

5.01 BENRALIZUMAB, 30 mg in 1 mL injection, Fasenra[®], AstraZeneca Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drug Program) listing for benralizumab subcutaneous injection for the treatment of uncontrolled severe eosinophilic asthma in patients aged 18 years and over. Benralizumab has not previously been considered by the PBAC.
- 1.2 Listing was requested on a cost-minimisation basis compared with mepolizumab and omalizumab.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults aged ≥ 18 years with uncontrolled severe eosinophilic asthma TGA/PBAC Parallel Process: The TGA delegate recommended that benralizumab be registered for use in patients ≥ 12 years; the Advisory Committee on Medicines agreed with this.
Intervention	Benralizumab 30 mg by SC injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter, as an add-on to ICS and LABA therapy.
Comparator	Mepolizumab 100 mg SC injection every 4 weeks; or Omalizumab SC injection every 2 or 4 weeks, dose depends on patient weight and IgE levels. The PBAC considered that mepolizumab was the appropriate main comparator.
Outcomes	Key outcome: annual asthma exacerbation rate (which aligned with “clinically significant asthma exacerbations” which was the key outcome accepted by the PBAC for mepolizumab). Secondary outcomes: reduction in OCS dose, ACQ score, safety.
Clinical claim	The submission claimed that benralizumab was non-inferior to mepolizumab and omalizumab in reducing asthma exacerbations and has a comparable safety profile.

Source: Table 1.1, p9 of the submission

ACQ = asthma control questionnaire; IgE = immunoglobulin E; ICS = inhaled corticosteroids; LABA = long acting beta-agonist; OCS = oral corticosteroid; PBAC = Pharmaceutical Benefits Advisory Committee; SC = subcutaneous

2 Requested listing

Initial treatment phase (abridged)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection (prefilled syringe)	1	4	Public (published): \$ [REDACTED] Private (published): \$ [REDACTED] Effective price: based on comparators	Fasenra® AstraZeneca Pty Ltd

Category/Program:	Section 100 Highly Specialised Drug Program - public and private
PBS indication:	Uncontrolled severe eosinophilic asthma
Treatment phase:	Initial
Restriction:	Authority Required – In Writing
Clinical criteria:	<p>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 6 weeks, 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 or mepolizumab.</p>
Population criteria:	<p>Patient must be aged 18 years or older. The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND (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>

Continuing treatment phase (abridged)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection (prefilled syringe)	1	2	Public (published): \$ [REDACTED] Private (published): \$ [REDACTED] Effective price: based on comparators	Fasenra® AstraZeneca Pty Ltd
Category/Program:	Section 100 Highly Specialised Drug Program - public and private			
PBS indication:	Uncontrolled severe eosinophilic asthma			
Treatment phase:	Continuing			
Restriction:	Authority Required – In Writing			
Clinical criteria:	Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised omalizumab or mepolizumab.			
Population criteria:	Patient must be aged 18 years or older. An adequate response to mepolizumab <i>benralizumab</i> treatment is defined as: (a) a reduction in the Asthma Control Questionnaire (ACQ-5) score of at least 0.5 from baseline, OR (b) maintenance OCS dose reduced by at least 25% from baseline, and no deterioration in ACQ-5 score from baseline.			

Grandfathering restriction (abridged): As proposed in the Pre-Sub-Committee Response

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection (prefilled syringe)	1	2	Public (published): \$ [REDACTED] Private (published): \$ [REDACTED] Effective price: based on comparators	Fasenra® AstraZeneca Pty Ltd
Category/Program:	Section 100 Highly Specialised Drug Program - public and private			
PBS indication:	Uncontrolled severe eosinophilic asthma			
Treatment phase:	Initial			
Restriction:	Authority Required – In Writing			
Clinical criteria:	Patient must have received non-PBS treatment with this drug for this condition prior to [DATE TO BE FINALISED], AND Patient must be receiving treatment with this drug for this condition at the time of application,			
Population criteria:	Patient must be aged 18 years or older.			

- 2.1 The submission proposed a special pricing arrangement for benralizumab with the price to be based on the effective price of the comparators, mepolizumab and omalizumab.
- 2.2 The proposed maximum quantity and repeats were based on a dosing regimen of one subcutaneous injection every four weeks for the first three doses, then every eight weeks thereafter. This aligned with the draft product information; however, the key clinical trials also included a treatment arm where patients were dosed every four weeks. The evaluation considered that it was not known whether the four-weekly regimen would be used in clinical practice, for example in patients with inadequate response to the eight-weekly regimen. While the risk of more frequent use would be minimised by the written authority requirement, it may limit the clinical benefits achieved in some patients.

- 2.3 The Pre-Sub-Committee Response (PSCR) noted there were two minor submissions on the March 2018 PBAC meeting agenda, both requesting changes to the PBS restrictions for biologics for severe uncontrolled asthma. The PSCR noted these submissions may have potential flow-on effects to the proposed restriction, which are discussed in the March 2018 PBAC Public Summary Documents (PSD) for mepolizumab and benralizumab.
- 2.4 The submission requested a separate grandfathering restriction for patients in ongoing studies and in a patient familiarisation program. Proposed wording for the restriction was provided in the PSCR, based on the grandfathering restriction for mepolizumab. The submission's financial estimates included five grandfathered patients from a safety extension study. The evaluation noted that this may have been an underestimate as it did not include patients in the patient familiarisation program.

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

3 Background

Registration status

- 3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Delegates Overview and Advisory Committee on Medicines Minutes were available. The Advisory Committee on Medicines Minutes stated that the committee considered benralizumab to have an overall positive benefit-risk profile for the relevant indication.
- 3.2 The draft indication, including the specified age group, changed throughout the TGA registration process. The sponsor initially proposed the following TGA indication: "[benralizumab] is indicated as an add-on maintenance treatment for severe asthma in patients with an eosinophilic phenotype." The pre-PBAC response stated that, following the Advisory Committee on Medicines meeting, the TGA Delegate had recommended the indication: "[benralizumab] is indicated as an add-on maintenance treatment in patients aged ≥ 12 years of age, with severe eosinophilic asthma (with blood eosinophil count of ≥ 300 cells/ μ L or ≥ 150 if on chronic OCS treatment)."
- 3.3 The pre-PBAC response noted that the TGA delegate recommended that benralizumab should be indicated in patients aged 12 years and over, which was broader than the age range included in the submission's proposed restriction (18 years and over), but was consistent with the PBS restriction for mepolizumab.

Previous PBAC considerations in severe eosinophilic asthma

- 3.4 Two monoclonal antibodies are PBS-listed for specific subtypes of severe uncontrolled asthma: mepolizumab and omalizumab. Mepolizumab was listed for eosinophilic asthma on 1 January 2017. It was recommended on a cost-minimisation basis to omalizumab. The key outcome presented was the rate of

clinically significant exacerbations. For the indirect comparison between mepolizumab and omalizumab (with standard of care as the common comparator) the rate ratio was 0.64 (95% confidence interval (CI): 0.45, 0.90) which statistically significantly favoured mepolizumab (Paragraph 6.15, Mepolizumab Public Summary Document, March 2016). The cost-minimisation analysis incorporated cost-offsets to account for costs associated with administration, the treatment of adverse events (anaphylaxis), and longer supervision due to the potential for anaphylaxis with omalizumab (Paragraph 7.3, Mepolizumab Public Summary Document, July 2016).

- 3.5 Omalizumab was first PBS-listed on 1 July 2011 for severe uncontrolled allergic asthma (elevated immunoglobulin E levels), which overlaps with eosinophilic asthma in some patients. It was recommended on a cost-effectiveness basis compared with standard of care.

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

4 Population and disease

- 4.1 Eosinophilic asthma occurs in response to inflammatory stimuli, usually has a late-onset (e.g. 20 years of age and over), and is often refractory to corticosteroid therapy. Benralizumab is a monoclonal antibody that targets the interleukin-5 pathway (i.e. eosinophil-mediated inflammation).
- 4.2 Benralizumab was proposed for use in patients with severe eosinophilic asthma that is uncontrolled with standard of care therapy. It is intended to be added-on to standard of care, which usually includes high-dose inhaled corticosteroids plus long-acting beta-agonists and, in some cases, oral corticosteroids.
- 4.3 The ESC noted that biologic therapies are intended for use as part of a comprehensive asthma management plan following optimisation of other therapies including assessment of patient compliance and inhaler technique.
- 4.4 The submission proposed that benralizumab would be an alternative to mepolizumab in patients with eosinophilic asthma, and to omalizumab in patients with overlapping eosinophilic and allergic asthma.
- 4.5 Benralizumab is administered, via subcutaneous injection, every eight weeks while mepolizumab is administered every four weeks, and omalizumab is administered every two to four weeks.

5 Comparator

- 5.1 The submission nominated mepolizumab as the main comparator. The key argument provided in support of this nomination was that mepolizumab was the only PBS-listed drug for the same indication and both drugs act on the interleukin-5 pathway. The ESC and the PBAC agreed that mepolizumab was the appropriate main comparator.

- 5.2 The submission nominated omalizumab as a secondary comparator because it is PBS-listed for allergic asthma, which overlaps with eosinophilic asthma in some patients (i.e. some patients have both allergic and eosinophilic asthma) so omalizumab would be a comparator in these patients. The nominated comparators were 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 health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the burden of illness associated with uncontrolled severe asthma and stated that effective biologic therapies can significantly improve quality of life. The comments highlighted the benefits of having an additional treatment option available. Further, Asthma Australia claimed that the less frequent administration requirements for benralizumab (every eight weeks versus every two to four weeks for alternative therapies) would reduce the logistical burden for some patients, particularly those in rural and remote areas.
- 6.3 The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

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

Table 2: Trials and associated reports presented in the submission

Trial ID/Author	Protocol title/ Publication title	Publication citation
Randomised controlled trial – benralizumab versus standard of care/placebo		
CALIMA	A multicentre, randomized, double-blind, parallel group, placebo-controlled, phase 3 study to evaluate the efficacy and safety of benralizumab in asthmatic adults and adolescents inadequately controlled on inhaled corticosteroid plus long-acting β 2 agonist (CALIMA). Clinical Study Report (CSR).	August 2016
Fitzgerald 2016	FitzGerald JM, Bleecker ER, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe uncontrolled, eosinophilic asthma (CALIMA): a randomised double-blind, placebo-controlled phase 3 trial.	Lancet 2016; 388:2128–41.
SIROCCO	Multicentre, randomized, double blind, parallel group, placebo controlled, phase 3 efficacy and safety study of benralizumab (MEDI 563) added to high dose inhaled corticosteroid plus long acting β 2 agonist in patients with uncontrolled asthma (SIROCCO). Clinical study report (CSR).	August 2016
Bleecker 2016	Bleecker ER, FitzGerald JM, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β 2-agonists (SIROCCO): A randomised, multicentre, placebo-controlled phase 3 trial.	Lancet 2016; 388:2115–27.
ZONDA	A multicenter, randomized, double-blind, parallel group, placebo-controlled, phase 3 efficacy and safety study of benralizumab (MEDI-563) to reduce oral corticosteroid use in patients with uncontrolled asthma on high dose inhaled corticosteroid plus long-acting β 2 agonist and chronic oral corticosteroid therapy (ZONDA). Clinical Study Report (CSR).	CSR, October 2016
Nair 2017	Nair P, Wenzel S, et al. Benralizumab significantly reduced oral corticosteroid dosages and asthma exacerbation rates for patients with severe, uncontrolled asthma: Results of the ZONDA phase III trial. Nair P, Wenzel S, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma.	American Journal of Respiratory and Critical Care Medicine 2017; 195: A4678. NEJM 2017; 376: 2448-5.
Randomised controlled trial – mepolizumab versus standard of care/placebo		
MUSCA	Chupp, GL, Bradford ES, 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-blinded, placebo controlled, parallel-group, multicentre, phase 3b trial.	Lancet Respir Med 2017; 5:390-400.
MENSA (Study 588)	Ortega HG, Liu MC, et al. Mepolizumab treatment in patients with severe eosinophilic asthma.	NEJM 2014; 371:1198-207.
SIRIUS (Study 575)	Bel EH, Wenzel SE, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.	NEJM 2014; 371:1189-97.

