

Cyclophosphamide IV Use for Non-Oncological Indications



<p>Areas where Protocol/Guideline applicable</p>	<p>SESLHD</p>
<p>Authorised Prescribers:</p>	<p>Senior medical officers (registrar or above) as recommended in Cytotoxic Medication and Handling CBR (POWH CLIN131).¹</p>
<p>Indication for use</p>	<p>Cyclophosphamide is used for a number of renal diseases, most commonly including:</p> <ol style="list-style-type: none"> 1. Lupus nephritis (WHO class III & class IV) 2. Crescentic glomerulonephritis <ul style="list-style-type: none"> - ANCA-associated vasculitis (including microscopic polyangiitis and granulomatosis with polyangiitis) - ANCA-negative, crescentic glomerulonephritis - Other immune complex-mediated crescentic glomerulonephritis - Goodpasture’s (anti-GBM) disease 3. Nephrotic syndrome <p>Cyclophosphamide is used for a number of neurological indications, including:</p> <ul style="list-style-type: none"> - Cerebral vasculitis - Inflammatory neuropathies - Inflammatory myositis - Myasthenia and related syndromes - Inflammatory cerebral amyloid angiopathy - Treatment-resistant limbic encephalitis - Autoimmune encephalitis <p>Cyclophosphamide may also be used for other autoimmune disorders, including:</p> <ul style="list-style-type: none"> - ANCA-associated vasculitis - Refractory, severe and/or organ threatening connective tissue diseases (e.g. systemic lupus erythematosus, CTD-interstitial lung disease) - Organ threatening systemic vasculitis (e.g. polyarteritis nodosa, IgA vasculitis) - Severe organ threatening autoimmune orphan diseases (e.g. pulmonary capillaritis, refractory Behcet’s disease, ocular cicatricial pemphigoid, scleritis, peripheral ulcerative keratitis) <p>Note that in a number of rare autoimmune conditions, the best evidence of cyclophosphamide is based on case reports or case series. This guideline is not for oncological indications.</p>
<p>Clinical condition Patient selection: Inclusion criteria (list investigations necessary and relevant results)</p>	<p>Investigations must clearly support one of the diagnoses mentioned above based on existing evidence.</p> <p>Decision to prescribe IV cyclophosphamide is dependent on severity of condition and individual patient factors (as per contraindications/precautions listed below).</p>

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<p>Proposed Place in Therapy</p> <p>State whether drug to be used as first, second or third line. When not first line, describe therapies to be used first. (Consider using algorithm)</p>	<p>IV cyclophosphamide may be used as first, second or third line therapy at the discretion of the treating physician depending on the severity of condition and individual patient factors (as per contraindications/precautions listed below).</p> <p>IV cyclophosphamide is a first line agent for cerebral vasculitis, but second line for the other neurological conditions. In most cases, immunosuppression with mycophenolate and a trial of intravenous immunoglobulin and possibly plasma exchange, would be used before considering cyclophosphamide. For myasthenia gravis, any thymoma must be removed and consideration given to surgical removal of thymic hyperplasia if present.</p>
<p>Adjunctive Therapy</p> <p>If part of combination therapy, list other drugs</p>	<p>Glucocorticoids</p> <p>IV methylprednisolone and/or oral prednisolone may be used as concurrent treatment depending on disease. Dosing at the discretion of the treating physician.</p> <p>Pneumocystis jiroveci pneumonia (PJP) Prophylaxis</p> <p>While on cyclophosphamide/glucocorticoids, PJP prophylaxis should be considered for all patients receiving IV cyclophosphamide where no contraindication exists.</p> <p>The most common PJP prophylaxis regimen is trimethoprim/sulfamethoxazole 160mg/800mg HALF a tablet daily or 1 tablet three times a week.² If unable to tolerate trimethoprim/sulfamethoxazole, consider dapsone 100mg daily (test for glucose-6-phosphate dehydrogenase (G6PD) deficiency before starting treatment with dapsone).²</p> <p>The optimal duration of PJP prophylaxis is uncertain. After stopping corticosteroids, it is recommended to continue PJP prophylaxis for at least 6 weeks.² Longer duration of prophylaxis may be required if patient remains on other immunosuppressive drugs. Assess the patient's level of immune compromise and risk of infection before stopping PJP prophylaxis. Review the benefit of ongoing prophylaxis regularly.²</p>
<p>Contra-indications³</p>	<ul style="list-style-type: none"> - Previous hypersensitivity to cyclophosphamide. - Active infection, which may lead to fatal complications as a result of immunosuppression induced by cytotoxic treatment. - Cystitis, acute systemic or urinary infection, urinary outflow obstruction, drug or radiation induced haemorrhagic cystitis. - Severely depressed bone marrow function (e.g. WCC < 2.5 x 10⁹ or Platelets < 50 x 10⁹/L) - Pregnancy (particularly the first trimester of pregnancy) or patients planning for pregnancy unless potential benefits outweigh the possible risks. - Breastfeeding - Cyclophosphamide therapy should not be commenced for 4 to 8 days after major surgery
<p>Precautions³</p>	<ul style="list-style-type: none"> - Adequate hydration must be maintained (pre- and post-hydration should be prescribed and patient should be encouraged to void frequently to protect against cyclophosphamide-induced urothelial toxicity) - Consider mesna to reduce the risk of haemorrhagic cystitis

