

**6.02 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<sup>®</sup>,  
Sanofi-Aventis Australia Pty Ltd.**

**1 Purpose of submission**

- 1.1 The submission requested a Section 100, Authority Required listing for dupilumab for the treatment of uncontrolled, severe type 2 asthma, both with and without oral corticosteroid (OCS) dependence. These populations have been previously considered by the PBAC for the listing of benralizumab, mepolizumab and omalizumab.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus three comparators: benralizumab, mepolizumab and omalizumab. The key components of the clinical issues addressed by the submission are summarised below.

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

| <b>Component</b> | <b>Description</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| Population       | <p>Patients aged ≥ 12 years with uncontrolled severe type 2 asthma.</p> <p>This includes:</p> <p>Dupilumab 200 mg: Patients with severe type 2 asthma, without OCS dependence</p> <ul style="list-style-type: none"> <li>- Submission subgroup 1a: Patients with severe eosinophilic asthma without OCS dependence</li> <li>- Submission subgroup 1b: Patients with severe allergic asthma without OCS dependence</li> </ul> <p>Dupilumab 300 mg: Patients with severe type 2 asthma, with OCS dependence</p> <ul style="list-style-type: none"> <li>- Submission subgroup 2a: Patients with severe eosinophilic asthma and OCS dependence</li> <li>- Submission subgroup 2b: Patients with severe allergic asthma and OCS dependence.</li> </ul> |
| Intervention     | <p>Population 1a and 1b: Dupilumab 400 mg loading dose followed by 200 mg Q2W;</p> <p>Population 2a and 2b: Dupilumab 600 mg loading dose followed by 300 mg Q2W.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Comparators      | <p>Subgroup 1a and 2a: Mepolizumab 100 mg SC injection Q4W and benralizumab 30 mg by SC injection Q4W for the first three doses, and then every eight weeks.</p> <p>Subgroup 1b and 2b: Omalizumab SC injection Q2W or Q4W (dose depends on patient weight and IgE levels) for patients with uncontrolled severe allergic asthma.</p>                                                                                                                                                                                                                                                                                                                                                                                                             |
| Outcomes         | <p>Key outcome: annual asthma exacerbation rate</p> <p>Secondary outcomes: change from baseline in FEV<sub>1</sub>, proportion reduction in OCS dose and safety.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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| Clinical claim | <p>In the treatment of patients aged <math>\geq 12</math> years with uncontrolled severe type 2 asthma, dupilumab is non-inferior in terms of efficacy and safety compared with omalizumab, mepolizumab and benralizumab</p> <p>More specifically,</p> <p>Dupilumab 200 mg has non-inferior efficacy and non-inferior safety compared to:</p> <ul style="list-style-type: none"> <li>- Benralizumab and mepolizumab in patients aged <math>\geq 12</math> years in patients with severe uncontrolled eosinophilic asthma without OCS dependence</li> <li>- Omalizumab in patients aged <math>\geq 12</math> years in patients with severe uncontrolled allergic asthma without OCS dependence</li> </ul> <p>Dupilumab 300 mg has non-inferior efficacy and non-inferior safety compared to:</p> <ul style="list-style-type: none"> <li>- Benralizumab and mepolizumab in patients aged <math>\geq 12</math> years in patients with severe uncontrolled eosinophilic asthma with OCS dependence</li> <li>- Omalizumab in patients aged <math>\geq 12</math> years in patients with severe uncontrolled allergic asthma with OCS dependence</li> </ul> |
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Source: Table 1.1 of the submission.

OCS = oral corticosteroids; Q2W = every 2 weeks; SC = subcutaneous; IgE = immunoglobulin E.

## 2 Background

### Registration status

- 2.1 Dupilumab was approved by the TGA in May 2019 for the treatment of patients aged 12 years and older with moderate to severe asthma with type 2 inflammation (elevated eosinophils or elevated exhaled nitric oxide concentration (FeNO)), as well as maintenance therapy for oral corticosteroid dependent asthma.
- 2.2 The TGA approved product information (PI) stated the recommended dose of dupilumab for adults and adolescents (12 years of age and older) with moderate to severe asthma with type 2 inflammation is:
  - Initial dose of 400 mg by subcutaneous injection (two 200 mg injections consecutively in different injection sites) followed by 200 mg given every other week.

Patients with oral corticosteroids-dependent asthma:

  - Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites) followed by 300 mg given every other week.
- 2.3 A black triangle warning accompanied the TGA approval, which encourages the reporting of adverse events. The TGA delegate's report proposed additional pharmacovigilance for the asthma indication, including ongoing paediatric studies, and expansion of the planned pregnancy registry study for atopic dermatitis to include asthma patients.
- 2.4 The PI for the comparators is for narrower therapeutic indications, as follow:
  - Benralizumab is indicated as add-on therapy in patients aged 12 years and over with severe eosinophilic asthma (blood eosinophil count  $\geq 300$  cells/ $\mu$ L or  $\geq 150$  cells/ $\mu$ L if on oral corticosteroid treatment).

- Mepolizumab is indicated as an add-on treatment for severe eosinophilic asthma in patients aged 12 years and over.
- Omalizumab is indicated as add-on therapy in children aged 6 to <12 years, to improve asthma control in patients with severe allergic asthma who have documented exacerbations despite daily high dose inhaled corticosteroids, and who have immunoglobulin E levels corresponding to the recommended dose range. Omalizumab is indicated in adults and adolescents  $\geq 12$  years of age for the management of moderate to severe allergic asthma, who are already being treated with inhaled steroids, and who have serum immunoglobulin E levels corresponding to the recommended dose range.

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

### 3 Requested listing

- 3.1 An abridged version of the requested listing is provided below (Prescribing Instructions and Administrative Advice are not included). Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

#### Treatment phase: Initial 1 and Initial 2

| Name, restriction, manner of administration, form               | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Dispensed price for maximum quantity                                 | Proprietary name and manufacturer |                                  |
|-----------------------------------------------------------------|---------------|--------------------------|--------------------------|----------------|----------------------------------------------------------------------|-----------------------------------|----------------------------------|
| DUPILUMAB<br><br>200 mg/1.14 mL injection, 2 x 1.14 mL syringes | NEW           | 1                        | 2                        | 8              | Public<br>= \$ [redacted]<br>Private<br>= \$ [redacted]<br>[SPA TBD] | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

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| <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                                                                                                                             |
| <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                                                                                                                          |
| <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                                                                                                                    |
| <b>Severity:</b><br><i>Uncontrolled severe</i>                                                                                                                                                                                                                                                |
| <b>Condition:</b><br><i>eosinophilic or allergic asthma</i>                                                                                                                                                                                                                                   |
| <b>PBS Indication:</b><br><i>Uncontrolled severe eosinophilic or allergic type 2 asthma without OCS dependence</i>                                                                                                                                                                            |
| <b>Treatment phase:</b><br><i>Initial treatment 1 – (New patient; or <del>Recommendation of patients recommencing treatment in a new treatment cycle following a break in PBS subsidised biological medicine therapy) after a break of more than 12 months, without OCS dependence.</del></i> |
| <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                 |
| <b>AND</b>                                                                                                                                                                                                                                                                                    |

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| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must be under the care of the same physician for at least 6 months; or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; or |
| Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have a duration of asthma of at least 1 year.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months, or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <i>Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids in the last 12 months, or</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 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 <i>in the last 12 months that is no more than 1 year old.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Population criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Patients must be aged 12 years or older.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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| <b>Category / Program:</b>                                          |
| Section 100 – Highly Specialised Drugs Program – public and private |
| <b>Prescriber type:</b>                                             |
| <input checked="" type="checkbox"/> Medical Practitioners           |
| <b>Restriction:</b>                                                 |
| <input checked="" type="checkbox"/> Authority Required - In Writing |
| <b>Severity:</b>                                                    |
| <i>Uncontrolled severe</i>                                          |

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| <b>Condition:</b><br><i>eosinophilic or allergic asthma</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>PBS Indication:</b><br><del>Uncontrolled severe type 2 eosinophilic or allergic asthma without OCS dependence</del>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Treatment phase:</b><br><del>Initial treatment – Initial 2 (change of treatment or patient recommencing after a break of less than 12 months) (Change of treatment)</del>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical criteria:</b><br>Patient must be under the care of the same physician for at least 6 months; or<br>Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical criteria:</b><br>Patient must have received prior PBS-subsidised treatment with a biological medicine for severe asthma in this treatment cycle.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical criteria:</b><br>Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug for severe asthma during the current treatment cycle.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical criteria:</b><br><del>Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months, Patient must have had a blood eosinophil count greater than or equal to 300 cells per microlitre measured is no older more than 12 months immediately prior to commencing PBS-subsidised biological medicine treatment for severe asthma; or</del><br><i>Patient must have had a blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids and that is no older than 12 months immediately prior to commencing PBS-subsidised biological medicine treatment for severe asthma; or</i> |
| <b>OR</b><br>Patient must have <i>had</i> a total serum human immunoglobulin E greater than or equal to 30 IU/mL <i>with a 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 severe asthma.</i>                                                                                                                                                                                                                                                                                                                                                  |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical criteria:</b><br>Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Clinical criteria:</b><br>The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Population criteria:</b><br>Patients must be aged 12 years or older.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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**Treatment phase: Continuing treatment**

| Name, restriction, manner of administration, form               | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Dispensed price for maximum quantity                               | Proprietary name and manufacturer |                                  |
|-----------------------------------------------------------------|---------------|--------------------------|--------------------------|----------------|--------------------------------------------------------------------|-----------------------------------|----------------------------------|
| DUPILUMAB<br><br>200 mg/1.14 mL injection, 2 x 1.14 mL syringes | NEW           | 1                        | 2                        | 5              | Public<br>=\$ [redacted]<br>Private<br>=\$ [redacted]<br>[SPA TBD] | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |
| 300 mg/2 mL injection, 2 x 2 mL syringes                        | NEW           | 1                        | 2                        | 5              | Public<br>=\$ [redacted]<br>Private<br>=\$ [redacted]<br>[SPA TBD] | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

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| <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                             |
| <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                          |
| <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                    |
| <b>Severity:</b><br><i>Uncontrolled severe</i>                                                                                                                                                |
| <b>Condition:</b><br><i>eosinophilic or allergic asthma</i>                                                                                                                                   |
| <b>PBS Indication:</b><br><del>Uncontrolled severe type 2 eosinophilic or allergic asthma without oral corticosteroid OCS dependence</del>                                                    |
| <b>Treatment phase:</b><br>Continuing treatment                                                                                                                                               |
| <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma. |
| <b>AND</b>                                                                                                                                                                                    |
| <b>Clinical criteria:</b><br>Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition.                                  |
| <b>AND</b>                                                                                                                                                                                    |
| <b>Clinical criteria:</b><br>The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                |
| <b>AND</b>                                                                                                                                                                                    |
| <b>Clinical criteria:</b><br>Patient must not receive more than 24 weeks of treatment under this restriction.                                                                                 |
| <b>Population criteria:</b><br>Patients must be aged 12 years or older                                                                                                                        |

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**Treatment phase: Initial 1 and Initial 2**

| Name, restriction, manner of administration, form | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Dispensed price for maximum quantity                               | Proprietary name and manufacturer |                                  |
|---------------------------------------------------|---------------|--------------------------|--------------------------|----------------|--------------------------------------------------------------------|-----------------------------------|----------------------------------|
| 300 mg/2 mL injection, 2 x 2 mL syringes          | NEW           | 1                        | 2                        | 8              | Public<br>=\$ [redacted]<br>Private<br>=\$ [redacted]<br>[SPA TBD] | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

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| <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Severity:</b><br><i>Uncontrolled severe</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Condition:</b><br><i>eosinophilic or allergic asthma</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>PBS Indication:</b><br><i>Uncontrolled severe type-2 eosinophilic or allergic asthma with OCS dependence</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Treatment phase:</b><br><i>Initial treatment 1 – (New patients; or Recommencement of patients recommencing treatment in a new treatment cycle following a break in PBS subsidised biological medicine therapy) treatment with an asthma biologic after a break of more than 12 months, with OCS dependence</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Clinical criteria:</b><br>Patient must be under the care of the same physician for at least 6 months; or<br>Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Clinical criteria:</b><br>Patient must not have received PBS-subsidised treatment with a biological medicine for severe asthma; or<br>Patient must have had a break in treatment from the most recently approved PBS-subsidised biological medicine for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Clinical criteria:</b><br>Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; or<br>Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma. |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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| Patient must have a duration of asthma of at least 1 year.                                                                                                                                                                               |
| <b>AND</b>                                                                                                                                                                                                                               |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                |
| <i>Patient must have been receiving regular maintenance oral corticosteroids (OCS) in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to treatment initiation.</i> |
| <b>AND</b>                                                                                                                                                                                                                               |
| Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroid in the last 12 months, or                                                                  |
| 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, that is no more than 1 year old. |
| <b>AND</b>                                                                                                                                                                                                                               |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                |
| 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.                                                  |
| <b>AND</b>                                                                                                                                                                                                                               |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                |
| Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                         |
| <b>AND</b>                                                                                                                                                                                                                               |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                |
| The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                        |
| <b>Population criteria:</b>                                                                                                                                                                                                              |
| Patients must be aged 12 years or older.                                                                                                                                                                                                 |

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| <b>Category / Program:</b>                                                                                                                                      |
| Section 100 – Highly Specialised Drugs Program – public and private                                                                                             |
| <b>Prescriber type:</b>                                                                                                                                         |
| <input checked="" type="checkbox"/> Medical Practitioners                                                                                                       |
| <b>Restriction:</b>                                                                                                                                             |
| <input checked="" type="checkbox"/> Authority Required - In Writing                                                                                             |
| <b>Severity:</b>                                                                                                                                                |
| <i>Uncontrolled severe</i>                                                                                                                                      |
| <b>Condition:</b>                                                                                                                                               |
| <i>eosinophilic or allergic asthma</i>                                                                                                                          |
| <b>PBS Indication:</b>                                                                                                                                          |
| Uncontrolled severe <del>type 2</del> eosinophilic or allergic asthma <del>with OCS dependence</del>                                                            |
| <b>Treatment phase:</b>                                                                                                                                         |
| Initial treatment – Initial 2 ( <del>change of treatment or patient recommencing after a break of less than 12 months</del> ) ( <i>Change of treatment</i> )    |
| <b>Treatment criteria:</b>                                                                                                                                      |
| Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma. |
| <b>AND</b>                                                                                                                                                      |
| <b>Clinical criteria:</b>                                                                                                                                       |
| Patient must be under the care of the same physician for at least 6 months; or                                                                                  |
| Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                              |
| <b>AND</b>                                                                                                                                                      |
| <b>Clinical criteria:</b>                                                                                                                                       |
| Patient must have received prior PBS-subsidised treatment with a biological medicine for severe asthma in this treatment cycle.                                 |
| <b>AND</b>                                                                                                                                                      |
| <b>Clinical criteria:</b>                                                                                                                                       |



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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug for severe asthma during the current treatment cycle.                                                                                                                                                                                                                                                                                                                              |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <del>Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre in the last 12 months, Patient must have had a blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids and that is no older than 12 months immediately prior to commencing PBS-subsidised biological medicine treatment for severe asthma; or</del>                                                          |
| Patient must have each of: i) total serum human immunoglobulin E greater than or equal to 30 IU/mL measured no more than 12 months prior to initiating PBS-subsidised treatment with a biological medicine for severe asthma, ii) past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE in the past 12 months or in the 12 months prior to initiating PBS-subsidised treatment with a biological medicine for severe asthma. |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <del>Patient must have received daily oral corticosteroids for at least 6 weeks</del>                                                                                                                                                                                                                                                                                                                                                                                             |
| Patient must have received regular maintenance oral corticosteroids (OCS) in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to treatment initiation.                                                                                                                                                                                                                                                       |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                 |
| <b>Population criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Patients must be aged 12 years or older.                                                                                                                                                                                                                                                                                                                                                                                                                                          |

**Treatment phase: Grandfather treatment**

| Name, restriction, manner of administration, form            | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Dispensed price for maximum quantity                               | Proprietary name and manufacturer |                                  |
|--------------------------------------------------------------|---------------|--------------------------|--------------------------|----------------|--------------------------------------------------------------------|-----------------------------------|----------------------------------|
| DUPILUMAB<br><br>300 mg/2 mL injection,<br>2 x 2 mL syringes | NEW           | 1                        | 2                        | 5              | Public<br>=\$ [REDACTED]<br>Private<br>=\$ [REDACTED]<br>[SPA TBD] | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

|                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------|
| <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                   |
| <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                |
| <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                          |
| <b>Severity:</b><br>Uncontrolled severe                                                                             |
| <b>Condition:</b><br>eosinophilic or allergic asthma                                                                |
| <b>PBS Indication:</b><br>Uncontrolled severe <del>type 2 eosinophilic or allergic asthma with OCS dependence</del> |
| <b>Treatment phase:</b><br><del>Continuing treatment (grandfathered patients)</del> Grandfather treatment           |

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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Treatment criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have received non-PBS-subsidised treatment with this biological medicine's <del>pre-filled syringe or pen device</del> for this <del>PBS-indica</del> condition prior to 1 June 2020 [listing date].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have demonstrated or sustained an adequate response to treatment with this drug if the patient has received at least the week 28 dose of this biological medicine.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must be receiving treatment with this drug for this condition at the time of application.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must be under the care of the same physician for at least 6 months; or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Patient must have been diagnosed with severe asthma by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; or |
| Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have had a <i>documented</i> blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids prior to <del>commencement</del> <i>initiating of a biological medicine treatment non-PBS subsidised treatment of this drug for severe asthma; or</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <i>Patient must have had a documented total serum human immunoglobulin E greater than or equal to 30 IU/mL measured no more than 12 months prior to initiating non-PBS-subsidised treatment with a biological medicine for severe asthma, 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 this drug for severe asthma.</i>                                                                                                                                                                                                                                                                                                                                                                                |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <i>Patient must have received regular maintenance oral corticosteroids (OCS) in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to commencement of a biological medicine treatment for severe asthma.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have a <i>documented</i> a duration of asthma of at least 1 year prior to commencement of this biological medicine.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Patient must have <i>documented a failure</i> <del>failed</del> to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, <i>prior to initiating non-PBS subsidised treatment with this drug for this condition. which has been documented.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical criteria:</b>                                                                                                                         |
| The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma. |
| <b>Population criteria:</b>                                                                                                                       |
| Patients must be aged 12 years or older.                                                                                                          |