Trial ID/Author	Protocol title/ Publication title	Publication citation
Randomised controlled trial – omalizumab versus standard of care/placebo		
INNOVATE	Humbert M, Berger SW, et al. Add on omalizumab improves day to day symptoms in inadequately controlled severe persistent allergic asthma.	Allergy 2008; 63:592 6.
Sthoeger 2007	Sthoeger ZM, Eiraz A, et al. The beneficial effects of Xolair® (omalizumab) as add on therapy in patients with severe persistent asthma who are inadequately controlled despite best available treatment (GINA 2002 step IV) – the Israeli arm of the INNOVATE study.	J Allergy Clin Immunol 2007; 9:472 5.
Humbert 2005	Humbert M, Beasley R, 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).	Allergy 2005; 60:309 16.
EXTRA	Hanania NA, Wenzel S, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Hanania NA, Alpan O, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial.	Am J Respir Crit Care Med. 2013; 187: 804-44. Ann Intern Med 2011; 154: 573-82.

Source: Table 2.2, p32 of the submission

- 6.5 The submission was based on indirect comparisons of benralizumab with mepolizumab and omalizumab, using standard of care/placebo as the common comparator. The indirect comparisons were based on five trials that reported asthma exacerbation rates. The key features of these trials are summarised in Table 3.

Table 3: Key features of the evidence used in the indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Benralizumab versus standard of care/placebo					
CALIMA	Total trial: 1,306 Efficacy population: 728 ^a	R, DB, MC 56 weeks	Low	Total trial: Severe uncontrolled asthma Efficacy population: EOS ≥ 300 + high-dose ICS	Annual asthma exacerbation rate, ACQ
SIROCCO	Total trial: 1,205 Efficacy population: 809 ^a	R, DB, MC 48 weeks	Low	Total trial: Severe uncontrolled asthma, on high-dose ICS Efficacy population: EOS ≥ 300	Annual asthma exacerbation rate, ACQ
Mepolizumab versus standard of care/placebo					
MENSA	576 ^a	R, DB, MC 32 weeks	Low	Severe uncontrolled refractory asthma on high-dose ICS, EOS ≥ 300 in past year or ≥ 150 at screening	Annual asthma exacerbation rate, ACQ
Omalizumab versus standard of care/placebo					
INNOVATE	419 ^b	R, DB, MC 28 weeks	Unclear ^c	Severe persistent allergic asthma	Exacerbation rate per 28 weeks, ACQ
EXTRA	848	R, DB, MC 48 weeks	Low	Severe uncontrolled allergic asthma	Exacerbation rate per 48 weeks, ACQ

Source: compiled during the evaluation

ACQ = asthma control questionnaire; DB = double blind; EOS = eosinophil; ICS = inhaled corticosteroid; MC = multi-centre; q4w = every four weeks; R = randomised

^a 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).

^b 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.

^c 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.

Benralizumab trials (CALIMA and SIROCCO)

- 6.6 The two key benralizumab trials (CALIMA and SIROCCO) recruited patients with severe, uncontrolled asthma taking inhaled corticosteroids plus long-acting beta-agonists.
- 6.7 For both CALIMA and SIROCCO, the submission focused on the “primary efficacy analysis populations”, which were the populations for which the trials were powered. This comprised patients with baseline eosinophils 300 cells/μL or higher (both trials) and those taking high-dose inhaled corticosteroids (in CALIMA only, as all patients in SIROCCO were taking high-dose inhaled corticosteroids). The Clinical Study Reports pre-specified this as the primary analysis and this group most closely reflected the proposed PBS population (which requires an eosinophil count 300 cells/μL or higher). Both trials recruited patients with eosinophil counts higher and lower than 300 cells/μL, in a two to one ratio. The group with eosinophil counts 300 cells/μL or higher were considered more likely to respond, while patients below this threshold were also included “in order to help understand efficacy and safety in this group”. The Clinical Study Reports did not report the total trial results, but rather reported the two groups separately.

- 6.8 CALIMA and SIROCCO had very similar designs, assessed the same interventions, were conducted over the same timeframe and measured the same outcomes. Both trials also had the same inclusion criteria for co-interventions other than inhaled corticosteroids: patients were required to be taking long-acting beta-agonists for at least 12 months (no minimum dose specified); and additional controller medicines were permitted if these had been taken for more than 30 days prior to study entry (e.g. tiotropium or maintenance oral corticosteroids).
- 6.9 Key differences were that the trials: were conducted in different countries (e.g. CALIMA included more patients from South and Central America than SIROCCO); and had different durations (56 weeks versus 48 weeks). Further, while both trials originally recruited patients taking high-dose inhaled corticosteroids (over 500 µg per day fluticasone), a protocol amendment to CALIMA allowed enrolment of patients taking medium-dose inhaled corticosteroids (over 250 µg per day); these patients were not included in the primary efficacy population.
- 6.10 Between the two benralizumab trials, CALIMA may have recruited patients with less severe asthma than SIROCCO as indicated by fewer patients on baseline oral corticosteroids (11% versus 17%, respectively) and fewer patients with prior exacerbations requiring hospitalisation (18% versus 26%). Further, CALIMA recruited more patients from South and Central America than SIROCCO (23% versus 12%), which may have affected access to background medications, though the direction of this bias was difficult to determine.
- 6.11 Both trials had three arms: benralizumab every four weeks; benralizumab every four weeks for the first three doses then every eight weeks thereafter; and standard of care/placebo. The submission used the results of the eight-weekly dosing regimen for the clinical claim, cost-minimisation analysis and financial estimates as this regimen was requested for PBS-listing. While the eight-weekly dose is the only one requested and being considered by the TGA, the results of the four-weekly dosing regimen are also presented.

Outcome used in the indirect comparison

- 6.12 The indirect comparison was based on the outcome of asthma exacerbations. In the benralizumab and mepolizumab trials, these were defined as exacerbations requiring: use of systemic corticosteroids for at least three days (or a single intra-muscular dose); an emergency department presentation; and/or hospital admission. This definition aligned with the outcome that the PBAC had previously considered for “clinically significant exacerbations” in its consideration of mepolizumab (March and July 2016). The definition of exacerbations in the omalizumab trials did not include emergency department or hospital admissions; however, the difference would likely be minimal as this level of severity would generally require systemic corticosteroids.
- 6.13 There were no precedents for non-inferiority margins for clinically significant asthma exacerbations in previous PBAC considerations. The submission proposed a

non-inferiority margin of 28% based on the EXTRA trial (omalizumab), which was powered to detect a 28% reduction in exacerbation rates. The submission considered that this was more conservative (in terms of demonstrating non-inferiority) than the benralizumab trials, which were powered to detect a 40% difference in exacerbation rates.

- 6.14 The evaluation considered that the non-inferiority margin chosen by the submission was poorly justified as it did not include consideration of other statistical methods or the clinical relevance of this difference. The PBAC Guidelines (Version 5.0) state that a submission should “justify the approach taken to establish the non-inferiority margin, noting that a statistical approach by itself is inadequate” (page 39). The evaluation considered that it was unclear whether a 28% difference in clinically significant exacerbations represents the smallest clinically meaningful difference given the seriousness of exacerbations.

Comparative effectiveness

- 6.15 Table 4 presents the annual asthma exacerbation rates for benralizumab versus standard of care for the primary efficacy population (eosinophil count 300 cells/ μ L or higher and high-dose inhaled corticosteroids) and the complement (patients with eosinophil count less than 300 cells/ μ L).

Table 4: Results of “primary efficacy population” and complement results

Trial ID	Dose	BEN n	SOC n	Annual exacerbation rate (95% CI)		RR (95% CI)	RD (95% CI)
				Benralizumab	Standard of care		
Primary efficacy population: EOS \geq 300 cells/μL, high dose ICS (SIROCCO were all high dose ICS)							
CALIMA	q8w	239	248	0.66 (0.54, 0.82)	0.93 (0.77, 1.12)	0.72 (0.54, 0.95)	-26% (-48%, 4%)
	q4w	241		0.60 (0.48, 0.74)			
SIROCCO	q8w	267	267	0.65 (0.53, 0.80)	1.33 (1.12, 1.58)	0.49 (0.37, 0.64)	-68% (-0.95, -0.41)
	q4w	275		0.73 (0.60, 0.89)			
Complement: EOS < 300 cells/μL, high dose ICS^a							
CALIMA	q8w	125	122	0.73 (0.55, 0.95)	1.21 (0.96, 1.52)	0.60 (0.42, 0.86)	-48% (-0.82, -0.14)
	q4w	116		0.78 (0.59, 1.02)			
SIROCCO	q8w	131	140	1.00 (0.78, 1.28)	1.21 (0.96, 1.52)	0.83 (0.59, 1.16)	-21% (-0.58, 0.16)
	q4w	124		0.85 (0.65, 1.11)			

Source: Table 2.15, pp74-75 of submission; CSR (CALIMA, SIROCCO)

BEN = benralizumab; CI = confidence interval; EOS = eosinophil; ICS = inhaled corticosteroid; q4w = every 4 weeks; q8w = every 8 weeks; RD = rate difference; RR = rate ratio; SOC = standard of care

^a Results were not available for “full complement” for CALIMA as results in the medium-dose ICS group were not available. Also note that the SOC exacerbation rate was identical in both trials for the complement.