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	<ul style="list-style-type: none"> - Creatinine clearance <30mL/min (dose reduction required)⁴ - Age >60 years (dose reduction required)⁴ - Immunocompromised patients (additional risk factors for infection) - Leucopenia (WCC < 4.0 x 10⁹) (dose reduction/delayed dose may be required)⁴ - Thrombocytopenia (Platelets < 100 x 10⁹/L) (dose reduction/delayed dose may be required)⁴ - Previous treatment with cyclophosphamide (cumulative doses >36g may increase risk of non-melanoma skin cancers, bladder cancer and myeloid leukaemia).⁵ - Recent major infection - Female patients of childbearing age should be offered goserelin 3.6mg subcutaneous implant every 28 days to reduce the risk of premature ovarian failure. - Effective contraception is required for female patients of childbearing age who are undergoing treatment with cyclophosphamide. - Adrenalectomised patients may require dose adjustment - Pre-existing cardiac disease as risk of cardiotoxicity may be increased - Consider withholding cyclophosphamide for up to 4 weeks prior to elective surgery to avoid risk of infection in the setting of neutropaenia.⁶ 																											
<p>Important Drug Interactions⁷</p>	<table border="1"> <thead> <tr> <th colspan="3" style="background-color: #cccccc;">Cyclophosphamide</th> </tr> <tr> <th></th> <th>Interaction</th> <th>Clinical management</th> </tr> </thead> <tbody> <tr> <td>CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)</td> <td>Increased toxicity of cyclophosphamide possible due to increased conversion to active (and inactive) metabolites</td> <td>Avoid combination or monitor for cyclophosphamide toxicity</td> </tr> <tr> <td>CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)</td> <td>Reduced efficacy of cyclophosphamide possible due to decreased conversion to active (and inactive) metabolites</td> <td>Avoid combination or monitor for decreased clinical response to cyclophosphamide</td> </tr> <tr> <td>Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)</td> <td>Additive nephrotoxicity</td> <td>Avoid combination or monitor kidney function closely</td> </tr> <tr> <td>Amiodarone</td> <td>Possible additive pulmonary toxicity with high-dose cyclophosphamide (i.e. doses used prior to stem cell transplant; 60 mg/kg daily or 120 to 270 mg/kg over a few days)</td> <td>Avoid combination or monitor closely for pulmonary toxicity</td> </tr> <tr> <td>Allopurinol, hydrochlorothiazide, indapamide</td> <td>Delayed effect. Increased risk of bone marrow depression; probably due to reduced clearance of active metabolites of cyclophosphamide</td> <td>Avoid combination, consider alternative antihypertensive therapy or monitor for myelosuppression</td> </tr> <tr> <td>Ciclosporin</td> <td>Reduced efficacy of ciclosporin due to reduced serum concentration</td> <td>Monitor ciclosporin levels; adjust dosage as appropriate; monitor response to ciclosporin</td> </tr> <tr> <td>Suxamethonium</td> <td>Prolonged apnoea due to marked and persistent inhibition of cholinesterase by cyclophosphamide</td> <td>Alert the anaesthetist if a patient has been treated with cyclophosphamide within ten days of planned general anaesthesia</td> </tr> </tbody> </table>	Cyclophosphamide				Interaction	Clinical management	CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Increased toxicity of cyclophosphamide possible due to increased conversion to active (and inactive) metabolites	Avoid combination or monitor for cyclophosphamide toxicity	CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Reduced efficacy of cyclophosphamide possible due to decreased conversion to active (and inactive) metabolites	Avoid combination or monitor for decreased clinical response to cyclophosphamide	Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely	Amiodarone	Possible additive pulmonary toxicity with high-dose cyclophosphamide (i.e. doses used prior to stem cell transplant; 60 mg/kg daily or 120 to 270 mg/kg over a few days)	Avoid combination or monitor closely for pulmonary toxicity	Allopurinol, hydrochlorothiazide, indapamide	Delayed effect. Increased risk of bone marrow depression; probably due to reduced clearance of active metabolites of cyclophosphamide	Avoid combination, consider alternative antihypertensive therapy or monitor for myelosuppression	Ciclosporin	Reduced efficacy of ciclosporin due to reduced serum concentration	Monitor ciclosporin levels; adjust dosage as appropriate; monitor response to ciclosporin	Suxamethonium	Prolonged apnoea due to marked and persistent inhibition of cholinesterase by cyclophosphamide	Alert the anaesthetist if a patient has been treated with cyclophosphamide within ten days of planned general anaesthesia
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<p>Dosage (Include dosage adjustment for specific patient groups)</p>	<p>EUVAS CYCLOPS protocol for rapidly progressive glomerulonephritis (crescentic)/ANCA-associated vasculitis⁴: IV cyclophosphamide pulse therapy at a dose of 15mg/kg (maximum pulse 1200mg) is given at weeks 0, 2, 4 and then every 3 weeks (weeks 7, 10, 13 etc) until remission and for a further 3 months (minimum of 6 months and maximum 12 months duration).</p>																											

