

## 6.19 MEPOLIZUMAB

### Powder for injection, 100 mg, Nucala<sup>®</sup>, GlaxoSmithKline Australia

#### 1 Purpose of Application

- 1.1 The minor submission requested extending the period of validity for the eosinophil blood test in the restriction of mepolizumab from 6 weeks to 12 months to align with the current IgE test validity period for the omalizumab restriction.

#### 2 Requested listing

- 2.1 The submission requested the following change to only the initial treatment phase. An abridged version of the initial treatment phase restriction is presented below, where the change is shown in **bold**.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
MEPOLIZUMAB 100 mg injection, 1 vial	1	7	Public: \$1638.00 Private: \$1685.15	Nucala GlaxoSmithKline Australia Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Uncontrolled severe eosinophilic asthma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

<b>Clinical criteria:</b>	<p>Patient must be under the care of the same physician for at least 12 months, AND</p> <p>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, AND</p> <p>Patient must have a duration of asthma of at least 1 year, AND</p> <p>Patient must have forced expiratory volume (FEV1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months, AND</p> <p>Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last <del>6 weeks</del>12 months, AND</p> <p>Patient must have signed a patient or parent/guardian acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment, AND</p> <p>Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented, AND</p> <p>The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised omalizumab.</p>
<b>Treatment criteria</b>	As per existing restriction (no changes proposed)
<b>Prescriber Instructions</b>	As per existing restriction (no changes proposed)
<b>Population criteria</b>	As per existing restriction (no changes proposed)
<b>Administrative Advice</b>	As per existing restriction (no changes proposed)

### 3 Background

- 3.1 Mepolizumab was TGA registered on 25 January 2016 for add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over.
- 3.2 The PBAC recommended the listing of mepolizumab under Section 100 Highly Specialised Drugs Program (HSD) for the treatment of severe eosinophilic asthma in patients aged 12 years and over at its July 2017 meeting on a cost-minimisation basis with omalizumab. Prior to this, mepolizumab was rejected by the PBAC for the same indication at its March 2016 meeting on the basis of high and uncertain cost-effectiveness in the comparison with standard of care, and inappropriate equi-effective doses proposed in the cost-minimisation analysis against omalizumab.
- 3.3 At its November 2010 meeting, the PBAC recommended expanding the listing of omalizumab for the treatment of severe allergic asthma in patients with a baseline

IgE of 30-75 IU/mL. Omalizumab was previously rejected by the PBAC for this indication at its November 2009 meeting.

## **4 Current situation**

- 4.1 Eosinophilic asthma is a Type 2 T helper driven asthma inflammation which differs from atopic and allergic asthma in that it is usually later-onset ( $\geq 20$  years), more severe, less allergic and is often refractory to corticosteroid therapy. Patients suffer from persistent symptoms and acute exacerbations despite treatment with high-dose inhaled corticosteroids plus additional controller therapy. Some patients who have eosinophilic asthma also have allergic asthma.
- 4.2 Mepolizumab is targeted at the IL-5 pathway (i.e. eosinophil-mediated inflammation) whereas omalizumab is targeted at immunoglobulin E (IgE)-driven asthma. Hence the biomarker of interest for mepolizumab and omalizumab are eosinophils and IgE, respectively.
- 4.3 Mepolizumab is used in combination with standard of care. It is given by subcutaneous (SC) injection once every four weeks.
- 4.4 The current initial treatment phase restriction for mepolizumab specifies that the 'patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 6 weeks'.
- 4.5 The current initial treatment phase restriction for omalizumab specifies that 'the initial IgE assessment must be no more than 12 months old at the time of application'.
- 4.6 The submission did not propose a change in clinical place in therapy.
- 4.7 A summary of the key differences between the initial treatment phase restrictions for mepolizumab and omalizumab are presented below in Table 1.