- 6.16 In CALIMA and SIROCCO, benralizumab every eight weeks was associated with a reduction in the annual asthma exacerbation rate of 28% and 51%, respectively, versus standard of care in the primary efficacy population (rate ratio of 0.72 [95% CI: 0.54, 0.95] and 0.49 [95% CI: 0.37, 0.64], respectively). The four weekly regimen was associated with a greater reduction in exacerbations in CALIMA, but not SIROCCO.

6.17 Whilst the trials were not powered to compare outcomes in the lower versus the higher eosinophil groups, a greater treatment effect was observed in patients with lower eosinophils than those with higher eosinophils in CALIMA, but the opposite was observed in SIROCCO. In CALIMA, this result may have been confounded by the higher exacerbation rate in the standard of care arm in the subgroup with lower eosinophils than higher eosinophils (1.21 versus 0.93).

Indirect comparison: Transitivity assumption

6.18 The submission conducted an indirect comparison between benralizumab (using the primary efficacy population) and the comparators for the outcome of asthma exacerbation rates using standard of care as the common reference. However the transitivity assumption was unlikely to hold due to differences in participant baseline characteristics, event rates in the common reference arm, and trial duration. These are each discussed in turn below.

6.19 Table 5 shows some of the key differences in inclusion criteria and baseline characteristics between the trials included in the indirect comparison.

Table 5: Key inclusion criteria and baseline characteristics that differed between the trials

	Benralizumab primary efficacy pop ^a		Mepolizumab	Omalizumab	
	CALIMA	SIROCCO	MENSA	INNOVATE	EXTRA
N	487	534	385	419	848
Inclusion criteria					
EOS count at baseline	≥ 300 cells/μL		≥ 150 cells/μL (or ≥300 in past 12 months)	Not applicable (inclusion was based on IgE levels instead)	
Prior ICS dose per day ^b	> 500 μg for ≥ 3 months		≥ 880 μg for ≥ 12 months	> 1,000 μg for ≥ 12 months	≥ 1,000 μg for ≥ 8 weeks
Baseline characteristics					
EOS count, mean cells/μL (SD)	632 (411)	620 (375)	305 (994)	NA	NA
Baseline ICS dose/ day mean ^b	966 μg	908 μg	NR	2,330 μg	NR
No. of exacerbations in past year, mean	2.7	3.0	3.7	2.5	2
% with ≥ 1 exacerbation requiring hospitalisation	18%	26%	17%	39%	NR
Time since asthma diagnosis, median yrs	17	14	20	23	24
% on maintenance OCS	11%	17%	25%	22%	17%

Source: Clinical study reports (p96-109 of SIROCCO; p94-108 of CALIMA); Ortega HG et al, 2014; Humbert et al 2008; Hanania et al 2011; Sthoeger et al 2007

EOS = eosinophils; ICS = inhaled corticosteroid; IgE = immunoglobulin E; NA = not applicable; NR = not reported; OCS = oral corticosteroids; pop = population; SD = standard deviation; yrs = years

^a Based on the primary efficacy population and the eight-weekly and placebo groups only

^b Fluticasone propionate dry powder inhaler or equivalent. Note these are the doses in patients aged ≥ 18 years only.

6.20 Patients in the mepolizumab trial (MENSA) may have had more severe asthma than patients in the benralizumab trials, especially CALIMA. Patients in MENSA had more

prior exacerbations (3.7 in the previous year versus 2.7 in CALIMA), were more likely to be on oral corticosteroids at baseline (25% versus 11% in CALIMA) and were likely to have a higher baseline dose of inhaled corticosteroids (the inclusion criteria were $\geq 880 \mu\text{g}$ versus $> 500 \mu\text{g}$ per day of fluticasone propionate). On the other hand, patients in MENSA had lower baseline eosinophils than those in the benralizumab trials. (This was, in part, due to lower thresholds in the inclusion criteria, which were $\geq 150 \text{ cells}/\mu\text{L}$ at baseline or ≥ 300 in the past year in MENSA, versus ≥ 300 at baseline in the benralizumab trials. The ESC noted that this may also have been due to higher rates of use of oral corticosteroids, which reduce eosinophil levels, in the MENSA trial.) While the overall direction of bias was likely to favour mepolizumab, there were many confounding factors which could be considered in any adjustment for bias. The key difference between patients in the omalizumab and benralizumab trials was that they recruited patients with a different type of asthma (allergic versus eosinophilic).

- 6.21 The exacerbation rates in the common reference arms (standard of care) differed substantially, as shown in Table 6. Exacerbation rates in the standard of care arms were much lower in the benralizumab trials than the other trials (0.93 and 1.33 exacerbations per year in CALIMA and SIROCCO respectively versus 1.74 per year in the MENSA trial of mepolizumab and 0.91 over 28 weeks in the INNOVATE trial of omalizumab). These differences likely reflect the effect of heterogeneity across the trials as discussed above.
- 6.22 With regard to trial duration, the omalizumab trials did not report annualised exacerbation rates and the INNOVATE trial was only 28 weeks, while EXTRA was 48 weeks. While the benralizumab and mepolizumab trials reported annualised exacerbation rates, differences in duration may affect results if exacerbation rates are not distributed homogeneously (e.g. due to seasonal exacerbations or patients spending longer at steady state).
- 6.23 The indirect comparison is presented in the table below. Rate differences were not presented in the submission, which may have been appropriate given the difference in trial durations.

Table 6: Indirect comparison of clinically significant exacerbations (primary efficacy population, q8w dose)

Trial	Benralizumab		SOC Exac rate/yr	Mepolizumab / Omalizumab		Indirect RR ^a (95% CI)
	RR (95% CI)	BEN Exac rate/yr		Exac rate/yr	RR (95% CI)	
Benralizumab (30 mg q8w) versus mepolizumab (100 mg SC)						
CALIMA (n = 487), efficacy population	0.72 (0.54, 0.95)	0.66 (0.54, 0.82)	0.93 (0.77, 1.12)	-	-	-
SIROCCO (n = 534) efficacy population	0.49 (0.37, 0.64)	0.65 (0.53, 0.80)	1.33 (1.12, 1.58)	-	-	-
MENSA (n = 385)	-	-	1.74	0.83	0.47 (0.35, 0.64)	-
Pooled random effects	0.59 (0.41, 0.86) ^b	-	-	-	0.47 (0.35, 0.64)	1.25 (0.78, 2.02)
Benralizumab (30 mg q8w) versus omalizumab						
INNOVATE (n = 419)	-	-	0.91 per 28 wks	0.68 ^c	0.74 (0.55, 1.00)	-
EXTRA (n = 848)	-	-	0.88 per 48 wks	0.66 ^c	0.75 (0.61, 0.92)	-
Pooled random effects	0.59 (0.41, 0.86) ^b	-	-	-	0.75 (0.63, 0.88) ^d	0.78 (0.52, 1.18)

Source: Table 2.34, p105 of the submission, Humbert 2005; Ital = values in italics were calculated or corrected during evaluation
 BEN = benralizumab; CI = confidence interval; exac = exacerbation; ICS = inhaled corticosteroid; q8w = every 8 weeks; RR = rate ratio;
 SOC = standard of care (placebo); yr = year

^a The submission did not present rate differences, which may have been appropriate given the difference in trial durations and also the differences in baseline risks across the trials.

^b Random effects model, using Generic Inverse Variance Method (natural log of rate ratios), RevMan 5.3. Result with Fixed Effects model was 0.59 (0.48, 0.72). $I^2 = 72\%$

^c Exacerbation rates were not annualised in INNOVATE (28 weeks) and EXTRA (48 weeks) trials

^d Heterogeneity = 0.931; $I^2 = 0\%$

- 6.24 The rate ratio for the difference in exacerbation rates between benralizumab and mepolizumab was 1.25 (95% CI: 0.78, 2.02). The ESC noted that the mean rate ratio (1.25) was close to the submission's proposed non-inferiority margin of 28%. Further, the upper bound of the 95% CI (202%) did not meet the non-inferiority margin proposed by the submission (28%). The indirect comparison was difficult to interpret due to significant transitivity concerns between the trials. However, given the seven-fold difference between the submission's proposed non-inferiority margin and the upper bound of the 95% CI, the evaluation considered that a conclusion of non-inferiority versus mepolizumab was not reasonable.
- 6.25 The PSCR acknowledged that there was heterogeneity between the studies and stated that this was biased against benralizumab and favoured mepolizumab.
- 6.26 The PBAC considered that the significant heterogeneity between the trials meant that the primary indirect comparison was difficult to interpret. The PBAC agreed that the overall direction of bias was likely to favour mepolizumab.
- 6.27 For the comparison with omalizumab, the rate ratio was 0.78 (95% CI: 0.52, 1.18), which would meet the 28% non-inferiority margin proposed by the submission. Again, this indirect comparison was difficult to interpret due to significant transitivity concerns between the trials.

6.28 During the evaluation, the indirect comparison was also conducted for benralizumab every four weeks, and the results were:

- versus mepolizumab: rate ratio 1.23 (95% CI: 0.88, 1.73).
- versus omalizumab: rate ratio 0.77 (95% CI: 0.62, 0.97).

The results were very similar between the two dosing regimens, with the four-weekly regimen being associated with narrower 95% confidence intervals, although the upper bound still exceeded the proposed non-inferiority margin compared to mepolizumab. Despite the similar results, there may be a risk of up-titration of doses in clinical practice in patients with inadequate response to the eight-weekly regimen.

6.29 Table 7 presents supplementary analyses conducted by the submission and during evaluation for the indirect comparison between benralizumab every eight weeks (primary efficacy population) and mepolizumab.

Table 7: Supplementary analyses - indirect comparison of the rate of clinically significant exacerbations

Trial	BEN q8w versus SOC		SOC Exac rate/yr	MEPO versus SOC		Indirect RR (95% CI)
	RR (95% CI)	BEN Exac rate/yr		MEPO Exac rate/yr	RR (95% CI)	
Excluding CALIMA: SIROCCO vs MENSA						
SIROCCO (n=534)	0.49 (0.37, 0.64)	0.65	1.33	-	-	-
MENSA (n = 385)	-	-	1.74	0.83	0.47 (0.35, 0.64)	-
Indirect comparison						1.04 (0.69, 1.56)
SIROCCO vs MENSA subgroup with EOS ≥ 300 cells/μL in 6 weeks prior to screening ^a						
SIROCCO (n=534)	0.49 (0.37, 0.64)	0.65	1.33	-	-	-
MENSA subgroup ^a (n = 206)	-	-	1.98	0.71	0.36 (0.24, 0.54)	-
Indirect comparison						1.36 (0.83, 2.22)
Including MUSCA (24 week trial of mepolizumab with primary outcome of ΔSGRQ)						
MUSCA (n = 551)			1.21	0.51	0.42 (0.31, 0.56)	
Pooled random effects	0.59 (0.41, 0.86)				0.44 (0.39, 0.49)	1.34 (0.91, 1.98)
OCS-sparing trials only (ZONDA vs SIRIUS)						
ZONDA (n=148)	0.30 (0.17, 0.53)	0.54	1.8	-	-	-
SIRIUS (n = 135)	-	-	2.1	1.4	0.68 (0.47, 0.99)	-
Pooled random effects						0.44 (0.22, 0.87)

Source: CSR (ZONDA Tables 11.2.1, 11.2.4.2); Mepolizumab Public Summary Document, March 2016, Table 5, p 9; text, pp1194-5 Bel 2014; Ital =analyses and values in italics were calculated during evaluation

BEN = benralizumab; CI = confidence interval; EOS = eosinophil; q8w = every 8 weeks; exac = exacerbation; MEPO = mepolizumab; OCS = oral corticosteroid; PBS = Pharmaceutical Benefits Scheme; SOC = standard of care; SRGC = St George's Respiratory Questionnaire; RR = rate ratio; yr = year

^a Subgroup: eosinophils of ≥ 300 cells/μL in the 6 weeks prior to screening (which the mepolizumab Public Summary Document stated to be more closely aligned with the PBS restriction). Source: Mepolizumab Public Summary Document March 2016, Table 5, p9.

