Guidelines for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH) through the Life Saving Drugs Program

This document outlines the criteria for initial and ongoing eligibility to receive Australian Government subsidised eculizumab (Soliris®) for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH) through the Life Saving Drugs Program.
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1. THE LIFE SAVING DRUGS PROGRAM

1.1 Aims of the Life Saving Drugs Program

Through the Life Saving Drugs Program (LSDP), the Australian Government provides subsidised access, for eligible patients, to expensive and potentially life saving drugs for very rare life-threatening conditions.

The supply of life saving drugs under this special non-statutory, administrative arrangement commenced in May 1995 and evolved from the former Act of Grace payment arrangements administered by the Department of Finance under section 34A of the Audit Act 1901. The Government provides funding each year for the LSDP under an annual appropriation item approved by Parliament.

The criteria for funding of a drug and the conditions for patient initial and ongoing subsidy are jointly approved by the Minister for Health and Ageing and the Minister for Finance and Deregulation. The Funding Criteria and Conditions for the LSDP are available at www.health.gov.au/lsdp.

A Departmental delegate of the Minister makes a final decision on eligibility and a separate committee of clinical experts in the relevant disease area is established for each of the medical conditions on the LSDP. Separate Guidelines have been established for each condition to govern initial access and continuation of treatment.

Patients with a disease condition treated through the LSDP are referred by their treating specialist for consideration for inclusion under the Program. Individual patients are assessed to determine initial eligibility and continuation of treatment by expert medical committees.

1.2 Drugs currently available through the Life Saving Drugs Program

Currently, funds are specifically made available on an annual basis for the following therapies:
   a) imiglucerase (Cerezyme®) & miglustat (Zavesca®) for the treatment of Gaucher disease
   b) agalsidase alfa (Replagal®) & agalsidase beta (Fabrazyme®) for the treatment of Fabry disease
   c) laronidase (Aldurazyme®) for the treatment of Mucopolysaccharidosis Type I disease
   d) idursulfase (Elaprase®) for the treatment of Mucopolysaccharidosis Type II disease
   e) galsulfase (Naglazyme®) for the treatment of Mucopolysaccharidosis Type VI disease
   f) alglucosidase alfa (Myozyme®) for the treatment of infantile-onset Pompe disease
   g) eculizumab (Soliris®) for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH)

1.3 Purpose of this document

The Department of Health and Ageing uses these Guidelines to administer Australian Government subsidised eculizumab for the treatment of PNH through the Life Saving Drugs Program. In addition, these Guidelines provide a framework and advice for clinicians who wish to apply for their patients to receive treatment through the LSDP. The Guidelines may also be of interest to patients and patients’ families.
2. **PNH - BACKGROUND INFORMATION**

2.1 **Scientific explanation of PNH**

PNH is an acquired clonal haemopoietic stem cell disorder that causes blood cells to be deficient of glycosylphosphatidylinositol (GPI)-linked membrane proteins. Red blood cells (RBC) deficient in GPI-anchored complement inhibitor proteins are susceptible to complement-mediated lysis leading to chronic intravascular haemolysis. This haemolysis can result in a spectrum of symptoms, from mild to severe.

2.2 **Types of PNH**

Through improved diagnostic techniques, it has been possible to differentiate subgroups of PNH. These subgroups were proposed in Parker and colleagues (2005)\(^1\), and have assisted in understanding progression of PNH through natural history studies, such as that of de Latour (2008)\(^2\). The subgroups are defined as follows:

a) **Classic PNH:**

   Patients in this subgroup have clinical evidence of intravascular haemolysis (diagnosed through abnormally raised lactate dehydrogenase (LDH) levels) but currently show little or no other bone marrow abnormality.

b) **PNH in the setting of another specified bone marrow disorder:**

   Patients in this subcategory have concomitant underlying bone marrow disorder, such as aplastic anaemia, myelodysplastic syndrome or another myelopathy (eg. myelofibrosis). In this patient group, bone marrow dysfunction causes further emphasis on the clone cells, because the bone marrow is unable to produce normal blood cells.

c) **Subclinical PNH:**

   Patients in this subcategory have no clinical or laboratory evidence of haemolysis, due to a low clone size.