- 3.2 The submission proposed a special pricing arrangement (SPA), which would be agreed upon after the confidential comparator prices are revealed to the sponsor.
- 3.3 The requested restriction is narrower than the TGA-approved indication, which included moderate asthma as well as severe asthma.
- 3.4 The submission requested listing for severe asthma with type 2 inflammation. Type 2 inflammation is defined as raised blood eosinophils (EOS) and/or raised FeNO. The requested initial restriction proposed the same measure of IgE (of more than or equal to 30IU/mL) as that in the omalizumab initial restriction for uncontrolled severe allergic asthma. It also proposed the same measures for EOS (of more than or equal to 150 cells per microlitre in patients receiving OCS; or more than or equal to 300 cells per microlitre) as that in the mepolizumab and benralizumab initial restrictions. As the requested restriction for dupilumab is consistent with that of omalizumab, benralizumab and mepolizumab it would be appropriate to use the same terminology i.e. uncontrolled severe allergic or eosinophilic asthma. The Pre-Sub-Committee Response (PSCR) stated that dupilumab represents an evolution in the treatment of uncontrolled severe asthma patients and argued that this is reflected in the breadth of the TGA restriction, which encompasses both allergic and eosinophilic asthma patients under the umbrella of type 2 asthma. The PSCR argued this terminology is routinely used in clinical practice and is consistent with the latest GINA guidelines. For these reasons, the PSCR stated that the sponsor considered it important that the type 2 endotype diagnosis is explicitly reflected in the PBS restriction. The ESC noted that the submission stated that dupilumab is not expected to increase the size of the asthma biologic market more than would otherwise be expected. As such, the ESC considered that it may be appropriate to amend the PBS indication to 'uncontrolled severe eosinophilic or allergic asthma' with reference to oral corticosteroid dependence reserved for the clinical criteria of the 300 mg formulation.
- 3.5 The proposed definition of OCS dependence was drawn from the definition used by currently listed biologic therapies: patients who received daily OCS for at least six weeks, whilst also on maximal inhaled therapy for at least 12 months. This is distinguished from the non-OCS dependent group, who may have had a cumulative dose of OCS of at least 500mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated. The PSCR considered that clarification of the meaning of OCS dependence by including the definition used in VENTURE may be appropriate. The ESC noted that this would involve the inclusion of the following clinical criterion in the dupilumab 300 mg restriction 'Patient must have received regular maintenance OCS in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to treatment initiation'.

- 3.6 The PSCR clarified that the ACQ-5 tool will be provided to prescribers in a manner consistent with current practice and hence the restrictions should include the following administrative advice 'For copies of the ACQ, please contact Sanofi Medical Information on 1800 818 806'.

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

## 4 Population and disease

- 4.1 Asthma is a heterogeneous disease characterised by chronic airway inflammation, which can lead to obstruction. The disease is characterised by respiratory wheeze, shortness of breath, chest tightness and cough that vary over time in intensity, together with variable airflow limitation which may become persistent. About 2.9 million people in Australia (11% of the total population) have asthma, based on self-reported data from 2017-18<sup>1</sup>.
- 4.2 The target population for dupilumab has 'severe refractory' asthma, where the disease remains uncontrolled despite adherence to high-dose inhaled corticosteroids (ICS) in combination with a second controller such as a long-acting beta agonist, and/or systemic corticosteroids, or whose asthma control deteriorates when these treatments are stepped down<sup>2</sup>. The ESC considered the target population to be appropriate.
- 4.3 Between 3% and 10% of all individuals with asthma are thought to have severe disease, and about 50% of these are associated with persistent elevation in markers of type 2 inflammation<sup>3</sup>. A multicentre study found 26% of Australian severe asthma patients were receiving background OCS therapy<sup>4</sup>.
- 4.4 Severe asthma is associated with a substantial burden. A study in the UK found around 2/3 individuals with severe asthma were unable to maintain full-time employment<sup>5</sup>, and in Australia, 73% of individuals with severe asthma reported being impaired at work due to their health in the previous week<sup>6</sup>. The requirement to use OCS represents further cumulative burden on current and future health<sup>7</sup>.
- 4.5 Dupilumab was proposed as an advanced therapy for both OCS-dependent and non-OCS dependent severe refractory type 2 asthma, where it could be used as an alternative to benralizumab or mepolizumab in patients with eosinophilic asthma, and

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<sup>1</sup> Australian Institute of Health and Welfare 2020. Asthma. Cat. no. ACM 33. Canberra: AIHW.

<sup>2</sup> Bel EH, Sousa A, Fleming L, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax*. 2011;66(10):910-917.

<sup>3</sup> Wenzel, S. Severe asthma phenotypes. *UpToDate*. March 2020.

<sup>4</sup> Data provided from the Severe Asthma Web-Based Database, at the request of the sponsor.

<sup>5</sup> Heaney LG, Brightling CE, Menzies-Gow A, Stevenson M, Niven RM; British Thoracic Society Difficult Asthma Network. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. *Thorax*. 2010;65(9):787-794.

<sup>6</sup> Hiles SA, Harvey ES, McDonald VM, et al. Working while unwell: Workplace impairment in people with severe asthma. *Clin Exp Allergy*. 2018;48(6):650-662.

<sup>7</sup> Sullivan, PW, Ghushchyan, VH, Globe, G, Schatz, M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *Asthma and Lower Airway Disease*. 2017; 141(1):110-116.E7

an alternative to omalizumab in patients with allergic asthma. It works through the dual inhibition of the interleukin- (IL) 4 and IL-13 pathways, which are common signalling pathways in both eosinophilic and allergic (IgE-mediated) subtypes of asthma.

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

## **5 Comparator**

- 5.1 The submission nominated three comparators: benralizumab, mepolizumab and omalizumab. These comparators represent the current treatment options for the target population. The ESC considered the nominated comparators appropriate.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (3) and organisations (5) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with dupilumab including a reduction in asthma exacerbations and hospitalisations and improvements in quality of life.

### ***Clinical trials***

- 6.3 Details of the trials presented in the submission are provided in Table 2 below.

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

| <b>Trial ID/ author</b>          | <b>Protocol title/ Publication title</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>Publication citation</b>                                                                                             |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| QUEST<br>EFC13579<br>NCT02528214 | A randomised, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma. Clinical study report.<br>Busse W, Maspero J, Rabe K, et al. Liberty asthma QUEST: Phase 3 randomised, double-blind, placebo-controlled, parallel-group study to evaluate dupilumab efficacy/safety in patients with uncontrolled, moderate-to-severe asthma.<br>Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. | November 2017<br><br><i>Adv Ther</i> 2018; 35(5):737-748<br><br><i>J Allergy Clin Immunol Pract</i> 2020; 8(2):516-526. |
| DRI2544                          | A randomised, double blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma. Clinical study report.<br>Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting $\beta_2$ agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial.                                                                          | February 2016<br><br><i>Lancet</i> 2016; 388:31-44.                                                                     |
| VENTURE<br>EFC13691              | A randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma. Clinical study report.<br>Rabe K, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma.                                                                                                                                                                                                                                                        | December 2017<br><br><i>N Engl J Med</i> 2018; 378:2475-85.                                                             |
| SIROCCO                          | Bleecker E, FitzGerald J, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting $\beta_2$ -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial.                                                                                                                                                                                                                                                                         | <i>Lancet</i> 2016; 388:2115-27.                                                                                        |
| CALIMA                           | FitzGerald J, Bleecker E, Nair, P, et al. Benralizumab, an anti-interleukin-5 receptor $\alpha$ monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial.                                                                                                                                                                                                                                                                             | <i>Lancet</i> 2016; 388:2128-41                                                                                         |
| ZONDA                            | Nair P, Wenzel S, Rabe K, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <i>N Engl J Med</i> 2017; 376:2448-58                                                                                   |
| MENSA                            | Ortega H, Liu M, Pavord I, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <i>N Engl J Med</i> 2014; 371:1198-207.                                                                                 |
| MUSCA                            | Chupp G, Bradford E, Albers F, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial.                                                                                                                                                                                                                                                                         | <i>Lancet Respir Med</i> 2017; 5:390-400.                                                                               |
| SIRIUS                           | Bel E, Wenzel S, Thompson P, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                            | <i>N Engl J Med</i> 2014; 371:1189-97.                                                                                  |
| EXTRA                            | Hanania N, Alpan O, Hamilos D, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy.                                                                                                                                                                                                                                                                                                                                                                                                                                | <i>Ann Intern Med</i> 2011; 154:573-582.                                                                                |
| INNOVATE                         | Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE                                                                                                                                                                                                                                                                                                                           | <i>Allergy</i> 2005; 60:309-16.                                                                                         |

Source: Table 2.7, pp 54 – 55 of the submission.

6.4 The key features of the trials are summarised in Table 3 below. Both QUEST and DRI12544 studied a patient population of moderate-to-severe uncontrolled asthma vs placebo, which is different to the 'severe uncontrolled asthma' populations of the

comparator studies. Efficacy for dupilumab should not be compared to placebo in patients who have moderate uncontrolled asthma; the appropriate comparator for this population in the Australian setting would be optimised asthma therapy, which consists of increasing the doses of inhaled therapies, with the addition of OCS (unless contraindicated or not tolerated). A proportion of patients may gain control with these measures; it is only in patients whose asthma remained uncontrolled despite optimised asthma therapy where placebo was the appropriate comparator at the time the trials were designed – this is the population studied in the comparator trials.

Table 3: Key features of the included evidence in the indirect comparisons

| Trial                              | N                                                           | Design/<br>duration   | Risk of<br>bias <sup>e</sup> | Patient population                                                                                                                      | Outcome(s)                                                                                      |
|------------------------------------|-------------------------------------------------------------|-----------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Dupilumab versus placebo</b>    |                                                             |                       |                              |                                                                                                                                         |                                                                                                 |
| QUEST                              | 952                                                         | R, DB, MC<br>52 weeks | Low                          | Moderate-to-severe uncontrolled asthma with medium-to-high dose ICS plus up to two additional controllers                               | Annualised rate of severe exacerbation events, FEV <sub>1</sub> change from baseline at week 12 |
| DRI12544                           | 308                                                         | R, DB, MC<br>24 weeks | Low                          | Moderate-to-severe uncontrolled asthma                                                                                                  | FEV <sub>1</sub> change from baseline at Week 12, annualised asthma exacerbation rate           |
| VENTURE                            | 150                                                         | R, DB, MC<br>24 weeks | Low                          | Patients who had been receiving asthma treatment with regular OCS in the previous 6 months (5-35mg per day of prednisone or equivalent) | Percentage reduction in OCS dose at week 24, annualised severe exacerbation rates               |
| <b>Benralizumab versus placebo</b> |                                                             |                       |                              |                                                                                                                                         |                                                                                                 |
| CALIMA                             | Total trial: 1,306<br>Efficacy population: 728 <sup>a</sup> | R, DB, MC<br>56 weeks | Low                          | Total trial: Severe uncontrolled asthma<br>Efficacy population: EOS ≥ 300 cells/μL + high-dose ICS                                      | Annual asthma exacerbation rate, ACQ                                                            |
| SIROCCO                            | Total trial: 1,205<br>Efficacy population: 809 <sup>a</sup> | R, DB, MC<br>48 weeks | Low                          | Total trial: Severe uncontrolled asthma, on high-dose ICS<br>Efficacy population: EOS ≥ 300 cells/μL                                    | Annual asthma exacerbation rate, ACQ                                                            |
| ZONDA                              | Total trial: 220 patients<br>Efficacy population: 148       | R, DB, MC<br>28 weeks | Low                          | Total trial: Severe uncontrolled asthma on OCS<br>Efficacy population: Benralizumab Q8W                                                 | Percentage reduction in OCS dose, annualized severe asthma exacerbations <sup>d</sup>           |
| <b>Mepolizumab versus placebo</b>  |                                                             |                       |                              |                                                                                                                                         |                                                                                                 |
| MENSA                              | 576 <sup>a</sup>                                            | R, DB, MC<br>32 weeks | Low                          | Severe uncontrolled refractory asthma, on high-dose ICS<br>Efficacy population: EOS ≥ 150 cells/μL at screening                         | Annual asthma exacerbation rate, ACQ                                                            |
| MUSCA                              | 551                                                         | R, DB, MC<br>28 weeks | Low                          | Severe uncontrolled eosinophilic asthma                                                                                                 | Mean change from baseline SGRQ, annualised severe exacerbations                                 |
| SIRIUS                             | 135                                                         | R, DB, MC<br>32 weeks | Low                          | Severe uncontrolled eosinophilic asthma with OCS dependence                                                                             | Reduction in OCS dose, annualised severe exacerbations                                          |
| <b>Omalizumab versus placebo</b>   |                                                             |                       |                              |                                                                                                                                         |                                                                                                 |
| INNOVATE                           | 419 <sup>b</sup>                                            | R, DB, MC<br>28 weeks | Unclear <sup>c</sup>         | Severe persistent allergic asthma                                                                                                       | Exacerbation rate per 28 weeks, ACQ                                                             |
| EXTRA                              | 848                                                         | R, DB, MC<br>48 weeks | Low                          | Severe uncontrolled allergic asthma                                                                                                     | Exacerbation rate per 48 weeks, ACQ                                                             |

Source: Data extracted from Table 2.20, p 109; Table 2.26, pp 121 – 127; Table 2.8, pp 62 – 64 of the submission, and Table 3, p 9 of the benralizumab March 2018 public summary document.

ACQ = Asthma control questionnaire; DB = double blind; EOS = eosinophils; FEV<sub>1</sub> = forced expiratory volume in the first second; ICS = inhaled corticosteroids; MC = multi-centre; OCS = oral corticosteroids; OL = open label; Q8W = every 8 weeks; R = randomised; SGRQ = St. George's Respiratory Questionnaire.

<sup>a</sup> Includes patients in all arms of the trial. For CALIMA and SIROCCO, this includes the q4w arm. For MENSA, this includes the 75mg intravenous arm, which is not registered in Australia (the N for patients in the relevant arms was 385).



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<sup>b</sup> INNOVATE enrolled 482 patients, but only 419 were included in the primary intention-to-treat population, which comprised patients randomised after a protocol amendment that adjusted for differences in pre-treatment exacerbation history.

<sup>c</sup> INNOVATE was considered during evaluation to have an unclear risk of selection bias because the method of randomisation was not reported and primary outcome was adjusted post hoc to account for differences in pre-treatment exacerbation history.

<sup>d</sup> ZONDA was not powered to assess secondary endpoints related to asthma exacerbations.

<sup>e</sup> Although the risk of bias within each trial was considered low (except for INNOVATE), there was potential for bias in the indirect comparison, given issues with transitivity of the trials.

6.5 As there were no head-to-head RCTs comparing dupilumab (the intervention) with benralizumab, mepolizumab and omalizumab (the comparators), the submission performed an indirect treatment comparison (ITC) of the primary efficacy and safety outcomes. Six comparisons were performed, to assess multiple comparators across the four nominated subgroups of the target population, as shown in Table 4 below.

**Table 4: Approach used in the submission for indirect treatment comparisons**

| Submission subgroup                | Asthma endotype | OCS dependence | Asthma phenotype | Intervention     | Key Evidence    | Comparator   | Key Evidence            | ITC |
|------------------------------------|-----------------|----------------|------------------|------------------|-----------------|--------------|-------------------------|-----|
| <b>Dupixent (dupilumab) 200 mg</b> |                 |                |                  |                  |                 |              |                         |     |
| 1a                                 | Type 2 asthma   | ✗              | Eosinophilic     | Dupilumab 200 mg | QUEST DRI 12544 | Benralizumab | SIROCCO CALIMA          | 1   |
|                                    |                 |                |                  |                  |                 | Mepolizumab  | MUSCA MENSA DREAM*      | 2   |
| 1b                                 | Type 2 asthma   | ✗              | Allergic         | Dupilumab 200 mg | QUEST DRI 12544 | Omalizumab   | EXTRA (M1, M2) INNOVATE | 3   |
| <b>Dupixent (dupilumab) 300 mg</b> |                 |                |                  |                  |                 |              |                         |     |
| 2a                                 | Type 2 asthma   | ✓              | Eosinophilic     | Dupilumab 300 mg | VENTURE         | Benralizumab | ZONDA                   | 4   |
|                                    |                 |                |                  |                  |                 | Mepolizumab  | SIRIUS                  | 5   |
| 2b                                 | Type 2 asthma   | ✓              | Allergic         | Dupilumab 300 mg | VENTURE         | Omalizumab   | EXTRA (M3)              | 6   |

Source: Table 2.91, p 291 of the submission.

ITC = Indirect treatment comparison; OCS = oral corticosteroids

\* The DREAM study is a mepolizumab study using an IV dose of 75 mg per 4 weeks which is not registered in Australia. DREAM was not included in the mepolizumab or benralizumab public summary documents.

6.6 The submission performed three steps to arrive at the ITCs to justify its clinical claim:

- Step 1 presented a comparison of the data using intention-to-treat (ITT) populations for dupilumab and the PBAC recommended populations for the comparators. This method had substantial transitivity issues which introduced substantial variation in baseline characteristics for potential effect modifiers (e.g., blood EOS levels, asthma exacerbation history, use of medium- or high-dose ICS, and use of maintenance OCS), and was methodologically inappropriate.
- Step 2 presented a summary of the data using eosinophilic and allergic subgroups for dupilumab which were stratified to align with the PBS restrictions. This method also yielded substantial imbalances in baseline disease characteristics due to the broad eligibility criteria in the dupilumab studies, and were consequently not appropriately matched to generate a reliable comparison of data.