6.30 SIROCCO versus MENSA: The CALIMA trial likely had the greatest transitivity issues versus the mepolizumab trial (MENSA) as it had the lowest event rate in the

standard of care arm. Exclusion of CALIMA reduced the rate ratio to 1.04 (95% CI: 0.69, 1.56). However, the evaluation noted that this still did not meet the 28% non-inferiority margin proposed by the submission and significant transitivity issues remained.

- 6.31 The PBAC acknowledged that the indirect comparison did not meet the non-inferiority margin, but considered this was likely due to the heterogeneity between the trials (the exacerbation rates in the common reference arms were 1.33 events per year for SIROCCO and 1.74 for MENSA) and a lack of statistical power for the analysis. The PBAC further noted that SIROCCO and MENSA reported similar results (noting both the point estimates and confidence intervals): the rate ratios for clinically significant asthma exacerbations were 0.49 (95% CI: 0.37, 0.64) in SIROCCO versus 0.47 (95% CI: 0.35, 0.64) in MENSA.
- 6.32 MENSA subgroup: A subgroup of MENSA (mepolizumab) that only included patients with eosinophils 300 cells/ μ L or higher in the six weeks prior to screening was reported in Table 5 of the Mepolizumab Public Summary Document, March 2016. This subgroup more closely aligned with the benralizumab trial inclusion criteria and the PBS restriction. The rate ratio for this indirect comparison was 1.36 (95% CI: 0.83, 2.22). However, this more highly favoured mepolizumab and thus still did not meet the 28% non-inferiority margin proposed by the submission and significant transitivity issues remained.
- 6.33 Inclusion of MUSCA: The submission excluded MUSCA, a trial of mepolizumab in which clinically significant exacerbations were a secondary outcome (the primary outcome was the change in St George's Respiratory Questionnaire score). The exclusion of MUSCA may not have been appropriate as it was identical to MENSA in terms of the inclusion and exclusion criteria and the definition of clinically significant asthma exacerbations. Further, the submission did not identify any additional, significant transitivity concerns that would arise from the inclusion of MUSCA. A sensitivity analysis conducted during evaluation indicated that the exclusion was not conservative for the point estimate. It was acknowledged that the trial was not powered to determine the difference in asthma exacerbations and the trial duration was shorter than the other trials included in the indirect comparison.
- 6.34 OCS sparing trials: The PSCR referred to an indirect comparison between two trials that the submission had excluded from its base case analysis. These trials were designed to assess reductions in oral corticosteroid doses: ZONDA (benralizumab); and SIRIUS (mepolizumab). The evaluation considered that these trials differed substantially from each other as they used different protocols for reducing the dose of oral corticosteroids and different inclusion criteria (especially with regard to baseline OCS maintenance doses and exacerbation history).
- 6.35 Matching-adjusted indirect comparison: The submission stated that a matching-adjusted indirect comparison had been conducted to adjust for the confounders;

however, the submission did not present the results as it included unregistered doses of mepolizumab (from the DREAM trial). The evaluation had stated that the results were only adjusted for baseline inhaled corticosteroid dose. The PSCR correctly identified that the matching-adjusted indirect comparison had been conducted for two sub-populations; patients on doses of fluticasone propionate >500 µg daily and ≥800 µg daily. It stated the variables that were adjusted for within the two ICS groups included the number of exacerbations in previous 12 months, OCS use at baseline, eosinophilic count (≥300 cells/µL), IgE count, gender, nasal polyps, body mass index and nicotine status. The PSCR reported the results of the comparison; however these could not be verified, as insufficient information was provided (as outlined on page 49 of the Guidelines for preparing a submission to the PBAC, Version 5.0, September 2016). Further, the ESC considered that this did not address the issue of the inclusion of unregistered doses of mepolizumab (which was the reason that the submission had not included the results).

- 6.36 The PBAC noted that the matching-adjusted indirect comparison included results from an unregistered dose of mepolizumab but noted that matching-adjusted indirect comparison reported a rate ratio of [REDACTED] (95% CI: [REDACTED]) for benralizumab versus mepolizumab in the sub population of patients on fluticasone propionate ≥880 µg daily. The PBAC noted that the results were within the 28% non-inferiority margin proposed by the submission. The PBAC noted the limitations of this analysis but considered the results were generally supportive of non-inferior efficacy between benralizumab and mepolizumab.

Comparative harms

- 6.37 Adverse events from the benralizumab trials are summarised in the table below for the whole trial population (i.e. regardless of eosinophil count or inhaled corticosteroid dose). Risk ratios were calculated during evaluation for the more common adverse events.

Table 8: Adverse events in the benralizumab randomised trials (on-treatment period, safety analysis set)

Whole trial population	CALIMA (56 weeks)			SIROCCO (48 weeks)		
	BEN q8w	BEN q4w	SOC	BEN q8w	BEN q4w	SOC
N	428	438	440	394	403	407
Any AEs, n (%)	320 (75%)	322 (74%)	342 (78%)	281 (71%)	293 (73%)	311 (76%)
RR (95% CI)	<i>0.96 (0.89, 1.04)</i>	<i>0.95 (0.88, 1.02)</i>	-	<i>0.93 (0.86, 1.01)</i>	<i>0.95 (0.88, 1.03)</i>	-
AE leading to discontinuation	10 (2%)	8 (2%)	4 (1%)	8 (2%)	9 (2%)	3 (1%)
RR (95% CI)	<i>2.57 (0.81, 8.13)</i>	<i>2.01 (0.61, 6.62)</i>	-	<i>2.75 (0.74, 10.31)</i>	<i>3.03 (0.83, 11.11)</i>	-
Any SAE	40 (9%)	45 (10%)	60 (14%)	52 (13%)	47 (12%)	55 (14%)
RR (95% CI)	<i>0.69 (0.47, 1.00)</i>	<i>0.75 (0.52, 1.08)</i>	-	<i>0.98 (0.69, 1.39)</i>	<i>0.86 (0.6, 1.24)</i>	-
Deaths	2 (< 1%)	2 (< 1%)	0	1 (< 1%)	2 (< 1%)	2 (< 1%)
Serious Infections	8 (2%)	6 (1%)	11 (3%)	10 (3%)	6 (2%)	8 (2%)
Hypersensitivity	13 (3%)	13 (3%)	17 (4%)	11 (3%)	13 (3%)	11 (3%)
Treatment-related AEs						
Any treatment-related AEs	54 (13%)	51 (12%)	36 (8%)	64 (16%)	55 (14%)	42 (10%)
Headache	6 (1%)	5 (1%)	4 (1%)	12 (3%)	8 (2%)	5 (1%)
Pyrexia	5 (1%)	7 (2%)	0	7 (2%)	7 (2%)	0

Source: Table 2.24 - 2.26, pp98 - 91 of the submission; Table 52, p203; Table 56, p211; Table 59, p219; Table 12.3.2.6.2; of the CALIMA CSR; Table 49, p197; Table 53, p206; Table 56, p213, Table 12.3.2.6.2; of the SIROCCO CSR; Table 40, p55; Table 45, p171; Table 11.3.2.1.2; Table 11.3.2.6.2 of the ZONDA CSR; Ital = values in italics were calculated during evaluation

AE = adverse event; BEN = benralizumab; CI = confidence interval; q8w = every eight weeks; q4w = every four weeks; RR = risk ratio; SOC = standard of care; SAE = serious adverse event

- 6.38 There were no statistically significant increases in adverse events between the benralizumab and standard of care arms of the trials. Further, there were no substantial differences in adverse events between the two benralizumab dose regimens.
- 6.39 Table 9 summarises adverse events in the trials included in the indirect comparison. For the benralizumab trials, this comparison uses the primary efficacy population and the eight-weekly dose regimen.

Table 9: Summary of adverse events for trials included in the indirect comparison

AEs	BEN q8w (EOS ≥ 300, high-dose ICS) ^a				Mepolizumab		Omalizumab			
	CALIMA (56 wks)		SIROCCO (48 wks)		MENSA (32 wks)		INNOVATE (28 wks)		EXTRA (48 wks)	
	BEN	SOC	BEN	SOC	MEPO	SOC	OMAL	SOC	OMAL	SOC
N	230	248	265	267	194	191	245	237	428	420
Any AEs	181 (79%)	188 (76%)	185 (70%)	203 (76%)	152 (78%)	158 (83%)	177 (72%)	179 (76%)	344 (80%)	334 (80%)
RR (95% CI)	1.04 (0.94, 1.14)		0.92 (0.83, 1.02)		0.95 (0.86, 1.05)		0.96 (0.86, 1.06)		1.01 (0.94, 1.08)	
Pooled ^b	0.98 (0.87, 1.10)				0.95 (0.86, 1.05)		0.99 (0.94, 1.05)			
Indirect comp, RR	<i>Benralizumab versus mepolizumab: 1.03 (0.88, 1.20)</i> <i>Benralizumab versus omalizumab: 0.99 (0.87, 1.13)</i>									
SAEs	25 (11%)	34 (14%)	33 (12%)	36 (13%)	16 (8%)	27 (14%)	29 (12%)	37 (16%)	40 (9%)	44 (11%)
RR (95% CI)	0.79 (0.49, 1.29)		0.92 (0.59, 1.44)		0.58 (0.32, 1.05)		0.76 (0.48, 1.19)		0.89 (0.59, 1.34)	
Pooled ^b	0.86 (0.62, 1.19)				0.58 (0.32, 1.05)		0.83 (0.61, 1.12)			
Indirect comp, RR	<i>Benralizumab versus mepolizumab: 1.48 (0.75, 2.92)</i> <i>Benralizumab versus omalizumab: 1.04 (0.66, 1.62)</i>									
Withdraw due to AE	6 (3%)	1 (<1%)	6 (2%)	2 (1%)	1 (<1%)	4 (2%)	11 (5%)	4 (2%)	16 (4%)	10 (2%)
RR (95% CI)	6.47 (0.78, 53.33)		3.02 (0.62, 14.84)		0.25 (0.03, 2.18)		2.66 (0.86, 8.24)		1.57 (0.72, 3.42)	
AE leading to death	2 (1%)	0	0	1 (<1%)	0	1 (<1%)	0	0	0	3 (<1%)

