing market script equivalence as 1.88, based on 20% usage of 75 mg and 80% usage of 150 mg. This was compared to the projected usage of dupilumab, based on the assumption that 94.1% of children will be treated with 300 mg dupilumab (half a script) every 4 weeks. This estimate of script equivalence depends on the accuracy of the assumptions about dose equivalence and usage of dupilumab which is assumed.

6.78 The submission presented its assumptions about the number of patients who would be grandfathered onto the PBS listed product following a patient familiarisation program. The ESC noted that the estimated number of patients to be treated through this program would appear to be larger than the current total market (based on the

estimates provided by the DUSC Secretariat). The PSCR stated that it presented the maximum feasible number of patients to be treated through this program to ensure a seamless transition but acknowledged that "the potential for any reduction in Grandfathering (GF) use would correspondingly diminish the overall impact to the cost to government".

6.79 The estimated use and financial implications as presented in the submission based on Subgroup A alone are shown in Table 14 based on the estimated effective AEMP of $ per pack for a second weekly dosing regimen and $ per pack for a 4 weekly dosing regimen. As noted above these prices are both overestimates, and the market size is an overestimate. The prices were weighted by the estimated utilisation in the public and private settings, based on the observed omalizumab utilisation in these settings (public 66.28%; private 33.72%).

6.80 The submission also included estimates of the change in prescription processing, and changes in the use of MBS items. The health care resource utilisation estimates were based on a survey of 17 clinicians and included use of GP and specialist visits, as well as nurse practitioner costs for training in the delivery of injections, and laboratory tests. These estimates appear to have been based on the epidemiological model for patient numbers only and were derived from the physician survey so are very uncertain.

Table 14: Estimated use and financial implications (placeholder effective EMP for dupilumab), market share model, based on the submission's estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of dupilumab						
Cost to PBS/RPBS less copayments	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimated financial implications for omalizumab						
Change in omalizumab scripts	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Cost to PBS/RPBS less copayments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to MBS/ Services Australia/other	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net cost to PBS/RPBS/MBS/ Services Australia}	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: Tables 4.17, 4.26, 4.33 of the submission.

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] $0 to < $10 million

[3] net cost saving

6.81 In the PSCR the sponsor stated that the additional DUSC data extracted from the PBS claims database was welcomed and that they updated the utilisation estimates in alignment with this supplementary information. These revised estimates are provided

in Table 15. The ESC noted these estimates would need to be revised with the corrected cost-minimised price for dupilumab.

Table 15: Amended use and financial implications (placeholder effective EMP for dupilumab), market share model

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of dupilumab						
Cost to PBS/RPBS less copayments	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Estimated financial implications for omalizumab						
Change in omalizumab scripts	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][4]	-[redacted][4]	-[redacted][4]
Cost to PBS/RPBS less copayments	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications based on the revised submission estimates						
Net cost to PBS/RPBS	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]
Net cost to MBS/ Services Australia/other*	NA	NA	NA	NA	NA	NA
Net cost to PBS/RPBS/MBS/ Services Australia}	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]	$[redacted][2]

Source: PSCR

*Given the UCM workbook requires nomination of a Duration of Treatment Group (DTG) in Sheet 7. Net Changes – MBS (cells R63-V66), and each DTG requires linkage to an 'Epidemiology' population, it was not possible to calculate the net cost to MBS/Services Australia for the 'Market Share' component of the workbook. Nonetheless, modest savings to the MBS would be expected each year, as detailed in the submission.

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$0 to < $10 million*

[3] *net cost saving*

[4] *500 to < 5,000*

6.82 The ESC noted the revised financial estimates provided for Subgroup A. The ESC considered the script estimates presented in the PSCR for Subgroup A to be more reliable than those presented in the submission. The ESC noted the additional net PBS/RPBS cost for Subgroup A was potentially inconsistent with listing being proposed on a CMA basis.

6.83 Financial estimates as presented in the submission for Subgroup B are presented in Table 16. The ESC noted that the dupilumab cost per script was the same as for Subgroup A and that this cost was overestimated in the CMA. The ESC noted based on the revised estimates in the PSCR for Subgroup A that the estimated cost for Subgroup B was higher than for Subgroup A.

Table 16: Estimated use and financial implications for Subgroup B of dupilumab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total patients (#)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated total volume of medicine	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total net cost (PBS + RPBS)	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]

Source: Derived from Table 4.14 of the submission.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $0 to < $10 million

Quality Use of Medicines

6.84 The submission described planned activities including an early access scheme/patient familiarisation program, educational meetings, and educational material. In addition, the submission stated that the sponsor is collaborating with the Thoracic Society of Australia and New Zealand to extend the Australasia Severe Asthma Registry to paediatric patients.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 Highly Specialised Drugs Program listing of dupilumab for the treatment of patients aged 6 to 11 years of age with uncontrolled severe asthma despite optimised asthma therapy who have total serum immunoglobulin E (IgE) $\geq$ 30 IU/mL and evidence of atopy, or blood eosinophils $\geq 150 \times 10^9$/L, or fractional exhaled nitric oxide (FeNO) $\geq$ 20 parts per billion (ppb).

7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of dupilumab would be acceptable if it were cost-minimised against omalizumab.