- Step 3 presented ITCs using dupilumab populations that aligned with the comparator populations. For this approach, subgroup data from the dupilumab trials were matched with subgroup data from the comparator trials, and Bucher pairwise ITCs were performed to reduce observed heterogeneity. The imbalances in prognostic characteristics were reduced from Steps 1 and 2 but the comparison in Step 3 still shows that background asthma severity was largely higher in the benralizumab and mepolizumab trials than in the dupilumab trials. The studies are therefore not transitive and the findings from the adjusted ITCs are therefore unlikely to accurately estimate the true effect of directly comparing dupilumab with its comparators – the gains from use of dupilumab will likely be over-estimated. The nominated non-inferiority margin was an annual exacerbation rate upper confidence interval of 1.28 (rate ratio), which was previously accepted by the PBAC (benralizumab public summary document (PSD), March 2018 PBAC meeting).
- 6.7 The key differences in trial and patient characteristics which might affect the transitivity assumption underpinning Step 3 ITCs are summarized in the table below.

**Table 5: Key differences that might influence the transitivity of the indirect comparisons**

|                                                                                          | Dupilumab                                                                                                                            | Comparator                                                                                 |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>ITC # 1: dupilumab vs. benralizumab in eosinophilic asthma without OCS dependence</b> |                                                                                                                                      |                                                                                            |
| Trials or relevant subgroups                                                             | QUEST (n=217)<br>DRI (n=74)                                                                                                          | SIROCCO (n=534)<br>CALIMA (n=583)                                                          |
| Mean ICS dose at baseline                                                                | QUEST: 788 vs 803 µg/day <sup>a</sup><br>DRI: NR <sup>c</sup>                                                                        | SIROCCO: 908 µg/day<br>CALIMA: 966 µg/day <sup>b</sup>                                     |
| Mean number of exacerbations in the previous year                                        | QUEST: 3.2 vs. 3.3 <sup>a</sup><br>DRI: 3.2 vs. 3.8 <sup>a</sup>                                                                     | SIROCCO: 3.0<br>CALIMA: 2.8 <sup>b</sup>                                                   |
| Concomitant treatment                                                                    | QUEST/DRI: transient increase in dose of ICS allowed in addition to reliever/rescue medication to treat acute symptoms of asthma     | On maintenance OCS:<br>SIROCCO: 17% of the ITT<br>CALIMA: 11% of the ITT                   |
| <b>ITC # 2: dupilumab vs. mepolizumab in eosinophilic asthma without OCS dependence</b>  |                                                                                                                                      |                                                                                            |
| Trials or relevant subgroups                                                             | QUEST (n=199)<br>DRI12544 (n=70)                                                                                                     | MENSA (n=576)<br>MUSCA (n=551)<br>DREAM (n=308)                                            |
| Geometric mean EOS level at baseline                                                     | QUEST: 400 vs. 404 cells/µL <sup>a</sup><br>DRI: 408 vs. 357 cells/µL <sup>a</sup>                                                   | MENSA: 305 cells/µL<br>MUSCA: 330 cells/µL<br>DREAM: 265 cells/µL                          |
| Concomitant treatment                                                                    | QUEST and DRI: transient increase in dose of ICS allowed in addition to reliever/rescue medication to treat acute symptoms of asthma | Taking baseline OCS:<br>MENSA: ~25% of the ITT<br>MUSCA: ~10% of the ITT                   |
| <b>ITC # 3: dupilumab vs. omalizumab in allergic asthma without OCS dependence</b>       |                                                                                                                                      |                                                                                            |
| Trials or relevant subgroups                                                             | QUEST (n=383)<br>DRI12544 (n=127)                                                                                                    | EXTRA (subgroups M1 and M2) (n=848)<br>INNOVATE (n=482)                                    |
| ICS/LABA dose at baseline, inclusion criteria                                            | Both trials: medium/high                                                                                                             | Both trials: high                                                                          |
| Mean ICS/LABA dose at baseline                                                           | QUEST: 719 v. 771 µg/day <sup>a</sup><br>DRI: NR <sup>c</sup>                                                                        | INNOVATE: 2,000 µg/day<br>EXTRA: NR                                                        |
| Mean IgE level at baseline                                                               | QUEST: 239 vs. 280 IU/mL <sup>a</sup><br>DRI: 268 vs. 277 IU/mL <sup>a</sup>                                                         | INNOVATE: 194 IU/mL<br>EXTRA: 177 IU/mL                                                    |
| Mean number of exacerbations in the previous year                                        | QUEST: 2.0 vs. 2.0 <sup>a</sup><br>DRI: 2.0 vs. 1.8 <sup>a</sup>                                                                     | INNOVATE: 2.5<br>EXTRA: 2.0                                                                |
| Concomitant treatment                                                                    | QUEST and DRI: transient increase in dose of ICS allowed in addition to reliever/rescue medication to treat acute symptoms of asthma | INNOVATE: 22% were taking baseline OCS.<br>EXTRA: No OCS were used in subgroups M1 and M2. |
| <b>ITC # 4: dupilumab vs. benralizumab in eosinophilic asthma with OCS dependence</b>    |                                                                                                                                      |                                                                                            |
| Trials or relevant subgroups                                                             | VENTURE (n=57)                                                                                                                       | ZONDA (n=148)                                                                              |
| Mean number of exacerbations in the previous year                                        | 2.53 vs. 2.70 <sup>a</sup>                                                                                                           | 3.1 vs. 2.5 <sup>a</sup>                                                                   |
| <b>ITC # 5: dupilumab vs. mepolizumab in eosinophilic asthma with OCS dependence</b>     |                                                                                                                                      |                                                                                            |
| Trials or relevant subgroups                                                             | VENTURE (n=132)                                                                                                                      | SIRIUS (n=135)                                                                             |
| Mean OCS dose pre-optimisation                                                           | 12.2 vs. 11.48 mg/day <sup>a</sup>                                                                                                   | 12.5 vs. 15.0 mg/day <sup>a</sup>                                                          |
| Mean number of exacerbations in the previous year                                        | 1.97 vs. 2.08 <sup>a</sup>                                                                                                           | 3.3 vs. 2.9 <sup>a</sup>                                                                   |
| <b>ITC # 6: dupilumab vs. omalizumab in allergic asthma with OCS dependence</b>          |                                                                                                                                      |                                                                                            |
| Trials or relevant subgroups                                                             | VENTURE (n=86)                                                                                                                       | EXTRA (M3 subgroup) (n=144)                                                                |
| OCS dose at baseline, inclusion criteria                                                 | 5-35 mg/day                                                                                                                          | 2-40 mg/day OR<br>5-80 mg every other day                                                  |
| Duration of treatment                                                                    | 24 wks                                                                                                                               | 48 wks                                                                                     |

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Source: Data extracted from Table 2.20, Table 2.25, of the submission, Table 10, Table 34, Table 44 in Attachment 7 ITC\_Final Report\_v7.1 Non-OCS Dependent Asthma Australia; Table 10, p23, Table 17, p32, Attachment 8 ITC\_Final Report\_v7.1 OCS-dependent Asthma Australia; Table 14, p 73 of the VENTURE CSR; Table 1, p 577 of Hanania et. al., 2011.

DRI = DRI12544; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; NR = not reported; ITT = intention-to-treat population; OCS = oral glucocorticoid; ppFEV1 = percent predicted forced expiratory volume in the first second

<sup>a</sup> Active treatment arm vs. placebo arm

<sup>b</sup> Relevant data not available for the medium ICS subgroup in CALIMA (n=96/583)

<sup>c</sup> 48% of the intention-to-treat population in DRI12544 took medium-dose ICS (defined as a minimum of 500µg/day)

- 6.8 The comparison of the relevant trial subpopulations was limited by the inadequate data provided by the submission, especially for trials subgroups included in #6 ITC. In addition, as placebo-based ITCs involving subgroups or trials do not preserve randomisation, the possibility of confounding from other unmeasured factors cannot be excluded. With the data available, there were major transitivity concerns, which was supported by the dissimilar event rates in the common comparator (placebo) arms across trials.
- 6.9 The ESC considered that treatment arms were not balanced in terms of prognostic factors and so the two populations in each ITC were not transitive. The dupilumab trials for non-OCS dependent asthma (QUEST and DRI12544) enrolled moderate-to-severe asthma, with medium-to-high dose ICS (nearly 50% of patients enrolled in both trials were on medium-dose ICS at baseline). This is a less severe form of asthma than studied in the comparator trials, and the target population.
- 6.10 Patients in QUEST and DRI12544 were allowed to receive a transient increase in dose of ICS in addition to reliever/rescue medication to treat acute symptoms of asthma, as per investigator's guidance. The ESC noted that this is not an option for patients on maximal ICS therapy, such as the target population, and considered this adds uncertainty to the applicability of the efficacy results.

### ***Comparative effectiveness***

- 6.11 Table 6 presents the annual asthma exacerbation rates for non-OCS dependent asthma. Table 7 presents the annual asthma exacerbation rates for OCS-dependent asthma. These comparisons correspond with the four population subgroups, defined as 1a, 1b, 2a, 2b, as described in Table 4 above. The benralizumab and mepolizumab trials had a higher rate of asthma exacerbations/year in the placebo groups, compared to the placebo groups in the dupilumab trials, despite having patients on higher doses of ICS and some patients on OCS; these patients likely had more severe disease. This metric alone may not accurately depict disease severity; if two patients have the same exacerbation rate, but one is on high-dose ICS and the other is on medium-dose ICS, then these patients do not suffer equivalent disease severity.

**Table 6: Asthma exacerbations – submission subgroups 1a and 1b; dupilumab 200 mg (ITT population) and comparators**

| Trial                                       | Dupilumab 200 mg Q2W    |                         | Placebo                 | Comparator              |                      |
|---------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|----------------------|
|                                             | RR (95%CI)              | Rate (exacerbations/yr) | Rate (exacerbations/yr) | Rate (exacerbations/yr) | RR (95%CI)           |
| <b>Dupilumab trials</b>                     |                         |                         |                         |                         |                      |
| QUEST (n =952; 631+321) ITT population      | 0.523<br>(0.413, 0.662) | 0.46<br>(0.39, 0.53)    | 0.87<br>(0.72, 1.05)    | -                       | -                    |
| DRI12544 (n= 308; 150 + 158) ITT population | 0.300<br>(0.159, 0.565) | 0.269<br>(0.157, 0.461) | 0.897<br>(0.619, 1.300) | -                       | -                    |
| <b>Benralizumab trials</b>                  |                         |                         |                         |                         |                      |
| SIROCCO (n = 534) efficacy population       | -                       | -                       | 1.33<br>(1.12, 1.58)    | 0.65<br>(0.53, 0.80)    | 0.49<br>(0.37, 0.64) |
| CALIMA (n = 487) efficacy population        | -                       | -                       | 0.93<br>(0.77, 1.12)    | 0.66<br>(0.54, 0.82)    | 0.72<br>(0.54, 0.95) |
| <b>Mepolizumab trials</b>                   |                         |                         |                         |                         |                      |
| MENSA (n = 385)                             | -                       | -                       | 1.74                    | 0.83                    | 0.47<br>(0.35, 0.64) |
| MUSCA (n = 551)                             | -                       | -                       | 1.21                    | 0.51                    | 0.42<br>(0.31, 0.56) |
| <b>Omalizumab trials</b>                    |                         |                         |                         |                         |                      |
| EXTRA M1, M2 (n = 704)                      | -                       | -                       | 0.88 per 48 weeks*      | 0.66 <sup>a</sup>       | 0.70<br>(0.55, 0.89) |
| INNOVATE (n = 419)                          | -                       | -                       | 0.91 per 28 weeks       | 0.68 <sup>a</sup>       | 0.74<br>(0.61, 0.92) |

Source: Table 2.92 of the submission.

CI = confidence interval; ITT = intention-to-treat; Q2W = every 2 weeks; RR = rate ratio.

\* This is the reported figure for subgroups M1, M2 and M3. M1 (n=310) included patients on inhaled corticosteroid (ICS) plus long-acting beta agonists (LABAs) alone; M2 (n=394) included patients on ICS plus LABAs plus 1 or more additional controller medications excluding oral corticosteroid (OCS); M3 (n=144) included patients on ICS plus LABAs plus OCS.

<sup>a</sup> Exacerbation rates were not annualised in EXTRA (48 weeks) and INNOVATE (28 weeks).**Table 7: Asthma exacerbations – submission subgroups 2a and 2b; dupilumab 300 mg (ITT population) and comparators**

| Trial                           | Dupilumab 300 mg Q2W    |                         | Placebo                 | Comparator              |                      |
|---------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|----------------------|
|                                 | RR (95%CI)              | Rate (exacerbations/yr) | Rate (exacerbations/yr) | Rate (exacerbations/yr) | RR (95%CI)           |
| <b>Dupilumab</b>                |                         |                         |                         |                         |                      |
| VENTURE (n= 210)                | 0.407<br>(0.263, 0.630) | 0.649<br>(0.442, 0.955) | 1.597<br>(1.248, 2.043) | -                       | -                    |
| <b>Benralizumab</b>             |                         |                         |                         |                         |                      |
| ZONDA (n = 148)                 | -                       | -                       | 1.83                    | 0.54                    | 0.30<br>(0.17, 0.53) |
| <b>Mepolizumab</b>              |                         |                         |                         |                         |                      |
| SIRIUS (n = 135)                | -                       | -                       | 2.12                    | 1.44                    | 0.68<br>(0.47, 0.99) |
| <b>Omalizumab</b>               |                         |                         |                         |                         |                      |
| EXTRA M3 <sup>a</sup> (n = 144) | -                       | -                       | NR                      | NR                      | 0.95<br>(0.63, 1.43) |

Source: Table 2.93, p 295 of the submission.

CI = confidence interval; ITT = intention-to-treat; NR = not reported; Q2W = every 2 weeks; RR = rate ratio.

<sup>a</sup> The M3 subgroup was not statistically powered to assess efficacy.

6.12 A summary of the base case Step 3 ITCs, which form the basis of the therapeutic conclusion and clinical claim, is provided in Table 8 below. The submission determined

that the patient populations included in the Step 3 ITC analyses were, overall, generally similar to the comparator trials after matching. This does not appear to be the case when comparing disease-modifying baseline characteristics of the selected dupilumab and comparator populations; all six comparisons were found to be non-transitive, as described in Table 5 above.

**Table 8: Results of the base case ITCs from Step 3**

| Analysis                        | Comparison                                      | RR (95% CI)       |
|---------------------------------|-------------------------------------------------|-------------------|
| <b>non-OCS dependent asthma</b> |                                                 |                   |
| 1                               | DUPI 200 mg vs. BENRA Q8W                       | 0.46 (0.32, 0.66) |
| 2 <sup>a</sup>                  | DUPI 200 mg vs. MEPO 75 mg-100 mg               | 0.68 (0.50, 0.93) |
| 3                               | DUPI 200 mg vs. OMA IgE 30-700 (no EOS cut-off) | 0.76 (0.35, 1.68) |
| <b>OCS dependent asthma</b>     |                                                 |                   |
| 4                               | DUPI 300 mg vs. BENRA Q8W                       | 0.86 (0.35, 2.13) |
| 5                               | DUPI 300 mg vs. MEPO 100 mg                     | 0.67 (0.36, 1.28) |
| 6 <sup>b</sup>                  | DUPI 300 mg vs. OMA                             | 0.29 (0.13, 0.68) |

Source: Table 2.107 of the submission.

BENRA = benralizumab; CI = confidence interval; DUPI = dupilumab; EOS = eosinophils; MEPO = mepolizumab; OCS = oral corticosteroids; OMA = omalizumab; Q8W = every eight weeks; RR = rate ratio.

<sup>a</sup> A sensitivity analysis which excluded patients treated with intravenous omalizumab increased the rate ratio to 0.75 (95% CI 0.53, 1.05)

<sup>b</sup> DUPI vs OMA for OCS dependent asthma was subject to substantial transitivity issues, with the omalizumab subgroup data not powered to assess efficacy. This result must be interpreted with additional caution.

- 6.13 The non-inferiority margin was met in ITC #1 and #2. In these comparisons, patients who had  $\geq 2$  severe exacerbations in the previous year were selected for comparison. This meant the populations were no longer representative of the target Australian population, which includes those with  $\geq 1$  severe exacerbations in the previous year. By excluding patients with 1 severe exacerbation in the previous year, the largest subgroup from QUEST (n=490, 52% of the 200 mg study population) was precluded from analyses. This subgroup also failed to demonstrate a significant improvement in exacerbations for dupilumab vs placebo (RR 0.771; 95%CI 0.525, 1.134), which generated an interaction effect (prior exacerbations: 1 vs.  $>1$ ), nominal p = 0.0114.
- 6.14 ITC #1 suggested dupilumab is non-inferior to benralizumab in patients with baseline blood eosinophils  $\geq 300$  cells/ $\mu$ L, based on the comparison of dupilumab data from QUEST (n=217), DRI12544 (n=64) and benralizumab data from SIROCCO (n=334) and CALIMA (n=583). For this comparison, patients receiving both medium- and high-dose ICS were included in the two dupilumab trials; the target Australian population would be on high-dose ICS only. The median ICS dose was lower in the dupilumab trial QUEST (~800 $\mu$ g/day) and not reported in DRI12544 (48% of the ITT population were taking medium-dose ICS at time of enrolment, defined as a minimum of 500 $\mu$ g/day), compared to the benralizumab trials SIROCCO and CALIMA (908 $\mu$ g/day and 966 $\mu$ g/day respectively). Patients in QUEST and DRI12544 were allowed to receive a transient increase in dose of ICS in addition to reliever/rescue medication to treat acute symptoms of asthma, as per investigator's guidance (it was unclear how often this occurred, and whether it occurred equally in treatment and placebo groups). Further, of the ITT populations, 17% from SIROCCO and 11% from CALIMA were on maintenance OCS. These imbalances suggest the dupilumab patients had less severe disease than the benralizumab patients at baseline. The PSCR argued that no

treatment-by-subgroup interaction was observed with a consistent reduction in the rate of severe asthma exacerbations with dupilumab versus placebo observed across both baseline ICS dose categories. The ESC considered that this may be the case for the ITT population, but the ITC was conducted on a small subset of patients from QUEST (217/1887 = 11.5%) and DRI12544 (64/325 = 19.7%).