Source: Table 12.3.2.1.2, CALIMA and SIROCCO CSR appendices;

AEs = adverse events; BEN = Benralizumab; CI = confidence interval; comp = comparison; EOS = eosinophil; ICS = inhaled corticosteroids; MEPO = mepolizumab 100mg; OMAL = omalizumab; q8w = every eight weeks; RR = risk ratio; SAEs = serious adverse events SOC = standard of care; wks = weeks; Ital = values in italics were calculated during evaluation

^aBased on the on-treatment period

^bMeta-analysis conducted in Review Manager 5.3, random effects, Mantel-Haenszel

6.40 Benralizumab was associated with a numerically greater, but statistically insignificant, risk of serious adverse events than mepolizumab (rate ratio for the indirect comparison of 1.48 (95% CI: 0.75, 2.92)). However, the most common serious adverse event reported in the benralizumab trials was asthma, which likely represented the condition being treated rather than an adverse event. There was a greater risk of withdrawal due to adverse events in the benralizumab trials than the mepolizumab trials, though the absolute numbers were small.

6.41 Overall, adverse events appeared similar between benralizumab, mepolizumab and omalizumab.

Clinical claim

6.42 The submission claimed that benralizumab was non-inferior to mepolizumab and omalizumab in terms of comparative efficacy and safety.

6.43 The evaluation considered that the claim of non-inferior efficacy was not adequately supported given that:

- the non-inferiority margin was not met for the primary comparison versus mepolizumab (upper bound of the 95% CI was 202% versus a proposed margin of 28%); and
 - there were significant transitivity concerns with the comparisons versus mepolizumab and omalizumab as highlighted by differences in the results for the common reference arms.
- 6.44 The PBAC considered that the primary indirect comparison was difficult to interpret due to the significant transitivity concerns, and considered that a range of supplementary analyses generally supported a conclusion of non-inferior efficacy. Overall, the PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.45 The ESC and the PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.46 The submission presented a cost-minimisation analysis of benralizumab versus mepolizumab, with cost-offsets for a reduction in health care resources. The equi-effective doses estimated by the submission were benralizumab 30 mg every eight weeks (6.5 doses per year) and mepolizumab 100 mg every four weeks (13 doses per year).
- 6.47 These were based on the fixed doses used in the key trials of benralizumab (CALIMA and SIROCCO) and mepolizumab (MENSA), based on the every eight week regimen of benralizumab. Only the maintenance phase was used.
- 6.48 Exclusion of the loading dose (30 mg every four weeks for the first three doses) was inconsistent with the method used to estimate the equi-effective doses of other biologics that require fixed induction doses such as ustekinumab in Crohn's disease (Paragraphs 6.31 and 7.9, Ustekinumab Public Summary Document, March 2017) and ixekizumab for chronic plaque psoriasis (Paragraph 7.4, Ixekizumab Public Summary Document, July 2016). The evaluation considered that inclusion of the loading dose over a one year time frame may have been appropriate as the duration of the key trials were around one year (CALIMA and SIROCCO were 56 and 48 weeks, respectively). Further, this would also align with the estimation of equi-effective doses for biologics in other conditions, which have used time periods between one and two years.
- 6.49 The ESC and the PBAC considered that the estimation of equi-effective doses should have included the fixed loading doses of benralizumab.
- 6.50 The submission considered that benralizumab would result in lower administration costs than mepolizumab due to less frequent dosing (eight-weekly versus four-weekly dosing). As shown in Table 10, the submission assumed each administration (of either benralizumab or mepolizumab) would require a specific

consult with a specialist, General Practitioner or nurse. The resource items, costs and proportions were based on those presented in the Public Summary Document for the cost-minimisation of mepolizumab to omalizumab (excluding those for anaphylaxis), which the PBAC considered were reasonable for that particular comparison (Paragraphs 6.22, 6.23 and 7.3, Mepolizumab Public Summary Document, July 2016). The PSCR noted that the basis for the proportions had been redacted from the Public Summary Document.

Table 10: Health care resource items used per administration of benralizumab or mepolizumab – per submission

Type of resource item	Unit cost	Proportion ^a	Source of unit cost
Specialist visit	\$75.50	█%	MBS 116
General Practitioner	\$37.05	█%	MBS 23 (Level B)
Nurse practitioner	\$8.20 ^b	█%	MBS 82200
Total	\$23.01	-	-

Source: text p113 of the submission; Table 4.14, p127 of the submission

MBS = Medicare Benefits Schedule

^a The basis for these proportions was not available in the Public Summary Documents.

^b The submission based the nurse administration costs on the 85% fee, rather than the full 100% fee. This was conservative.

6.51 The evaluation and the ESC considered that the cost offsets for administration of benralizumab were overestimated because:

- it was unreasonable to assume that █% of patients would visit a specialist solely for the purpose of administration of a subcutaneous injection;
- some of the General Practitioner visits may not be just for the purposes of medication administration alone, particularly given the severity of the asthma and the need for continuous monitoring in this patient group; and
- the ESC considered that it may not have been reasonable to base the cost-offsets for administration on those for the cost-minimisation of mepolizumab to omalizumab. The ESC noted that patients are observed following administration of omalizumab due to the risk of anaphylaxis, while mepolizumab and benralizumab are associated with a lower risk of anaphylaxis. While ‘supervision post dose for anaphylaxis’ was included in the proposed cost-minimisation of mepolizumab to omalizumab (Paragraph 6.22, Mepolizumab Public Summary Document, July 2016) this may not have fully captured the level of professional attendance and clinical experience required.

6.52 The results of the cost-minimisation analysis presented in the submission are outlined in Table 11.

Table 11: Results of the cost-minimisation analysis presented in the submission (published prices)

Component	Benralizumab	Mepolizumab
Number of doses per year (maintenance phase)	█	█
Calculation of mepolizumab price per year (including administration costs)		
AEMP per dose of mepolizumab (published).	-	\$ █
Drug costs per year (published)	-	\$ █
Administration cost per year (per Table 10)	\$ █	\$ █
Total annual cost		\$ █
Calculation of benralizumab price		
Total annual cost (based on mepolizumab)	\$ █	
Total cost per dose (drug + administration)	\$ █	
Difference in administration costs per year	\$ █ per year; \$ █ per injection	
AEMP per dose of benralizumab (published, proposed)	\$ █	

Source: Table 3.3, p113 of the submission
AEMP = approved ex-manufacturer price

6.53 The submission estimated that, based on the published price of mepolizumab, the approved ex-manufacturer price of mepolizumab would be \$ █ per dose. This may not be reasonable as it excluded the fixed loading doses and over-estimated the administration offsets.

6.54 The pre-PBAC response proposed revised benralizumab administration costs that excluded the costs of specialist visits. This resulted in administration costs of \$17.18 per administration, based on the costs used in Table 10 and maintaining the ratio of General Practitioner to nurse administrations (31% General Practitioner Level B, and 69% nurse administrations). Per Table 12 below this would result in a AEMP of \$ █ per dose. This aligned with one of the sensitivity analyses conducted during evaluation (Table 13).

Table 12: Results of the cost-minimisation analysis – revised base case in pre-PBAC response (published prices)

Component	Benralizumab	Mepolizumab
Number of doses per year (maintenance phase)	█	█
Calculation of mepolizumab price per year (including administration costs)		
AEMP per dose of mepolizumab (published).	-	\$ █
Drug costs per year (published)	-	\$ █
Administration cost per year (\$17.18 per dose, per Paragraph 6.52)	\$ █	\$ █
Total annual cost		\$ █
Calculation of benralizumab price		
Total annual cost (based on mepolizumab)	\$ █	
Total cost per dose (drug + administration)	\$ █	
Difference in administration costs per year	\$ █ per year; \$ █ per injection	
AEMP per dose of benralizumab (published, proposed)	\$ █	

Source: Constructed based on page 3 of the pre-PBAC response
AEMP = approved ex-manufacturer price

6.55 Table 13 presents sensitivity analyses conducted during the evaluation to assess the impact of administration costs, inclusion of the loading dose and use of the four weekly dosing regimen.

Table 13: Sensitivity analyses conducted during evaluation

Component	AEMP, published
Base case	\$ [REDACTED]
Administration offsets (base case = \$23.01 per administration)	
Removal of specialist visits (31% GP Level B, 69% nurse administrations) = \$17.18 (Revised base case in the pre-PBAC response)	\$ [REDACTED]
Use only nurse consults (MBS Item 82200) = \$9.60	\$ [REDACTED]
Including the loading dose of benralizumab (base case = 6.5 doses per year in maintenance phase)	
Costed over a 1-year period (7.5 doses in Year 1, including 1 additional loading dose)	\$ [REDACTED]
Costed over a 2-year period (benralizumab = 7.5 doses in Year 1, 6.5 doses in Year 2; mepolizumab = 26 doses per 2 years)	\$ [REDACTED]
Every four week regimen used in practice (base case = only the every eight week regimen would be used)	
Every four week regimen used in half of patients (avg. 9.75 doses per year)	\$ [REDACTED]
Multivariate sensitivity analyses	
Inclusion of loading dose costed over a 1 year period (7.5 doses of benralizumab to 13 doses of mepolizumab) plus no specialist administration (\$17.18 per administration)	\$ [REDACTED]

Source: Compiled during evaluation

AEMP = approved ex-manufacturer price; GP = General Practitioner; MBS = Medicare Benefits Schedule

6.56 During evaluation, a multivariate sensitivity analysis was conducted in which:

- benralizumab loading doses were included, based on a one year time frame for estimation of the equi-effective doses; and
- specialist costs were removed from the administration offsets, reducing the cost per administration to \$ [REDACTED]. This generally aligns with the cost of a Level A GP consult (\$16.95, MBS Item 3). This remained conservative as it assumed the GP consults and nurse visits would be for the sole purpose of administering the medication.

This resulted in an Approved Ex-Manufacturer Price of \$ [REDACTED] (a [REDACTED]% reduction to the proposed price). This may have been a more appropriate method for calculating the cost-minimisation analysis.