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Dose reduction is required for age > 60 years and/or serum creatinine > 150µmol/L according to the table below.

Age (years)	Serum Creatinine (µmol/L)	
	150-300	300-500
<60	15mg/kg/pulse	12.5mg/kg/pulse
60-70	12.5mg/kg/pulse	10mg/kg/pulse
>70	10mg/kg/pulse	7.5mg/kg/pulse

Check full blood count (FBC) prior to treatment and adjust dose according to table below:

White cell count	Neutrophil count	Dosage adjustment
Less than 4x10 ⁹ /L	Less than 2x10 ⁹ /L	Withhold temporarily and repeat blood tests weekly until WCC is greater than 4x10 ⁹ /L and neutrophil greater than 2x10 ⁹ /L. Reduce next dose by 25%.

Check FBC 10 to 14 days after IV cyclophosphamide.

If WCC nadir is less than 3x10⁹/L, adjust dose according to table below (even if WCC immediately prior to treatment is greater than 4x10⁹/L):

White cell count	Neutrophil count	Dosage adjustment
2-3x10 ⁹ /L	1-2x10 ⁹ /L	Reduce next dose of cyclophosphamide by 20%.
1-2x10 ⁹ /L	0.5-1x10 ⁹ /L	Reduce next dose of cyclophosphamide by 40%.

Euro-Lupus protocol for lupus nephritis⁸:

IV cyclophosphamide 500mg every 2 weeks for a total of 6 doses.

NIH protocol⁹:

Doses range between 500-1000mg/m² for monthly pulse therapy.

Dose adjustment for age and/or renal impairment:

Consider dose reduction of cyclophosphamide to 500 mg/m² if age is greater than 60 years or if eGFR is <20 mL/min. In severe renal impairment, full dose may be warranted for aggressive disease with dosing guided by toxicity.