- 6.15 ITC #2 suggested dupilumab is non-inferior to mepolizumab, based on the comparison of dupilumab data from QUEST (n=199), DRI12544 (n=70) and mepolizumab data from MENSA (n=576), MUSCA (n=551) and DREAM (n=308). For this comparison, the baseline EOS level for inclusion was  $\geq 150$  cells/ $\mu\text{L}$ , which is not consistent with the PBS requirement of  $\geq 300$  cells/ $\mu\text{L}$  in the previous year. In MENSA and MUSCA, all enrolled patients had EOS  $\geq 150$  cells/ $\mu\text{L}$  at enrolment or  $\geq 300$  cells/ $\mu\text{L}$  in the previous 12 months. The mean EOS levels were generally higher in the dupilumab trials ( $\sim 400$  cells/ $\mu\text{L}$ ) compared to the mepolizumab trials ( $\sim 300$  cells/ $\mu\text{L}$ ); as dupilumab and mepolizumab appear more efficacious in patients with higher EOS levels, this difference may over-represent the apparent efficacy of dupilumab. The ITC used data from intravenous (IV) mepolizumab 75 mg (the DREAM trial), a formulation not available in Australia. Data from MENSA suggested the IV dose is inferior to the SC dose at reducing serious exacerbations<sup>8</sup>, making its inclusion inappropriate; a sensitivity analysis excluding IV groups was performed, which yielded an ITC RR 0.75 (95% CI 0.53, 1.05). Finally, of the ITT populations, approximately 25% of the MENSA patients and around 10% of MUSCA patients were taking baseline OCS, suggesting they had a more severe form of asthma compared to the dupilumab patients.
- 6.16 ITC #3 showed dupilumab failed to meet the non-inferiority margin versus omalizumab, based on the comparison of dupilumab data from QUEST (n=383), DRI12544 (n=127) and omalizumab data from INNOVATE (N=419) and EXTRA (N=848) with a baseline immunoglobulin E (IgE) of 30-700 IU/mL. This result was produced when the dupilumab group had lower mean baseline ICS dose in QUEST (719 $\mu\text{g/day}$ ) than the omalizumab groups in INNOVATE and EXTRA (2,000 $\mu\text{g/day}$  and 1169 $\mu\text{g/day}$  respectively). Baseline ICS doses were not provided for dupilumab patients from DRI12544 (48% of the ITT population were taking medium-dose ICS at time of enrolment, defined as a minimum of 500 $\mu\text{g/day}$ ). In addition, patients in QUEST had a lower mean baseline exacerbation rate in the previous year compared to patients in INNOVATE (2.0 vs 2.5 respectively). These imbalances suggest the dupilumab patients may have had less severe disease than the omalizumab patients at baseline. The submission speculated that a lack of statistical power and low patient numbers were responsible for the failure to meet the pre-specified non-inferiority margin, as the selected subgroup of the dupilumab ITT populations made up only 40% (510/1260) of the study patients. This is an unlikely explanation, as ITC #3 had the highest number of dupilumab patients out of all the ITCs performed in Step 3. The PSCR acknowledged that the upper confidence interval for ITC #3 exceeded the nominated MCID of 28%

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<sup>8</sup> Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma [published correction appears in *N Engl J Med*. 2015 Apr 30;372(18):1777]. *N Engl J Med*. 2014;371(13):1198-1207

but argued that it is more accurate to say that the non-inferiority conclusion is uncertain with the point estimate favouring dupilumab. In addition, the PSCR argued that when making its decision to recommend benralizumab in March 2018 the PBAC considered a similar ITC to ITC #3 where benralizumab did not meet the nominated MCID vs. the main comparator mepolizumab (RR 1.25 [0.78, 2.02]) (Table 6, benralizumab PSD, March 2018 PBAC meeting).

- 6.17 ITC #4 showed dupilumab failed to meet the non-inferiority margin with benralizumab, based on the comparison of dupilumab data from VENTURE (n=57) and benralizumab data from ZONDA (n=148), with 24 and 28 weeks of follow-up respectively. The dupilumab patient cohort had fewer baseline exacerbations in the prior year compared to the benralizumab group (2.53 vs 3.1), suggesting the benralizumab patients had more severe disease at baseline. Overall, the low numbers and short follow-up make it difficult to meaningfully interpret these results.
- 6.18 ITC #5 showed dupilumab achieved borderline non-inferiority with mepolizumab, based on the comparison of dupilumab data from VENTURE (n=132) and mepolizumab data from SIRIUS (n=135), with only 24 weeks of follow-up for each group. Patients in the dupilumab arm of VENTURE had a lower mean baseline exacerbation rate in the previous year compared to patients in the mepolizumab arm of SIRIUS (1.97 vs 3.3 respectively), and the placebo arm of VENTURE had both a lower baseline daily OCS dose compared to the placebo arm of SIRIUS (11.48 vs 15 respectively) and fewer exacerbations in the last year (2.08 vs 2.9). These imbalances suggest patients in SIRIUS suffered a more severe form of asthma compared to VENTURE, which adds uncertainty to the borderline non-inferiority finding.
- 6.19 ITC #6 could not be performed with the same framework as the other 5 ITCs, due to the absence of a dedicated phase 3 study in OCS-dependent patients taking omalizumab. As such, dupilumab data from VENTURE (dupilumab) and omalizumab data from EXTRA (M3 subgroup) cohorts were compared, which suggested dupilumab was non-inferior to omalizumab. This comparison is based on incomplete and imbalanced data. The M3 group of EXTRA (n=144) comprised 60 patients who had received daily or alternate-day OCS at baseline, and 84 patients who had  $\geq 4$  asthma exacerbations during the previous year requiring treatment with OCS. As such, the majority of this group had a high number of previous exacerbations. The result incorporated substantial transitivity issues, and is highly uncertain; these trials used different inclusion criteria, and a lot of the baseline characteristics for these subgroups were unknown. In addition, the M3 subgroup was not statistically powered to assess efficacy. The PSCR acknowledged that the lack of omalizumab evidence in this population introduced uncertainty into the results of ITC #6. However, the PSCR argued that patients with severe uncontrolled allergic asthma with OCS-dependence continue have a significant unmet need with only one reimbursed treatment option currently available.
- 6.20 The PSCR argued that overall the evaluation suggested that patients in the dupilumab studies may have had less severe disease than patients in the comparator studies and



the evaluation indicated that this ultimately favoured dupilumab. The PSCR stated that this conclusion is inconsistent with previous evaluations and PBAC recommendations for severe asthma biologics which suggest that for ITCs the treatment arm with more severe disease is likely favoured (paragraphs 6.20 and 6.26, benralizumab PSD, March 2018 PBAC meeting). The ESC considered that an important difference was that patients with moderate asthma in the QUEST and DRI12544 trials could transiently increase the dose of their ICS to manage exacerbations. As such, the ESC considered that the impact on the efficacy of dupilumab observed in the QUEST and DRI12544 trials is unknown as the submission did not provide information on how frequently a transient increase of ICS dose occurred during the study period or whether it occurred equally in the treatment and placebo arms. The ESC disagreed with the PSCR that the evaluation's conclusion is inconsistent with the PBACs March 2018 recommendations for benralizumab. The ESC noted that the disease severity of patients included in the trials considered as part of the March 2018 evaluation of benralizumab was confined to patients with severe asthma who had already maximised their inhaled asthma therapies. The ESC considered this is distinct from the 'moderate severity' patients in QUEST and DRI12544, who had not achieved 'optimised asthma therapy'.

- 6.21 The pre-PBAC response acknowledged that for the non-OCS dependent ITCs both the evaluator and the ESC raised concerns regarding the inclusion of medium-dose ICS patients, patients with lower blood EOS and the exclusion of patients who experienced one severe exacerbation in the previous year. To address these concerns the pre-PBAC response provided two supplementary ITCs:

- ITC 1a: Non-OCS dependence: dupilumab vs. benralizumab (high-dose ICS, EOS  $\geq 300$  cells/ $\mu$ L, 1+ exacerbations).
- ITC 2a: Non-OCS dependence: dupilumab vs mepolizumab (high-dose ICS, EOS  $\geq 300$  cells/ $\mu$ L, 1+ exacerbations).

The results of ITC 1a and ITC 2a are presented in Table 9. The pre-PBAC response argued that the results from ITC 1a show a favourable point estimate for dupilumab versus benralizumab in the Australian PBS population with an upper 95% CI that is below the nominated MCID of 28%. The pre-PBAC response argued that the point estimate for ITC 2a is approximately 1, indicating non-inferiority of dupilumab vs. mepolizumab in this population. The pre-PBAC response noted that ITC in the submission included 1,704 patients across the treatment arms compared with only 586 in ITC 2a and that the upper 95% CI exceeded the nominated MCID of 28%. However, the pre-PBAC response argued that the results of submission ITCs 1, 2, 4 and 5 and supplementary ITC 1a show that dupilumab is an effective treatment for eosinophilic asthma regardless of background therapy with OCS. Further, the pre-PBAC response argued that the upper 95% CI of ITC 2a (2.097) is similar to the upper 95% CI previously accepted by the PBAC for benralizumab at the March 2018 PBAC

meeting (RR 1.25 [0.78, 2.02]), noting the point estimate is much closer to 1.0 (Table 6, benralizumab PSD, March 2018 PBAC meeting).

- 6.22 The pre-PBAC response stated that it was not possible to conduct an additional ITC versus omalizumab in high-dose ICS allergic asthma patients with 1+ exacerbations in the previous year due to a lack of clinical data availability in the populations for which omalizumab is currently PBS reimbursed. However, the pre-PBAC response reiterated that the submission had also included an allergic asthma sensitivity analysis ITC (ITC 3a) which, like the current PBS initiation criteria, did not have an upper limit of IgE (Table 9), unlike the base case ITC 3 which mirrored the upper limit in the omalizumab clinical trial setting of  $\geq 700$  IU/mL. The pre-PBAC response argued that in ITC 3a dupilumab was found to be non-inferior to omalizumab using the nominated 28% MCID.

**Table 9: Results of ITC 1a, ITC 2a and ITC 3a**

| Analysis                        | Comparison (n)                         | RR (95% CI)       |
|---------------------------------|----------------------------------------|-------------------|
| <b>non-OCS dependent asthma</b> |                                        |                   |
| 1a <sup>a</sup>                 | DUPI 200 mg vs. BENRA Q8W              | 0.71 (0.41, 1.23) |
| 2a <sup>b</sup>                 | DUPI 200 mg vs. MEPO 75 mg-100 mg      | 1.08 (0.55, 2.10) |
| 3a                              | DUPI 200 mg vs. OMA no IgE upper limit | 0.80 (0.61, 1.05) |

Source: Table 3, Table 5 of the pre-PBAC response.

BENRA = benralizumab; CI = confidence interval; DUPI = dupilumab; MEPO = mepolizumab; OCS = oral corticosteroids; OMA = omalizumab; Q8W = every eight weeks; RR = rate ratio.

<sup>a</sup> A subgroup analysis of the QUEST and DRI12544 trial patients who were treated with high-dose ICS at baseline, had EOS  $\geq 300$  cells/ $\mu$ L and experienced  $\geq 1$  severe exacerbations in the previous year were identified and compared via an ITC with the Q8W "primary efficacy population" presented in the March 2018 benralizumab PSD (Table 4).

<sup>b</sup> The same subgroup analysis of the QUEST and DRI12544 trial patients from ITC 1a were compared via an ITC with the  $\geq 300$  cells/ $\mu$ L subgroup of the mepolizumab clinical trial Study 588 (MENSA) detailed in Table 5 of the March 2016 mepolizumab PSD.

## Comparative harms

- 6.23 Dupilumab was generally well tolerated, with no strong signals regarding treatment-emergent adverse events identified, as summarised in Table 10 and Table 11 below. The most common adverse events were viral upper respiratory tract infections, bronchitis, injection site erythema and headache. More patients had a treatment-emergent adverse event leading to permanent discontinuation in the 300 mg Q2W cohort compared to the 200 mg cohort in QUEST (7% vs 3% respectively). The incidence of treatment-emergent adverse events leading to death was very low across the three dupilumab trials, with no deaths considered related to the study drug.

**Table 10: Overview of adverse event profile of Dupilumab in non-OCS dependent patients; Treatment-emergent adverse events and deaths (any cause) - safety population**

| n (%)                                                                 | QUEST             |                    |                    |                    | DRI12544         |                          |                          |
|-----------------------------------------------------------------------|-------------------|--------------------|--------------------|--------------------|------------------|--------------------------|--------------------------|
|                                                                       | 200 mg Q2W        |                    | 300 mg Q2W         |                    | Placebo<br>N=158 | Q2W                      |                          |
|                                                                       | Placebo<br>N=313  | Dupilumab<br>N=631 | Placebo<br>N=321   | Dupilumab<br>N=632 |                  | Dupilumab<br>200mg N=148 | Dupilumab<br>300mg N=156 |
| Patients with any TEAE                                                | 257 (82.1%)       | 508 (80.5%)        | 270 (84.1%)        | 515 (81.5%)        | 118 (74.7%)      | 119 (80.4%)              | 121 (77.6%)              |
| RR (95% CI)                                                           | 0.98 (0.92, 1.05) |                    | 0.97 (0.91, 1.03)  |                    | -                | 1.08 (0.95, 1.21)        | 1.04 (0.92, 1.18)        |
| Patients with any treatment emergent SAE                              | 26 (8.3%)         | 49 (7.8%)          | 27 (8.4%)          | 55 (8.7%)          | 9 (5.7%)         | 10 (6.8%)                | 13 (8.3%)                |
| RR (95% CI)                                                           | 0.93 (0.59, 1.47) |                    | 1.03 (0.67, 1.61)  |                    | -                | 1.19 (0.50, 2.84)        | 1.46 (0.64, 3.32)        |
| Patients with any TEAE leading to permanent treatment discontinuation | 19 (6.1 %)        | 19 (3.0%)          | 10 (3.1%)          | 44 (7.0%)          | 5 (3.2 %)        | 6 (4.1%)                 | 4 (2.6%)                 |
| RR (95% CI)                                                           | 0.50 (0.27, 0.92) |                    | 2.23 (1.14, 4.38)  |                    | -                | 1.28 (0.40, 4.11)        | 0.81 (0.22, 2.96)        |
| Patients with any TEAE leading to death                               | 3 (1%)            | 1 (0.2%)           | 0                  | 4 (0.6%)           | 0                | 0                        | 0                        |
| RR (95% CI)                                                           | 0.17 (0.02, 1.58) |                    | 4.06 (0.22, 76.62) |                    | -                | -                        | -                        |

Source: Data extracted from Table 2.75 of the submission. Risk ratios calculated during the evaluation.

CI = confidence interval; OCS = oral corticosteroids; RR = risk ratio; TEAE = treatment-emergent adverse event; SAE = serious adverse event

Note: n (%) = number and percentage of patients with at least one TEAE

**Table 11: Overview of adverse event profile of Dupilumab in OCS-dependent patients; Treatment-emergent adverse events and deaths (any cause) - safety population**

| n (%)                                                                 | VENTURE          |                              | RR (95% CI)       |
|-----------------------------------------------------------------------|------------------|------------------------------|-------------------|
|                                                                       | Placebo<br>N=107 | Dupilumab 300mg Q2W<br>N=103 |                   |
| Patients with any TEAE                                                | 69 (64.5 %)      | 64 (62.1%)                   | 0.96 (0.78, 1.18) |
| Patients with any treatment emergent SAE                              | 6 (5.6%)         | 9 (8.7%)                     | 1.56 (0.57, 4.22) |
| Patients with any TEAE leading to permanent treatment discontinuation | 4 (3.7%)         | 1 (1.0%)                     | 0.26 (0.03, 2.29) |
| Patients with any TEAE leading to death                               | 0                | 0                            | -                 |

Source: Table 2.75 of the submission.

CI = confidence interval; OCS = oral corticosteroids; TEAE = treatment-emergent adverse event; SAE = serious adverse event

Note: n (%) = number and percentage of patients with at least one TEAE

- 6.24 The submission noted that omalizumab must be monitored for anaphylaxis; that is not the case with dupilumab, which recorded one case of anaphylaxis in its asthma trials.
- 6.25 The submission performed ITCs of dupilumab versus comparators for any adverse events, serious adverse events and adverse events leading to treatment withdrawal. The submission concluded that no statistically significant differences between dupilumab and the three comparators were identified. ITC risk ratio point estimates, and the majority of the 95% confidence intervals, were >1 for serious adverse events (dupilumab vs all comparators) and discontinuation due to adverse events (dupilumab vs mepolizumab). This suggests a trend of inferior safety of dupilumab for these outcomes, and the upper limits of the confidence intervals represent clinically

meaningful differences. These data are provided in Table 12, with key data presented in the forest plot Figure 1 below.

