



CENTRE OF EXCELLENCE IN
SEVERE ASTHMA

Innovative solutions for severe asthma

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CLINICAL RECOMMENDATIONS FOR THE USE OF BENRALIZUMAB IN SEVERE EOSINOPHILIC ASTHMA

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ABOUT THE TREATMENT

INTRODUCTION

Benralizumab (Fasenra) is indicated as an add-on therapy for people with uncontrolled severe eosinophilic asthma, aged ≥ 12 years.

MECHANISM OF ACTION

Benralizumab is an IgG1 antibody directed against the interleukin 5 receptor-alpha (IL-5R α). IL-5 is a major cytokine responsible for the growth, differentiation, recruitment, activation and survival of eosinophils.

Benralizumab blocks the effect of IL-5 on eosinophils and induces antibody-mediated cell cytotoxicity, causing eosinophil cell death. As a result, eosinophil numbers are reduced in the blood and airways following benralizumab exposure (1, 2).

PHARMACODYNAMIC EFFECTS (MODIFIED FROM FASENRA PRODUCTION INFORMATION)

In a 12-week Phase 2 trial (3), treatment of patients with mild-moderate asthma caused the rapid depletion of blood eosinophils within 24-hours, for all 3 doses assessed [25 mg, 100 mg or 200 mg subcutaneous]. Treatment was administered every 4 weeks for a total of 3 doses. There were no changes in median blood eosinophil numbers in the placebo group. Blood eosinophil depletion was maintained throughout the 12-week dosing period.

In patients with $\geq 2.5\%$ sputum eosinophils, a single dose of benralizumab treatment also reduced eosinophil numbers in airway mucosa tissue, in a Phase 1 trial (1). Further, 3 monthly benralizumab treatments (100 or 200 mg subcutaneous) resulted in a median reduction in airway mucosa eosinophil numbers of 96% from baseline levels (compared to a 47% reduction from baseline in the placebo group; $p=0.06$).

Blood basophil numbers were also reduced in the Phase 1 trial and eosinophil granule proteins (serum eosinophil derived neurotoxin (EDN) and eosinophil cationic protein (ECP)) were also reduced in the Phase I and II trials (3).

In the two pivotal Phase 3 asthma trials (SIROCCO and CALIMA), patients were treated by subcutaneous benralizumab injection (30mg; or matching placebo) every 4 or 8 weeks, following 3 initial 4-weekly doses, for 48 weeks (SIROCCO) or 56 weeks (CALIMA) (4, 5). Benralizumab treatment reduced median absolute blood eosinophil counts to 0 cells/ μL (a median reduction of 100%) (4, 5). This reduction was present at the first assessment timepoint (4 weeks) and was maintained throughout the treatment period (48 or 56 weeks depending on the study).

IMMUNOGENICITY (MODIFIED FROM FASENRA PRODUCTION INFORMATION)

Anti-drug antibody (ADA) responses developed in 107 out of 809 (13%) patients treated with benralizumab at the recommended dosing regimen during the 48 to 56-week treatment period. In a majority of cases, in vitro neutralizing antibodies were detected. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high ADA titers. There is no apparent correlation between ADA development and treatment efficacy or adverse effects.

CLINICAL BENEFIT

In a meta-analysis of 7 RCT publications involving 2,321 patients with severe asthma, benralizumab treatment reduced exacerbation frequency, with an odds ratio of 0.63 (95% CI; 0.52-0.76, $p<0.00001$)(6). There was no trend for improvement in lung function (FEV $_1$), asthma control (ACQ) or asthma related quality of life (AQLQ). Safety data indicated benralizumab administration resulted in no increased incidence of adverse effects (RR: 1.00, 95% CI; 0.95-1.05, $p=0.96$). In the ZONDA trial, benralizumab treatment significantly reduced oral corticosteroid use by 75%, compared to 25% in the placebo treatment group (7).

