Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)
Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy: CP98
Eculizumab for Atypical Haemolytic Uraemic Syndrome (aHUS)

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Policy Statement

Background	Atypical haemolytic-uremic syndrome (aHUS) is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. aHUS is characterized by three major features related to abnormal clotting: haemolytic anaemia, thrombocytopenia, and kidney failure. aHUS often results from a combination of environmental and genetic factors. Mutations in at least seven genes appear to increase the risk of developing the disorder. Mutations in a gene called CFH are most common; they have been found in about 30 percent of all cases of atypical haemolytic-uremic syndrome. Mutations in the other genes have each been identified in a smaller percentage of cases.
Summary of Access Criteria	Access criteria are outlined in section 3 of this policy.
Responsibilities	Referring physicians should: • Inform the patient that this treatment is not funded outside the criteria in this policy and • Refer via the agreed pathway Clinician considering treatment should: • Discuss all the alternative treatment with the patient ensuring that the patient is given the opportunity to make an informed decision based on potential side effects and risks of treatment; • Advise the patient on the potential clinical scenarios in an informed, open and transparent manner; • Inform the patient that treatment is not funded outside of the criteria in the policy

Contents

1. Aim

1.1 Introduction

The document has been developed as the policy for the planning of for Welsh patients. The policy applies to residents of all seven Health Boards in Wales.

The purpose of this document is to:

- Specify the clinical circumstances under which patients will be able to access Eculizumab for Atypical Haemolytic Uraemic Syndrome (aHUS)*;*
- Clarify the referral process; and
- Define the clinical criteria that patients must meet in order to access treatment.

1.2 Relationship with other Policies and Service Specifications

This document should be read in conjunction with the following documents:

- All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR).

2. Scope

2.1 Definitions

2.1.1 Atypical Haemolytic Uraemic Syndrome (aHUS) is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. Atypical haemolytic-uremic syndrome is characterized by three major features related to abnormal clotting: haemolytic anaemia, thrombocytopenia, and kidney failure. Atypical haemolytic-uremic syndrome should be distinguished from a more common condition called typical haemolytic-uremic syndrome. The two disorders have different causes and different signs and symptoms. Unlike the atypical form, the typical form is caused by infection with certain strains of Escherichia coli bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized by severe diarrhoea and most often affects children younger than 10. The typical form is less likely than the atypical form to involve recurrent attacks of kidney damage that lead to end-stage renal failure (ESRD).

2.1.2 A Disintegrin and Metalloproteinase with a Thrombospondin type 1 motif, member 13 (ADAMTS13), also known as von Willebrand

factor-cleaving protease (VWFCP), is a zinc-containing metalloprotease enzyme that cleaves von Willebrand factor (vWf), a large protein involved in blood clotting. It is secreted in blood and degrades large vWf multimers, decreasing their activity. Thrombotic thrombocytopenic purpura (TTP) is a rare disease (5–10 cases per million persons per year) characterised by the massive formation of platelet rich-thrombi in the microcirculation of multiple organs. It affects both sexes, although the incidence is two to three times higher among females. The possibility of using plasma ADAMTS13 values to manage TTP patients stems from the current availability of ADAMTS13 assays to measure ADAMTS13 activity, ADAMTS13 antigen and neutralising or non-neutralising anti-ADAMTS13 autoantibodies.

2.1.3 End Stage Renal Disease (ESRD) The stages of CKD (Chronic Kidney Disease) are mainly based on measured or estimated GFR (Glomerular Filtration Rate). There are five stages but kidney function is normal in Stage 1, and minimally reduced in Stage 2. In Stage 4 CKD is severely reduced kidney function, 15-30% (eGFR 15-29ml/min/1.73m2) Stage 5 CKD is very severely reduced kidney function (end stage or ESRF/ESRD), less than 15% (eGFR less than 15 ml/min).

2.1.4 Thrombotic microangiopathy (TMA) is a pathological process involving thrombocytopenia, microangiopathic haemolytic anaemia and microvascular occlusion. TMA leads to end-organ ischaemia and infarction affecting particularly the kidney and brain. Patients may present with acute renal failure and/or cerebral dysfunction, although cardiac, gastrointestinal and other organ involvement can also occur. TMA is common to haemolytic uraemic syndrome (HUS) associated with shiga toxin or invasive pneumococcal infection, atypical HUS (aHUS), thrombotic thrombocytopenic purpura (TTP) and other disorders including malignant hypertension.