**Table 12: ITCs performed for AEs, SAEs and withdrawal due to AE, dupilumab vs comparators**

|                                  | Dupilumab            |     |                      |     |                      |     | Benralizumab                        |     |                       |     |                      |     | Mepolizumab                        |     |                      |     |                      |     | Omalizumab                        |     |                      |     |
|----------------------------------|----------------------|-----|----------------------|-----|----------------------|-----|-------------------------------------|-----|-----------------------|-----|----------------------|-----|------------------------------------|-----|----------------------|-----|----------------------|-----|-----------------------------------|-----|----------------------|-----|
|                                  | QUEST                |     | DRI                  |     | VENTURE              |     | SIROCCO                             |     | CALIMA                |     | ZONDA                |     | MENSA                              |     | MUSCA                |     | SIRIUS               |     | EXTRA                             |     | INNOVATE             |     |
|                                  | DUPI                 | PBO | DUPI                 | PBO | DUPI                 | PBO | BENRA                               | PBO | BENRA                 | PBO | BENRA                | PBO | MEPO                               | PBO | MEPO                 | PBO | MEPO                 | PBO | OMA                               | PBO | OMA                  | PBO |
| Study N                          | 1263                 | 634 | 304                  | 158 | 103                  | 107 | 265                                 | 267 | 230                   | 248 | 73                   | 75  | 194                                | 191 | 273                  | 278 | 69                   | 66  | 428                               | 420 | 245                  | 237 |
| Any Adverse Event                |                      |     |                      |     |                      |     |                                     |     |                       |     |                      |     |                                    |     |                      |     |                      |     |                                   |     |                      |     |
| n                                | 1,023                | 527 | 240                  | 118 | 64                   | 69  | 185                                 | 203 | 181                   | 188 | 55                   | 62  | 152                                | 158 | 192                  | 207 | 57                   | 61  | 344                               | 334 | 177                  | 179 |
| %                                | 81%                  | 83% | 79%                  | 75% | 62%                  | 64% | 70%                                 | 76% | 79%                   | 76% | 75%                  | 83% | 78%                                | 83% | 70%                  | 74% | 83%                  | 92% | 80%                               | 80% | 72%                  | 76% |
| RR (95%CI) <sup>a</sup>          | 0.97<br>(0.93, 1.02) |     | 1.06<br>(0.95, 1.18) |     | 0.96<br>(0.78, 1.18) |     | 0.92<br>(0.83, 1.02)                |     | 1.04<br>(0.94, 1.14)  |     | 0.91<br>(0.77, 1.08) |     | 0.95<br>(0.86, 1.05)               |     | 0.94<br>(0.85, 1.05) |     | 0.89<br>(0.79, 1.02) |     | 1.01<br>(0.94, 1.08)              |     | 0.96<br>(0.86, 1.06) |     |
| Pooled RR (95%CI) <sup>a,c</sup> | 0.99 (0.95, 1.03)    |     |                      |     |                      |     | 0.96 (0.88, 1.05)                   |     |                       |     |                      |     | 0.93 (0.88, 0.99)                  |     |                      |     |                      |     | 0.99 (0.94, 1.05)                 |     |                      |     |
| ITC RR (95%CI) <sup>b</sup>      | -                    |     |                      |     |                      |     | DUPI vs BENRA: 1.031 (0.936, 1.136) |     |                       |     |                      |     | DUPI vs MEPO: 1.065 (0.991, 1.143) |     |                      |     |                      |     | DUPI vs OMA: 1.000 (0.934, 1.071) |     |                      |     |
| Serious Adverse Events           |                      |     |                      |     |                      |     |                                     |     |                       |     |                      |     |                                    |     |                      |     |                      |     |                                   |     |                      |     |
| n                                | 104                  | 53  | 23                   | 9   | 9                    | 6   | 33                                  | 36  | 25                    | 34  | 7                    | 14  | 16                                 | 27  | 15                   | 22  | 1                    | 12  | 40                                | 44  | 29                   | 37  |
| %                                | 8%                   | 8%  | 8%                   | 6%  | 9%                   | 6%  | 12%                                 | 13% | 11%                   | 14% | 10%                  | 19% | 8%                                 | 14% | 5%                   | 8%  | 1%                   | 18% | 9%                                | 10% | 12%                  | 16% |
| RR (95%CI) <sup>a</sup>          | 0.99<br>(0.72, 1.35) |     | 1.33<br>(0.63, 2.8)  |     | 1.56<br>(0.58, 4.22) |     | 0.92<br>(0.59, 1.44)                |     | 0.79<br>(0.49, 1.29)  |     | 0.51<br>(0.22, 1.2)  |     | 0.58<br>(0.32, 1.05)               |     | 0.69<br>(0.37, 1.31) |     | 0.08<br>(0.01, 0.6)  |     | 0.89<br>(0.59, 1.34)              |     | 0.76<br>(0.48, 1.19) |     |
| Pooled RR (95%CI) <sup>a</sup>   | 1.07 (0.81, 1.41)    |     |                      |     |                      |     | 0.81 (0.59, 1.09)                   |     |                       |     |                      |     | 0.51 (0.25, 1.04)                  |     |                      |     |                      |     | 0.83 (0.61, 1.12)                 |     |                      |     |
| ITC RR (95%CI) <sup>b</sup>      | -                    |     |                      |     |                      |     | DUPI vs BENRA: 1.321 (0.874, 1.998) |     |                       |     |                      |     | DUPI vs MEPO: 2.098 (0.977, 4.508) |     |                      |     |                      |     | DUPI vs OMA: 1.289 (0.854, 1.945) |     |                      |     |
| Withdrawal due to Adverse Event  |                      |     |                      |     |                      |     |                                     |     |                       |     |                      |     |                                    |     |                      |     |                      |     |                                   |     |                      |     |
| n                                | 63                   | 29  | 10                   | 5   | 1                    | 4   | 6                                   | 2   | 6                     | 1   | 3                    | 2   | 1                                  | 4   | 2                    | 3   | 3                    | 3   | 16                                | 10  | 11                   | 4   |
| %                                | 5%                   | 5%  | 3%                   | 3%  | 1%                   | 4%  | 2%                                  | 1%  | 3%                    | 0%  | 4%                   | 3%  | 1%                                 | 2%  | 1%                   | 1%  | 4%                   | 5%  | 4%                                | 2%  | 4%                   | 2%  |
| RR (95%CI) <sup>a</sup>          | 1.09<br>(0.71, 1.68) |     | 1.04<br>(0.36, 2.99) |     | 0.26<br>(0.03, 2.28) |     | 3.02<br>(0.62, 14.84)               |     | 6.47<br>(0.78, 53.33) |     | 1.54<br>(0.27, 0.03) |     | 0.25<br>(0.03, 2.18)               |     | 0.68<br>(0.11, 4.03) |     | 0.96<br>(0.2, 4.57)  |     | 1.57<br>(0.72, 3.42)              |     | 2.66<br>(0.86, 8.24) |     |
| Pooled RR (95%CI) <sup>a</sup>   | 1.03 (0.7, 1.53)     |     |                      |     |                      |     | 2.88 (1.03, 8.06)                   |     |                       |     |                      |     | 0.63 (0.22, 1.77)                  |     |                      |     |                      |     | 1.86(0.98, 3.53)                  |     |                      |     |
| ITC RR (95%CI) <sup>b</sup>      | -                    |     |                      |     |                      |     | DUPI vs BENRA: 0.358 (0.119, 1.075) |     |                       |     |                      |     | DUPI vs MEPO: 1.635 (0.537, 4.978) |     |                      |     |                      |     | DUPI vs OMA: 0.554 (0.261, 1.173) |     |                      |     |

Source: Data extracted from Table 2.108 of the submission.

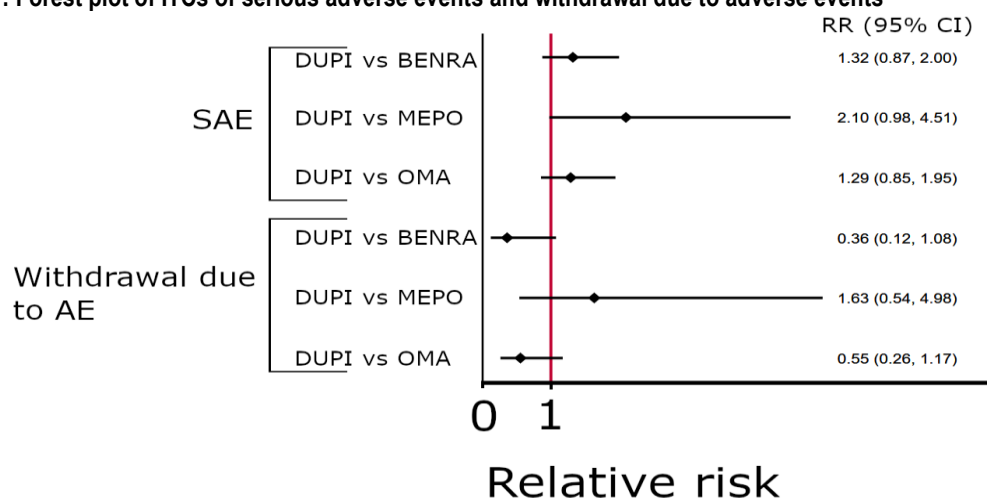
AE = adverse event; CI = confidence interval; DUPI = dupilumab; BENRA = benralizumab; MEPO = mepolizumab; ITC = indirect treatment comparison; OMA = omalizumab; PBO = placebo; RR = risk ratio; SAE = serious adverse event.

<sup>a</sup> A RR <1 favours active, a RR >1 favours placebo

<sup>b</sup> A RR <1 favours dupilumab, a RR >1 favours comparator

<sup>c</sup> Meta-analysis conducted in Review Manager 5.3, random effects, Mantel-Haenszel

**Figure 1: Forest plot of ITCs of serious adverse events and withdrawal due to adverse events**



Source: Forest plot generated during the evaluation in STATA 15.1, using unmodified data from Table 2.108 of the submission.

CI = confidence interval; DUPI = dupilumab; BENRA = benralizumab; MEPO = mepolizumab; ITC = indirect treatment comparison; OMA = omalizumab; AE = adverse event; RR = risk ratio; SAE = serious adverse event.

Note: A RR < 1 favours dupilumab, a RR > 1 favours comparator.

### **Clinical claim**

- 6.26 The clinical claim presented by the submission was that dupilumab treatment for patients aged  $\geq 12$  years with uncontrolled severe type 2 asthma was non-inferior in terms of efficacy and safety compared with omalizumab, mepolizumab and benralizumab. The submission presented six ITCs which indirectly compared the efficacy of dupilumab with the three comparators, in both OCS-dependent and non-OCS dependent asthma patients. This formed the evidence base used by the submission to support this claim.
- 6.27 To reduce the observed heterogeneity between trials, six Bucher pairwise ITCs were performed on matched subgroup data. About 50% of the study populations in the dupilumab trials QUEST and DRI12544 were taking medium-dose ICS at baseline; this is problematic for two reasons, (1) placebo is not a reasonable comparator for patients who have not maximised their inhaled asthma therapies, and (2) the comparator trials studied uncontrolled severe asthma only. The key issue was that despite the additional matching, the comparisons remained largely non-transitive as the comparator populations generally had a more severe form of asthma compared to the dupilumab populations. The PSCR argued that the suggestion that the evidence presented favoured dupilumab as the intervention studies may have had less severe disease is inconsistent with previous PBAC evaluations and recommendations for severe asthma biologics (see paragraph 6.20). The ESC considered that an important difference was that patients with moderate asthma in the QUEST and DRI12544 trials could transiently increase the dose of their ICS to manage exacerbations. The ESC considered the impact of this on the efficacy observed in QUEST and DRI12544 is unknown and highly likely to favour dupilumab.
- 6.28 In addition, in selecting better-matched subgroups, the ITC study populations were shifted away from the proposed PBS target population.
- 6.29 The evidence for non-inferiority in non-OCS dependent asthma was not robust; the non-inferiority margin was not met for dupilumab vs omalizumab (#3). Whilst the non-inferiority margin was achieved for dupilumab vs benralizumab and vs mepolizumab (#1 and #2), these study populations were not representative of the target population, and differences in patient characteristics suggested dupilumab patients had less severe disease.
- 6.30 There was a paucity of evidence to suggest dupilumab is non-inferior to benralizumab, mepolizumab or omalizumab in OCS-dependent severe refractory asthma. The comparison with benralizumab (#4) failed to meet the non-inferiority margin, and the comparison with mepolizumab (#5) was borderline non-inferior with imbalances in baseline characteristics which made this finding uncertain. The comparison with

omalizumab (#6) incorporated substantial transitivity issues, which made interpretation highly uncertain.

- 6.31 The claim of non-inferior safety for dupilumab was uncertain, based on currently available safety data for dupilumab and its comparators and the ITC presented by the submission. It is plausible that dupilumab was inferior to the comparators for serious adverse events, and inferior to mepolizumab for adverse events leading to discontinuation, but the ITC was unable to significantly delineate these differences. It is also possible that data presented by the submission, drawn from around 3,300 patients exposed to dupilumab, is not powerful enough to detect rare but serious adverse events; it is noted that detection of the risk for anaphylaxis in patients treated with omalizumab occurred after the Food and Drug Administration reviewed 124 cases out of an estimated 57,300 exposed patients (~0.2% of treated patients)<sup>9</sup>. The ESC noted the trend of inferior safety for serious adverse events, and agreed with the evaluation that the non-inferior safety claim for dupilumab against its comparators was uncertain. The pre-PBAC response argued that there was variation in terms of safety follow-up duration across the included trials, with definitions being poorly reported in some instances and none being powered to detect differences in safety outcomes. Despite this, the pre-PBAC response argued that presented clinical evidence (including a periodic benefit risk evaluation report which provided information on cumulative post marketing exposure to dupilumab of 161,582 patient years) suggested the benefit-risk balance of dupilumab is favourable in patients with asthma and certainly non-inferior to the nominated submission comparators.
- 6.32 The PBAC noted the supplementary ITCs (ITC 1a and ITC 2a) provided in the pre-PBAC response to address concerns raised by the evaluator and ESC regarding the inclusion of medium-dose ICS patients, patients with lower blood EOS and the exclusion of patients who experienced one severe exacerbation in the previous year in the dupilumab trials (see paragraph 6.21). In addition, the PBAC noted the allergic asthma sensitivity analysis ITC (ITC 3a) highlighted by the pre-PBAC response which, like the current PBS initiation criteria, did not have an upper limit of IgE (see paragraph 6.22). Overall, the PBAC considered that the claim of non-inferior comparative effectiveness was uncertain but reasonable.
- 6.33 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

- 6.34 The submission presented a cost-minimisation analysis of dupilumab versus a weighted combination of benralizumab, mepolizumab and omalizumab, with cost-offsets for a reduction in use of health care resources (compared with omalizumab). This approach was consistent with the submission's claim that dupilumab is non-

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<sup>9</sup> Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol*. 2007 Dec;120(6):1378-81.

inferior to benralizumab, mepolizumab and omalizumab in terms of both effectiveness and safety.

6.35 The equi-effective doses estimated by the submission were:

In patients with eosinophilic asthma, dupilumab 400 mg subcutaneous injection (two injections consecutively in two different injection sites) followed by 200 mg given every 2 weeks in the non-OCS dependent population and dupilumab 600 mg subcutaneous injection (two injections consecutively in two different injection sites) followed by 300 mg given every 2 weeks in the OCS dependent population are equi-effective to:

- benralizumab 30 mg subcutaneous injection every 4 weeks for the first three doses, and every 8 weeks thereafter, and
- mepolizumab 100 mg subcutaneous injection every 4 weeks.

In patients with allergic asthma, dupilumab 400 mg subcutaneous injection (two injections consecutively in two different injection sites) followed by 200 mg given every 2 weeks in the non-OCS dependent population and dupilumab 600 mg subcutaneous injection (two injections consecutively in two different injection sites) followed by 300 mg given every 2 weeks in the OCS dependent population are equi-effective to:

- omalizumab 398 mg every 4 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.

6.36 These equi-effective doses were based on the fixed doses used in the key trials of dupilumab (QUEST, DRI12544 and VENTURE), benralizumab (SIROCCO, CALIMA and ZONDA) and mepolizumab (MUSCA, MENSA and SIRIUS). The dose and dosing frequency relating to omalizumab therapy were determined by patient body weight and baseline serum total IgE level, measured before the start of treatment. The equi-effective dose for omalizumab used in the cost-minimisation analysis, i.e. 398 mg per 4 weeks, was the mean omalizumab dose derived from Trial INNOVATE, which has been accepted by the PBAC (paragraphs 6.16 and 7.12, mepolizumab PSD, July 2016 PBAC meeting). The proposed equi-effective doses for the comparators, namely benralizumab, mepolizumab and omalizumab, were consistent with the Therapeutic Relativity Sheets (1 November 2019)<sup>10</sup>.

6.37 In the cost-minimisation analysis, the loading dose(s) relating to the dupilumab therapy and the benralizumab therapy were also taken into account. The inclusion of the fixed loading doses in estimating the equi-effective doses was consistent with previous PBAC consideration (paragraphs 6.49 and 7.11, benralizumab, PSD, March 2018 PBAC meeting).

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<sup>10</sup> [www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets](http://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets)

- 6.38 Therapies with dupilumab and its comparators were costed over 3 years. This time frame was not justified and was much longer than the treatment duration in the clinical trials (24-52 weeks in the dupilumab studies vs. 24-56 weeks in the comparator trials). When the benralizumab submission was considered at the March 2018 meeting, the PBAC noted that a 1-year time horizon was appropriate as it aligned with the duration of the key trials (56 weeks in CALIMA and 48 weeks in SIROCCO) (paragraphs 6.48 and 7.11, benralizumab, PSD, March 2018 PBAC meeting).
- 6.39 In the cost-minimisation analysis, the submission took into account the one-off cost for subcutaneous injection training (MBS item 82215) for patients treated with dupilumab, benralizumab and mepolizumab. In all patients receiving omalizumab, services relating to subcutaneous administration by a nurse practitioner (MBS item 82200), monitoring of anaphylaxis events (MBS item 82210) following each injection and treatment of anaphylaxis (PBS item 8698T) were costed. The inclusion of the above costs in the cost-minimisation analysis was consistent with previous asthma biologic submissions and/or previous PBAC considerations. However, with respect to the omalizumab administration costs, when the PBAC considered the benralizumab submission at the March 2018 meeting, the Committee noted that subcutaneous injections would likely be administered by practice nurses, for whom MBS item codes do not apply, and the use of the MBS item for nurse practitioners as a proxy may overestimate this cost (paragraphs 6.57 and 7.13, benralizumab, PSD, March 2018 PBAC meeting). In addition, the omalizumab Product Information states that after proper training in subcutaneous injection technique, patients or the caregiver may self-inject omalizumab via pre-filled syringe if a physician determines that it is appropriate (as for dupilumab, benralizumab and mepolizumab).
- 6.40 The results of cost-minimisation analysis, based on the published prices for benralizumab, mepolizumab and omalizumab, are presented in the table below. Of note, the MBS fees used in the analysis have been updated during the evaluation.