PBS ELIGIBILITY FOR BENRALIZUMAB ACCESS

[Accessed 05 December 2018; please check <https://www.humanservices.gov.au/organisations/health-professionals/enablers/eosinophilic-asthma> for any recent changes]



CHECKLIST	
<input type="checkbox"/>	Age \geq 12 years
<input type="checkbox"/>	<p>Is not receiving benralizumab treatment in combination with or within 6 months with PBS subsidised omalizumab or mepolizumab</p> <p>AND</p> <p>Has received prior PBS subsidised benralizumab or mepolizumab treatment (provide date treatment stopped)</p> <p>OR</p> <p>Has not received prior PBS subsidised benralizumab or mepolizumab treatment.</p>
<input type="checkbox"/>	<p>Has had asthma for at least 12 months</p> <p>AND</p> <p>Has forced expiratory volume (FEV₁) \leq 80% predicted documented on one or more occasions in the last 12 months</p> <p>AND</p> <p>Has blood eosinophil count \geq300 cells/μL (\geq0.3 x 10⁹ cells/L) in the last 12 months</p> <p>AND</p> <p>Has been under the care of the same physician for at least 6 months</p> <p>OR</p> <p>Has been diagnosed by a multidisciplinary severe asthma clinic team</p>
<input type="checkbox"/>	<p>Has a diagnosis of asthma defined by standard clinical features, including (1 or more of the following):</p> <p>a. FEV₁ reversibility \geq 12% and \geq 200mL at baseline within 30 minutes after administration of salbutamol (200-400μg),</p> <p>OR</p> <p>b. Airway hyper-responsiveness (AHR) defined as >20% decline in FEV₁ during a direct bronchial provocation test or >15% decline during an indirect test,</p> <p>OR</p> <p>c. Peak Expiratory Flow (PEF) variability of >15% between the 2 highest and 2 lowest peak expiratory flow rates during 14 days</p>
<input type="checkbox"/>	<p>The patient has received optimised asthma therapy including adherence to high dose¹ inhaled corticosteroid (ICS) for at least 12 months</p> <p>AND</p> <p>Adherence to long-acting beta-2 agonist (LABA) for at least 12 months</p> <p>AND</p> <p>Treatment with oral corticosteroids (OCS) (either as daily OCS for at least 6 weeks or a cumulative dose of oral corticosteroids of \geq 500mg prednisolone equivalent in the previous 12 months)</p>
<input type="checkbox"/>	<p>Failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, as indicated by:</p> <p>a. Asthma Control Questionnaire (ACQ-5) score \geq2 in the past month</p> <p>AND</p> <p>While receiving optimised asthma therapy in the previous 12 months, has experienced:</p> <p>i. \geq1 admission to hospital for a severe asthma exacerbation</p> <p>OR</p> <p>ii. \geq1 severe asthma exacerbation requiring documented use of systemic corticosteroids (OCS initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician.</p>

Some exemptions to the above treatment requirements, based on toxicity, are possible. See <https://www.humanservices.gov.au/organisations/health-professionals/enablers/severe-asthma-toxicity-criteria-and-severity-descriptors> for details.

1. For definitions of high dose ICS for adults, see <http://www.asthmahandbook.org.au/table/show/22>

SAFETY PROFILE

(Extracted from Fasenna Product Information (PI), for further information not included here refer to the PI)

PRECAUTIONS

Benralizumab should not be used to treat acute asthma exacerbations. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with benralizumab. Reductions in inhaled and oral corticosteroid doses, if warranted, should be gradual and performed under the supervision of a physician. Abrupt discontinuation of asthma medication (including inhaled and oral corticosteroids or long acting beta agonists) after initiation of benralizumab therapy is not recommended.

ADVERSE EFFECTS

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions (e.g. urticaria, urticaria papular, rash) have occurred following administration of benralizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (ie. days).

In the event of a hypersensitivity reaction, benralizumab should be discontinued.

PARASITIC INFECTIONS

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if benralizumab may influence a patient's response against helminth infections. **Treat patients with pre-existing helminth infections before initiating therapy with benralizumab [See Appendix B].** If patients become infected while receiving treatment with benralizumab and do not respond to anti-helminth treatment, discontinue treatment with benralizumab until infection resolves.

EFFECTS ON FERTILITY

No fertility studies have been conducted with benralizumab in humans or animals.

USE IN PREGNANCY (CATEGORY B1):

It is preferable to avoid the use of benralizumab during pregnancy, especially during the third trimester due to the potential for eosinophil depletion in the newborn. Administration of benralizumab to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. IgG antibodies such as benralizumab are increasingly transported across the placenta as pregnancy progresses; therefore, greater foetal exposure occurs in the third trimester of pregnancy.

The effect of benralizumab on human pregnancy is unknown.

USE IN LACTATION:

It is unknown whether benralizumab is excreted in human milk. Since antibodies can be secreted in human milk a risk to the breastfed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from benralizumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

PAEDIATRIC USE:

The safety and efficacy of benralizumab in children under the age of 12 years has not yet been established.

