



CENTRE OF EXCELLENCE IN
SEVERE ASTHMA

Innovative solutions for severe asthma

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CLINICAL RECOMMENDATIONS FOR THE USE OF MEPOLIZUMAB IN SEVERE ASTHMA

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ABOUT THE TREATMENT

INTRODUCTION

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

MECHANISM OF ACTION

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human IL-5 with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils.

Mepolizumab inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

PHARMACODYNAMIC EFFECTS

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with mepolizumab. The magnitude and duration of this reduction was dose-dependent. Following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced to a geometric mean count of 40 cells/ μ L (0.04×10^9 cells/L). This corresponds to a geometric mean reduction of 84% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period.

CLINICAL BENEFIT

In a meta-analysis the relative rate reduction for hospitalisations compared to placebo was 0.49; 95% CI, 0.30-0.80; $P = 0.004$ and for hospitalisation/emergency room visit the relative rate was, 0.49; 95% CI, 0.33-0.73; $P < 0.001$ (1). It also has an oral-steroid sparing effect, permitting an average OCS dose reduction of 50% in patients with severe OCS dependent eosinophilic asthma (2). Responding patients are adults and adolescents with severe asthma, who experience persistent asthma exacerbations despite optimal inhaled therapy, and with evidence of eosinophilia from blood eosinophil counts (≥ 300 cells/ μ L or $\geq 0.3 \times 10^9$ cells/L) or sputum eosinophilia ($>3\%$)(3).

The safety and efficacy of mepolizumab has not been established in adolescents weighing < 45 kg.

PBS ELIGIBILITY FOR MEPOLIZUMAB ACCESS

[Accessed 10.03.2020; please check www.humanservices.gov.au/organisations/health-professionals/enablers/eosinophilic-asthma for any recent changes]

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

CHECKLIST	
<input type="checkbox"/>	Age ≥ 12 years
<input type="checkbox"/>	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.
<input type="checkbox"/>	<p>Patient must not have received PBS-subsidised treatment with a biological medicine for severe asthma; OR</p> <p>Patient must have had a break in treatment from the most recently approved PBS-subsidised biological medicine for severe asthma AND</p> <p>The treatment must not be used in combination with and within 4 weeks of another PBS-subsidised biological medicine prescribed for severe asthma.</p>
<input type="checkbox"/>	<p>Has had asthma for at least 12 months AND</p> <p>$FEV_1 \leq 80\%$ predicted documented on one or more occasions in the last 12 months AND</p> <p>Has blood eosinophil count ≥ 300 cells/μL ($\geq 0.3 \times 10^9$ cells/L) in the last 12 months OR patient must have blood eosinophil count greater than or equal to 150 cells per microlitre while receiving treatment with oral corticosteroids in the last 12 months AND</p> <p>Under the care of the same physician for 6 months OR</p> <p>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> <ul style="list-style-type: none"> a. FEV_1 reversibility $\geq 12\%$ and ≥ 200mL at baseline within 30 minutes after administration of salbutamol (200-400μg), <p>OR</p> <ul style="list-style-type: none"> b. Airway hyper-responsiveness (AHR) defined as $>20\%$ decline in FEV_1 during a direct bronchial provocation test or $>15\%$ decline during an indirect test, <p>OR</p> <ul style="list-style-type: none"> c. Peak Expiratory Flow (PEF) variability of $>15\%$ between the 2 highest and 2 lowest peak expiratory flow rates during 14 days <p>OR</p> <ul style="list-style-type: none"> d. Patient must have a diagnosis of asthma from at least two physicians experienced in the management of patients with severe asthma
<input type="checkbox"/>	<p>The patient has received optimised asthma therapy including adherence to high dose¹ inhaled corticosteroid (ICS) and adherence to long-acting beta-2 agonist (LABA) for at least 12 months and treatment with oral corticosteroids (OCS) (either as daily OCS for at least 6 weeks or a cumulative dose of oral corticosteroids of ≥ 500mg prednisolone equivalent in the previous 12 months)</p>
<input type="checkbox"/>	<p>Failed to achieve adequate control with optimized asthma therapy, despite formal assessment of and adherence to correct inhaler technique, as indicated by:</p> <ul style="list-style-type: none"> a. Asthma Control Questionnaire (ACQ-5) score ≥ 2 AND b. One of the following experienced in the previous year: <ul style="list-style-type: none"> i. ≥ 1 admission to hospital for a severe asthma exacerbation, OR ii. ≥ 1 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.

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

SAFETY PROFILE

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

PRECAUTIONS

Mepolizumab should not be used to treat acute asthma exacerbations.

Asthma-related adverse events or exacerbations may occur during treatment with Mepolizumab. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with Mepolizumab.

Abrupt discontinuation of asthma medication (including inhaled and oral corticosteroids or long acting beta agonists) after initiation of Mepolizumab therapy is not recommended. Reductions in inhaled and oral corticosteroid doses, if warranted, should be gradual and performed under the supervision of a physician.

ADVERSE EFFECTS

HYPERSENSITIVITY AND ADMINISTRATION REACTIONS

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., days). These reactions may occur for the first time after a long duration of treatment. In the event of a hypersensitivity reaction, mepolizumab should be discontinued.

PARASITIC INFECTIONS

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in the clinical programme. **Patients with pre-existing helminth infections should be treated for their infection prior to mepolizumab therapy.** If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of mepolizumab should be considered.

OPPORTUNISTIC INFECTIONS: HERPES ZOSTER

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with mepolizumab versus none in the placebo group.