2.1.5 Thrombotic thrombocytopenic purpura (TTP) is a rare blood condition characterised by the formation of small clots (thrombi) within the circulation, which results in the consumption of platelets and thus a low platelet count (thrombocytopenia).

2.2 Codes

The clinical coding for atypical haemolytic uraemic syndrome is not currently well described.

Thrombotic microangiopathy:

- M31.1 is an ICD-10-CM code that can be used to indicate a diagnosis for reimbursement purposes: this code will be used in all correspondence with WHSSC.

3. Access Criteria

3.1 Clinical Indications

Eculizumab is indicated for the treatment of aHUS for adults and children. The condition needs to be distinguished from TTP and typical HUS where Eculizumab is not indicated. The patient should meet the clinical criteria for treatment outlined below.

3.2 Criteria for Treatment

3.2.1 Inclusion Criteria

1. Thrombocytopaenia - Platelet count <150,000/mm or >25% Decrease from baseline;

AND

2. Microangiopathic Haemolysis – Schistocytes and/or Elevated LDH and/or Decreased haptoglobin and/or Decreased haemoglobin;

PLUS 1 OR MORE of the following:

- Renal Impairment - Elevated creatinine, Decreased eGFR
- Neurological Symptoms - Confusion and/or Seizures, other cerebral abnormalities
- Gastrointestinal Symptoms – Diarrhoea and/or Abdominal pain.

AND

>5% ADAMTS13 Activity (In the absence of ADAMTS13 results, a serum creatinine >150–200 µmol/L (>1.7–2.3 mg/dL) or a platelet count >30,000 mm almost eliminates a diagnosis of severe ADAMTS13 deficiency) (TTP)

AND

Absence of a Positive Shiga-toxin/EHEC

Eculizumab should be initiated urgently in all patients diagnosed with aHUS. Earlier treatment with eculizumab has been associated with improved clinical outcomes.

Genetic testing is not required for diagnosis of aHUS or eculizumab initiation. Genetic testing may be useful for longer-term management decisions, especially when investigating potential familial linkages.

ADAMTS13 testing is available via laboratory services at Cardiff and Vale University Health Board and should be marked for urgent processing and reporting.

All patients should receive meningococcal prophylaxis prior to treatment with Eculizumab. Patients must be vaccinated at least 2 weeks prior to receiving Eculizumab. Patients who are treated with Eculizumab less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients must be re-vaccinated according to current medical guidelines for vaccination use. Tetravalent vaccines against serotypes A, B, C, Y and W135 are strongly recommended, preferably conjugated ones.

3.2.2 Exclusion Criteria
Any patient not meeting the required pre-testing and diagnostic criteria to confirm a positive diagnosis of aHUS will not be considered appropriate for initiation of treatment.

3.3 Monitoring and Treatment Continuation

Eculizumab is agreed for patients meeting the clinical criteria described in the policy on a 6-month basis. Confirmation of clinical benefit will be submitted to WHSSC following a 6-month assessment. Without confirmation of clinical benefit funding will stop.

Disorders of complement regulation include mutations and copy number variation in the genes encoding factor H (*CFH*), membrane cofactor protein (*MCP*), factor I (*CFI*), factor B (*CFB*), C3 (*C3*) and factor H related proteins 1-5 (*CFHR1-5*). Life-long therapy may be appropriate in patients with aHUS who have mutations associated with poor outcomes (e.g. *CFH* or *C3/CFB* gain of function mutations). However, eculizumab may be reasonably withdrawn in subgroups with isolated MCP mutations who have fully recovered from aHUS or in patients due to adverse events or lack of clinical response to treatment.

Mutational analysis and genetic testing should be consistent and compliant with the *Clinical Practice Guidelines for the management of Atypical Haemolytic Uraemic Syndrome in the United Kingdom.* Access to the service is via referral through WHSSC to:

Professor T H J Goodship, Institute of Human Genetics, Newcastle University, Central Parkway, Newcastle upon Tyne NE1 3BZ.

The mutational status of all aHUS patients funded by WHSSC is expected to be reported at 12 months to allow for a clinical discussion about continuation of therapy as part of the patients annual review.

3.3.1 Monitoring for treatment efficacy and treatment response
Monitoring for treatment efficacy and treatment response will be carried out as follows:

1. Weekly monitoring of FBC, reticulocyte count, U&Es, LFTS and LDH for the first 4 weeks;
2. Two weekly monitoring (as above) for the next 8 weeks; and
3. Monitoring according to clinical response with a minimum of 6 monthly assessment thereafter

3.3.2 Clinical parameters

Clinical parameters will be measured to demonstrate effectiveness of eculizumab following 6 months of treatment:

3.3.2.1 Inhibition of thrombotic microangiopathy, demonstrated by one or more of the following:
- Increase or normalisation of platelet count;
- Decrease in haemolysis – decreased LDH, or increased haptoglobin, or increased haemoglobin.