6.57 The PBAC noted that the proposed offsets included the cost of administration by nurse practitioners, per the Public Summary Document for the cost-minimisation of mepolizumab to omalizumab. However, the PBAC considered that in practice, subcutaneous injections would likely be administered by practice nurses, for whom MBS item codes do not apply. While the PBAC acknowledged that there would be a cost associated with administration of injections by practice nurses, the PBAC considered that the use of the MBS item for nurse practitioners as a proxy may overestimate this cost.

- 6.58 Omalizumab, which was nominated as a secondary comparator, has an established equi-effective dose of: omalizumab 398 mg equals mepolizumab 100 mg. Thus the equi-effective doses proposed by the submission were: benralizumab 100 mg every eight weeks (6.5 doses per year) equals omalizumab 398 mg every four weeks (13 doses per year). Omalizumab would be an appropriate pricing comparator, though the prices between mepolizumab and omalizumab were at parity at the time of evaluation (once administration offsets were included).

Drug cost/patient/year: \$ [REDACTED] (at the price proposed in the submission)

- 6.59 The drug cost per patient per year was based on the submission's proposed published dispensed price per maximum quantity (DPMQ) of \$ [REDACTED] (Public) and \$ [REDACTED] (Private), assuming [REDACTED] doses including the initial loading dose, and [REDACTED]% of use through public hospitals.
- 6.60 This compares with a drug cost per patient of \$ [REDACTED] for mepolizumab (13 doses, 67% of use through public hospitals).

Estimated PBS usage & financial implications

- 6.61 This submission was not considered by DUSC.
- 6.62 An epidemiological approach was used to estimate the number of patients who would be eligible for benralizumab. The submission did not include cost-offsets for reduced use of mepolizumab or omalizumab (due to patients switching or otherwise having been treated with the comparators). This resulted in a significant estimated net cost despite listing being requested on a cost-minimisation basis. This was not reasonable given the proposed population was the same as mepolizumab.
- 6.63 The PSCR stated that it was difficult to estimate the extent to which benralizumab would substitute for mepolizumab and omalizumab. The PSCR also noted that there are two minor submissions on the agenda for the March 2018 PBAC meeting which both request changes to the time period for switching between biologics in asthma. The PSCR stated that this would impact the uptake estimates.

Table 14: Estimated use and financial implications (based on price proposed in the submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
No. of patients treated						
No. of scripts dispensed ^a						
Estimated financial implications of benralizumab						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Copayments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost to MBS – <i>without GP and nurse costs</i>	\$	\$	\$	\$	\$	\$
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$	\$

Source: Tables 4.8, 4.9, p129 of the submission; “3b. Impact – PUB” worksheet, “Utilisation-and-cost-model_benralizumabMar18PBAC meeting.xlsx”; Ital = values in italics were re-calculated during the evaluation to reflect the 85% benefit rather than the full fee for specialists consults and also to remove GP and nurse administration costs as these would be unlikely to be realised in clinical practice. GP = general practitioner; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme; MBS = Medicare Benefits Schedule

^a Assuming 6.5 scripts per year for continuing patient and 5 scripts per year for initiating patients as estimated by the submission.

6.64 The submission estimated that less than 10,000 patients would use benralizumab in Year 6. The submission estimated that the net cost to the PBS/RPBS would be \$10 - \$20 million in Year 6 and \$40 - \$60 million over six years. This was based on the price proposed in the submission.

6.65 The cost of listing benralizumab was substantially overestimated as cost-offsets from reductions in use of mepolizumab and omalizumab were not included.

6.66 Overall, the evaluation considered that the submission likely overestimated the number of treated patients because the prevalent population was double-counted. The submission assumed that 80% of prevalent patients from each previous year would continue (cumulatively), plus a new prevalent pool was assumed to commence each year. This likely outweighed the impact of two factors which would have reduced the number of eligible patients:

- an unnecessary step was included in the estimation of the proportion of patients with exacerbations (an adjustment was made for the proportion of patients taking high-dose inhaled corticosteroids, however this adjustment was also made in a subsequent step); and
- the proportion of patients with refractory asthma appeared to have been underestimated. The submission assumed that only 30% of patients with uncontrolled asthma would have good adherence and correct inhaler technique.

Quality Use of Medicines

6.67 The submission stated that the risk of incorrect administration or dosing of benralizumab would be minimised because it is a pre-filled syringe intended to be administered by health care professionals.

Financial Management – Risk Sharing Arrangements

- 6.68 The submission anticipated that there was a Risk Sharing Arrangement in place for mepolizumab and omalizumab, and expected that benralizumab would be added to this agreement, including any existing price-volume caps.
- 6.69 The submission also stated that benralizumab was likely to grow the market for biologics in asthma because: it was suitable for some different sub-types of asthma compared with omalizumab; it provides an additional treatment option; and a minor submission was being submitted to amend the restriction to enable a shorter wash-out period. However, the evaluation considered that benralizumab would be unlikely to significantly grow the market compared with mepolizumab because the proposed population was the same as mepolizumab and no additional patient groups would be eligible.

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 benralizumab for the treatment of uncontrolled severe eosinophilic asthma. The PBAC recommended the listing on a cost-minimisation basis with mepolizumab. In making this recommendation, the PBAC noted the clinical need for additional treatment options in uncontrolled severe asthma.
- 7.2 The PBAC welcomed the input from health care professionals and organisations, which described the burden of illness associated with uncontrolled severe asthma and highlighted the benefits of having an additional treatment option available given the severity of the condition.
- 7.3 The PBAC recommended that the restrictions for benralizumab should be consistent with those for mepolizumab for the treatment of uncontrolled severe eosinophilic asthma.
- 7.4 The PBAC noted that the submission had initially requested listing in patients aged 18 years and over, but subsequently the TGA delegate had recommended that the registered indication should include patients aged 12 years and over. The PBAC noted that mepolizumab is PBS-listed in patients aged 12 years and over, and considered that the PBS restriction for benralizumab should be consistent with the TGA indication (once finalised) regarding patient age.
- 7.5 The PBAC considered that a grandfathering restriction would be appropriate and recommended that the grandfather restriction be consistent with the PBS population for benralizumab.
- 7.6 The PBAC considered that mepolizumab was the appropriate main comparator.
- 7.7 The PBAC noted the significant heterogeneity between the trials used in the

indirect comparisons (e.g. differences in participant baseline characteristics and trial duration) which were highlighted by the large differences in event rates in the common reference arms. The PBAC considered that these differences favoured mepolizumab and meant that the indirect comparisons were difficult to interpret.

- 7.8 The PBAC noted the range of supplementary analyses that had been conducted by the submission. The PBAC considered that the most informative was the indirect comparison of SIROCCO (benralizumab versus standard of care) versus MENSA (mepolizumab versus standard of care), which had the most similar event rates in the common reference arm. The PBAC noted that the two trials reported similar results: the rate ratios for clinically significant asthma exacerbations were 0.49 (95% CI: 0.37, 0.64) in SIROCCO versus 0.47 (95% CI: 0.35, 0.64) in MENSA. Further, the PBAC noted that a matching-adjusted indirect comparison conducted by the submission was generally supportive of a conclusion of non-inferior efficacy. The PBAC noted the limitations of the available evidence but considered that direct evidence comparing benralizumab and mepolizumab was unlikely to become available in the future.
- 7.9 Overall, the PBAC concluded that benralizumab is non-inferior to mepolizumab in terms of comparative efficacy and safety. In forming this view the PBAC considered, in addition to the evidence presented, the clinical need for additional treatment options for uncontrolled severe asthma.
- 7.10 The PBAC recommended the listing of benralizumab on a cost-minimisation basis with mepolizumab.
- 7.11 The PBAC considered that the estimation of equi-effective doses should include the fixed loading doses of benralizumab, which would be consistent with methods used to estimate the equi-effective doses of other biologics (in other conditions) that require induction doses. The PBAC considered that it would be appropriate to include the loading dose over a one year time frame consistent with the duration of the key trials (CALIMA and SIROCCO).
- 7.12 Thus, the PBAC considered that the equi-effective doses were:
- benralizumab 30 mg every four weeks for the first three doses, then every eight weeks (7.5 doses over one year); and
 - mepolizumab 100 mg every four weeks (13 doses over one year).
- 7.13 The PBAC noted that the submission's cost-minimisation analysis included cost-offsets for reduced administration costs as benralizumab is administered less frequently than mepolizumab (eight weekly versus four weekly dosing). The PBAC noted that the pre-PBAC response had proposed revised administration costs, which appropriately removed the costs of specialist visits. The PBAC considered that the revised cost-offsets may remain overestimated as benralizumab would likely be administered by practice nurses, rather than under the Nurse Practitioner MBS item code.