7.3 The PBAC noted the comments from health care professionals and organisations in support of PBS listing of dupilumab in paediatric patients, including the potential for home initiation of treatment and a reduction in injection frequency.

7.4 The PBAC noted the advice from the sponsor hearing that whilst increased IgE is typical for most childhood Type 2 asthma cases, there exists a small number of children with uncontrolled asthma with low IgE in the presence of other elevated Type 2 markers such as blood eosinophils or FeNO, and considered a clinical need existed for these patients.

7.5 The PBAC noted the submission had requested a grandfather clause to allow patients enrolled in a Patient Familiarisation Programme to transition to PBS-subsidised use of dupilumab, and considered this was appropriate.

7.6 The PBAC noted the submission had proposed an alternative restriction that aligned with the characteristics of patients enrolled in the VOYAGE trial rather than with the

current omalizumab restriction. The PBAC noted for continuing therapy this alternative restriction removed reference to (i) a reduction in the maintenance dose of corticosteroids by at least 25% from baseline and (ii) no deterioration in the Asthma Control Questionnaire or ACQ-IA from baseline. The PBAC considered it inappropriate to remove these criteria.

7.7 The PBAC considered a written authority level was appropriate.

7.8 The submission proposed the comparator of omalizumab for patients with IgE of ≥ 30 IU/mL. The PBAC considered the nominated comparator was appropriate, noting that while tiotropium is a possible comparator based on the GINA Guidelines that it is not included in the National Asthma Council guidelines and, as noted in the PSCR, omalizumab was not considered to be an appropriate comparator for tiotropium when it was considered by the PBAC in 2018.

7.9 The submission proposed the comparator of placebo (representing standard of care) for patients with IgE < 30 IU/mL. The PBAC considered the nominated comparator was appropriate.

7.10 The PBAC noted the submission was based on indirect treatment comparisons (ITCs) of one randomised controlled trial (RCT) of dupilumab versus placebo (VOYAGE) and one RCT of omalizumab versus placebo (IA-05). The PBAC noted the submission had excluded three other trials of omalizumab from the ITC and considered that while Odajima 2015 had been appropriately excluded (given it was an uncontrolled study) that it was inappropriate for the submission to have excluded Busse 2011 and Milgram 2001. However, the PBAC considered that the excluded studies were not critical for the assessment of the clinical claims.

7.11 The PBAC noted that both dupilumab and omalizumab were effective in reducing the rate of exacerbations, although the primary outcome was assessed over 52 weeks in VOYAGE compared to over 24 weeks in IA-05. The PBAC noted another key difference between the trials was that patients in IA-05 were required to have an IgE of ≥ 30 IU/mL whereas there were no IgE criteria in VOYAGE.

7.12 The PBAC noted that two ITCs were presented in the submission. The first used the VOYAGE subgroup of patients with elevated eosinophils or FeNO and the IA-05 ITT population. The Committee noted that for this ITC the rate ratio for the annualised rates of severe exacerbations for dupilumab vs placebo was 0.41 (95% CI: 0.22, 0.75) at 52 weeks, and for omalizumab vs placebo was 0.69 (95% CI: 0.53, 0.90) at 24 weeks. The indirect estimate for dupilumab vs omalizumab was 0.59 (0.31, 1.15). The second ITC used the VOYAGE subgroup of patients with elevated eosinophils or FeNO and high-dose ICS+LABA and the IA-05-EU (high-dose ICS+LABA) population. For this ITC the rate ratios were 0.37 (95% CI: 0.15, 0.81) for dupilumab vs placebo at 52 weeks and 0.66 (95% CI: 0.44, 0.0995) for omalizumab vs placebo at 24 weeks. The indirect estimate for dupilumab vs omalizumab was 0.52 (0.20, 1.35).

7.13 The Committee noted that the point estimates for the ITCs favoured dupilumab

however the confidence intervals were wide and included one, and the efficacy of omalizumab appeared to be better at 52 weeks, compared to the 24-week time point used in the ITCs.

7.14 The PBAC considered the adverse event profile for patients treated with dupilumab or omalizumab in VOYAGE and IA-05 to be similar but noted that while the adverse event of eosinophilia > 3.0 x 10^9/L was not reported for omalizumab, that 5.9% of patients treated with dupilumab had eosinophilia > 3.0 x 10^9/L compared to 0.7% for patients treated with placebo in the VOYAGE trial. The Committee noted that cases of eosinophilic pneumonia and of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA) reported in adults receiving dupilumab, but that causation had not been established.

7.15 For patients meeting the current criteria for omalizumab (i.e., those with serum IgE of ≥ 30 IU/mL), the PBAC noted that there were transitivity issues due to differences in baseline characteristics of patients between the trials but considered that on balance the claim of non-inferior comparative effectiveness and safety for dupilumab compared to omalizumab was likely to be reasonable.

7.16 The PBAC noted the submission's proposed PBS restriction was broader than the approved TGA indication where patients must have high serum IgE and evidence of atopy together with either elevated eosinophils or FeNO. The PBAC noted that the submission's claim of superior effectiveness for patients with IgE of < 30 IU/mL was based on seven patients enrolled in VOYAGE. The PBAC considered there was insufficient evidence presented to determine whether the claim of superior comparative effectiveness and non-inferior safety for dupilumab compared to standard of care was reasonable. However, the PBAC noted that for this population there were no PBS-listed biologic treatments and the number of patients and cost were expected to be small, and overall considered that dupilumab was likely to be effective with similar safety as for those with an IgE ≥ 30 IU/mL.