Consistent with the PBAC recommendations of August 2010, only patients with Classic PNH will be eligible to receive treatment through the LSDP. In cases where it is unclear, committee members can be approached by treating physicians to discuss potential patient eligibility.

2.3 **Clinical presentation of PNH**

Patients with PNH suffer a range of symptoms, which all result from haemolysis. The clone size dictates the range and severity of symptoms that a patient may display, including thromboembolism, renal dysfunction, and pulmonary arterial hypertension (PAH), abdominal pain, smooth muscle spasm-related symptoms (e.g. dysphagia, oesophageal spasms and erectile dysfunction), severe anaemia and haemolysis driven fatigue independent of anaemia. In patients with a granulocyte clone size greater than 10% in particular, these symptoms can be life threatening.

PNH can present at any age, with the median age in the early to mid thirties, affecting males and females equally.


2.4 Prevalence of PNH

Data presented by Hill et al (2006), based on the incidence and prevalence of 3.7 million people living in Yorkshire (United Kingdom) between 1991 and 2006 found an incidence of 0.13/100,000/year, and prevalence of 1.59/100,000 over 15 years.

2.5 Available treatments for PNH

2.5.1 Pre-complement inhibitor treatment

Treatment of PNH before monoclonal antibody focused on transfusions of red blood cells, iron and/or folic acid therapy, steroids (eg. androgens, glucocorticoids) and anticoagulants (to treat thrombotic complications such as Budd-Chiari syndrome).

Haemopoietic stem cell transplantation has occasionally been used, but carries significant risk.

2.5.2 Complement inhibitor treatment

Treatment of PNH by complement inhibitor represents a major advance in treatment. The currently available complement inhibitor (eculizumab) is a monoclonal antibody that is administered through intravenous infusion.

2.5.3 eculizumab (Soliris®)

Eculizumab (Soliris®) was registered in Australia by the Therapeutic Goods Administration on 20 March 2009 ‘for the treatment of patients with PNH to reduce haemolysis’ (see Section 9).

Eculizumab has been subsidised through the Life Saving Drugs Program for the treatment of PNH since 2010.

2.5.4 Therapies in development

It is noted that clinical trials must be conducted to test and research the efficacy and safety of any new product being developed. Australian patients may be offered involvement in international clinical trials of new therapies for the treatment of PNH by their treating doctors.

Patients participating in a clinical trial are not eligible for subsidised treatment through the LSDP. Previous involvement in a clinical trial does not impede eligibility for subsidised treatment through the LSDP. Patients, however, will only be assessed for eligibility to receive drugs subsidised through the LSDP, once the patient is off the clinical trial. Eligibility to participate in a clinical trial does not entitle patients to receive drugs subsidised through the LSDP.

2.5.5 Potential adjunctive therapies

Supportive treatments can be continued during eculizumab therapy if the treating haematologist considers it appropriate. For a haemolytic crisis, narcotic pain relief and fluids may be appropriate. Blood transfusions may be required to support haemoglobin levels.

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3. ELIGIBILITY CRITERIA FOR TREATMENT THROUGH THE LSDP

3.1 LSDP eligibility criteria

A patient must meet the Life Saving Drugs Program Criteria and Conditions in order to be eligible for eculizumab for the treatment of PNH through the LSDP. The Program Criteria and Conditions can be found on the LSDP website at: [www.health.gov.au/lsdp](http://www.health.gov.au/lsdp).

3.2 Additional eligibility criteria for PNH – initial treatment

In addition to the LSDP funding criteria and conditions, the patient must meet each of the following additional eligibility criteria specific for PNH for initial treatment:

3.2.1 Diagnosis

The diagnosis of PNH must have been established by flow cytometry (see section 9). The proportion of circulating cells of each type which are GPI-deficient and hence of the PNH clone is quantitated by flow cytometry. To be eligible for subsidised treatment, patients must have a PNH granulocyte clone size equal to or greater than 10% and a raised LDH (value at least 1.5 times the upper limit of normal for the reporting laboratory).