Fixed low dose regimen for neurology indications¹⁰:

IV cyclophosphamide 500 to 1000mg IV monthly.

Dose adjustment for renal impairment:

- GFR 10-20mL/min reduce to 75% of standard dose.
- GFR <10mL/min begin with 50% of standard dose.

Dose adjustment for liver impairment:

- Serum bilirubin 3.1 to 5 mg/dL (53-85 µmol/L) or transaminases > 3x ULN reduce to 75% of the standard dose.
- Bilirubin > 5 mg/dL (85 µmol/L) avoid use.

For other indications and doses outside this range, seek specialist advice. Alternative dosing regimens may be used at the discretion of the treating physician.

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Duration of therapy	Dependent on indication and clinical response (refer to dosage section for further information).
Prescribing Instructions	<p>Anti-emetics:</p> <ul style="list-style-type: none"> - IV cyclophosphamide is moderately emetogenic at doses <math><1500\text{mg}/\text{m}^2</math> and all patients should be prescribed ondansetron 8mg PO/IV 30-60 minutes prior to receiving IV cyclophosphamide.⁷ - For patients not receiving concurrent steroid therapy, consider the addition of dexamethasone 4 to 8mg IV or hydrocortisone 50 to 100mg IV.⁷ - Patients may also require PRN anti-emetics to be prescribed following the infusion (ondansetron 4-8mg BD PRN or metoclopramide 10mg TDS PRN) <p>Pre-Hydration:</p> <ul style="list-style-type: none"> - Prescribe 500-1000mL sodium chloride 0.9% over 1-2 hours. Fluids may be given over a longer duration depending on patient comorbidities/circumstances. <p>Mesna:</p> <ul style="list-style-type: none"> - Cyclophosphamide metabolites are toxic to the urothelium and can cause haemorrhagic cystitis in the short term and malignancy in the long term. Mesna binds to acrolein, a toxic metabolite of cyclophosphamide rendering it non-toxic to reduce risk of haemorrhagic cystitis. - The total recommended dose of mesna is 60% of the cyclophosphamide dose.⁴ - Mesna (20% of cyclophosphamide dose) diluted in 50-100mL sodium chloride 0.9% IV over 15-30mins administered prior to commencement of cyclophosphamide - Mesna (remaining 40% of cyclophosphamide dose) may be administered with IV post-hydration (see below). - Alternatively, the patient can take oral mesna at 2 hours and 6 hours after the completion of cyclophosphamide infusion (oral dose is twice the IV dose, tablets are available as 400mg and 600mg strength). Take with a full glass of water. - The patient should be encouraged to void frequently to protect against cyclophosphamide-induced urothelial toxicity. <p>Cyclophosphamide:</p> <ul style="list-style-type: none"> - Prescribe required dose diluted in 500mL sodium chloride 0.9% to be infused over 1 hour. <p>Post-Hydration:</p> <ul style="list-style-type: none"> - Mesna (40% of cyclophosphamide dose) diluted in 500-1000mL sodium chloride 0.9% IV over 1-2 hours. - Mesna to be omitted from IV post-hydration if oral mesna is prescribed.
Administration Instructions	<p>Safe handling requirements: Cyclophosphamide is a cytotoxic medication. Personal protective equipment (PPE) must be worn during administration and related waste handled as directed in POWH CBR Cytotoxic Medication and Handling CBR (POWH CLIN131) or SGH/TSH CBR Cytotoxic Medication including Staff Training, Administration, Extravasation and Post Administration CBR (SGH-TSH</p>