7.17 The PBAC noted the submission presented a cost-minimisation approach (CMA) of dupilumab to omalizumab for patients with IgE ≥ 30 IU/mL and evidence of atopy.

7.18 The Committee noted the submission also presented a CMA of dupilumab to omalizumab for patients with IgE < 30 IU/mL rather than a cost-effectiveness analysis versus standard of care. The Committee considered the submission's approach was likely reasonable, noting the limited evidence for patients with IgE < 30 IU/mL and that the approach was consistent with that used for mepolizumab for uncontrolled severe eosinophilic asthma (para 7.11, mepolizumab PSD, March 2016 PBAC meeting).

7.19 The PBAC considered the equi-effective doses to be dupilumab 300 mg given by subcutaneous injection every 4 weeks for patients weighing < 60 kg, or 200 mg given by subcutaneous injection every 2 weeks for patients weighing ≥ 30 kg, is therapeutically equivalent to omalizumab 375 mg given every 4 weeks by subcutaneous injection, either as one dose given every 4 weeks or split into two equal doses given every 2 weeks.

7.20 The PBAC noted that the submission proposed the same 4-weekly treatment cost for a patient treated with dupilumab at a dose of 300 mg every 4 weeks (Q4W) or 200 mg every 2 weeks (Q2W) and that this required the cost per syringe for the Q2W regimen to be half that for the Q4W regimen. The PBAC noted that in the submission it was estimated that the Q2W regimen was assumed to be used in 5.9% of patients based on American age-weight charts and an assumption that for patients with a weight of 30-60 kg that the Q2W regimen would be used in 10% of patients. The PBAC considered the extent of use of the Q2W regimen should be estimated with consideration of Australian weight charts. The PBAC noted it was important that the use of the Q2W regimen was not underestimated as this would result in the cost of dupilumab being higher than the cost of omalizumab. Alternatively, the PBAC noted that it may be possible to avoid calculating a weighted price if the cost of the Q2W syringe, which is used Q2W, is half that of the 300 mg syringe, which is used Q4W.

7.21 The PBAC noted the equi-effective dose of omalizumab of 375 mg every 4 weeks for the cost-minimisation was consistent with that used for the July 2016 consideration of omalizumab (para 6.16, omalizumab PSD, July 2016 PBAC Meeting). The PBAC agreed with ESC that cost of omalizumab should be consistent with that calculated for the July 2016 consideration, and noted that it would be inappropriate to round up the average number of syringes when calculating the cost (paragraph 6.77). The PBAC noted the pre-PBAC response agreed with the approach in the ESC advice.

7.22 The PBAC noted the submission had used a market share approach to estimate utilisation in patients with IgE ≥ 30 IU/mL and evidence of atopy. The Committee considered the DUSC Secretariat data on current use of omalizumab, mepolizumab, benralizumab and dupilumab in patients under the age of 12 years should be used to inform the market size. The Committee considered the estimate of a 50% market share to be reasonable. The Committee considered dupilumab may also replace a small proportion of the tiotropium use. The PBAC agreed with the sponsor that ease of use with dupilumab associated with a reduced number of monthly injections and reduced dosing complexity may lead to market growth. The PBAC noted the growth assumptions included in the submission's financial estimates were % in year 1, % in year 2 reducing to % in year 6. The high growth in year 1 was stated in the submission to be due to 'unlocking of disengaged market'. The PBAC considered the growth in year 1 was substantially overestimated.

7.23 The PBAC noted that an epidemiological approach had been used to estimate utilisation in patients with IgE < 30 IU/mL but considered the estimates to be substantially overestimated given that the submission's estimate of the proposed number of patients was larger than for patients with IgE ≥ 30 IU/mL. The PBAC considered the use in this population should be estimated based on the dupilumab trial population i.e., approximately 15% of patients in the trial did not have high IgE and Type 2 inflammation.

7.24 The PBAC noted that at the time of consideration, the recommendation for the PBS listing of dupilumab for patients aged 6 to 11 years with atopic dermatitis from the

March 2022 PBAC meeting had not been implemented and considered there was potential for overlap in patient eligibility. The PBAC noted that the written authority listing for asthma would minimise the risk of use in a broader population.

7.25 The requested restriction is considered to be complex.

7.26 The PBAC recommended that the grandfather listing be in operation for 12 months to transition patients commenced on non-PBS subsidised treatment to PBS subsidised supply, where these patients would otherwise have met the initial treatment criteria.