In Phase 3 studies, the treatment responses in adolescent patients (12 to 17 years of age) were less than that observed in adults, however they were not powered to detect a response in this sub-group. The adverse event profile in adolescents was generally similar to the overall population in these studies of up to 56 weeks duration. The longer term adverse effects in this age group are unknown.

USE IN THE ELDERLY:

No dose adjustment is required for use in elderly patients.



DOSAGE

The recommended dose of benralizumab is 30mg, administered by subcutaneous injection every four weeks for the first three doses, and then every 8 weeks thereafter.

STORAGE

Benralizumab is provided in prefilled syringes and should be stored at 2°C to 8°C (do not freeze). Do not shake. Do not use if frozen. The syringe should be stored in its original packaging.

Prior to administration, allow benralizumab to reach room temperature (approximately 30 minutes). Keep benralizumab in the carton until ready to administer to protect it from light. Administer within 24 hours after taking the syringe out of the refrigerator or discard into sharps container.

PROCEDURES

The patient should remain for one hour after the first benralizumab injection in an area under direct staff observation. For subsequent doses, an observation period of 30 minutes is required.

Benralizumab should be administered by a health care professional. Monitoring of patients after administration of biological agents is recommended.

BEFORE THE FIRST INJECTION

Initial injections will generally be administered in the specialist's clinic or private rooms, day hospital or day procedure unit, for the first 2 to 3 doses. In some situations, the initiation and continued administration of monoclonal antibodies may be considered in primary care, provided specific conditions are met (see Appendix A). This approach may be reasonable where the patient has to travel long distances to the specialist's clinic or where no ready access to a day procedure unit or outpatient clinic is available.

1. Obtain Strongyloides serology for all patients being considered for benralizumab treatment. If serology is positive, treat for Strongyloides before commencing benralizumab (*for more details, see Appendix B*). For pre-existing helminth infection, manage accordingly (see precautions), prior to initiation of benralizumab.
2. Complete PBS benralizumab application including ACQ5 and blood eosinophil count (within the last 12 months). Initial treatment forms can be downloaded at: <http://www.humanservices.gov.au/health-professionals/forms/pb194>
 - a. For information on grandfather treatment, for patients who received non-PBS subsidised benralizumab treatment before 01 December 2018, see the DHS website: <https://www.humanservices.gov.au/organisations/health-professionals/services/medicare/written-authority-required-drugs/drug-program-or-condition/asthma-severe-eosinophilic-asthma>
3. Complete an authority script prescribing benralizumab 30 mg SCI injection every 4 weeks for the first 3 doses and every 8 weeks after this (4 repeats total; 32 weeks) for the first prescription. Subsequent prescriptions will require 2 repeats.
4. Send the completed application form, authority prescription form, copy of ACQ5 and copy of blood eosinophil pathology report to:

Department of Human Services Complex Drugs Programs

Reply Paid 9826 HOBART TAS 7001

Alternatively, submit the completed application documents through a Provider Digital Access (PRODA) account. More information on registration and management of a PRODA account can be found here:

<https://www.humanservices.gov.au/organisations/health-professionals/services/medicare/proda>

5. Once approval is received invite the patient to attend the clinic for their first dose and arrange for the medication to be ordered and obtained according to your hospital's policy. Allow time for the patient to receive the script and the pharmacy to order stock.

INJECTION DAY

An assessment of the patient's current asthma and general health should be made before each injection to determine whether there were any recent health changes that might require withholding treatment. This assessment should include vital signs, exacerbation history and spirometry.

Patients should be reminded to continue to take their other asthma medications unless the regimen is changed by their managing physician.

Procedure can only take place in an area where there is access to emergency procedures and adequate medical support.

Ensure rescue medication such as adrenaline, salbutamol MDI and spacer or nebuliser therapy, antihistamines and systemic corticosteroids are accessible.

Ensure benralizumab has been ordered by the respiratory physician on an approved medication chart.

Confirm that the patient has taken their usual asthma medications.

Assess current asthma control and exacerbation status and manage as required.

Assess clinical progress by recording medication requirements and changes since last visit.

Perform baseline observations (HR, RR, BP, SpO2 and Temp).