3.2.2 Severity of PNH

Patients with a clone size greater than 10% also require at least one of the following criteria to be eligible for treatment with eculizumab:

a) Thrombosis:
   This is a thrombotic or embolic event which required the institution of therapeutic anticoagulant therapy.

b) Transfusions:
   Evidence that the patient has been transfused with at least four units of red blood cells in the last twelve months.

c) Anaemia:
   Chronic or recurrent anaemia where causes other than haemolysis have been excluded and demonstrated by more than one measure of less than or equal to 70g/L or by more than one measure of less than or equal to 100 g/L with concurrent symptoms of anaemia.

d) Pulmonary insufficiency:
   Debilitating shortness of breath and/or chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded.

e) Renal insufficiency:
   History of renal insufficiency, demonstrated by an eGFR less than or equal to 60mL/min/1.73m², where causes other than PNH have been excluded.

f) Smooth muscle spasm:
   Recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded.
3.2.3 Other eligibility requirements

3.2.3.1 Risk of Meningococcal infection
Eculizumab increases a patient’s susceptibility to serious meningococcal infections (septicaemia and/or meningitis). All patients must receive meningococcal vaccination with a tetravalent vaccine (ACWY) at least two weeks prior to receiving the first dose of eculizumab.

Revaccination must occur every 2.5 - 3 years or according to NHMRC recommendations. Treating physicians will be required to complete and submit a ‘vaccination form’ on an annual basis in order for their patients to continue to be eligible for treatment with eculizumab.

3.3 Continuation criteria

Therapy can be withdrawn at the request of the patient or their parent/guardian at any time. Notification of withdrawal from therapy must be made by the treating physician or patient in writing to the LSDP.

Patient eligibility will be reviewed six months after commencing therapy and every six months thereafter.

Continued eligibility will be subject to the assessment of evidence, in accordance with the monitoring requirements at section 4, which demonstrates:

a) Clinical improvement in the patient, or

b) Stabilisation of the patient’s condition.

The assessment of eligibility will be made with regard to the natural course and stage of the disease, and any exceptional circumstances that may apply.

Further, subsidised treatment may continue unless one or more of the following situations apply:

a) the patient or treating physician fails to comply adequately with treatment or measures, including monitoring requirements, taken to evaluate the effectiveness of the therapy;

b) if therapy fails to relieve the symptoms of disease that originally resulted in the patient being approved for subsidised treatment;

Note: these clauses are consistent with, and don’t exclude those general clauses in the Patient Conditions for Initial and Ongoing Subsidy available at www.health.gov.au/lsdp.

Treating doctors will be advised by the LSDP if their patient is at risk of being withdrawn from treatment for failure to comply with the requirements of the program, or other perceived ‘non-compliance’. Following this advice, if the situation is not adequately addressed to the Department of Health and Ageing and the Committee’s satisfaction, including the provision of data for review, treatment may be withdrawn.

3.4 Exclusion criteria

Patients are not eligible for treatment with eculizumab for the treatment of PNH through the LSDP if they meet any of the following criterion.
a) Small granulocyte clone size - the treatment of patients with a granulocyte clone size below 10% will not be eligible for treatment; or

b) Aplastic anaemia with two or more of the following: neutrophil count below 0.5 x 10^9/L, platelet count below 20 x 10^9/L, reticulocytes below 25 x 10^9/L, or severe bone marrow hypocellularity; or

c) Patients with a presence of another life threatening or severe disease where the long term prognosis is unlikely to be influenced by therapy (for example acute myeloid leukaemia or high-risk myelodysplastic syndrome); or

d) The presence of another medical condition that might reasonably be expected to compromise a response to therapy.

### 3.5 Precautions

Please refer to the drug Product Information for full information on precautions.