7.27 The PBAC noted that the following changes will be required to the omalizumab 75 mg/0.5 mL injection, 0.5 mL syringe (items 10967F, 10956P, 11958J, 11962N, 11946R, 11952C), and omalizumab 150 mg/mL injection, 1 mL syringe (items 10968G, 10973M, 11950Y, 11932B, 11945Q, 11953D) restrictions to allow for eligible patients to switch between omalizumab and dupilumab during a treatment cycle:

- The Overarching Note of 'Treatment of paediatric patients with uncontrolled severe asthma' will be required for omalizumab.
- The addition of an initial 2 restriction is required for omalizumab to allow for eligible patients to be able to switch from dupilumab to omalizumab within a treatment cycle if required.
- The restrictions for omalizumab will require the following Prescriber Instruction to be changed from 'A patient who fails to respond to a course of PBS-subsidised omalizumab for the treatment of uncontrolled severe allergic asthma will not be eligible to receive further PBS-subsidised treatment with omalizumab for this condition within 6 months of the date on which treatment was ceased' to 'A patient who fails to demonstrate a response to treatment with this drug for this condition will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle'.
- The restrictions for omalizumab will require an update in its Prescriber Instructions to reflect that 'A treatment break in PBS-subsidised biological medicine therapy of at least 12 months must be observed in a patient who has failed to achieve or sustain a response to treatment with 2 biological medicines within the same treatment cycle.' The PBAC reaffirmed that a patient can only fail any biologics for severe asthma/severe allergic asthma once within a treatment cycle. In addition, the PBAC reaffirmed that there is no limit to the number of treatment cycles in a lifetime for biological medicines for uncontrolled severe asthma/uncontrolled severe allergic asthma.
- The PBAC noted that currently the only available biological treatment option for paediatric patients is omalizumab, and for these patients, completion of a treatment cycle is defined as when the patient has trialled and failed omalizumab once. The PBAC noted that this currently must then be followed by at least 6 months exclusion before the patient can re-start a new treatment cycle with omalizumab. Given these patients will now have an extra choice of dupilumab,

the PBAC considered that the treatment break should be extended to 12 months once they have trialled and failed both omalizumab and dupilumab within a treatment cycle.

- In the context of a treatment cycle, the PBAC also considered that since the proposed dupilumab restriction encompassed patients who would be eligible for omalizumab, but was also broader in that it would allow for patients with IgE levels of < 30 IU/mL without allergic asthma to also be treated with dupilumab, the restrictions should ensure that while eligible patients treated with omalizumab should be able to switch to dupilumab, only eligible patients treated with dupilumab who initially qualified based on IgE levels should be able to switch to omalizumab.

7.28 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because dupilumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over omalizumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

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

Outcome:
Recommended

8 Recommended listing

8.1 Add new items as follows:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
DUPILUMAB					
dupilumab 200 mg/1.14 mL injection, 2 x 1.14mL	NEW (Public) NEW (Private)	1	2	7	Dupixent
dupilumab 300 mg/2 mL injection, 2 x 2mL syringes	NEW (Public) NEW (Private)	1	2	3	Dupixent
Restriction Summary edit / Treatment of Concept: edit					
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (in writing only via post/HPOS upload)				
	Administrative Advice: See overarching administrative note below.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice:				

	Special Pricing Arrangements apply.
	Indication: Uncontrolled Severe Asthma
	Treatment Phase: Initial treatment 1 – (New patient; or Recommencement of treatment in a new treatment cycle following a break in PBS-subsidised biological medicine therapy)
	Clinical criteria:
	Patient must not have received PBS-subsidised treatment with a biological medicine for either: (i) severe asthma, (ii) severe allergic asthma; or
	Patient must have had a break in treatment from the most recently approved PBS-subsidised biological medicine for either: (i) severe asthma, (ii) severe allergic asthma
	AND
	Clinical criteria:
	Patient must have a diagnosis of asthma confirmed and documented in the patient's medical records by either: (i) a paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist, (iv) paediatrician or general physician experienced in the management of patients with severe asthma in consultation with a respiratory physician, defined by at least one of the following standard clinical features: (a) forced expiratory volume (FEV1) reversibility, (b) airway hyperresponsiveness, (c) peak expiratory flow (PEF) variability,
	AND
	Clinical criteria:
	Patient must have a duration of asthma of at least 1 year
	AND
	Clinical criteria:
	Patient must have total serum human immunoglobulin E of at least 30 IU/mL with past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE in the last 12 months, OR
	Patient must have blood eosinophil count of at least 150 cells per microlitre in the last 12 months; OR
	Patient must have a fractional exhaled nitrous oxide of at least 20 ppb in the last 12 months
	AND
	Clinical criteria:
	Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented in the patient's medical records,
	AND
	Clinical criteria:
	Patient must not receive more than 32 weeks of treatment under this restriction,
	AND
	Clinical criteria:
	Patient must be under the care of the same physician for at least 6 months.
	AND
	Clinical criteria:
	The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for either: (i) severe asthma, (ii) severe allergic asthma
	Treatment criteria:
	Must be treated by a medical practitioner who is either: (i) paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist; (iv) paediatrician or general physician experienced in the management of patients with severe asthma, in consultation with a respiratory physician.
	Population criteria:
	Patient must be aged 6 to less than 12 years.