3.3.2.2 Cessation of plasma infusion/exchange (in patients who were previously receiving plasma infusion/exchange)

3.3.2.3 Maintenance or improvement of renal function
- Maintenance of renal function (demonstrating prevention of further renal impairment);
- Improvement in renal function (may be achieved in some patients).

3.3.2.4 Prevention of sequelae of systemic thrombotic microangiopathy
- Lack of further neurological, gastrointestinal and other extra-renal organ damage.

3.3.3 Recommended Dosage Regimen – aHUS

Eculizumab should only be administered as an intravenous infusion at the recommended dosage regimen time points, or within two days of these time points.

3.3.3.1 *Recommended Adult Dosage Regimen*

For patients 18 years of age and older, Eculizumab therapy consists of:
- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

3.3.3.2 *Recommended Paediatric/Adolescent Dosage Regimen*

For patients less than 18 years of age, administer Eculizumab based upon body weight, according to the following schedule in Table 1.

Table 1.

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

3.3.3.3 *Supplemental dose of Eculizumab in the setting of PE/PI:* Concomittant Eculizumab therapy is **not approved** for funding in the clinical context of PE/PI.

3.3.3.4 *Rationale for the aHUS dosing regimen*

- Eculizumab blocks complement activation by specifically binding to complement protein C5.
- Complete and sustained complement inhibition requires adequate serum concentration of Eculizumab. The half-life of Eculizumab in aHUS patients is approximately 12 days.
- The aHUS dose and schedule was designed, and validated in the aHUS clinical trials, to achieve complete complement inhibition in the vast majority of the population at all times, including trough serum concentrations prior to the next dose of Eculizumab;

3.4 Responsibilities

Referrers should:

- Inform the patient that this treatment is not funded outside the criteria in this policy; and
- Refer via the agreed pathway. The agreed pathway includes named physicians, identified by WHSSC, for the purposes of ensuring consistency to this policy and appropriate engagement with the Nationally Designated Centre for advice, opinion and potential genetic testing where considered clinically appropriate:
  - Deputy Medical Director, WHSSC;
  - WHSSC nominated renal physician;
  - Medical Director, WHSSC
- Any physician considering management of a patient (paediatric or adult) with confirmed or suspected aHUS is requested to contact whssc.ipc@wales.nhs.uk before initiating Eculizumab therapy. A member of WHSSC will contact the physician and discuss required information and the management strategy prior to a funding decision being made.

Clinician considering treatment should:

- Discuss all the alternative treatment with the patient;
- Advise the patient of any side effect and risks of the potential treatment;
- Inform the patient that treatment is not routinely funded outside of the criteria in the policy.

Clinicians should refer to:

- The Newcastle protocol (2013): *Prophylactic Eculizumab for Adult Patients with Atypical Haemolytic Uraemic Syndrome Undergoing Kidney Transplantation*

  The protocol makes recommendations about the management of patients with atypical haemolytic uraemic syndrome (aHUS) who are being considered for transplantation. The protocol has been developed specifically to consider the use of prophylactic Eculizumab in preventin recurrence of aHUS after transplantation.

4. Quality and Safety

4.1 Clinical Outcome and Quality Measures

4.1.1 International aHUS registry

All Physicians managing patients with aHUS are mandated to be included into the aHUS registry. This includes all patients of any age diagnosed with aHUS, regardless of treatment.

Diagnosis is defined by:

- Clinical diagnosis of aHUS
- Patients with or without an identified complement regulatory factor genetic mutation or anti-complement factor antibody
- ADAMTS13 >5%

4.1.2 Clinical outcomes

Physician-Reported Data

Data will be collected at initiation of therapy and every 6 months thereafter for all patients in the study.

Data entry includes information on demographics, medical and disease history, TMA complications, aHUS diagnosis, symptomology, clinical outcomes, concomitant medication, and safety. Pregnancy and lactation data will also be collected (if applicable).

All necessary information will be gathered from patient medical records and will be entered via a secure web portal and maintained anonymously. It is expected that the Nationally designated centre will be responsible for the reporting of outcomes to commissioners. The exact details of this arrangement will be discussed with the Nationally Designated Centre once it has been identified by NHS England.