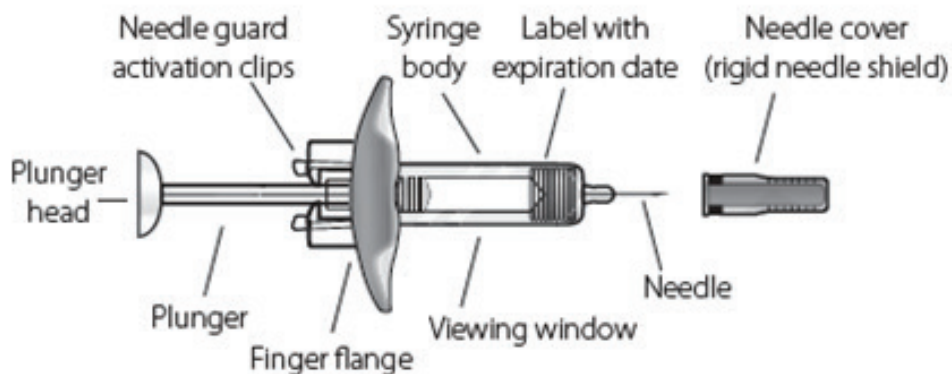
Spirometry assessment should be performed at baseline and PBS continuation assessment. At other visits it may be performed according to the physician's discretion.

Record all information in patient's medical record.



ADMINISTRATION (FROM FASENRA PRODUCT INFORMATION)

Figure 1. Fasenra prefilled syringe



To prevent premature activation of the needle safety guard, do not touch the needle guard activation clips.

1. Grasp the syringe body, not the plunger, to remove prefilled syringe from the tray. Check the expiry date on the syringe.

Visually inspect for particulate matter and discolouration prior to administration. Benralizumab is clear, colourless to slightly yellow and may contain translucent or white to off-white particles. Do not use benralizumab if liquid is cloudy, discoloured or if it contains large particles or foreign particulate matter.

The syringe may contain a small air bubble; this is normal. Do not expel the air bubble prior to administration.

2. Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (e.g. dropped without the needle cover in place), discard and use a new prefilled syringe.
3. Gently pinch the skin and insert the needle at the recommended injection site (i.e. upper arm, thighs or abdomen).
4. Inject all of the medication by pushing in the plunger all the way until the plunger head is completely between the needle guard activation clips. **This is necessary to activate the needle guard.**
5. After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. Do not re-cap the prefilled syringe.
6. Discard the used syringe into a sharps container.

POST ADMINISTRATION

The patient must be observed directly by a suitably qualified clinician administering the injection for at least one hour after the first dose and 30 minutes thereafter, looking for adverse effects from the medication.

If the patient refuses to wait the recommended period of time he or she must sign a waiver, and a discussion with the treating physician is to precede the next administration booking.

While a formal review of response is not required for PBS approval until 6 months after commencement of treatment, a review of clinical progress at around 3 months is recommended.

This review should assess asthma control, adverse events and medication adherence. This review can occur through a face-to-face meeting or by phone

ASSESSING RESPONSE

All applications for continuing treatment must include a measurement of response to the prior course of therapy. The assessment of the patient's response to an initial course of treatment must be made at around **26 to 30 weeks** after the first dose. For second and subsequent treatment courses, the assessment must be made around **18 to 22 weeks** of treatment.

The same physician who initiated treatment with benralizumab should also complete the application for the first assessment. Continuing applications must include an ACQ5 calculation sheet.

An adequate response to treatment is defined as:

- A reduction in ACQ5 scores of at least 0.5 from baseline **OR**
- Maintenance OCS dose reduced by at least 25% from baseline and no deterioration of ACQ5 score from baseline

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.

For patients receiving grandfather PBS treatment or for second and subsequent courses, the assessment must be made around 18 to 22 weeks of treatment.

Continuation forms can be downloaded at: <https://www.humanservices.gov.au/health-professionals/forms/pb195>.

PROTOCOL DEVELOPED BY:

Professor Vanessa McDonald – Centre of Excellence in Severe Asthma

Professor Peter Gibson – Centre of Excellence in Severe Asthma

Steven Maltby – Research Academic, Centre of Excellence in Severe Asthma

Investigators from the Centre of Excellence in Severe Asthma – **Professor John Upham**

John Harrington - Respiratory Clinical Nurse Consultant John Hunter Hospital

Dr Edmond Lau

Dr Rebecca Davis

Dr Raymond Chan

Dr Erin Harvey

RESOURCES USED

Benralizumab Product Information - <http://www.medicines.org.au/files/appfasen.pdf> (date accessed 05-12-2018)