**Table 1: Key differences between the initial restrictions for mepolizumab and omalizumab**

Component	Mepolizumab July 2016 (listed January 2017)	Omalizumab July 2016 (listed December 2016)
PBS indication	Uncontrolled severe eosinophilic asthma	Uncontrolled severe allergic asthma
Program	Section 100 (Highly Specialised Drug (HSD) Program), authority required in writing	
Treatment criteria	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.	
Clinical criteria	<p>Patient must be under the care of the same physician for at least 12 months,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p>Patient must have a duration of asthma of at least 1 year,</p> <p>AND</p> <p>Patient must have forced expiratory volume (FEV1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months,</p> <p>AND</p> <p><b>Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last 6 weeks,</b></p> <p>AND</p> <p>Patient must have signed a patient or parent/guardian acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p><b>The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised omalizumab.</b></p>	<p>Patient must be under the care of the same physician for at least 12 months,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p>Patient must have a duration of asthma of at least 1 year,</p> <p>AND</p> <p>Patient must have forced expiratory volume (FEV1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months,</p> <p>AND</p> <p><b>Patient must have past or current evidence of atopy, documented by skin prick testing or RAST,</b></p> <p>AND</p> <p><b>Patient must have total serum human immunoglobulin E greater than or equal to 30 IU/mL,</b></p> <p>AND</p> <p>Patient must have signed a patient or parent/guardian acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment,</p> <p>AND</p> <p>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,</p> <p>AND</p>

Component	Mepolizumab July 2016 (listed January 2017)	Omalizumab July 2016 (listed December 2016)
		<p><b>Patient must not receive more than 28 weeks of treatment under this restriction,</b> AND <b>The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised mepolizumab.</b></p>
Population criteria	Patient must be aged 12 years or older.	
Prescriber instructions	<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>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><b>The Asthma Control Questionnaire (5 item version) assessment of the patient must be made at time of application for treatment (to establish baseline score) and again around 26 to 30 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed.</b></p> <p><b>This assessment at around 26 to 30 weeks, which will be used to determine eligibility for continuing treatment, must be submitted within 4 weeks of</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>The initial IgE assessment must be no more than 12 months old at the time of application.</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><b>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, must be made at around 22 to 26 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed.</b></p>

Component	Mepolizumab July 2016 (listed January 2017)	Omalizumab July 2016 (listed December 2016)
	<p>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 within this timeframe, the patient will be deemed to have failed to respond to treatment with mepolizumab.</p> <p>A patient who fails to respond to a course of PBS-subsidised mepolizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with mepolizumab or omalizumab within 6 months of the date on which treatment was ceased.</p> <p><b>At the time of the authority application, medical practitioners should request 7 repeats to provide for an initial course of mepolizumab sufficient for 32 weeks of therapy.</b></p> <p><b>Mepolizumab and omalizumab may not be used concurrently or within 6 months of each other. A patient is required to have ceased treatment with omalizumab for 6 months prior to initiating treatment with mepolizumab.</b></p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and  <b>(b) a completed Severe Eosinophilic Asthma Initial PBS Authority Application - Supporting Information Form,</b>  which includes the following:</p> <p>(i) details of prior optimised asthma drug therapy (date of commencement and duration of therapy); and  (ii) details of severe exacerbation/s experienced in the past 12 months while receiving optimised asthma therapy (date and treatment); and  (iii) the signed patient or parent/guardian acknowledgement; and  <b>(c) a copy of the eosinophil pathology report;</b> and  (d) a completed Asthma Control Questionnaire (ACQ-5) calculation sheet including the date of assessment of the patient's symptoms.</p>	<p>This assessment, which will be used to determine eligibility for continuing treatment, must 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 within this timeframe, the patient will be deemed to have failed to respond to treatment with omalizumab.</p> <p>A patient who fails to respond to a course of PBS-subsidised omalizumab for the treatment of uncontrolled severe allergic asthma will not be eligible to receive further PBS-subsidised treatment with omalizumab or mepolizumab for this condition within 6 months of the date on which treatment was ceased.</p> <p><b>At the time of the authority application, medical practitioners should request the appropriate maximum quantity and number of repeats to provide for an initial course of omalizumab consisting of the recommended number of doses for the baseline IgE level and body weight of the patient (refer to the TGA-approved Product Information) to be administered every 2 or 4 weeks.</b></p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and  <b>(b) a completed Severe Allergic Asthma PBS Authority Application - Supporting Information Form,</b>  which includes the following:</p> <p>(i) details of prior optimised asthma drug therapy (date of commencement and duration of therapy); and  (ii) details of severe exacerbation/s experienced in the past 12 months while receiving optimised asthma therapy (date and treatment); and  (iii) the signed patient or parent/guardian acknowledgement; and  <b>(c) the IgE pathology report;</b> and  (d) a completed Asthma Control Questionnaire (ACQ-5) calculation sheet including the date of assessment of the patient's symptoms.</p>
Administrative advice	<p>The Department of Human Services website (<a href="http://www.humanservices.gov.au">www.humanservices.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>For copies of the ACQ, please contact</b></p>	<p>The Department of Human Services website (<a href="http://www.humanservices.gov.au">www.humanservices.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>For copies of the ACQ and the calculation sheets</b></p>