	Prescribing Instructions: Optimised asthma therapy includes: (i) Adherence to optimal inhaled therapy, including high dose inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) therapy for at least six months. If LABA therapy is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative; AND (ii) treatment with at least 2 courses of oral or IV corticosteroids (daily or alternate day maintenance treatment courses, or 3–5-day exacerbation treatment courses), in the previous 12 months unless contraindicated or not tolerated. If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications (including those specified in the relevant TGA-approved Product Information) and/or intolerances of a severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance must be provided in the Authority application.
	Prescribing Instructions: The initial IgE assessment, blood eosinophil count or fractional exhaled nitrous oxide measurement must be no more than 12 months old at the time of application.
	Prescribing Instructions: The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) An Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month (for children aged 6 to 10 years it is recommended that the Interviewer Administered version – the ACQ-IA be used), AND (b) while receiving optimised asthma therapy in the previous 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. The Asthma Control Questionnaire (5 item version) or ACQ-IA assessment of the patient's response to this initial course of treatment, the assessment of oral corticosteroid dose, and the assessment of exacerbation rate should be made at around 28 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. This assessment, which will be used to determine eligibility for continuing treatment, should be submitted within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a response assessment is not undertaken and submitted, the patient will be deemed to have failed to respond to treatment with this drug for this condition. A patient who fails to demonstrate a response to treatment with this drug will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle. A treatment break in PBS-subsidised biological medicine therapy of at least 12 months must be observed in a patient who has either failed to achieve or sustain a response to treatment with 2 biological medicines within the same treatment cycle. The length of the break in therapy is measured from the date of the most recent treatment with a PBS-subsidised biological medicine was administered until the date of the first application for recommencement of treatment with a biological medicine under the new treatment cycle. 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 dupilumab of up to 32 weeks.

	Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: The following must be provided at the time of application and documented in the patient's medical records: (a) details of prior optimised asthma drug therapy (dosage, date of commencement and duration of therapy); and (b) details of severe exacerbation/s experienced in the past 12 months while receiving optimised asthma therapy (date and treatment); and (c) the IgE, blood eosinophil or the fractional exhaled nitrous oxide result and date; and (d) Asthma Control Questionnaire (ACQ-5) score; or (e) Asthma Control Questionnaire interviewer administered version (ACQ-IA) score.
	Administrative Advice: The Services Australia website (www.servicesaustralia.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.
	Administrative Advice: For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
	Administrative Advice: It is recommended that an application for continuing treatment is submitted at the of the 28-week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug for this condition.
	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
	Administrative Advice: 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 authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Restriction Summary / Treatment of Concept	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
	Indication: Uncontrolled severe asthma
	Treatment Phase: Initial treatment – Initial 2 (Change of treatment)

	Clinical criteria:
	Patient must have had a total serum human immunoglobulin E of at least 30 IU/mL with past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE no more than 12 months prior to initiating PBS-subsidised treatment with a biological medicine for either: (i) severe asthma, (ii) severe allergic asthma; or
	Patient must have had a blood eosinophil count of at least 150 cells per microlitre no more than 12 months prior to initiating PBS-subsidised treatment with a biological medicine for either: (i) severe asthma, (ii) severe allergic asthma; or
	Patient must have had a fractional exhaled nitrous oxide of at least 20 ppb no more than 12 months prior to initiating PBS-subsidised treatment with a biological medicine for either: (i) severe asthma, (ii) severe allergic asthma
	AND
	Clinical criteria:
	Patient must not receive more than 32 weeks of treatment under this restriction.
	AND
	Clinical criteria:
	Patient must be under the care of the same physician for at least 6 months.
	AND
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine in this treatment cycle for either: (i) severe asthma, (ii) severe allergic asthma,
	AND
	Clinical criteria:
	Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle
	AND
	Clinical criteria:
	The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for either: (i) severe asthma, (ii) severe allergic asthma
	Treatment criteria:
	Must be treated by a medical practitioner who is either a: (i) paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist; (iv) paediatrician or general physician experienced in the management of patients with severe asthma, in consultation with a respiratory physician
	Population criteria:
	Patient must be aged 6 to less than 12 years.

	Prescribing Instructions: An application for a patient who has received PBS-subsidised biological medicine treatment for severe asthma or severe allergic asthma who wishes to change therapy to this biological medicine, must be accompanied by the results of an ACQ-5 (or ACQ-5-IA) assessment of the patient's most recent course of PBS-subsidised biological medicine treatment. The assessment must have been made not more than 4 weeks after the last dose of biological medicine. Where a response assessment was not undertaken, the patient will be deemed to have failed to respond to treatment with that previous biological medicine. An ACQ-5 (or ACQ-5-IA) assessment of the patient may be made at the time of application for treatment (to establish a new baseline score), but should be made again around 28 weeks after the first PBS-subsidised dose of this biological medicine under this restriction so that there is adequate time for a response to be demonstrated and for the application for the first continuing therapy to be processed. This assessment at around 28 weeks, which will be used to determine eligibility for the first continuing treatment, should be conducted within 4 weeks of the last dose of biological medicine. To avoid an interruption of supply for the first continuing treatment, the assessment should be submitted no later than 2 weeks prior to the patient completing their current treatment course, unless the patient is currently on a treatment break. Where a response assessment is not undertaken and submitted, the patient will be deemed to have failed to respond to treatment with this biological medicine. A patient who fails to respond to a course of PBS-subsidised treatment with this drug for uncontrolled severe asthma will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within 12 months of the date on which treatment was ceased. 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 dupilumab sufficient for up to 32 weeks of therapy.
	Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: The following must be provided at the time of application and documented in the patient's medical records: (a) the IgE, blood eosinophil or fractional exhaled nitrous oxide result and date; and (b) Asthma Control Questionnaire (ACQ-5) score; or (c) Asthma Control Questionnaire interviewer administered version (ACQ-IA) score. (d) the details of prior biological medicine treatment including the details of date and duration of treatment; and (e) the reason for switching therapy (e.g. failure of prior therapy, partial response to prior therapy, adverse event to prior therapy).
	Administrative Advice: The Services Australia website (www.servicesaustralia.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.
	Administrative Advice: For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
	Administrative Advice: It is recommended that an application for continuing treatment is submitted at the 28-week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug for this condition.

	Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
	Administrative Advice: 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 authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
DUPILUMAB					
dupilumab 200 mg/1.14 mL injection, 2 x 1.14mL	NEW (Public) NEW (Private)	1	2	0	Dupixent
dupilumab 300 mg/2 mL injection, 2 x 2mL syringes	NEW (Public) NEW (Private)	1	2	0	Dupixent

Restriction Summary / Treatment of Concept:	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/electronic)
	Administrative Advice: See overarching administrative note below
	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).
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Uncontrolled Severe Asthma
	Treatment Phase: Initial 1 (New patient; or Recommencement of treatment in a new treatment cycle following a break in PBS-subsidised biological medicine therapy), Initial 2 (Change of treatment), Continuing treatment, or transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements - Balance of Supply
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the Initial 1 (New patient; or Recommencement of treatment in a new treatment cycle following a break in PBS-subsidised biological medicine therapy) restriction to complete 32 weeks of treatment; OR
	Patient must have received insufficient therapy with this drug for this condition under the Initial 2 (Change of treatment) restriction to complete 32 weeks of treatment; OR

	Patient must have received insufficient therapy with this drug for this condition under the Continuing treatment restriction to complete 24 weeks of treatment; OR
	Patient must have received insufficient therapy with this drug for this condition under the transitioning from non-PBS to PBS-subsidised supply – Grandfather arrangements restriction to complete 24 weeks of treatment.
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 32 weeks treatment available under the Initial 1 and Initial 2 restriction; OR
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the Continuing and transitioning from non-PBS to PBS-subsidised supply-Grandfather arrangements restriction.
	Treatment criteria:
	Must be treated by a medical practitioner who is either a: (i) paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist; (iv) paediatrician or general physician experienced in the management of patients with severe asthma, in consultation with a respiratory physician.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
DUPILUMAB					
dupilumab 200 mg/1.14 mL injection, 2 x 1.14mL	NEW (Public) NEW (Private)	1	2	5	Dupixent
dupilumab 300 mg/2 mL injection, 2 x 2mL syringes	NEW (Public) NEW (Private)	1	2	2	Dupixent

Restriction Summary / Treatment of Concept:		
Concept ID (for internal Dept. use)		**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
		Administrative Advice: See overarching administrative note below
		Administrative Advice: For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806 or MedInfo.Australia@sanofi.com
		Administrative Advice: Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).
		Administrative Advice: 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 authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to:

		Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Indication: Uncontrolled Severe Asthma
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have a documented history of severe asthma
		AND
		Clinical criteria:
		Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must not receive more than 24 weeks of treatment under this restriction,
		Treatment criteria:
		Must be treated by a medical practitioner who is either a: (i) paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist; (iv) paediatrician or general physician experienced in the management of patients with severe asthma, in consultation with a respiratory physician.
		Population criteria:
		Patient must be aged 6 to less than 12 years.
		Prescribing Instructions: An adequate response to this biological medicine is defined as: (a) a reduction in the Asthma Control Questionnaire (ACQ-5) or ACQ-IA score of at least 0.5 from baseline, OR (b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 or ACQ-IA score from baseline, OR (c) a reduction in the time-adjusted exacerbation rates compared to the 12 months prior to baseline.
		Prescribing Instructions: All applications for continuing treatment this biological medicine must include a measurement of response to the prior course of therapy. The Asthma Control Questionnaire (5 item version) or Asthma Control Questionnaire interviewer administered version (ACQ-IA) assessment of the patient's response to the prior course of treatment, the assessment of systemic corticosteroid dose, and the assessment of time-adjusted exacerbation rate must be made at around 20 weeks after the first dose of PBS-subsidised dose of this drug so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. The first assessment should, where possible, be completed by the same physician who initiated treatment with this drug. This assessment, which will be used to determine eligibility for continuing treatment, should be submitted within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a response assessment is not undertaken and submitted, the patient will be deemed to have failed to respond to treatment with this drug for this condition. A patient who fails to demonstrate a response to treatment with this drug for this condition will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle.