**Table 13: Results of cost-minimisation analysis using published prices and the updated MBS fees**

| Parameter                                                                                                                                    | Dupilumab   | Mepolizumab | Benralizumab | Omalizumab         |
|----------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|--------------|--------------------|
| <b>Year 1</b>                                                                                                                                |             |             |              |                    |
| A. Dose size per administration                                                                                                              | 200mg/300mg | 100mg       | 30mg         | 398mg <sup>a</sup> |
| B. Drug cost per administration (published ex-manufacturer price)                                                                            | ████████    | ████████    | ████████     | ████████           |
| C. Number of doses in Year 1                                                                                                                 | 27          | 13          | 7.5          | 13                 |
| D. Total annual drug cost (=BxC)                                                                                                             | ████████    | ████████    | ████████     | ████████           |
| E. Subcutaneous injection training (MBS item 82215)                                                                                          | \$60.40     | \$60.40     | \$60.40      | \$0.00             |
| F. Cost for administration cost per year (MBS item 82200, 17.5 administrations for omalizumab <sup>b</sup> )                                 | \$0.00      | \$0.00      | \$0.00       | \$173.04           |
| G. Cost for post-administration monitoring of anaphylaxis event per year (MBS item 82210, 17.5 administrations for omalizumab <sup>b</sup> ) | \$0.00      | \$0.00      | \$0.00       | \$716.62           |
| H. Cost of adrenaline syringe for anaphylaxis per year (PBS item 8698T, one syringe per 1.5 year)                                            | \$0.00      | \$0.00      | 0.00         | \$56.17            |
| I. Total annual cost per patient (=D+E+F+G+H)                                                                                                | ████████    | ████████    | ████████     | ████████           |
| <b>Subsequent years</b>                                                                                                                      |             |             |              |                    |



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| Parameter                                   | Dupilumab | Mepolizumab | Benralizumab | Omalizumab |
|---------------------------------------------|-----------|-------------|--------------|------------|
| J. Number of doses per year                 | 26        | 13          | 6.5          | 13         |
| K. Total annual drug cost (=BxJ)            |           |             |              |            |
| L. Total annual cost per patient (=K+F+G+H) |           |             |              |            |
| M. Total cost over 3 years (=Lx2)           |           |             |              |            |
| N. In eosinophilic asthma population        |           |             | <sup>c</sup> | –          |
| O. In allergic asthma population            |           |             | –            |            |
| P. In overall population                    |           |             | <sup>d</sup> |            |

Source: Analysis performed during the evaluation, based on Table 3.5, Table 3.6, Table, Table 3.9, and Table 3.11 of the submission, the "Sanofi Dupilumab CMA FINAL" Excel workbook

<sup>a</sup> This is the mean omalizumab dose per 4 week, not the dose per administration. Omalizumab can be administered every 2 weeks or every 4 weeks. The number of omalizumab administrations every 4 weeks (1.34) were determined on the basis of the DUSC report (2014) on the utilisation of omalizumab in the 24 months after listing (1 July 2011 to 30 June 2013), which provided data on both baseline IgE level and patient weight.

<sup>b</sup>  $17.5 = 1.34 \times (52/4)$

<sup>c</sup> Weighted on the basis that 42.1% of the eosinophilic asthma patients receive benralizumab, and the remaining 57.9% receive mepolizumab

<sup>d</sup> Weighted using a ratio of 68.3%: 31.7% for eosinophilic asthma vs. allergic asthma.

6.41 The 3-year treatment cost, based on the current MBS fees, was estimated to be \$[REDACTED] for dupilumab, \$45,264 for omalizumab, \$63,942 for mepolizumab, and \$67,936 for benralizumab. The [REDACTED] price of dupilumab for the 200 mg and 300 mg syringe (i.e. \$[REDACTED]) was calculated using the costs of the comparators weighted by their relative use, based on the recent PBS statistics from Services Australia and the 10% PBS sample data. The submission's approach resulted in dupilumab therapy being more expensive than omalizumab for treatment of uncontrolled severe allergic asthma, despite the non-inferiority clinical claim. The PBAC Guidelines (Version 5.0) state that, under the *National Health Act 1953*, Section 101 (3B), the PBAC cannot make a positive recommendation for a medicine that is substantially more costly than an alternative medicine unless it is satisfied that the proposed medicine also provides a significant improvement of health. The PSQR stated that as all currently reimbursed asthma biologics were cost-minimised to omalizumab it is expected that the price of dupilumab will be no higher or lower than any of the nominated comparators once the effective prices of comparators are disclosed.

6.42 Results from the sensitivity analysis indicated that the ex-manufacturer price for dupilumab would be \$[REDACTED] per 200 mg or 300 mg syringe (i.e. [REDACTED] per pack) on the basis of cost-minimisation compared to omalizumab (vs. \$748.22 in the base case). If a shorter time frame was used in the cost-minimisation analysis, the dupilumab price would be slightly higher than the base case (\$[REDACTED] vs. \$[REDACTED]). In a scenario where all patients receive omalizumab therapy via self-injection, the per syringe price would be around \$2 lower than the base case estimate (i.e. \$[REDACTED]).

Table 14: Sensitivity analyses conducted during evaluation

| Component                                                                                         | Ex-manufacturer price for dupilumab per 200mg or 300mg syringe |
|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Base case                                                                                         | [REDACTED]                                                     |
| Cost-minimising to omalizumab therapy                                                             | [REDACTED]                                                     |
| Using 1-year time frame                                                                           | [REDACTED]                                                     |
| Assuming that omalizumab would be self-injected (including one-off training cost, MBS item 82215) | [REDACTED]                                                     |

Source: Sensitivity analyses performed during the evaluation.

**Drug cost/patient/year**

- 6.43 The per patient drug costs for dupilumab and its comparators are presented in the table below. The drug cost for dupilumab was estimated to be \$ [REDACTED], based on the submission's proposed published dispensed price per maximum quantity (DPMQ) of \$ [REDACTED] (Public) and \$ [REDACTED] (Private), assuming 27 doses including the initial loading doses, and 71.8% of use through public hospitals.
- 6.44 This compares with a drug cost per patient of \$ [REDACTED] for benralizumab (7.5 doses including initial loading doses), \$ [REDACTED] for mepolizumab (13 doses) and \$ [REDACTED] for omalizumab (398 mg every 4 weeks for 13 4-week periods).

**Table 15: Drug cost per patient for proposed and comparator drugs**

|                                   | Dupilumab                                                    |                            |                            | Comparators                                                                                           |                                                                                                       |                                                                                                       |
|-----------------------------------|--------------------------------------------------------------|----------------------------|----------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
|                                   | Trial dose and duration                                      | Cost-minimisation analysis | Financial estimates        | Trial dose and duration                                                                               | Cost-minimisation analysis                                                                            | Financial estimates                                                                                   |
| Mean dose                         | 400mg, followed by 200mg Q2W or 600mg, followed by 300mg Q2W | As in the trials           | Not estimated              | Ben: 30mg Q4W for 3 doses, followed by Q8W<br>Mep: 100mg Q4W<br>Oma: 398mg per 4 weeks                | As in the trials                                                                                      | Ben and Mep: Not estimated<br>Oma: 545.5mg                                                            |
| Treatment duration                | 24-52 weeks                                                  | 3 years                    | Not estimated              | Ben: 28-56 weeks<br>Mep: 24-32 weeks<br>Oma: 28-48 weeks                                              | 3 years                                                                                               | Not estimated                                                                                         |
| Cost/patient/4 weeks <sup>a</sup> | \$ [REDACTED] <sup>b</sup>                                   | \$ [REDACTED] <sup>c</sup> | \$ [REDACTED] <sup>b</sup> | Ben: \$ [REDACTED] <sup>b</sup><br>Mep: \$ [REDACTED] <sup>b</sup><br>Oma: \$ [REDACTED] <sup>b</sup> | Ben: \$ [REDACTED] <sup>c</sup><br>Mep: \$ [REDACTED] <sup>c</sup><br>Oma: \$ [REDACTED] <sup>c</sup> | Ben: \$ [REDACTED] <sup>b</sup><br>Mep: \$ [REDACTED] <sup>b</sup><br>Oma: \$ [REDACTED] <sup>b</sup> |
| Cost/patient/year <sup>d</sup>    | \$ [REDACTED] <sup>b</sup>                                   | \$ [REDACTED] <sup>c</sup> | \$ [REDACTED] <sup>b</sup> | Ben: \$ [REDACTED] <sup>b</sup><br>Mep: \$ [REDACTED] <sup>b</sup><br>Oma: \$ [REDACTED] <sup>b</sup> | Ben: \$ [REDACTED] <sup>c</sup><br>Mep: \$ [REDACTED] <sup>c</sup><br>Oma: \$ [REDACTED] <sup>c</sup> | Ben: \$ [REDACTED] <sup>b</sup><br>Mep: \$ [REDACTED] <sup>b</sup><br>Oma: \$ [REDACTED] <sup>b</sup> |

Source: Table compiled during the evaluation, based on Table 2.20, Table 2.25 of the submission, the "Sanofi Dupilumab CMA FINAL" Excel workbook, the "UCM-Workbook-dupilumab asthma FINAL" Excel workbook.

Ben = benralizumab; Mep = mepolizumab; Oma = omalizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks

<sup>a</sup> Initial loading doses not considered

<sup>b</sup> The drug cost as in the clinical trials and in the financial analysis was based on the (proposed) published dispensed prices, weighted by assuming that 71.8% of the asthma biologic prescriptions scripts would be dispensed in a public setting and 28.2% dispensed in a private setting

<sup>c</sup> The drug cost in the cost-minimisation analysis was calculated on the basis of the published ex-manufacturer prices (i.e. dispensed prices in a public setting) for benralizumab, mepolizumab and omalizumab and the price of dupilumab from the cost-minimisation analysis (i.e. \$ [REDACTED] per 200mg/300mg syringe).

<sup>d</sup> In the first year of treatment, where initial loading doses of the dupilumab and benralizumab therapy are taken into account.

**Estimated PBS usage & financial implications**

- 6.45 This submission was not considered by DUSC. The submission took a market share approach to estimate the extent of use and financial implications associated with the listing of dupilumab. The key inputs in the financial analysis are outlined in the table below.

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**Table 16: Key inputs for financial estimates**

| Parameter                                                                                          | Value applied and source                                                                                                                                                                                                                                                                                                                                                 | Comment                                                                                                                            |
|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Number of prescriptions for PBS items relating to benralizumab, mepolizumab and omalizumab         | Benralizumab: 6,357<br>Mepolizumab: 14,454<br>Omalizumab: 53,027<br>Medicare prescription data (April 2019-March 2020)                                                                                                                                                                                                                                                   | Appropriate data source.                                                                                                           |
| Expected growth of asthma biologic market                                                          | Benralizumab: 50% in 2020, decreasing to 13% in Year 6 of listing (2026)<br>Mepolizumab: 26% in 2020, decreasing to 10% in Year 6 of listing<br>Omalizumab: 9% in 2020, varying between 9% and 15% in Years 1-6<br>Assuming a liner projection based on 10% PBS sample data from April 2018 to Mar 2020                                                                  | The submission's assumption that the listing of dupilumab would not affect the growth of the asthma biologic market was uncertain. |
| Uptake rate of dupilumab                                                                           | Eosinophilic asthma patients receiving benralizumab or mepolizumab: 7% in Year 1, increasing by 2%-3% per year in subsequent years<br>Allergic asthma patients receiving omalizumab: 9% in Year 1, increasing by 6% per year in subsequent years<br>Submission's assumption                                                                                              | An area of uncertainty.                                                                                                            |
| Predicted utilisation of dupilumab 200mg dose vs. 300mg dose                                       | 60% 200mg vs. 40% 300mg<br>McDonald et al. (2018), the submission's assumption                                                                                                                                                                                                                                                                                           | This would not affect the results given the proposed flat price for 200mg and 300mg doses.                                         |
| Proportion of initiating and continuing prescriptions for benralizumab, mepolizumab and omalizumab | Benralizumab: 48% initiating vs. 52% continuing<br>Mepolizumab and omalizumab: 29% initiating vs. 79% continuing<br>Medicare prescription data (April 2019-March 2020). As omalizumab initiating and continuing prescriptions used the same PBS codes before December 2019. It was assumed that the initiating/continuing split for omalizumab was equal to mepolizumab. | Reasonable data source.                                                                                                            |
| Ex-manufacturer prices                                                                             | Dupilumab: \$ [REDACTED] per 2 x 200mg or 300mg syringes<br>Benralizumab: \$ [REDACTED] per 30mg syringe/pen device<br>Mepolizumab: \$ [REDACTED] per 100mg pen device/vial<br>Omalizumab: \$ [REDACTED] per 150mg syringe, \$205.00 per 75mg syringe<br>(Proposed) published prices. The effective prices for the comparators were unknown to the Sponsor.              | Reasonable.                                                                                                                        |
| Medical services costs                                                                             | Training of injection technique: MBS item 82212 (\$60.40)<br>Subcutaneous injection: MBS item 82200 (\$9.90)<br>Monitoring of anaphylaxis events: MBS item 82210 (\$41.00)                                                                                                                                                                                               | Appropriate data source.                                                                                                           |

Source: Table compiled during the evaluation, based on Table 4.1 and information provided in Sections 4.1-4.5 of the submission.

- 6.46 The submission assumed that the growth of the asthma biologic market from April 2020 until the end of Year 6 of dupilumab listing (2026) would not be affected by the availability of dupilumab, as the proposed restriction criteria ensure that patients eligible for treatment with dupilumab would also currently qualify for treatment with benralizumab, mepolizumab or omalizumab. The 10% PBS sample data indicated that, despite the similar PBS restrictions of benralizumab to those of mepolizumab, the reimbursement of benralizumab accelerated the growth of the asthma biologic market, which meant that the availability of additional treatment option attracted new patients who otherwise would not receive asthma biologics. This might also occur following the listing of dupilumab, especially in the allergic asthma population, for

whom only one treatment (omalizumab) is currently available, and dupilumab therapy is associated with a more straightforward posology with no need for post-injection monitoring of anaphylaxis events. The PSCR argued that at the time of listing dupilumab, benralizumab will have been listed for 2 years, and claimed that it reasonably expected that all biologic naïve patients suitable for IL-5 therapy will have initiated therapy.

- 6.47 The estimated use and financial implications are summarised in the table below. Referencing errors were identified in the financial analysis Excel workbook: Cells E203:J203 and E215:J215 in the 'Scripts – market' spreadsheet, "UCM-Workbook-dupilumab asthma FINAL" workbook. An uptake rate of 7%-21% (as that for benralizumab and mepolizumab) was applied to omalizumab PBS items 10109C and 10110D, rather than 9%-39% as stated in the submission and used for other omalizumab PBS items. This was corrected during the evaluation. The PBAC noted the estimated costs for dupilumab would be lower when incorporating effective prices.

**Table 17: Estimated use and financial implications**

|                                                                                      | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--------------------------------------------------------------------------------------|--------|--------|--------|--------|--------|--------|
| <b>Estimated extent of use</b>                                                       |        |        |        |        |        |        |
| Number of scripts dispensed                                                          | 1      | 2      | 3      | 3      | 4      | 5      |
| Revised <sup>a</sup>                                                                 | 1      | 2      | 3      | 3      | 4      | 5      |
| <b>Estimated financial implications of dupilumab</b>                                 |        |        |        |        |        |        |
| Cost to PBS/RPBS less copayments                                                     | \$ 6   | \$ 7   | \$ 7   | \$ 8   | \$ 9   | \$ 10  |
| Revised <sup>a</sup>                                                                 | \$ 6   | \$ 7   | \$ 7   | \$ 8   | \$ 9   | \$ 11  |
| <b>Estimated financial implications for benralizumab, mepolizumab and omalizumab</b> |        |        |        |        |        |        |
| Cost to PBS/RPBS less copayments                                                     | \$ 6   | \$ 7   | \$ 7   | \$ 8   | \$ 9   | \$ 10  |
| Revised <sup>a</sup>                                                                 | \$ 6   | \$ 7   | \$ 8   | \$ 8   | \$ 9   | \$ 11  |
| <b>Net financial implications</b>                                                    |        |        |        |        |        |        |
| Net cost to PBS/RPBS                                                                 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 |
| Revised <sup>a</sup>                                                                 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 |
| Net cost to MBS                                                                      | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 |
| Revised <sup>a</sup>                                                                 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 |
| Net cost to PBS/RPBS/MBS                                                             | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 |
| Revised <sup>a</sup>                                                                 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 | -\$ 12 |

Source: Table 4.9, Table 4.13, Table 4.16, Table 4.20 of the submission.

<sup>a</sup> Revised by correcting the referencing errors (regarding the uptake of dupilumab in patients receiving omalizumab) in the financial analysis Excel workbook: Cells E203:J203 and E215:J215 in the 'Scripts – market' spreadsheet, "UCM-Workbook-dupilumab asthma FINAL" workbook.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 10,000 to < 20,000

<sup>4</sup> 20,000 to < 30,000

<sup>5</sup> 30,000 to < 40,000

<sup>6</sup> \$0 to < \$10 million

<sup>7</sup> \$10 million to < \$20 million

<sup>8</sup> \$20 million to < \$30 million

<sup>9</sup> \$30 million to < \$40 million

<sup>10</sup> \$40 million to < \$50 million

<sup>11</sup> \$50 million to < \$60 million

<sup>12</sup> Net cost saving

- 6.48 It was estimated that the listing of dupilumab would result in a net cost saving to the PBS/RPBS in Year 6, and a total of \$0 to < \$10 million savings in the first 6 years of listing. This was based on the proposed published price for dupilumab and the PBS-listed prices for benralizumab, mepolizumab and omalizumab.
- 6.49 The estimated net cost saving to the PBS/RPBS was primarily due to the higher dosage for omalizumab used in the financial analysis (based on the 10% PBS sample data) compared with that used in the cost-minimisation analysis (from Trial INNOVATE) (545.5 mg vs. 398 mg). This resulted in a greater cost offset associated with the substitution of omalizumab therapy with dupilumab therapy for treatment of uncontrolled severe allergic asthma. However, the ESC agreed with the evaluation that the assumed net cost saving to the PBS/RPBS might not be realised in clinical practice if the reimbursement of dupilumab accelerates the growth of the asthma biologic market.
- 6.50 The PBAC noted that the financial estimates would need to be recalculated to take into account the outcome of its considerations regarding the cost-minimisation analysis.