Component	Mepolizumab July 2016 (listed January 2017)	Omalizumab July 2016 (listed December 2016)
	<p><b>GlaxoSmithKline Medical Information on 1800 033 109.</b></p> <p>It is recommended that an application for continuing treatment is submitted at the time of the 26 to 30 week assessment, to ensure continuity of treatment for those patients who meet the continuation criteria for PBS-subsidised mepolizumab treatment.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Programs Reply Paid 9826 HOBART TAS 7001</p> <p><b>TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA</b></p> <p>Patients are eligible to commence a '<b>mepolizumab treatment cycle</b>' (initial treatment course with or without continuing treatment course/s) if they satisfy the eligibility criteria as detailed under the initial treatment restriction.</p> <p>Once a patient has either failed to achieve or maintain a response to <b>mepolizumab</b>, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 6 month break in PBS-subsidised mepolizumab therapy before they are eligible to commence the next <b>mepolizumab treatment cycle</b> or, if eligible, an '<b>omalizumab treatment cycle</b>'. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised <b>mepolizumab</b> is stopped to the date of the first application for initial treatment with <b>mepolizumab</b> under the new treatment cycle.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p> <p>(1) How to prescribe PBS-subsidised <b>mepolizumab</b> therapy:</p> <p>(a) Initial treatment:</p>	<p><b>please contact Novartis Medical Information on 1800 671 203 or <a href="mailto:medinfo.phauno@novartis.com">medinfo.phauno@novartis.com</a></b></p> <p>It is recommended that an application for continuing treatment is submitted at the time of the 22 to 26 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised omalizumab treatment.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p><b>TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE ALLERGIC ASTHMA</b></p> <p>Patients are eligible to commence an '<b>omalizumab treatment cycle</b>' (initial treatment course with or without continuing treatment course/s) if they satisfy the eligibility criteria as detailed under the initial treatment restriction.</p> <p>Once a patient has either failed to achieve or maintain a response to <b>omalizumab</b>, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 6 month break in PBS-subsidised omalizumab therapy before they are eligible to commence the next <b>omalizumab treatment cycle</b> or, if eligible, a '<b>mepolizumab treatment cycle</b>'. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised <b>omalizumab or mepolizumab</b> treatment is stopped to the date of the first application for initial treatment with <b>omalizumab or mepolizumab</b> under the new treatment cycle.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p>