- 7.14 The PBAC considered that the number of treated patients was overestimated for the reasons outlined in Paragraph 6.66.
- 7.15 At the same meeting, the PBAC also considered two minor submissions that requested changes to the current PBS restrictions for biologics for uncontrolled severe asthma (refer to items 6.11 and 6.16 for details). As part of these considerations, the PBAC recommended amending the clinical criterion stipulating that a "patient must be under the care of the same physician for at least 12 months". The PBAC recommended that this criterion be replaced with a requirement for patients to be either under the care of the same physician for at least six months, or be diagnosed as having uncontrolled severe asthma by a multidisciplinary severe asthma clinic team. The PBAC considered that these changes should be made to all biologics for uncontrolled, severe asthma.
- 7.16 The PBAC recommended that benralizumab should be treated as interchangeable on an individual patient basis with mepolizumab.
- 7.17 The PBAC advised that benralizumab is not suitable for prescribing by nurse practitioners.
- 7.18 The PBAC recommended that the Early Supply Rule should apply.
- 7.19 The PBAC noted that flow-on changes would be required to the mepolizumab and omalizumab restrictions for the treatment of uncontrolled severe eosinophilic asthma and uncontrolled severe allergic asthma respectively to clarify that they cannot be used in combination with, or within 6 months of treatment with, PBS subsidised benralizumab. The PBAC noted that the restriction was complex.
- 7.20 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection, (prefilled syringe)	1	4	Fasenra® AstraZeneca Pty Ltd
Category / Program	Section 100 Highly Specialised Drugs Program – public and private		
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
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 6 months, OR Patient must have been diagnosed by a multidisciplinary severe asthma clinic team, 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 12 months, 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 or mepolizumab.</p>
Population criteria	Patient must be aged 12 years or older.
Prescriber Instructions	<p>Optimised asthma therapy includes: (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; AND (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>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 24 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.</p> <p>This assessment at around 24 weeks, 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 benralizumab.</p> <p>A patient who fails to respond to a course of PBS-subsidised benralizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with benralizumab, mepolizumab or omalizumab within 6 months of the date on which treatment was ceased.</p> <p>A multidisciplinary severe asthma clinic team comprises of:</p> <ul style="list-style-type: none"> • A respiratory physician; and • A pharmacist, nurse or asthma educator. <p>At the time of the authority application, medical practitioners should request 4 repeats to provide for an initial course of benralizumab sufficient for 32 weeks of therapy.</p> <p>Benralizumab may not be used concurrently with mepolizumab or omalizumab or within 6 months of each other. A patient is required to have ceased treatment with mepolizumab or omalizumab for 6 months prior to initiating treatment with benralizumab.</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 Asthma Initial PBS Authority Application - Supporting Information Form,</p> <p>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 signed patient or parent/guardian acknowledgement; and</p> <p>(c) a copy of the eosinophil pathology report; and</p> <p>(d) a completed Asthma Control Questionnaire (ACQ-5) calculation sheet including the date of assessment of the patient's symptoms.</p>
<p>Administrative Advice</p>	<p>The Department of Human Services website (www.humanservices.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.</p> <p>For copies of the ACQ, please contact AstraZeneca on [phone number to be advised].</p> <p>It is recommended that an application for continuing treatment is submitted at the time of the 24 week assessment, to ensure continuity of treatment for those patients who meet the continuation criteria for PBS-subsidised benralizumab 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 www.humanservices.gov.au</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>TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA</p> <p>Patients are eligible to commence a 'benralizumab treatment cycle' (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 benralizumab, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 6 month break in PBS-subsidised benralizumab therapy before they are eligible to commence the next 'benralizumab treatment cycle', or if eligible, a 'mepolizumab treatment cycle' or an 'omalizumab treatment cycle'. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised benralizumab is stopped to the date of the first application for initial treatment with benralizumab, mepolizumab or omalizumab 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 benralizumab therapy:</p> <p>(a) Initial treatment: Applications for initial treatment should be made where:</p> <ul style="list-style-type: none">i) A patient has received no prior PBS-subsidised benralizumab treatment and wishes to commence such therapy; orii) A patient wishes to recommence treatment with benralizumab following a break in PBS-subsidised therapy of more than 6 months; oriii) A patient has received prior PBS-subsidised mepolizumab or omalizumab and wishes to commence treatment with benralizumab after a treatment break of 6 months. <p>All applications for initial treatment for non-grandfather patients will be limited to provide for a maximum of 32 weeks of therapy for benralizumab.</p> <p>(b) Grandfather patients: For patients who commenced treatment with benralizumab for uncontrolled severe eosinophilic asthma prior to <i>[insert date of listing]</i> 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 benralizumab 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 benralizumab 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>(c) Continuing treatment: Following the completion of the initial treatment course with benralizumab, a patient may qualify to receive up to a further 24 weeks of continuing treatment with benralizumab providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing benralizumab treatment in courses of up to 24 weeks providing they continue to sustain the response.</p> <p>(2) Baseline measurements to determine response: 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 benralizumab. 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: A patient who wishes to trial a second or subsequent benralizumab treatment cycle, or an initial mepolizumab or 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. Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.humanservices.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130). No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>
--	---

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection, (prefilled syringe)	1	4	Fasenra® AstraZeneca Pty Ltd

Category / Program	Section 100 Highly Specialised Drugs Program – public and private
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 – balance of supply
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Streamlined
Treatment criteria	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.

Public Summary Document – March 2018 PBAC Meeting

Clinical criteria:	Patient must have received insufficient therapy with this drug under the Initial treatment restriction to complete 32 weeks treatment, AND The treatment must provide no more than the balance of up to 32 weeks treatment available under the above restriction.
Population criteria	Patient must be aged 12 years or older.
Administrative Advice	Authority approval for sufficient therapy to complete a maximum of 32 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Written application for authority approval for sufficient therapy to complete a maximum of 32 weeks of treatment should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA <i>(Per note for initial treatment)</i> No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection, (prefilled syringe)	1	2	Fasenra® AstraZeneca Pty Ltd

Category / Program	Section 100 Highly Specialised Drugs Program – public and private
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:	Continuing 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
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:	Patient must have demonstrated or sustained an adequate response to PBS subsidised treatment with this drug, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS subsidised omalizumab or mepolizumab.

Population criteria	Patient must be aged 12 years or older.
Prescriber Instructions	<p>An adequate response to benralizumab treatment is defined as:</p> <p>(a) a reduction in the Asthma Control Questionnaire (ACQ 5) score of at least 0.5 from baseline,</p> <p>OR</p> <p>(b) maintenance oral corticosteroid dose reduced by at least 25% from baseline, and no deterioration in ACQ 5 score from baseline.</p> <p>All applications for continuing treatment with benralizumab 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, and the assessment of oral corticosteroid dose, must be made at around 24 weeks after the first dose of PBS subsidised benralizumab 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 first assessment should, where possible, be completed by the same physician who initiated treatment with benralizumab. 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 benralizumab.</p> <p>A patient who fails to respond to a course of PBS subsidised benralizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS subsidised treatment with benralizumab for this condition within 6 months of the date on which treatment was ceased.</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 benralizumab sufficient for 24 weeks of therapy.</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 Asthma Continuing PBS Authority Application Supporting Information Form which includes details of maintenance oral corticosteroid dose; and</p> <p>(c) a completed Asthma Control Questionnaire (ACQ 5) calculation sheet including the date of assessment of the patient's symptoms</p>
Administrative Advice	<p>If the same physician cannot assess the patient please call the Department of Human Services on 1800 700 270.</p> <p>It is recommended that second and subsequent applications for continuing treatment are submitted at the time of a 16 week assessment, to ensure continuity of treatment for those patients who meet the continuation criteria for PBS subsidised benralizumab 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 www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

Public Summary Document – March 2018 PBAC Meeting

Administrative (additional note)	advice	For copies of the ACQ, please contact AstraZeneca on [phone number to be advised]. TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA <i>(Per note for initial treatment)</i> No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
---	---------------	---

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection, (prefilled syringe)	1	2	Fasenra® AstraZeneca Pty Ltd
Category / Program	Section 100 Highly Specialised Drugs Program – public and private		
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:	Continuing treatment – balance of supply		
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Streamlined		
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:	Patient must have received insufficient therapy with this drug under the continuing treatment restriction to complete 24 weeks treatment, AND The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction.		
Population criteria	Patient must be aged 12 years or older.		
Administrative Advice	Authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Written application for authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA <i>(Per note for initial treatment)</i> No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.		

Public Summary Document – March 2018 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BENRALIZUMAB 30 mg in 1 mL injection, (prefilled syringe)	1	2	Fasenra® AstraZeneca Pty Ltd
Category / Program	Section 100 Highly Specialised Drugs Program – public and private		
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 – grandfather patients		
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		
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 have received non-PBS treatment with this drug for this condition prior to [Date to be finalised], AND Patient must be receiving treatment with this drug for this condition at the time of application, AND Patient must have had, prior to commencement of benralizumab, 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 had blood eosinophil count greater than or equal to 300 cells per microlitre prior to commencement of benralizumab, AND Patient must have had a duration of asthma of at least 1 year prior to commencement of benralizumab, AND Patient must have failed to achieve adequate control with optimised asthma therapy prior to benralizumab therapy despite formal assessment of and adherence to correct inhaler technique, which has been documented, AND Patient must have demonstrated an adequate response to treatment with benralizumab, AND The treatment must not be used in combination with mepolizumab or omalizumab.</p>		
Population criteria	Patient must be aged 12 years or older.		

<p>Prescriber Instructions</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>A review of the patient's records should be conducted to extract pre- and post-benralizumab data on symptoms, quality of life, medication doses, exacerbations and hospitalisations. Parameters to establish response are: (i) a reduction in Asthma Control Questionnaire (ACQ-5) score of at least 0.5; and/or (ii) maintenance oral corticosteroid dose reduced by at least 25% from baseline.</p> <p>The assessment of the patient's response to the initial PBS subsidised course of treatment must be made at around 16 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. The same parameters used to establish response to non-PBS-subsidised therapy with benralizumab should be used for the assessment.</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 benralizumab.</p> <p>Patients will be eligible to receive continuing courses of benralizumab treatment of up to 24 weeks providing they continue to demonstrate an adequate response to treatment.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p> <p>A patient who fails to respond to a course of PBS-subsidised benralizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with benralizumab, mepolizumab or omalizumab within 6 months of the date on which treatment was ceased.</p> <p>At the time of the authority application, medical practitioners should request the appropriate maximum quantity and number of repeats to provide for a continuing course of benralizumab sufficient for 24 weeks of therapy.</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 Asthma Grandfather PBS Authority Application - Supporting Information Form,</p> <p>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 pre- and post-benralizumab data on symptoms, quality of life, medication doses, severe exacerbation/s and hospitalisations, and</p> <p>(iii) the signed patient or parent/guardian acknowledgement; and</p> <p>(c) a copy of the pre-benralizumab eosinophil pathology report.</p>
<p>Administrative Advice</p>	<p>The Department of Human Services website (www.humanservices.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.</p>

	<p>It is recommended that an application for continuing treatment is submitted at the time of the 16 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS subsidised benralizumab 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 www.humanservices.gov.au</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>Formal assessment and correction of inhaler technique should be performed in accordance with the National Asthma Council (NAC) Information Paper for Health Professionals on Inhaler Technique (available at www.humanservices.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).</p>
<p>Administrative advice (additional note)</p>	<p>For copies of the ACQ, please contact <i>AstraZeneca</i> on [phone number to be advised]. TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA (Per note for initial treatment)</p> <p>No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.</p>

8.2 Flow-ons to the following mepolizumab and omalizumab restrictions. Note that no changes are required to the 'balance of supply' restrictions.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
MEPOLIZUMAB 100 mg injection, 1 vial	1	7	Nucala® GlaxoSmithKline Australia Pty Ltd
Category / Program	Section 100 Highly Specialised Drugs Program – public and private		
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		
Treatment criteria	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.		