Asthma – Severe eosinophilic asthma DHS website - <https://www.humanservices.gov.au/organisations/health-professionals/services/medicare/written-authority-required-drugs/drug-program-or-condition/asthma-severe-eosinophilic-asthma> (date accessed 07-03-2019)

Adolescent and adult severe eosinophilic asthma Initial PBS authority application. <https://www.humanservices.gov.au/organisations/health-professionals/forms/pb194> (date accessed 05-12-2018)

Adolescent and adult severe eosinophilic asthma Continuing PBS authority application <https://www.humanservices.gov.au/health-professionals/forms/pb195> (date accessed 05-12-2018)

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APPENDIX A: INITIATION OF MONOCLONAL ANTIBODIES FOR SEVERE ASTHMA IN PRIMARY CARE

Specialists are responsible for assessing suitability for monoclonal antibody treatment in severe asthma, and for preparing written applications to the PBS for supply of these medications. Initial injections will generally be administered in the specialist's clinic or private rooms, day hospital or day procedure unit. If there are no untoward reactions after the first 3 injections, the specialist will often arrange for subsequent injections to be administered in primary care by a practice nurse, or in a local health care facility.

In some instances, it may be reasonable to initiate monoclonal antibody injections in primary care or local health care facility, especially where the patient might have to travel long distances to the specialist's clinic or office, or where there is no ready access to a day procedure unit or hospital outpatient clinic.

For this to occur in a way that optimises good patient care, the following criteria should be met:

- The prescribing specialist maintains oversight of the treatment programme and is readily contactable in the event of an asthma exacerbation or adverse reaction.
- The prescribing specialist communicates clearly to the general practitioner about what is involved in giving the injections, the necessary precautions, and what to do in the event of an adverse reaction.
- The patient is fully informed and involved in the decision making.

Specialist review

1. It is recommended that the prescribing specialist reviews the patient 2 to 3 months after starting monoclonal antibody treatment to:
 - a. Assess asthma control and lung function,
 - b. Review inhaler therapy, adherence and oral steroid use
 - c. Assess adverse events.
2. The prescribing specialist will review the patient again at around 5-7 months after starting the monoclonal antibody to determine if the treatment has had the desired impact on asthma control and if so, prepare a written application to the PBS for ongoing supply of medication (see "Assessing Response").



APPENDIX B:

PARASITIC INFECTIONS AND BENRALIZUMAB TREATMENT

Parasitic infections are relevant when considering benralizumab treatment, because anti-IL5 \square treatment could theoretically lead to disseminated parasitic infection. Further, parasitic infections are a common cause of mild peripheral eosinophilia, particularly in those who had visited/come from tropical areas. For example, a UK study determined that 64% of people with elevated eosinophil numbers (>500 cells/ μ L blood) had at least one underlying parasitic helminth infection². Parasitic infections were found in 39% of Caucasian travellers returning to the UK who had blood eosinophil counts >450/ μ L³; and 76% of immigrants to southern Spain who had blood eosinophil counts >500/ μ L⁴.

In Australia, for patients with eosinophilia, the most important parasitic infection to consider before starting benralizumab treatment is *Strongyloides stercoralis*, because:

- Chronic *Strongyloides* infection is usually asymptomatic, so a negative history for gastro-intestinal symptoms does not exclude infection^{5,6}
- *Strongyloides* infection can be present for many decades if untreated^{5,6}
- Many Australians have travelled to areas endemic for *Strongyloides* (including northern Australia, South Asia, and South and Central America).
- The consequences of disseminated *Strongyloides* infection are more serious than for many other parasitic infections (the Centre for Disease Control states that case fatality rates for disseminated *Strongyloides* infection are close to 90%)⁶.

There are no validated screening questionnaires for parasitic infection. Australian infectious diseases specialists therefore recommend that, until further data are available, *Strongyloides* serology should be obtained for all patients being considered for anti-IL5 therapies, regardless of travel or GIT history. If serology is positive, the patient should be treated⁶ before commencing benralizumab treatment, regardless of whether or not they have symptoms.

It should be noted that *Strongyloides* infection should also be considered before commencing patients on oral corticosteroids.

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2. J. Whetham et al. *Investigation of Tropical Eosinophilia; Assessing a Strategy Based on Geographical Area. Journal of Infection* (2003) 46: 180-185
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 6. *Centres for Disease Control and Prevention, Resources for Health Professionals, Parasites - Strongyloides* https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html



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Innovative solutions for severe asthma