Component	Mepolizumab July 2016 (listed January 2017)	Omalizumab July 2016 (listed December 2016)
	<p>Applications for initial treatment should be made where:</p> <ul style="list-style-type: none"> <li>i) a patient has received no prior PBS-subsidised <b>mepolizumab</b> treatment and wishes to commence such therapy; or</li> <li>ii) A patient wishes to recommence treatment with <b>mepolizumab</b> following a break in PBS-subsidised therapy of more than 6 months; or</li> <li>iii) <b>A patient has received prior PBS-subsidised omalizumab and wishes to commence treatment with mepolizumab after a treatment break of 6 months.</b></li> </ul> <p>All applications for initial treatment for non-grandfather patients will be limited to provide for a maximum of 32 weeks of therapy for mepolizumab.</p> <p><b>(b) Grandfather patients:</b></p> <p>For patients who commenced treatment with mepolizumab for uncontrolled severe eosinophilic asthma prior to 1 January 2017 and who continues to receive treatment at the time of application, may qualify for treatment under the initial 'grandfather' treatment restriction. A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment with mepolizumab will be authorised under this criterion. Approval will be based on the criteria included in the relevant restriction. Following completion of the Initial PBS-subsidised course, further applications for treatment with mepolizumab will be assessed under the continuing treatment restriction.</p> <p>'Grandfather' arrangements will only apply for the first treatment cycle (initial treatment course with or without continuing treatment course/s). If a 'Grandfathered' patient recommences on second and subsequent cycles after a treatment break, the 'Grandfathered' patient must re-qualify for Initial treatment under the criteria that apply to a new patient. See 'Re-commencement of treatment after a 6 month break in PBS-subsidised therapy' below for further details.</p> <p><b>(c) Continuing treatment:</b></p> <p>Following the completion of the initial treatment course with mepolizumab, a patient may qualify to receive up to a further 24 weeks of continuing treatment with mepolizumab providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing mepolizumab treatment in courses of up to 24 weeks</p>	<p>(1) How to prescribe PBS-subsidised <b>omalizumab</b> therapy:</p> <p><b>(a) Initial treatment:</b></p> <p>Applications for initial treatment should be made where:</p> <ul style="list-style-type: none"> <li>i) A patient has received no prior PBS-subsidised <b>omalizumab</b> treatment and wishes to commence such therapy; or</li> <li>ii) <b>A patient wishes to recommence treatment with omalizumab following a break in PBS-subsidised therapy of at least 6 months; or</b></li> <li>iii) <b>A patient has received prior PBS-subsidised mepolizumab and wishes to commence treatment with omalizumab after a treatment break of at least 6 months.</b></li> </ul> <p>All applications for initial treatment for non-grandfathered patients will be limited to provide for a maximum of 28 weeks of therapy of omalizumab.</p> <p><b>(b) Continuing treatment:</b></p> <p>Following the completion of the initial treatment course with omalizumab, a patient may qualify to receive up to a further 24 weeks of continuing treatment with omalizumab providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing omalizumab treatment in courses of up to 24 weeks providing they continue to sustain the response.</p> <p><b>(2) Baseline measurements to determine response:</b></p> <p>The Department of Human Services will determine whether a response to treatment has been demonstrated based on the baseline measurements of the Asthma Control Questionnaire (ACQ; 5 item version) or oral corticosteroid dose submitted with the Initial authority application for <b>omalizumab</b>. 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 the Department of Human Services will assess response according to these revised baseline</p>

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	<p>providing they continue to sustain the response.</p> <p>(2) Baseline measurements to determine response:</p> <p>The Department of Human Services will determine whether a response to treatment has been demonstrated based on the baseline measurements of the Asthma Control Questionnaire (ACQ; 5 item version) and oral corticosteroid dose, submitted with the Initial authority application for <b>mepolizumab</b>. However, prescribers may provide new baseline measurements when a new Initial treatment authority application is submitted and the Department of Human Services will assess response according to these revised baseline measurements.</p> <p>(3) Re-commencement of treatment after a 6 month break in PBS-subsidised therapy:</p> <p>A patient who wishes to trial a second or subsequent <b>mepolizumab</b> treatment cycle, or an initial omalizumab treatment cycle, following a break in PBS-subsidised therapy of at least 6 months, must re-qualify for initial treatment with respect to the indices of disease severity (oral corticosteroid dose, Asthma Control Questionnaire (ACQ-5) score, and relevant exacerbation history). Patients must have received optimised standard therapy, at adequate doses and for the minimum period specified, immediately prior to the time the new baseline assessments are performed.</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.humanservices.gov.au">www.humanservices.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>No increase in maximum quantity or number of units may be authorized</b></p> <p><b>No increase in the maximum number of repeats may be authorized.</b></p> <p>Special pricing arrangements apply.</p>	<p>measurements.</p> <p>(3) Re-commencement of treatment after a 6 month break in PBS-subsidised therapy:</p> <p>A patient who wishes to trial a second or subsequent <b>omalizumab</b> treatment cycle, or an initial mepolizumab treatment cycle, following a break in PBS-subsidised therapy of at least 6 months, must re-qualify for initial treatment with respect to the indices of disease severity (oral corticosteroid dose, Asthma Control Questionnaire (ACQ-5) score, and relevant exacerbation history). Patients must have received optimised standard therapy, at adequate doses and for the minimum period specified, immediately prior to the time the new baseline assessments are performed.</p> <p><b>(4) Monitoring of patients:</b></p> <p><b>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.</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.humanservices.gov.au">www.humanservices.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>Special Pricing Arrangements apply.</p>