<p>Clinical criteria:</p>	<p><i>Patient must be under the care of the same physician for at least 42 6 months,</i> OR <i>Patient must have been diagnosed by a multidisciplinary severe asthma clinic team</i> 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 12 months, 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 or benralizumab.</p>
<p>Population criteria</p>	<p>Patient must be aged 12 years or older.</p>
<p>Prescriber Instructions</p>	<p>Optimised asthma therapy includes: (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; AND (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. 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. The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND (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</p>

	<p>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 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.</p> <p>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 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 benralizumab.</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, <i>benralizumab</i> or omalizumab within 6 months of the date on which treatment was ceased.</p> <p>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.</p> <p><i>A multidisciplinary severe asthma clinic team comprises of:</i></p> <ul style="list-style-type: none"> • <i>A respiratory physician; and</i> • <i>A pharmacist, nurse or asthma educator.</i> <p>Mepolizumab and omalizumab may not be used concurrently with <i>benralizumab</i> or <i>omalizumab</i>, or within 6 months of each other. A patient is required to have ceased treatment with <i>benralizumab</i> or omalizumab for 6 months prior to initiating treatment with mepolizumab.</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 Asthma Initial PBS Authority Application - Supporting Information Form,</p> <p>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 signed patient or parent/guardian acknowledgement; and</p> <p>(c) a copy of the eosinophil pathology report; and</p> <p>(d) a completed Asthma Control Questionnaire (ACQ-5) calculation sheet including the date of assessment of the patient's symptoms.</p>
<p>Administrative Advice</p>	<p>The Department of Human Services website (www.humanservices.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.</p> <p>For copies of the ACQ, please contact GlaxoSmithKline Medical Information on 1800 033 109.</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</p>

	<p>documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</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>TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA</p> <p>Patients are eligible to commence a 'mepolizumab treatment cycle' (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 mepolizumab, 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 mepolizumab treatment cycle, or if eligible, a '<i>benralizumab treatment cycle</i>' or an '<i>omalizumab treatment cycle</i>'. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised mepolizumab is stopped to the date of the first application for initial treatment with mepolizumab, <i>benralizumab</i> or <i>omalizumab</i> 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 mepolizumab therapy:</p> <p>(a) Initial treatment:</p> <p>Applications for initial treatment should be made where:</p> <p>i) A patient has received no prior PBS-subsidised mepolizumab treatment and wishes to commence such therapy; or</p> <p>ii) A patient wishes to recommence treatment with mepolizumab following a break in PBS-subsidised therapy of more than 6 months; or</p> <p>iii) A patient has received prior PBS-subsidised <i>benralizumab</i> or <i>omalizumab</i> and wishes to commence treatment with mepolizumab after a treatment break of 6 months.</p> <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) Grandfather patients:</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>(eb) Continuing treatment:</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</p>
--	---

	<p>remains eligible to receive continuing mepolizumab treatment in courses of up to 24 weeks providing they continue to sustain the response.</p> <p>(2) Baseline measurements to determine response: 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 mepolizumab. 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: A patient who wishes to trial a second or subsequent mepolizumab treatment cycle, or an initial <i>benralizumab</i> or 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 www.humanservices.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
--	--

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
MEPOLIZUMAB 100 mg injection, 1 vial	1	5	Nucala® GlaxoSmithKline Australia Pty Ltd
Category / Program	Section 100 Highly Specialised Drugs Program – public and private		
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:	Continuing 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		
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 have demonstrated or sustained an adequate response to PBS subsidised treatment with this drug, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS subsidised <i>benralizumab</i> or <i>omalizumab</i>.</p>
Population criteria	<p>Patient must be aged 12 years or older.</p>
Prescriber Instructions	<p>An adequate response to mepolizumab treatment is defined as: (a) a reduction in the Asthma Control Questionnaire (ACQ 5) score of at least 0.5 from baseline, OR (b) maintenance OCS dose reduced by at least 25% from baseline, and no deterioration in ACQ 5 score from baseline.</p> <p>All applications for continuing treatment with mepolizumab 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, and the assessment of oral corticosteroid dose, must be made at around 26 to 30 weeks after the first dose of PBS subsidised mepolizumab 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 first assessment should, where possible, be completed by the same physician who initiated treatment with mepolizumab. 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 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 for this condition within 6 months of the date on which treatment was ceased.</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 mepolizumab sufficient for 24 weeks of therapy.</p> <p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> (a) a completed authority prescription form; and (b) a completed Severe Eosinophilic Asthma Continuing PBS Authority Application Supporting Information Form which includes details of maintenance oral corticosteroid dose; and (c) a completed Asthma Control Questionnaire (ACQ 5) calculation sheet including the date of assessment of the patient's symptoms
Administrative Advice	<p>If the same physician cannot assess the patient please call the Department of Human Services on 1800 700 270.</p> <p>It is recommended that second and subsequent applications for continuing treatment are submitted at the time of an 18 to 22 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 www.humanservices.gov.au</p>

Public Summary Document – March 2018 PBAC Meeting

	Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001 Authority Required Uncontrolled severe eosinophilic asthma
Administrative advice (additional note)	For copies of the ACQ, please contact GlaxoSmithKline Medical Information on 1800 033 109. TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA (Per note for initial treatment) No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
OMALIZUMAB 75 mg in 0.5 mL injection, 1 syringe	1	0	Xolair® Novartis Pharmaceuticals Australia Pty Ltd
OMALIZUMAB 150 mg in 1 mL injection, 1 syringe	1	0	
Category / Program	Section 100 Highly Specialised Drugs Program – public and private		
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 allergic 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		
Treatment criteria	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.		

<p>Clinical criteria:</p>	<p>Patient must be under the care of the same physician for at least 426 months, OR Patient must have been diagnosed by a multidisciplinary severe asthma clinic team 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 past or current evidence of atopy, documented by skin prick testing or RAST, AND Patient must have total serum human immunoglobulin E greater than or equal to 30 IU/mL, 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 Patient must not receive more than 28 weeks of treatment under this restriction, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised mepolizumab or benralizumab.</p>
<p>Population criteria</p>	<p>Patient must be aged 12 years or older.</p>
<p>Prescriber Instructions</p>	<p>Optimised asthma therapy includes: (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; AND (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. 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. The initial IgE assessment must be no more than 12 months old at the time of 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>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.</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 or <i>benralizumab</i> for this condition within 6 months of the date on which treatment was ceased.</p> <p>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.</p> <p><i>A multidisciplinary severe asthma clinic team comprises of:</i></p> <ul style="list-style-type: none"> • <i>A respiratory physician; and</i> • <i>A pharmacist, nurse or asthma educator.</i> <p><i>Omalizumab may not be used concurrently with benralizumab or mepolizumab, or within 6 months of each other. A patient is required to have ceased treatment with benralizumab or mepolizumab for 6 months prior to initiating treatment with omalizumab.</i></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 Allergic Asthma PBS Authority Application - Supporting Information Form,</p> <p>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 signed patient or parent/guardian acknowledgement; and</p> <p>(c) the IgE pathology report; and</p> <p>(d) a completed Asthma Control Questionnaire (ACQ-5) calculation sheet including the date of assessment of the patient's symptoms.</p>
<p>Administrative Advice</p>	<p>The Department of Human Services website (www.humanservices.gov.au) has details of the accepted toxicities, including severity, which will be accepted for the purposes of exempting a patient from the requirement of treatment with optimised asthma therapy.</p> <p>For copies of the ACQ and the calculation sheets please contact Novartis Medical</p>

	<p>Information on 1800 671 203 or medinfo.phauno@novartis.com</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 www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>Note:</p> <p>TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE ALLERGIC ASTHMA</p> <p>Patients are eligible to commence an 'omalizumab treatment cycle' (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 omalizumab, 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 omalizumab treatment cycle, or if eligible, a 'mepolizumab treatment cycle' or a 'benralizumab treatment cycle'. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised omalizumab, or mepolizumab or benralizumab is stopped to the date of the first application for initial treatment with omalizumab, or mepolizumab or benralizumab 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 omalizumab therapy:</p> <p>(a) Initial treatment:</p> <p>Applications for initial treatment should be made where:</p> <p>i) A patient has received no prior PBS-subsidised omalizumab treatment and wishes to commence such therapy; or</p> <p>ii) A patient wishes to recommence treatment with omalizumab following a break in PBS-subsidised therapy of more than 6 months; or</p> <p>iii) A patient has received prior PBS-subsidised mepolizumab or benralizumab and wishes to commence treatment with omalizumab after a treatment break of 6 months.</p> <p>All applications for initial treatment for non-grandfather patients will be limited to provide for a maximum of 28 weeks of therapy of omalizumab.</p> <p>(b) Continuing treatment:</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>(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</p>
--	---

	<p>Questionnaire (ACQ; 5 item version) or oral corticosteroid dose submitted with the Initial authority application for omalizumab. 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 measurements.</p> <p>(3) Re-commencement of treatment after a 6 month break in PBS-subsidised therapy: A patient who wishes to trial a second or subsequent omalizumab treatment cycle, or an initial mepolizumab <i>or benralizumab</i> 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>(4) Monitoring of patients: 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.</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 www.humanservices.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).</p> <p>Special Pricing Arrangements apply.</p>
--	--

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
OMALIZUMAB 75 mg in 0.5 mL injection, 1 syringe	1	0	Xolair® Novartis Pharmaceuticals Australia Pty Ltd
OMALIZUMAB 150 mg in 1 mL injection, 1 syringe	1	0	

Category / Program	Section 100 Highly Specialised Drugs Program – public and private
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 allergic asthma
Treatment phase:	Continuing 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

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 have a documented history of severe allergic asthma, AND Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug, AND Patient must not receive more than 24 weeks of treatment under this restriction, AND The treatment must not be used in combination with, or within 6 months of treatment with, PBS-subsidised mepolizumab <i>or benralizumab</i>.</p>
Population criteria	Patient must be aged 12 years or older.
Prescriber Instructions	<p>An adequate response to omalizumab treatment 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</p> <p>(c) a reduction in the time-adjusted exacerbation rates compared to the 12 months prior to baseline (this criterion is only applicable for patients transitioned from the paediatric to the adolescent/adult restriction).</p> <p>All applications for continuing treatment with omalizumab 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, the assessment of oral corticosteroid dose, and the assessment of time adjusted exacerbation rate must be made at around 18 to 22 weeks after the first dose of PBS-subsidised omalizumab 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 first assessment should, where possible, be completed by the same physician who initiated treatment with omalizumab. 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 for this condition within 6 months of the date on which treatment was ceased.</p> <p>At the time of the authority application, medical practitioners should request the appropriate quantity and number of repeats to provide for a continuing course of 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), sufficient for 24 weeks of therapy.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form(s); and</p> <p>(b) a completed Severe Allergic Asthma PBS Authority Application and Supporting Information Form which includes details of maintenance oral corticosteroid dose; and</p> <p>(c) a completed Asthma Control Questionnaire (ACQ-5) calculation sheet including the date of assessment of the patient's symptoms and is endorsed with the signature of the prescriber; for patients transitioned from the paediatric to the adolescent/adult restrictions an exacerbation calculation sheet may be submitted.</p>

Administrative Advice	<p>If the same physician cannot assess the patient please call the Department of Human Services on 1800 700 270.</p> <p>For copies of the ACQ and the calculation sheets please contact Novartis Medical Information on 1800 671 203 or medinfo.phauno@novartis.com</p> <p>It is recommended that an application for continuing treatment is submitted at the time of the 18 to 22 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 www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE ALLERGIC ASTHMA <i>(Per note for initial treatment)</i></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 www.humanservices.gov.au or www.nationalasthma.org.au); the assessment and adherence to correct technique should be documented in the patient's medical records. Patients can obtain support with inhaler technique through their local Asthma Foundation (1800 645 130).</p> <p>Special Pricing Arrangements apply.</p>
------------------------------	---

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

The sponsor had no comment.