4.1.3 Patient demographics and medical history

- Date of disease onset
- Number of TMA complications of aHUS since diagnosis
- Details on first TMA complication and either most recent occurrence prior to enrolment or prior to start of eculizumab,
- Vital statistics: height and weight
- Family history of aHUS
- Co-morbidities e.g. cancer, systemic disease
- Historical and current therapies and/or concomitant medications used to treat aHUS e.g.
- Plasma exchange/plasma infusion
- Dialysis
- Immunosuppressive therapy

4.2 Quality of Life

Patient Reported Outcomes

- Patients complete questionnaires at study enrollment and every six months thereafter
  - Paper copies completed by patient
- Patient Reported Outcomes include:
  - Patient Reported aHUS Symptoms
  - Patient Questionnaire
    - Resource Utilization
    - General Health
    - Work Status
- FACIT-Fatigue

4.3 Targeted lab results

- Anti-hypertensive medication use
- Kidney status e.g. CKD or transplant information if applicable eGFR, Proteinuria
- Child Pugh classification in patients with history of hepatic dysfunction e.g. cirrhosis, chronic hepatitis
- Patient Reported Outcomes (PROs)
- Eculizumab use
- Historical occurrence of targeted events of interest (at baseline)

4.4 6-month follow-up results

6 monthly follow up results may be requested by WHSSC

4.5 Patient status

- Height and weight for pediatric patients <40 kg as well as head circumference for patients up to 3 years of age
- Clinical status of aHUS:
- TMA complications of aHUS
- Therapies and/or concomitant medications used to treat aHUS
- Targeted lab results
- Anti-hypertensive medication use and other relevant concomitant medications
- Kidney status
- Child Pugh classification in patients with hepatic dysfunction
- PROs
- Eculizumab dose and frequency of administration, and reason for discontinuation or dose adjustment if applicable
- Serious Adverse Events
- Targeted events of interest

4.6 Clinical Audit Programme

This will be agreed with the nationally designated centre as part of the National Auditing requirements for these patients. All patients are required to be entered into the aHUD registry.

4.7 Quality Standards

4.7.1 Patient Experience

Providers will be expected to provide an annual statement in relation to patient experience as part of the Quality Framework for WHSSC.

Patient experience will be included in the departmental audit programme.

4.8 Putting Things Right: Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided. The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern:

- When a patient or their representative is unhappy with the decision that the patient does not meet the criteria for treatment further information can be provided demonstrating exceptionality. The request will then be considered by the All Wales IPFR Panel.
- If the patient or their representative is not happy with the decision of the All Wales IPFR Panel the patient and/or their representative has a right to ask for this decision to be

reviewed. The grounds for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated. The review should be undertaken, by the patient's Local Health Board;

- When a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (welsh).

This policy has been subjected to an Equality Impact Assessment. The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex (i) Checklist

CP98: Eculizumab for Atypical Haemolytic Uraemic Syndrome (aHUS)

The following checklist should be completed for ***all*** *patients to whom the policy applies*, before treatment, by the responsible clinician:

Patient NHS No:			
Patient is Welsh Resident: Yes/No	Post Code:		
Patient is English Resident registered with NHS Wales GP	GP Code:		

Patient meets following access criteria for treatment (see section 3.)	**Yes**	**No**
Thrombocytopaenia - Platelet count <150,000/mm or >25% Decrease from baseline; **AND**		
Microangiopathic Haemolysis – Schistocytes and/or Elevated LDH and/or Decreased haptoglobin and/or Decreased haemoglobin;		
Plus 1 or more of the following: • Renal Impairment - Elevated creatinine, Decreased eGFR [define measurement] • Neurological Symptoms - Confusion and/or Seizures, other cerebral abnormalities [define] • Gastrointestinal Symptoms – Diarrhoea and/or Abdominal pain. **AND**		
• >5% ADAMTS13 Activity (In the absence of ADAMTS13 results, a serum creatinine >150–200 µmol/L (>1.7–2.3 mg/dL) or a platelet count >30,000 mm almost eliminates a diagnosis of severe ADAMTS13 deficiency) (TTP) **AND** • Absence of a Positive Shiga-toxin/EHEC		
Patient does not meet access criteria but has exceptional clinical circumstances		
An Individual Patient Funding Request (IPFR) must be completed and submitted to WHSSC for approval prior to treatment. *The form must clearly demonstrate why funding should be provided as an exception. The form can be found at http://www.wales.nhs.uk/sites3/docopen.cfm?orgid=898&id=181455*		

Please complete the appropriate boxes

Name: _____

Designation: _____

Signature: _____ **Date:** _____

Appendix A References

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