## 5 Comparator

5.1 As a minor submission, there was no economic comparison.

## 6 Consideration of the evidence

### ***Sponsor hearing***

6.1 There was no hearing for this item as it was a minor submission.

### ***Consumer comments***

6.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical trials***

6.3 As a minor submission no new clinical data was presented.

6.4 The pivotal trial presented in the March 2016 and July 2016 mepolizumab submissions was Study 588 (n=580), a 32-week phase III randomised double-blind trial comparing mepolizumab with standard of care in the treatment of severe uncontrolled refractory asthma.

6.5 The submission indicated that the 6 week eosinophil blood test validity period specified in the current mepolizumab restriction is based on the 6 week run-in period post eosinophil screening to treatment initiation applied in Study 588.

6.6 The PBAC noted that the key eligibility criteria for Study 588 includes peripheral blood eosinophil count greater than or equal to 300 cells per microlitre in the past 12 months.

6.7 The omalizumab listing for the treatment of uncontrolled severe allergic asthma was largely based on the data from Trial 2306 (INNOVATE); a 28-week phase III randomised double-blind trial assessing the efficacy of omalizumab + optimal asthma therapy versus placebo + optimal asthma therapy. Two open label studies Trial 2425 (EXALT) and Trial IA04 (ETOPA) was provided as supporting evidence in the omalizumab submissions.

6.8 The submission argued that the 12 month IgE test validity period currently specified in the omalizumab restriction for the treatment of uncontrolled severe allergic asthma was not based on evidence from the omalizumab clinical trials noting that the timing of baseline IgE assessments prior to initial treatment for these trials ranged from 4 to 9 weeks.

6.9 The submission presented the clinical claim that IgE levels varied in a comparable manner to blood eosinophil levels such that a validity period of 12 months, if imposed on eosinophil assessments, would affect eligibility for PBS funded mepolizumab similarly to PBS funded omalizumab. Two studies (a retrospective analysis by Mummadi et al 2012 and a prospective study by Hatipoglu et al 2016) based in the United States were presented in the submission in support of IgE variability. The submission presented Study 997 and 558 in support of eosinophil variability. Both of these studies were previously presented in the mepolizumab submissions.

### **Basis of request**

- 6.10 The basis of the minor submission's request was clinician support for the validity period of the eosinophil blood test to be extended to 12 months in the mepolizumab PBS eligibility criteria to align with the IgE test validity period of 12 months in the PBS eligibility criteria for omalizumab.
- 6.11 The submission included clinical opinion from three Australian respiratory specialists regarding the burden on patients and prescribers imposed by the current 6 week eosinophil blood test validity period in the mepolizumab PBS eligibility criteria and why IgE and eosinophils should be subject to the same test validity period of 12 months. The submission noted that eosinophil measurements would be available within the 12 month period before application. The PBAC considered this to be reasonable.
- 6.12 According to clinical opinion in the submission, prescribers reduce or withdraw oral corticosteroids to maximise the likelihood of obtaining an eosinophil blood count of  $\geq 300$  cells per microliter within the 6 week period despite that it is widely acknowledged that this action puts patients at risk of asthma exacerbation. Consequently, if there was an exacerbation, prescribers would have to administer high dose of oral corticosteroids which in turn would suppress the eosinophil count and subsequently delay access to treatment.
- 6.13 Clinical opinion on the proportion of patients requiring a second test to confirm eosinophil blood levels of  $\geq 300$  cells per microlitre for the purposes of an application for a PBS approval was mixed, but it was agreed that a retest would further delay access to mepolizumab treatment in addition to logistical and administrative burden. The submission did not provide estimates of the proportion of patients requiring a second eosinophil blood test to meet the PBS eligibility criteria for treatment with mepolizumab.
- 6.14 The submission noted that although the analyses were not directly comparable due to differences in study designs, the submission claimed it could be considered that the results were broadly similar. The submission noted that based on the results of Hatipoglu et al 2016, 18% of patients who may have been eligible for omalizumab treatment at different time points, had IgE concentration measures at other time points which would have deemed them ineligible for treatment. The submission noted that ■% of patients in Study 997 did not maintain average eosinophil blood levels  $\geq 300$  cells per microlitre over the subsequent 56 weeks and inferred that ■% of patients were likely to have been ineligible for mepolizumab at a subsequent time point had the eosinophil assessment been conducted at a visit post screening.
- 6.15 The clinical opinion was mixed regarding the level of fluctuation for eosinophil levels over time. One clinician stated that there were studies which supported stability of eosinophil counts over a longer period. For example, data from the DREAM study showed that on average, subsequent measurements of eosinophils were still above the original screening level ( $> 150$  cells per microlitre in 85% of patients). However, the clinician noted that it is not known if stability would be similar if an eosinophil threshold of  $> 300$  cells per microlitre is used.