Eculizumab carries a ‘Category B2’ pregnancy rating in Australia.

It is recommended that women who intend to become pregnant discuss the need for treatment during pregnancy with their treating physician. The product information for eculizumab advises that Soliris should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

In relation to breast feeding, the product information for eculizumab advises that consideration should be given to avoiding breast feeding for the first 24 hours after birth. The product information also advises that Soliris should be given to a breastfeeding woman only if clearly needed and after a careful risk/benefit analysis has been conducted.
4. MONITORING REQUIREMENTS

Patients must demonstrate ongoing eligibility, as required by section 3.2.3, by providing recent clinical data on the following monitoring requirements*. Patients are monitored at intervals of six months by the PNH Disease Advisory Committee and Department.

Data are to be entered directly into the PNH Registry (see section 8.3).

4.1 New patient requirements

As described in application form

4.2 Information required every six months

The following information is required by the LSDP and PNH Disease Advisory Committee every 6 months:

   a) Lactate dehydrogenase (LD);
   b) Full blood count and reticulocytes;
   c) Transfusion history for previous six months;
   d) Iron studies;
   e) Urea, electrolytes and eGFR; and
   f) Recent clinical history

4.3 Information required every 12 months

The following information is required by the LSDP and PNH Disease Advisory Committee every 12 months:

   a) Certificate to confirm that the patient has been vaccinated (meningococcal);
   b) Progress reports on the clinical symptoms that formed the basis of initial eligibility (as defined in section 3.2.2);
   c) Quality of life, through clinical narrative; and
   d) Granulocyte clone size (by flow cytometry) (or more frequently if required)

4.4 Increased monitoring during pregnancy

As outlined in section 3.5, treatment with eculizumab should be carefully considered. Monitoring should be increased during pregnancy (the suggested frequency of blood counts and LD is monthly with 2-3 monthly clone size determination), regardless of whether treatment is continued, as dilutional effects may confound interpretation of tests and there may be a requirement for larger doses of eculizumab in pregnancy to suppress haemolysis and reduce the risk of thrombotic events.

* Monitoring and testing is not funded or subsidised by the LSDP, however some tests may be subsidised through Medicare or available through the treating public hospital.
5. APPLICATIONS

Application and consent forms are available from the LSDP website at www.health.gov.au/lsdp. Completed application forms may be mailed, faxed or emailed to the LSDP Secretariat (see section 8.2).

5.1.1 Application requirements

Applications for subsidised therapy with eculizumab for the treatment of PNH, through the LSDP, will only be considered on:

a) Receipt of a completed application form;

b) Receipt of signed consent forms; and

c) Receipt of diagnostic test results.

The application form must be filled out by a patient’s treating physician, with the consent of the patient (or parent/guardian).

5.1.2 Consent forms

Patients or their parent/guardian are required to sign consent and agreement forms, to be submitted at the time of application, prior to the start of subsidised treatment.

Once a patient has reached 18 years of age, he or she will be required to complete the adult version of these forms.
6. **APPEALS**

If a patient, their parent/guardian, or treating physician is unhappy with a decision made under the LSDP, it may be discussed with the LSDP Secretariat. This process provides parties with an opportunity to correct any misunderstandings and to present any new information or evidence.

If the matter remains unresolved, a review of the decision may be requested within 60 days of the original decision being made.

All applications for review must be in writing and addressed to the LSDP Secretariat. An application for review must include:

- a) the complainant’s name and contact details;
- b) relevant reference numbers (if applicable);
- c) an outline of the decision appealed;
- d) an explanation as to why the original decision is considered to be wrong; and
- e) any evidence or additional documentation which assists the appeal.

It is important to keep a copy of the application for review and then post or scan and email to the LSDP Secretariat (see section 8.2).

The First Assistant Secretary, Pharmaceutical Benefits Division, is responsible for reviewing decisions.
7. DOSAGE

7.1 Initial dose

For the first four weeks of treatment, the dose is 600mg once per week.