	At the time of authority application, medical practitioners should request the appropriate quantity and number of repeats to provide for a continuing course of dupilumab, sufficient for 24 weeks therapy.
	Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: The following must be provided at the time of application and documented in the patient's medical records: (a) maintenance oral corticosteroid dose; and (b) Asthma Control Questionnaire (ACQ-5) score; or (c) Asthma Control Questionnaire interviewer administered version (ACQ-IA) score.
Restriction Summary / Treatment of Concept: [	
Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Highly Specialised Drugs Program (Public/Private)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
	Indication: Uncontrolled severe asthma
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – Grandfathering arrangements
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this PBS-indication prior to [list date]
	AND
	Clinical criteria:
	Patient must have a diagnosis of asthma confirmed and documented in the patient's medical records by either a: (i) paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist; (iv) paediatrician or general physician experienced in the management of patients with severe asthma in consultation with a respiratory physician, defined by at least one of the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility, (ii) airway hyperresponsiveness, (iii) peak expiratory flow (PEF) variability,
	AND
	Clinical criteria:
	Patient must have had a duration of asthma of at least 1 year prior to commencement of non-PBS subsidised treatment with this drug
	AND
	Clinical criteria:
	Patient must have had a documented total serum human immunoglobulin E of at least 30 IU/mL measured no more than 12 months prior to initiation of non-PBS-subsidised treatment with this drug for this condition, with past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE no more than 12 months prior to initiation of PBS-subsidised treatment with this drug for this condition; OR
	Patient must have had a blood eosinophil count of at least 150 cells per microlitre in the 12 months prior to initiation of non-PBS-subsidised treatment with this drug for this condition; OR
	Patient must have had a fractional exhaled nitrous oxide of at least 20 ppb in the 12 months prior to initiation of non-PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:

	Patient must have documented a failure to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, prior to initiating non-PBS-subsidised treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have demonstrated or sustained an adequate response to treatment with this drug if the patient has received at least 28 weeks of treatment with this drug for this condition.
	AND
	Clinical criteria:
	Patient must not receive more than 24 weeks of treatment under this restriction.
	Treatment criteria:
	Must be treated by a medical practitioner who is either a: (i) paediatric respiratory physician, (ii) clinical immunologist, (iii) allergist; (iv) paediatrician or general physician experienced in the management of patients with severe asthma, in consultation with a respiratory physician
	Population criteria:
	Patient must be aged 6 to less than 12 years.
	Prescribing Instructions: Optimised asthma therapy includes: (i) Adherence to optimal inhaled therapy, including high dose inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) therapy for at least six months. If LABA therapy is contraindicated, not tolerated or not effective, montelukast, cromoglycate or nedocromil may be used as an alternative; AND (ii) treatment with at least 2 courses of oral or IV corticosteroids (daily or alternate day maintenance treatment courses, or 3–5-day exacerbation treatment courses), in the previous 12 months unless contraindicated or not tolerated. If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications (including those specified in the relevant TGA-approved Product Information) and/or intolerances of a severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance must be provided in the Authority application.
	Prescribing Instructions: An adequate response to this biological medicine is defined as: (a) a reduction in the Asthma Control Questionnaire (ACQ-5) or ACQ-IA score of at least 0.5 from baseline, OR (b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 or ACQ-IA score from baseline, OR (c) a reduction in the time-adjusted exacerbation rates compared to the 12 months prior to baseline.
	Prescribing Instructions: The following initiation criteria indicate failure to achieve adequate control with optimised asthma therapy and must be demonstrated in all patients at the time of the application: (a) An Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed prior to non-PBS-subsidised treatment with this drug for this condition (for children aged 6 to 10 years it is recommended that the Interviewer Administered version – the ACQ-IA be used), AND (b) while receiving optimised asthma therapy in the prior to non-PBS-subsidised treatment with this drug for this condition 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. The Asthma Control Questionnaire (5 item version) or Asthma Control Questionnaire interviewer administered version (ACQ-IA) assessment, the assessment of systemic corticosteroid dose, and the assessment of time-adjusted exacerbation rate to determine whether the patient has achieved or

	sustained an adequate response to non-PBS subsidised treatment, must be conducted immediately (no later than 4 weeks after the last dose of non-PBS-subsidised treatment) prior to this application if the treatment duration has been at least 28 weeks. All applications for continuing treatment with this biological medicine must include a measurement of response to the prior course of therapy. The Asthma Control Questionnaire (5 item version) or Asthma Control Questionnaire interviewer administered version (ACQ-IA) assessment of the patient's response to the prior course of treatment, the assessment of systemic corticosteroid dose, and the assessment of time-adjusted exacerbation rate must be made at around 20 weeks after the first dose of PBS-subsidised treatment with this drug under this restriction so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. The first assessment should, where possible, be completed by the same physician who initiated treatment with this drug. This assessment, which will be used to determine eligibility for continuing treatment, should be submitted within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an interruption to supply. Where a response assessment is not undertaken and submitted, the patient will be deemed to have failed to respond to treatment with this drug for this condition. A patient who fails to demonstrate a response to treatment with this drug for this condition will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle. At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats to provide for a continuing course of dupilumab, sufficient for 24 weeks of therapy.
	Prescribing Instructions: The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: The following must be provided at the time of application and documented in the patient's medical records: (a) prior optimised asthma drug therapy (date of commencement and duration of therapy); and (b) IgE, blood eosinophils or fractional exhaled nitrous oxide results and date from prior to initiating non-PBS-subsidised treatment with this drug; and (c) date of commencing non-PBS-subsidised treatment with this drug for this condition. (d) If applicable, maintenance oral corticosteroid dose; and (e) the Asthma Control Questionnaire (ACQ-5) scores, including the date of assessment of the patient's symptoms; or (f) the Asthma Control Questionnaire interviewer administered version (ACQ-IA) scores, including the date of assessment of the patient's symptoms.
	Prescribing Instructions: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: The Services Australia website (www.servicesaustralia.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