- 6.16 Overall, the clinicians argued that there were no clinical grounds to have a 12 month validity period for IgE tests and 6 weeks validity period for eosinophil blood tests to inform eligibility for omalizumab and mepolizumab, respectively.

### **Economic analysis**

- 6.17 As a minor submission, there was no economic comparison presented.

### **Estimated PBS usage & financial implications**

- 6.18 The minor submission estimated there to be no financial implications to the PBS/changes in PBS usage as the submission does not expect the change in restriction to change uptake numbers.
- 6.19 The pre-PBAC response (p1) stated the extension of the validity period would not expand the mepolizumab patient population as the patients would have to meet the other requirements within the current restriction. The change would ensure timely access to eligible patients and reduce the risk of exacerbations due to unnecessary modification of oral corticosteroid dose. Additionally, the pre-PBAC response reiterated that the change could potentially reduce health care costs given the reduction in blood testing and clinician appointments to retest patients as well as decrease hospitalisations because of the reduced risk of exacerbations due to modifications to patient corticosteroid doses to meet the target eosinophil count. The PBAC considered these arguments to be reasonable.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended extending the eosinophil blood test validity period from 6 weeks to 12 months in the mepolizumab listing to align with the omalizumab listing for uncontrolled severe allergic asthma.
- 7.2 The PBAC noted the clinical support for extending the validity period of eosinophil blood test to 12 months was to allow timely access to mepolizumab treatment and reduce the logistical and administrative burden on patients and clinicians. The PBAC considered that the change may reduce the risk of asthmatic exacerbations due to withdrawal or reduction of corticosteroids to maximise the likelihood of obtaining the target results within 6 weeks.
- 7.3 Consistent with the existing arrangements for current listing of mepolizumab, the PBAC advised that mepolizumab should not be treated as interchangeable with any other drugs.
- 7.4 The PBAC advised that Section 100 medicines are currently considered out of scope for prescribing by nurse practitioners.
- 7.5 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 listings. Should this change in the future, the Committee recalled that it would be appropriate for the Early Supply Rule to apply to mepolizumab.

7.6 The PBAC noted that this submission is not eligible for an Independent Review because it has received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name	Manufacturer
MEPOLIZUMAB 100 mg injection, 1 vial	1	7	Nucala	GlaxoSmithKline Australia Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Uncontrolled severe eosinophilic asthma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

<b>Clinical criteria:</b>	<p>Patient must be under the care of the same physician for at least 12 months, AND 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, AND Patient must have a duration of asthma of at least 1 year, AND Patient must have forced expiratory volume (FEV1) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months, AND Patient must have blood eosinophil count greater than or equal to 300 cells per microlitre in the last <del>6 weeks</del> <b>12 months</b>, AND Patient must have signed a patient or parent/guardian acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment, AND Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised omalizumab.</p>
<b>Treatment criteria</b>	As per existing restriction (no changes proposed)
<b>Prescriber Instructions</b>	As per existing restriction (no changes proposed)
<b>Population criteria</b>	As per existing restriction (no changes proposed)
<b>Administrative Advice</b>	As per existing restriction (no changes proposed)

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 10 Sponsor's Comment

GSK welcomes the PBAC recommendation.