### **Quality Use of Medicines**

- 6.51 The submission outlined a number of activities to promote the safe and effective use of dupilumab in clinical practice, such as conducting health care professional educational meetings, developing clinician and patient educational materials, and supporting the development of clinical research networks and registers to assist the clinical management of patients with severe asthma and to facilitate a post-marketing surveillance study.

*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 Drug Program Authority Required (in writing) listing of dupilumab for the treatment of uncontrolled severe eosinophilic or allergic asthma, both with and without oral corticosteroid (OCS) dependence.
- 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 the least costly biologic for asthma over a 1-year time frame.
- 7.3 The PBAC noted the input from individuals, health care professionals and organisations supporting the listing of dupilumab for this indication.
- 7.4 The PBAC noted that the PBS indication requested was uncontrolled severe type 2 asthma with or without OCS dependence depending on the dupilumab strength. As

outlined in paragraph 3.4, the PBAC noted that the proposed restrictions included the same measure of IgE as that in the omalizumab restriction for severe allergic asthma and the same measures of eosinophils as in the mepolizumab and benralizumab restrictions for severe eosinophilic asthma. The PBAC agreed with the ESC that the PBS indication should be amended to 'uncontrolled severe eosinophilic or allergic asthma' with reference to oral corticosteroid dependence reserved for the clinical criteria of the 300 mg dupilumab formulation. The PBAC also agreed with the ESC that it would be appropriate to include the definition of OCS dependence from the VENTURE trial in the clinical criteria of the 300 mg dupilumab formulation. The PBAC considered that as patients taking OCS are not excluded from using the 200 mg dupilumab formulation the clinical criteria 'Patient must have blood eosinophil count greater than or equal to 150 cells per microliter while receiving treatment with oral corticosteroids in the last 12 months' could be retained for consistency with the existing mepolizumab and benralizumab restrictions.

- 7.5 The PBAC considered the three nominated comparators of benralizumab, mepolizumab and omalizumab were appropriate.
- 7.6 The PBAC noted the submission presented indirect treatment comparisons (ITCs) which compared the efficacy of dupilumab with the three comparators. The PBAC noted that subgroup data from the dupilumab trials were matched with subgroup data from the comparator trials to reduce observed heterogeneity and Bucher pairwise ITCs were performed. The PBAC agreed with the ESC that a key issue was that, despite the additional matching, the transitivity of the comparisons presented in the submission was uncertain as the comparator populations generally had a more severe form of asthma compared to the dupilumab populations (see paragraph 6.20). In addition, the PBAC agreed with the evaluation that selecting better matched subgroups in terms of prior number of severe exacerbations (see paragraph 6.13) raised concerns regarding applicability to the target Australian population. The PBAC noted the supplementary ITCs (ITC 1a and ITC 2a) provided in the pre-PBAC response to address concerns raised regarding the inclusion of medium-dose ICS patients and the exclusion of patients who experienced one severe exacerbation in the previous year (see paragraph 6.21). The PBAC also noted the allergic asthma sensitivity analysis ITC (ITC 3a) highlighted in the pre-PBAC response which provided a comparison in a population likely more applicable to the target Australian population than that presented in ITC 3 (see paragraph 6.22). Overall, the PBAC considered that the claim of non-inferior comparative effectiveness was uncertain but reasonable.
- 7.7 The PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 7.8 The PBAC noted that the submission presented a cost-minimisation analysis of dupilumab versus a weighted combination of the nominated comparators. The PBAC noted that the analysis was weighted using a ratio of 68.3%:31.7% for eosinophilic asthma versus allergic asthma, with the eosinophilic asthma patient group being subject to a further weighting with 42.1% assumed to receive benralizumab (see Table

13). The PBAC recalled that omalizumab, mepolizumab and benralizumab for the treatment of severe asthma were cost-minimised to each other and considered that the cost-minimisation analysis should be against the least costly biologic for asthma rather than a weighted combination of the nominated comparators.

7.9 In addition, the PBAC noted that therapies were costed over three years with loading dose(s) for dupilumab and benralizumab taken into account. The PBAC noted that the 3 year time frame was longer than the treatment duration in the dupilumab (24-52 weeks) and comparator (24-56 weeks) clinical trials. The PBAC recalled that it had recommended a one year time horizon in its March 2018 consideration of benralizumab as it aligned with the duration of the key trials (paragraphs 6.48 and 7.11, benralizumab, PSD, March 2018 PBAC meeting). The PBAC advised that dupilumab and its comparators should be costed over a one year time horizon with the loading dose for dupilumab and benralizumab included.

7.10 Thus, the PBAC considered the equi-effective doses for eosinophilic asthma were:

- dupilumab 400 mg subcutaneous injection followed by 200 mg given every 2 weeks in the non-OCS dependent population (27 doses over one year); and
- dupilumab 600 mg subcutaneous injection followed by 300 mg given every 2 weeks in the OCS dependent population (27 doses over one year); and
- benralizumab 30 mg subcutaneous injection every 4 weeks for the first three doses, and every 8 weeks thereafter (7.5 doses over one year), and
- mepolizumab 100 mg subcutaneous injection every 4 weeks (13 doses over one year).

The PBAC considered the subcutaneous injection administration cost-offsets for omalizumab were overestimated as it would likely be administered by practice nurses, rather than under the Nurse Practitioner MBS item code. The PBAC further noted that the Product Information for omalizumab, benralizumab and mepolizumab state that after proper training in subcutaneous injection technique, patients or the caregiver may self-inject via pre-filled syringe if a physician determines that it is appropriate (as for dupilumab), and noted that MBS costs were not considered as part of the costs of administration for dupilumab. The PBAC noted that in relation to the self-injection of omalizumab the Product Information recommended the first three doses be administered under the supervision of a healthcare professional. As such the PBAC considered that it appropriate for the subcutaneous injection administration cost-offsets and the costs for post-administration monitoring of anaphylaxis to be included for the first three doses of omalizumab only. In addition, the PBAC considered that a one-off cost for subcutaneous injection training should also be included for omalizumab to allow for self-injection after the initial three doses. The PBAC considered the equi-effective doses in patients with allergic asthma were:

- dupilumab 400 mg subcutaneous injection followed by 200 mg given every 2 weeks in the non-OCS dependent population (27 doses over one year); and

- dupilumab 600 mg subcutaneous injection followed by 300 mg given every 2 weeks in the OCS dependent population (27 doses over one year); and
  - omalizumab 398 mg every 4 weeks subcutaneous injection, either as one dose or split into two equal doses depending on patient weight and IgE level (13 doses over one year).
- 7.11 The PBAC noted that the financial estimates were based on the proposed published price for dupilumab and the cost for benralizumab, mepolizumab and omalizumab and would need to be recalculated to take into account effective prices and the outcome of its considerations regarding the cost-minimisation analysis.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The requested restriction is considered to be complex.
- 7.14 The PBAC noted that the following changes will be required to the omalizumab, benralizumab, mepolizumab restrictions:
- The overarching note of ‘Treatment of adult and adolescent patients with uncontrolled severe eosinophilic or allergic asthma’ to the existing omalizumab, mepolizumab and benralizumab listings for severe asthma will need to be amended to include dupilumab.
  - The individual comparator drug’s restrictions 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 either failed to achieve or sustain a response to treatment with 4 biological medicines within the same treatment cycle....’ The PBAC reaffirmed that a patient can only fail any biologics for severe 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 eosinophilic or allergic asthma.
  - The PBAC noted that currently, in a patient, whose only available treatment option is omalizumab, 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. The PBAC noted that this change would be consistent with the existing requirements for patients eligible for benralizumab and mepolizumab.
- 7.15 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 benralizumab,



mepolizumab or 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 2009 for Pricing Pathway A were not met.

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

**Outcome:**

Recommended

## 8 Recommended listing

- 8.1 Add new items as follows:

**Treatment phase: Initial 1 and Initial 2**

| Name, restriction, manner of administration, form                  | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |                                  |
|--------------------------------------------------------------------|---------------|--------------------------|--------------------------|----------------|-----------------------------------|----------------------------------|
| DUPILUMAB<br><br>200 mg/1.14 mL injection,<br>2 x 1.14 mL syringes | NEW           | 1                        | 2                        | 8              | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

|            |                                                                                                                                                                                               |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Concept ID | <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                             |
|            | <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                          |
|            | <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                    |
|            | <b>Severity:</b><br>Uncontrolled severe                                                                                                                                                       |
|            | <b>Condition:</b><br>eosinophilic or allergic asthma                                                                                                                                          |
|            | <b>PBS Indication:</b><br>Uncontrolled severe eosinophilic or allergic asthma                                                                                                                 |
|            | <b>Treatment phase:</b><br>Initial treatment 1 – (New patient; or Recommencement of treatment in a new treatment cycle following a break in PBS subsidised biological medicine therapy)       |
|            | <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma. |
|            | <b>AND</b>                                                                                                                                                                                    |
|            | <b>Clinical criteria:</b><br>Patient must be under the care of the same physician for at least 6 months; or                                                                                   |
|            | Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                            |
|            | <b>AND</b>                                                                                                                                                                                    |
|            | <b>Clinical criteria:</b><br>Patient must not have received PBS-subsidised treatment with a biological medicine for severe asthma; or                                                         |

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|  | Patient must have had a break in treatment from the most recently approved PBS-subsidised biological medicine for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; or |
|  | Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have a duration of asthma of at least 1 year.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 12 months, or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids in the last 12 months, or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | <b>Population criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|  | Patients must be aged 12 years or older.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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|  | <p><b>Prescribing instructions</b></p> <p>The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application:</p> <p>(a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND</p> <p>(b) while receiving optimised asthma therapy in the past 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.</p> <p>The Asthma Control Questionnaire (5 item version) assessment of the patient's response to this initial course of treatment, and the assessment of oral corticosteroid dose, should be made at around 28 weeks after the first PBS-subsidised dose of this drug 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.</p> <p>This assessment, which will be used to determine eligibility for the first 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.</p> <p>If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle.</p> <p>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 4 biological medicines within the same treatment cycle.</p> <p>The length of the break in therapy is measured from the date 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.</p> <p>There is no limit to the number of treatment cycles that a patient may undertake in their lifetime.</p> <p>A multidisciplinary severe asthma clinic team comprises of:</p> <ul style="list-style-type: none"> <li>• A respiratory physician; and</li> <li>• A pharmacist, nurse or asthma educator.</li> </ul> <p>At the time of the authority application, medical practitioners should request up to 8 repeats to provide for an initial course of dupilumab sufficient for up to 32 weeks of therapy, at a dose of 400 mg as an initial dose, followed by 200 mg every 2 weeks thereafter.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe eosinophilic or allergic asthma Initial PBS Authority Application - Supporting Information Form, which includes the following:</p> <p>(i) details of prior optimised asthma drug therapy (date of commencement and duration of therapy); and</p> <p>(ii) details of severe exacerbation/s experienced in the past 12 months while receiving optimised asthma therapy (date and treatment); and</p> <p>(iii) the eosinophil count and date; or</p> <p>(iv) the IgE result; and</p> <p>(iv) Asthma Control Questionnaire (ACQ-5) score.</p> |
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|  | <p><b>Prescribing instructions:</b></p> <p>Optimised asthma therapy includes:</p> <p>(i) Adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy for at least 12 months, unless contraindicated or not tolerated;</p> <p>AND</p> <p>(ii) treatment with oral corticosteroids, either daily oral corticosteroids for at least 6 weeks, OR a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated.</p> <p>If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications according to 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.</p> |
|  | <p><b>Administrative Advice:</b></p> <p>The Services Australia website (<a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a>) 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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | <p><b>Administrative Advice:</b></p> <p>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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> or <a href="http://www.nationalasthma.org.au">www.nationalasthma.org.au</a>); 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).</p>                                                                                                                                                                                                                                                                                                           |
|  | <p><b>Note:</b></p> <p>For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| Concept ID | <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                                                                                                                                                                |
|            | <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                                                                                                                                                             |
|            | <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                                                                                                                                                       |
|            | <b>Severity:</b><br>Uncontrolled severe                                                                                                                                                                                                                                                                                          |
|            | <b>Condition:</b><br>eosinophilic or allergic asthma                                                                                                                                                                                                                                                                             |
|            | <b>PBS Indication:</b><br>Uncontrolled severe eosinophilic or allergic asthma                                                                                                                                                                                                                                                    |
|            | <b>Treatment phase:</b><br>Initial treatment – Initial 2 (Change of treatment)                                                                                                                                                                                                                                                   |
|            | <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                                                    |
|            | <b>AND</b>                                                                                                                                                                                                                                                                                                                       |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                        |
|            | Patient must be under the care of the same physician for at least 6 months; or                                                                                                                                                                                                                                                   |
|            | Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                                                               |
|            | <b>AND</b>                                                                                                                                                                                                                                                                                                                       |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                        |
|            | Patient must have received prior PBS-subsidised treatment with a biological medicine for severe asthma in this treatment cycle.                                                                                                                                                                                                  |
|            | <b>AND</b>                                                                                                                                                                                                                                                                                                                       |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                        |
|            | Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug for severe asthma during the current treatment cycle.                                                                                                                                                                             |
|            | <b>AND</b>                                                                                                                                                                                                                                                                                                                       |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                        |
|            | Patient must have had a blood eosinophil count greater than or equal to 300 cells per microlitre measured no more than 12 months immediately prior to commencing PBS-subsidised biological medicine treatment for severe asthma; or                                                                                              |
|            | Patient must have had a blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids and that is no older than 12 months immediately prior to commencing PBS-subsidised biological medicine treatment for severe asthma; or                                      |
|            | OR                                                                                                                                                                                                                                                                                                                               |
|            | Patient must have had a total serum human immunoglobulin E greater than or equal to 30 IU/mL with a 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 severe asthma. |
|            | <b>AND</b>                                                                                                                                                                                                                                                                                                                       |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                        |
|            | Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                 |
|            | <b>AND</b>                                                                                                                                                                                                                                                                                                                       |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                        |
|            | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                |
|            | <b>Population criteria:</b><br>Patients must be aged 12 years or older.                                                                                                                                                                                                                                                          |

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|  | <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Uncontrolled severe eosinophilic or allergic asthma Initial PBS Authority Application - Supporting Information Form, which includes the following:</p> <p>(i) Asthma Control Questionnaire (ACQ-5 item version) score (where a new baseline is being submitted or where the patient has responded to prior treatment); and</p> <p>(ii) the details of prior biological medicine treatment including the details of date and duration of treatment; and</p> <p>(iii) eosinophil count and date; and</p> <p>(iv) the dose of the maintenance oral corticosteroid (where the response criteria or baseline is based on corticosteroid dose); or</p> <p>(v) the IgE results; and</p> <p>(vi) the reason for switching therapy (e.g. failure of prior therapy, partial response to prior therapy, adverse event to prior therapy).</p> <p>An application for a patient who has received PBS-subsidised biological medicine treatment for severe asthma who wishes to change therapy to this biological medicine, must be accompanied by the results of an ACQ-5 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.</p> <p>An ACQ-5 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.</p> <p>This assessment at around 28 weeks, which will be used to determine eligibility for the first 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 biological medicine.</p> <p>At the time of the authority application, medical practitioners should request up to 8 repeats to provide for an initial course of dupilumab sufficient for up to 32 weeks of therapy, at a dose of 400 mg as an initial dose, followed by 200 mg every 2 weeks thereafter.</p> <p>A multidisciplinary severe asthma clinic team comprises of:</p> <ul style="list-style-type: none"> <li>• A respiratory physician; and</li> <li>• A pharmacist, nurse or asthma educator.</li> </ul> |
|  | <p><b>Note:</b></p> <p>For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

**Treatment phase: Continuing treatment**

| Name, restriction, manner of administration, form | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |                                  |
|---------------------------------------------------|---------------|--------------------------|--------------------------|----------------|-----------------------------------|----------------------------------|
| DUPILUMAB                                         |               |                          |                          |                |                                   |                                  |
| 200 mg/1.14 mL injection, 2 x 1.14 mL syringes    | NEW           | 1                        | 2                        | 5              | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |
| 300 mg/2 mL injection, 2 x 2 mL syringes          | NEW           | 1                        | 2                        | 5              | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

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| <b>Concept ID</b> | <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                                                                                                                                                                                                                                                         |
|                   | <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                                                                                                                                                                                                                                                      |
|                   | <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                                                                                                                                                                                                                                                |
|                   | <b>Severity:</b><br>Uncontrolled severe                                                                                                                                                                                                                                                                                                                                                                                   |
|                   | <b>Condition:</b><br>eosinophilic or allergic asthma                                                                                                                                                                                                                                                                                                                                                                      |
|                   | <b>PBS Indication:</b><br>Uncontrolled severe eosinophilic or allergic asthma                                                                                                                                                                                                                                                                                                                                             |
|                   | <b>Treatment phase:</b><br>Continuing treatment                                                                                                                                                                                                                                                                                                                                                                           |
|                   | <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                                                                                                                                             |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                 |
|                   | Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug for this condition.                                                                                                                                                                                                                                                                                           |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                 |
|                   | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                         |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                 |
|                   | Patient must not receive more than 24 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                          |
|                   | <b>Population criteria:</b><br>Patients must be aged 12 years or older                                                                                                                                                                                                                                                                                                                                                    |
|                   | <b>Prescribing instructions:</b><br>An adequate response to this biological medicine is defined as:<br>(a) a reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 0.5 from baseline,<br>OR<br>(b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 score from baseline or an increase in ACQ-5 score from baseline less than or equal to 0.5. |