7.2 Continued dose

From week five of treatment, the standard dose for eculizumab is 900mg once every two weeks.
8. RESOURCES FOR PNH

8.1 The PNH Disease Advisory Committee

The Government has established a PNH Disease Advisory Committee to provide advice on the treatment of PNH patients with eculizumab through the LSDP.

The PNH Disease Advisory Committee meets twice per year to review patients for continued eligibility to receive Australian Government subsidised treatment for PNH. Applications for new patients are reviewed out of session at any time of the year, along with other ad hoc business.

The PNH Disease Advisory Committee is comprised of the following specialists:

Chair:

Professor Jeffrey Szer
Director
Department of Clinical Haematology and Bone Marrow Transplant Service
Royal Melbourne Hospital
Melbourne, Victoria

Members:

Dr Paul Cannell
Director of Cancer and Neurosciences Division
Royal Perth Hospital
Perth, Western Australia

Dr Anthony Mills
Clinical Haematologist
Division of Cancer Services
Princess Alexandra Hospital, Queensland and
Greenslopes Private Hospital, Queensland

Dr John Norman
Clinical Haematologist
Department of Medicine
The Queen Elizabeth Hospital, South Australia

Professor Hatem Salem
Director of Haematology
The Alfred Hospital
Melbourne, Victoria

Dr Pauline Warburton
Director
Department of Haematology
Wollongong Hospital
Wollongong, New South Wales
8.2 LSDP Secretariat

All information for the PNH Disease Advisory Committee must be sent to the Life Saving Drugs Program Secretariat at:

Phone:   (02) 6289 2336  
Fax:      (02) 6289 8537  
Address: Life Saving Drugs Program (MDP 953)  
          Pharmaceutical Benefits Division  
          PO Box 9848 Canberra ACT 2606  
Email:    lsdp@health.gov.au

8.3 PNH Registry

The International PNH Interest Group supported the development of a worldwide patient registry to generate more detailed epidemiological data and to gain greater insight into both the natural history of the disease and the outcomes of therapy.

The Australian Government supports the use of data Registries for the LSDP, provided that they can report and present data for the benefit of medical advisors who must review data (namely the Advisory Committee and the Senior Medical Advisor of the Pharmaceutical Benefits Division).
9. FLOW CYTOMETRY

Flow cytometry is the required method of diagnosis for patients with PNH disease. Analysis of expression on granulocytes better determines the PNH clone size in an individual, as granulocytes that are deficient in glycosyl phosphatidylinositol do not lyse prematurely unlike erythrocytes (red blood cells) do.

Flow cytometry categorises erythrocytes into three categories, depending on the number of glycosyl phosphatidylinositol - anchored proteins (GPI-AP) on the cells surface:

a) PNH-III
erthrocytes with a complete deficiency of GPI-AP’s

b) PNH-II
erthrocytes with subtotal deficiency of GPI-AP’s

c) PNH-I
erthrocytes with normal expression of GPI-AP’s
10. TGA REGISTRATION FOR Eculizumab (SOLIRIS®)

### Public Summary

**Summary for ARTG Entry:** 13885  
**SOLIRIS eculizumab (mrc) 300mg/30mL concentrated solution for intravenous infusion vial**

**ARTG Entry for:** Medicine Regulated  
**Sponsor:** Aventis Pharmaceuticals Australia Pty Ltd  
**Postal Address:** 7 McDonald Crescent, STRATHFIELD, NSW, 2135  
**ARTG Start Date:** 20/03/2009

### Conditions

Conditions applicable to all therapeutic goods as specified in the document “Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 26 of the Therapeutic Goods Act 1989” effective 1 July 1990.

Conditions applicable to the relevant category and class of therapeutic goods as specified in the document “Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 26 of the Therapeutic Goods Act 1989” effective 1 July 1995.

### Products

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### Warnings

See Product Information and Consumer Medicine Information for this product

### Standard Indications

No Standard Indications included or included

### Special Instructions

For the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis.

### Additional Product Information

### Container Information

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### Active Ingredients

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