OVERARCHING ADMINISTRATIVE NOTE

	Administrative Advice: TREATMENT OF PAEDIATRIC PATIENTS WITH UNCONTROLLED SEVERE ASTHMA AND UNCONTROLLED SEVERE ALLERGIC ASTHMA The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines dupilumab for uncontrolled severe asthma and omalizumab for uncontrolled severe allergic asthma. Therefore, where the term 'biological medicine' appears in notes and restrictions, it refers to dupilumab and omalizumab only. A patient is eligible for PBS-subsidised treatment with only 1 of the above biological medicine at any one time. A patient receiving PBS-subsidised treatment for uncontrolled severe asthma or uncontrolled severe allergic asthma is able to commence a treatment cycle where they may trial a biological medicine without having to experience a disease flare when swapping to an alternate biological medicine within the same treatment cycle. Under these arrangements, within a treatment cycle, a patient may receive long-term treatment with a biological medicine as long as they sustain a response to therapy. A patient currently receiving PBS-subsidised treatment as of [dupilumab list date] is considered to have started a cycle of treatment. Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to the same PBS-subsidised biological more than once. Therefore, once a patient fails to meet the response criteria for a PBS-subsidised biological medicine, they must change to an alternate biological medicine if they wish to continue PBS-subsidised biological treatment. Once a patient has either failed to achieve or sustain a response to treatment 2 times, they are deemed to have completed a single treatment cycle. They must have at least a 12-month break in PBS-subsidised biological medicine therapy before they are eligible to recommence another new treatment cycle [further details are under 'Recommencement of treatment after a break in PBS-subsidised therapy' below]. The length of the break in therapy is measured from the date the most recent treatment with a PBS-subsidised biological medicine is ceased until the date of the first application for recommencement of treatment with a biological medicine under the new treatment cycle. There is no limit to the number of treatment cycles that a patient may undertake in their lifetime. How to prescribe PBS-subsidised biological medicine treatment for uncontrolled severe asthma/uncontrolled severe allergic asthma. (1) Initial treatment: Applications for initial treatment should be made where: (i) a patient has not received prior PBS-subsidised biological medicine treatment and wishes to commence such therapy (Initial 1 restriction); or (ii) a patient has received prior PBS-subsidised treatment with a biological medicine and wishes to recommence a new treatment cycle with this biological medicine following a treatment break in PBS-subsidised therapy (Initial 1 restriction); or (iii) a patient has received prior PBS-subsidised biological medicine therapy and wishes to trial an alternate biological medicine within the same treatment cycle (Initial 2 restriction) – [further details are under 'Swapping therapy' below].

	All applications for initial treatment will be limited to provide for a maximum of 32 weeks of therapy of dupilumab and a maximum of 28 weeks of therapy of omalizumab. It is recommended that a patient be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological medicine supply. (2) Continuing treatment: Following the completion of an initial treatment course with a specific biological medicine, a patient may qualify to receive up to 24 weeks of continuing treatment with that biological medicine providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing biological medicine treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. It is recommended that a patient be reviewed the month prior to completing their current course of treatment to ensure uninterrupted biological medicine supply. (3) Baseline measurements to determine response: Baseline measurements of the Asthma Control Questionnaire (ACQ, ACQ-IA; 5 item version), systemic corticosteroid dose and time adjusted exacerbation rate, submitted with the Initial authority application for a biological medicine must be used to determine whether an adequate response to treatment has been achieved or sustained. However, prescribers may provide new baseline measurements when a new Initial treatment authority application is submitted and these new baseline measurements may be used to assess response. (4) Swapping therapy within the same treatment cycle. Once initial treatment with the first PBS-subsided biological medicine is approved, a patient may swap to an alternate biological medicine at any time by qualifying under an Initial 2 restriction, provided they meet all of the restriction criteria. However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug with the same treatment cycle. Within the same treatment cycle a patient may alternate between therapy with either biological medicine of their choice (1 at a time) providing: (i) they have not received PBS-subsided treatment with that particular biological medicine previously; or (ii) they have demonstrated an adequate response to that particular biological medicine if they have previously trialled it on the PBS; and (iii) they have not previously failed to respond to treatment with either 2 biological medicines in this treatment cycle. (5) Re-commencement of a new treatment cycle after a treatment break in PBS-subsidised therapy: A patient who wishes to trial a second or subsequent new treatment cycle, following a break in PBS-subsidised therapy of at least 12 months (in patients who have failed to achieve or ceased to sustain a response to treatment 2 times within a treatment cycle), must re-qualify through an Initial 1 restriction. (6) Monitoring of patients (Omalizumab only): Anaphylaxis and anaphylactoid reactions have been reported following first or subsequent administration of omalizumab (see Product Information). Patients should be monitored post-injection, and medication for the treatment of anaphylactic reactions should be available for immediate use following administration of omalizumab. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

8.2 Flow-on changes to the omalizumab restriction are required to include this Overarching Note, and details to allow for patients to switch between dupilumab and omalizumab as part of a treatment cycle (including the creation of an initial 2 restriction).

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.