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|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p><b>Prescribing instructions:</b></p> <p>All applications for second and subsequent continuing treatments with this drug must include a measurement of response to the prior course of therapy. The Asthma Control Questionnaire (5 item version) assessment of the patient's response to the prior course of treatment or the assessment of oral corticosteroid dose, should be made at around 20 weeks after the first dose of PBS-subsidised dose of 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.</p> <p>The 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.</p> <p>Where treatment was ceased for clinical reasons despite the patient experiencing improvement, an assessment of the patient's response to treatment made at the time of treatment cessation or retrospectively will be considered to determine whether the patient demonstrated or sustained an adequate response to treatment.</p> <p>A patient who fails to respond to treatment with this biological medicine for uncontrolled severe asthma will not be eligible to receive further PBS subsidised treatment with this biological medicine for severe asthma within the current treatment cycle.</p> |
|  | <p><b>Prescribing instructions:</b></p> <p>At the time of the authority application, medical practitioners should request the appropriate number of repeats to provide for a continuing course of this drug sufficient for up to 24 weeks of therapy. The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Uncontrolled severe eosinophilic or allergic asthma Continuing PBS Authority Application - Supporting Information Form which includes:</p> <p>(i) details of maintenance oral corticosteroid dose; or</p> <p>(ii) a completed Asthma Control Questionnaire (ACQ-5) score.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | <p><b>Note:</b></p> <p>For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

**Treatment phase: Initial 1 and Initial 2**

| Name, restriction, manner of administration, form | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |                                  |
|---------------------------------------------------|---------------|--------------------------|--------------------------|----------------|-----------------------------------|----------------------------------|
| 300 mg/2 mL injection, 2 x 2 mL syringes          | NEW           | 1                        | 2                        | 8              | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

|            |                                                                                                              |
|------------|--------------------------------------------------------------------------------------------------------------|
| Concept ID | <p><b>Category / Program:</b></p> <p>Section 100 – Highly Specialised Drugs Program – public and private</p> |
|            | <p><b>Prescriber type:</b></p> <p><input checked="" type="checkbox"/> Medical Practitioners</p>              |
|            | <p><b>Restriction:</b></p> <p><input checked="" type="checkbox"/> Authority Required - In Writing</p>        |
|            | <p><b>Severity:</b></p> <p>Uncontrolled severe</p>                                                           |
|            | <p><b>Condition:</b></p> <p>eosinophilic or allergic asthma</p>                                              |
|            | <p><b>PBS Indication:</b></p> <p>Uncontrolled severe eosinophilic or allergic asthma</p>                     |
|            | <p><b>Treatment phase:</b></p>                                                                               |



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|  | Initial treatment 1 – (New patients; or Recommencement of treatment in a new treatment cycle following a break in PBS subsidised biological medicine therapy)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|  | <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must be under the care of the same physician for at least 6 months; or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; or |
|  | Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have a duration of asthma of at least 1 year.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have been receiving regular maintenance oral corticosteroids (OCS) in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to treatment initiation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | Patient must have blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroid in the last 12 months, or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | 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, that is no more than 1 year old.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | <b>Population criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|  | <p>Patients must be aged 12 years or older.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|  | <p><b>Prescribing instructions:</b><br/> Optimised asthma therapy includes:<br/> (i) Adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy for at least 12 months, unless contraindicated or not tolerated;<br/> AND<br/> (ii) treatment with oral corticosteroids as outlined in the clinical criteria.<br/> If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications according to 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.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|  | <p><b>Prescribing instructions</b><br/> The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application:<br/> (a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND<br/> (b) while receiving optimised asthma therapy in the past 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.<br/> The Asthma Control Questionnaire (5 item version) assessment of the patient's response to this initial course of treatment, and the assessment of oral corticosteroid dose, should be made at around 28 weeks after the first PBS-subsidised dose of this drug 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.<br/> This assessment, which will be used to determine eligibility for the first 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.<br/> If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle.<br/> 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 4 biological medicines within the same treatment cycle.<br/> The length of the break in therapy is measured from the date the most recent treatment with a PBS-subsidised biological medicine was administered until the date of the first application for commencement of treatment with a biological medicine under the new treatment cycle.<br/> There is no limit to the number of treatment cycles that a patient may undertake in their lifetime.<br/> A multidisciplinary severe asthma clinic team comprises of:</p> <ul style="list-style-type: none"> <li>• A respiratory physician; and</li> <li>• A pharmacist, nurse or asthma educator.</li> </ul> <p>At the time of the authority application, medical practitioners should request up to 8 repeats to provide for an initial course of dupilumab sufficient for up to 32 weeks of therapy, at a dose of 600 mg as an initial dose, followed by 300 mg every 2 weeks thereafter.<br/> The authority application must be made in writing and must include:<br/> (a) a completed authority prescription form; and<br/> (b) a completed Uncontrolled severe eosinophilic or allergic asthma Initial PBS Authority Application - Supporting Information Form, which includes the following:<br/> (i) details of prior optimised asthma drug therapy (date of commencement and duration of therapy); and<br/> (ii) details of severe exacerbation/s experienced in the past 12 months while receiving optimised asthma therapy (date and treatment); and<br/> (iii) the eosinophil count and date; or<br/> (iv) the IgE result; and</p> |

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|  | (iv) Asthma Control Questionnaire (ACQ-5) score.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|  | <b>Administrative Advice:</b><br>The Services Australia website ( <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> ) 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.                                                                                                                                                                                                                                                                                |
|  | <b>Administrative Advice:</b><br>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 <a href="http://www.servicesaustralia.gov.au">www.servicesaustralia.gov.au</a> or <a href="http://www.nationalasthma.org.au">www.nationalasthma.org.au</a> ); 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). |
|  | <b>Note:</b><br>For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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| <b>Concept ID</b> | <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                                                                                                                           |
|                   | <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                                                                                                                        |
|                   | <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                                                                                                                  |
|                   | <b>Severity:</b><br>Uncontrolled severe                                                                                                                                                                                                                                                     |
|                   | <b>Condition:</b><br>eosinophilic or allergic asthma                                                                                                                                                                                                                                        |
|                   | <b>PBS Indication:</b><br>Uncontrolled severe eosinophilic or allergic asthma                                                                                                                                                                                                               |
|                   | <b>Treatment phase:</b><br>Initial treatment – Initial 2 (Change of treatment)                                                                                                                                                                                                              |
|                   | <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                                                                                               |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                  |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                   |
|                   | Patient must be under the care of the same physician for at least 6 months; or                                                                                                                                                                                                              |
|                   | Patient must have been diagnosed by a multidisciplinary severe asthma clinic team.                                                                                                                                                                                                          |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                  |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                   |
|                   | Patient must have received prior PBS-subsidised treatment with a biological medicine for severe asthma in this treatment cycle.                                                                                                                                                             |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                  |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                   |
|                   | Patient must not have failed, or ceased to respond to PBS-subsidised treatment with this drug for severe asthma during the current treatment cycle.                                                                                                                                         |
|                   | <b>AND</b>                                                                                                                                                                                                                                                                                  |
|                   | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                   |
|                   | Patient must have had a blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids and that is no older than 12 months immediately prior to commencing PBS-subsidised biological medicine treatment for severe asthma; or |

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|  | Patient must have each of: i) total serum human immunoglobulin E greater than or equal to 30 IU/mL measured no more than 12 months prior to initiating PBS-subsidised treatment with a biological medicine for severe asthma, ii) past or current evidence of atopy, documented by skin prick testing or an in vitro measure of specific IgE in the past 12 months or in the 12 months prior to initiating PBS-subsidised treatment with a biological medicine for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | Patient must have received regular maintenance oral corticosteroids (OCS) in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to treatment initiation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | Patient must not receive more than 32 weeks of treatment under this restriction.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|  | <b>Population criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | Patients must be aged 12 years or older.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | <p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> <li>(a) a completed authority prescription form; and</li> <li>(b) a completed Uncontrolled severe eosinophilic or allergic asthma Initial PBS Authority Application - Supporting Information Form, which includes the following: <ul style="list-style-type: none"> <li>(i) Asthma Control Questionnaire (ACQ-5 item version) score (where a new baseline is being submitted or where the patient has responded to prior treatment); and</li> <li>(ii) the details of prior biological medicine treatment including the details of date and duration of treatment; and</li> <li>(iii) eosinophil count and date; and</li> <li>(iv) the dose of the maintenance oral corticosteroid (where the response criteria or baseline is based on corticosteroid dose); or</li> <li>(v) the IgE results; and</li> <li>(vi) the reason for switching therapy (e.g. failure of prior therapy, partial response to prior therapy, adverse event to prior therapy).</li> </ul> </li> </ul> <p>An application for a patient who has received PBS-subsidised biological medicine treatment for severe asthma who wishes to change therapy to this biological medicine, must be accompanied by the results of an ACQ-5 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.</p> <p>An ACQ-5 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.</p> <p>This assessment at around 28 weeks, which will be used to determine eligibility for the first 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 biological medicine.</p> <p>At the time of the authority application, medical practitioners should request up to 8 repeats to provide for an initial course of dupilumab sufficient for up to 32 weeks of therapy at a dose of 600 mg as an initial dose, followed by 300 mg every 2 weeks thereafter.</p> <p>A multidisciplinary severe asthma clinic team comprises of:</p> <ul style="list-style-type: none"> <li>• A respiratory physician; and</li> <li>• A pharmacist, nurse or asthma educator.</li> </ul> |

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|  | <b>Note:</b><br>For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806. |
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**Treatment phase: Grandfather treatment**

| Name, restriction, manner of administration, form         | PBS item code | Maximum quantity (packs) | Maximum quantity (units) | No. of repeats | Proprietary name and manufacturer |                                  |
|-----------------------------------------------------------|---------------|--------------------------|--------------------------|----------------|-----------------------------------|----------------------------------|
| DUPILUMAB<br><br>300 mg/2 mL injection, 2 x 2 mL syringes | NEW           | 1                        | 2                        | 5              | Dupixent®                         | Sanofi-Aventis Australia Pty Ltd |

|            |                                                                                                                                                                                                              |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Concept ID | <b>Category / Program:</b><br>Section 100 – Highly Specialised Drugs Program – public and private                                                                                                            |
|            | <b>Prescriber type:</b><br><input checked="" type="checkbox"/> Medical Practitioners                                                                                                                         |
|            | <b>Restriction:</b><br><input checked="" type="checkbox"/> Authority Required - In Writing                                                                                                                   |
|            | <b>Severity:</b><br>Uncontrolled severe                                                                                                                                                                      |
|            | <b>Condition:</b><br>eosinophilic or allergic asthma                                                                                                                                                         |
|            | <b>PBS Indication:</b><br>Uncontrolled severe eosinophilic or allergic asthma                                                                                                                                |
|            | <b>Treatment phase:</b><br>Grandfather treatment                                                                                                                                                             |
|            | <b>Treatment criteria:</b><br>Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.                |
|            | <b>AND</b>                                                                                                                                                                                                   |
|            | <b>Clinical criteria:</b><br>Patient must have received non-PBS-subsidised-treatment with this biological medicine-for this condition prior to [listing date].                                               |
|            | <b>AND</b>                                                                                                                                                                                                   |
|            | <b>Clinical criteria:</b><br>Patient must have demonstrated or sustained an adequate response to treatment with this drug if the patient has received at least the week 28 dose of this biological medicine. |
|            | <b>AND</b>                                                                                                                                                                                                   |
|            | <b>Clinical criteria:</b><br>Patient must be receiving treatment with this drug for this condition at the time of application.                                                                               |
|            | <b>AND</b>                                                                                                                                                                                                   |
|            | <b>Clinical criteria:</b><br>Patient must be under the care of the same physician for at least 6 months; or                                                                                                  |
|            | Patient must have been diagnosed with severe asthma by a multidisciplinary severe asthma clinic team.                                                                                                        |
|            | <b>AND</b>                                                                                                                                                                                                   |
|            | <b>Clinical criteria:</b>                                                                                                                                                                                    |

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|  | Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features: (i) forced expiratory volume (FEV1) reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 micrograms), or (ii) airway hyperresponsiveness defined as a greater than 20% decline in FEV1 during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; or |
|  | Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have had a documented blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids prior to initiating non-PBS subsidised treatment of this drug for severe asthma; or                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | Patient must have had a documented total serum human immunoglobulin E greater than or equal to 30 IU/mL measured no more than 12 months prior to initiating non-PBS-subsidised treatment with a biological medicine for severe asthma, 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 this drug for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                       |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have received regular maintenance oral corticosteroids (OCS) in the last 6 months with a stable daily OCS dose of 5 to 35 mg/day of prednisolone or equivalent over the 4 weeks prior to commencement of a biological medicine treatment for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | Patient must have a documented a duration of asthma of at least 1 year prior to commencement of this biological medicine.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|  | <b>AND</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|  | <b>Clinical criteria:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|  | The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|  | <b>Population criteria:</b><br>Patients must be aged 12 years or older.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|  | <b>Prescribing instructions:</b><br>Optimised asthma therapy includes:<br>(i) Adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy for at least 12 months, unless contraindicated or not tolerated;<br><b>AND</b><br>(ii) treatment with oral corticosteroids as outlined in the clinical criteria.<br>If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications according to 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.                                                                                                     |

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|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p><b>Prescribing instructions</b></p> <p>The following initiation criteria indicate failure to achieve adequate control with optimised asthma therapy and must be declared to have been met at the time of the application:</p> <p>(a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0 prior to commencement with a biological medicine for severe asthma; AND</p> <p>(b) while receiving optimised asthma therapy in the 12 months prior to commencing treatment with a biological medicine for severe asthma, 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.</p> <p>An Asthma Control Questionnaire (5 item version) assessment and/or an assessment of a reduction in the patient's maintenance oral corticosteroid dose 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 28 weeks or greater.</p> <p>If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within the same treatment cycle.</p> <p>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 4 biological medicines within the same treatment cycle.</p> <p>The length of the break in therapy is measured from the date the most recent treatment with a PBS-subsidised biological medicine was administered until the date of the first application for commencement of treatment with a biological medicine under the new treatment cycle.</p> <p>There is no limit to the number of treatment cycles that a patient may undertake in their lifetime.</p> <p>A multidisciplinary severe asthma clinic team comprises of:</p> <ul style="list-style-type: none"> <li>• A respiratory physician; and</li> <li>• A pharmacist, nurse or asthma educator.</li> </ul> |
|  | <p><b>Prescribing instructions:</b></p> <p>An adequate response to this biological medicine is defined as:</p> <p>(a) a reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 0.5 from baseline, OR</p> <p>(b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 score from baseline or an increase in ACQ-5 score from baseline less than or equal to 0.5.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|  | <p><b>Prescribing instructions:</b></p> <p>A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|  | <p><b>Prescribing instructions:</b></p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Uncontrolled severe eosinophilic or allergic asthma Grandfather PBS Authority Application - Supporting Information Form which seeks details of the following (if not already provided):</p> <p>(i) prior optimised asthma drug therapy (date of commencement and duration of therapy); and</p> <p>(ii) a eosinophil pathology report (eosinophil counts and dates) prior to initiating non-PBS-subsidised treatment with this drug; and an eosinophil pathology report (eosinophil counts and dates) no more than 4 weeks old at the time of application; or</p> <p>(iii) IgE results prior to initiating non-PBS-subsidised treatment with this drug; and IgE results no more than 4 weeks old at the time of application; and</p> <p>(iv) ACQ-5 scores including the date of assessment of the patient's symptoms, or details of the maintenance oral corticosteroid dose; and</p> <p>(v) Date of commencing non-PBS subsidised treatment with this drug</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|  | <p><b>Administrative advice:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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|  | This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.        |
|  | <b>Note:</b><br>For copies of the ACQ and the calculation sheets please contact Sanofi Medical Information on 1800 818 806. |

- 8.2 Follow on changes to the Overarching Note for this indication are required as are changes to omalizumab, benralizumab, mepolizumab restrictions as outlined below.

**FLOW ON CHANGES TO THE OVERARCHING NOTE:**

[24994] requires edits as below. Applicable to omalizumab, benralizumab and mepolizumab.

**Note**

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).

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at [www.servicesaustralia.gov.au](http://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](http://www.servicesaustralia.gov.au/hpos)

Or mailed to:

Services Australia

Complex Drugs

Reply Paid 9826

HOBART TAS 7001

**Note**

TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC OR ALLERGIC ASTHMA

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines benralizumab and mepolizumab for adult and adolescent patients with uncontrolled severe eosinophilic asthma; omalizumab for adult and adolescent patients with uncontrolled severe allergic asthma; and dupilumab for uncontrolled severe eosinophilic or allergic asthma. Therefore, where the term 'biological



medicine' appears in notes and restrictions, it refers to dupilumab, benralizumab, mepolizumab, and omalizumab only.

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

A patient receiving PBS-subsidised treatment for uncontrolled severe eosinophilic or allergic asthma or 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 [PBS listing date of dupilumab] 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 medicine 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 **4** times, they are deemed to have completed a single treatment cycle. They must have at least a 12-month break in PBS-subsidised biological medicine therapy before they are eligible to recommence another new treatment cycle [further details are under 'Recommencement of treatment after a treatment break in PBS-subsidised therapy' below].

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 eosinophilic or 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 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; 5 item version) or oral corticosteroid dose 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.

For patients transitioned from the paediatric to the adolescent/adult restriction, the exacerbation history may also be used to determine response.

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-subsidised 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 within the same treatment cycle.

Within the same treatment cycle a patient may alternate between therapy with any biological medicine of their choice (1 at a time) providing:

(i) they have not received PBS-subsidised 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 all 4 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 12 months (in patients who have failed to achieve or ceased to sustain a response to treatment 4 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 medications 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.

Note

Special Pricing Arrangements apply.

FLOW ON CHANGES TO OMALIZUMAB, BENRALIZUMAB AND MEPOLIZUMAB:

Flow on change required – change the numeral ‘3’ to ‘4’ for the following PBS items:

1. Applicable to omalizumab 10109C, 10122R, 10110D, 10118M

[25384] edits required to ‘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 3 biological medicines for severe asthma within the same treatment cycle.’

2. Applicable to benralizumab 11994G, 11997K, 11523L, 11549W

[25459] edits required to ‘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 3 biological medicines within the same treatment cycle.’

3. Applicable to mepolizumab 10996R, 11003D, 12007Y, 12051G

[25450] edits required to ‘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 3 biological medicines within the same treatment cycle.’

## **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.