USE IN PREGNANCY (CATEGORY B1):

The effect of mepolizumab on human pregnancy is unknown. No treatment related effects on embryofetal or postnatal development have been shown in animal studies.

Mepolizumab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

USE IN LACTATION:

There are no data regarding the excretion of mepolizumab in human milk. A decision should be made whether to discontinue breast-feeding or discontinue mepolizumab, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother.

PAEDIATRIC USE:

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

USE IN THE ELDERLY:

No formal studies have been conducted in elderly patients.

DOSAGE

The recommended dose of mepolizumab is 100mg, administered by subcutaneous injection every four weeks.

STORAGE

Unopened vials should be refrigerated at temperatures between 2-8°C (Do not freeze). The vial should be stored in its original packaging.

After reconstitution with Water for Injection, the solution is stable for up to 6 hours if stored below 30°C. Protection from light is not necessary during administration.



PROCEDURES

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

Mepolizumab should be reconstituted and 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 mepolizumab treatment, when blood is being drawn for eosinophil count. If serology is positive, treat for Strongyloides before commencing mepolizumab (*for more details, see the Appendix B*). For pre-existing helminth infection, manage accordingly (see precautions), prior to initiation of mepolizumab.
2. Complete PBS mepolizumab application including ACQ5 and blood eosinophil count (within the last 12 months). Initial treatment forms can be downloaded at: www.humanservices.gov.au/health-professionals/forms/pb194.
3. Complete an authority script prescribing mepolizumab 100mg SCI injection every 4 weeks, with 7 repeats for the first prescription. Subsequent prescriptions will require 5 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 mepolizumab 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.



RECONSTITUTION

Mepolizumab is provided as a lyophilised powder in a single-use vial for subcutaneous injection only and should be reconstituted by a healthcare professional using standard aseptic techniques as follows:

Preparation in a laminar flow hood is not indicated in any product information nor supported by evidence.

1. Reconstitute the mepolizumab powder in the vial with 1.2 mL of sterile Water for Injections preferably using a 2 to 3 mL syringe and a 21G needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab.
2. The stream of sterile water for injections should be directed vertically onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion, followed by resting the vial for 5 seconds, until the powder is dissolved. *Note: **Do not shake** the reconstituted solution during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 -10 minutes after the sterile water has been added, but it may take additional time.*

You may need to tip the vial on its side and roll gently to dissolve all of the dose.

3. *If a mechanical reconstitution device (swirler) is used to reconstitute MEPOLIZUMAB, reconstitution can be accomplished by swirling at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1000 rpm for no longer than 5 minutes is acceptable.*
4. Following reconstitution, mepolizumab should be visually inspected for particulate matter and clarity prior to use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution should not be used.

RECONSTITUTED SOLUTION

- Mepolizumab is for single use in one patient only and contains no antimicrobial agent. To reduce microbiological hazard, use as soon as practicable after reconstitution. Discard any unused solution.
- If storage is necessary, store below 30°C for not more than 6 hours

ADMINISTRATION

1. For subcutaneous administration a 1 mL polypropylene syringe fitted with a disposable needle, 25-27G is preferable.
2. Just prior to administration, remove 1 mL of reconstituted mepolizumab. Do not shake the reconstituted mepolizumab solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

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 for 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 mepolizumab 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>.



AUSTRALIAN MEPOLIZUMAB REGISTRY

The Australian Mepolizumab Registry collects and reports on data from people with severe refractory eosinophilic asthma who receive mepolizumab.

The Registry will provide a mechanism for sharing information which will help researchers and clinicians to better understand the use, efficacy, and safety associated with the treatment of severe asthma with mepolizumab. All information collected from participating sites will be securely stored in the main data repository. Access to the Register will be restricted to authorised users. The Registry will report regularly on characteristics and outcomes for this population.

The Australian Mepolizumab Registry is an investigator initiated study supported by a clinical research grant from GlaxoSmithKline [dated 21st October 2016; protocol 207455] covering the period 1/10/2016 until 1/10/2021].

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RESOURCES USED

Mepolizumab Product Information - https://au.gsk.com/media/351182/nucala_pi_au_002_approved.pdf (date accessed 06-12-2018)

Adolescent and adult severe eosinophilic asthma Initial PBS authority application. <https://www.humanservices.gov.au/health-professionals/forms/pb194>. (date accessed 06-12-2018)

Adolescent and adult severe eosinophilic asthma Continuing PBS authority application <https://www.humanservices.gov.au/health-professionals/forms/pb195>. (date accessed 06-12-2018)

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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 2 or 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 program 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 review 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. Document adverse events.
4. 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 MEPOLIZUMAB TREATMENT

Parasitic infections are relevant when considering mepolizumab treatment, because anti-IL5 treatment could theoretically lead to disseminated parasitic infection, and because parasitic infections are a common cause of mild peripheral eosinophilia (e.g. they were found in 64% of people investigated in UK for eosinophils >500),² particularly in those who had visited/come from tropical areas (e.g. parasitic infections found in 39% of Caucasian travelers returning to UK who had eosinophils >450³; and 76% of immigrants to southern Spain who had eosinophils >500⁴).

In Australia, for patients with eosinophilia, the most important parasitic infection to consider before starting mepolizumab 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^{4,5}
- 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%)⁵

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 mepolizumab, regardless of travel or GIT history. If serology is positive, the patient should be treated⁵ before commencing mepolizumab, 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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 5. Page W and Spear R, *Chronic strongyloidiasis – Don't look and you won't find. Australian Family Physician* Vol.45, No.1-2, Jan-Feb 2016
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