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	<p>BR201).^{1,11} All spills/unprotected exposure involving cyclophosphamide must be handled according to SESLHD Procedure Health Monitoring for Occupational Exposures other than Infectious Diseases (SESLHDPR/378).¹²</p> <p>Administration instructions:</p> <ul style="list-style-type: none"> - Infuse over 1 hour - Bag prepared by sterile pharmacy in 500mL - It is recommended to commence cyclophosphamide infusion in the morning so that frequent voiding occurs and cyclophosphamide metabolites do not rest in the bladder for prolonged periods. <p>Nursing observations prior to administration of cyclophosphamide:</p> <ul style="list-style-type: none"> - Check patient's blood results to ensure WBC is $> 4 \times 10^9$ - Check venous access device is patent and there are no signs of redness or inflammation - Perform full set of vital signs within 30 minutes of commencement of infusion - Check PIVC at least every 15 minutes during the infusion for swelling and / or patient complaints of discomfort at the site. If pain or swelling occurs immediately stop the infusion and assess PIVC site, notify medical officer - Observe patient for presence of macroscopic haematuria, notify medical officer if macroscopic haematuria occurs. <p>Nursing training requirements for administration:</p> <ul style="list-style-type: none"> - To be administered by a RN who is trained in the safe handling of cytotoxic agents – please refer to POWH Cytotoxic Medication Administration and Handling CBR (POWH CLIN131) or SGH/TSH Cytotoxic Medication including Staff Training, Administration, Extravasation and Post Administration CBR (SGH-TSH BR 201) for further details.^{1,11}
<p>Adverse effects³</p>	<ul style="list-style-type: none"> - Haemorrhagic cystitis (encourage optimal oral hydration as clinically appropriate/tolerated and frequent voiding, including emptying the bladder before going to bed and during the night if necessary) - Bone marrow suppression (nadir 10 to 14 days following first dose) - Hepatotoxicity - SIADH – less than 0.1% incidence - Alopecia (dose related) - Nausea and vomiting - Headache - Dermatitis - Increased risk of infection - Gonadal suppression and foetal toxicity

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<p>Monitoring requirements</p> <p>Safety</p> <p>Effectiveness (state objective criteria)</p>	<p>Infection screening prior to treatment initiation: Hepatitis B, Hepatitis C, HIV and Tuberculosis.</p> <p>Pathology requirements:</p> <ul style="list-style-type: none"> - Baseline: FBC, UEC, CMP, LFTs, urine dipstick or microscopy. - Prior to each treatment (within 48 hours prior): FBC, UEC, LFTs, urine dipstick or microscopy. - Dose of cyclophosphamide may need to be adjusted according to renal function or leukopaenia. <p>Clinical assessment:</p> <ul style="list-style-type: none"> - Fluid status - IV access - Assess clinical response by organ involvement as per treating specialist, e.g. renal function, urine ACR, Birmingham Vasculitis Activity Score (BVAS) - Monitoring of cardiac function should be considered, particularly for patients receiving doses > 1.5g.
<p>Management of Complications</p>	<p>To be monitored by specialist and referral/escalation as required.</p>
<p>Basis of Protocol/Guideline: (including sources of evidence, references)</p>	<ol style="list-style-type: none"> 1. POWH CBR: Cytotoxic Medication Administration and Handling (POWH CLIN131). 2. <i>Primary prophylaxis in immunocompromised adults without HIV infection. eTGs Antibiotic.</i> 3. <i>Cyclophosphamide (Endoxan) Power for Injection Product Information. Accessed via: https://app.emimselite.com.acs.hcn.com.au/medicineview?id=22b5e943-0577-44a9-9ad0-a53300fdb3fb&type=abppi</i> 4. <i>European Vasculitis Study Group (EUVAS), Clinical Trial Protocol – CYCLOPS: Randomised trial of daily oral versus pulse cyclophosphamide as therapy for ANCA-associated systemic vasculitis. November 2006.</i> 5. <i>Faurschou, M. et al. Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis. Rheumatology. August 2015, Volume 54, Issue 8, 1345-50.</i> 6. <i>Russell, L.A. et al. Preoperative Management of Medications for Rheumatologic and HIV Diseases: Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement. Mayo Clinic Proceedings, August 2022, Volume 97, Issue 8, 1551-71.</i> 7. <i>eviQ Cancer Treatments Online, Cancer Institute NSW, viewed 5 November 2025, https://www.eviq.org.au/</i> 8. <i>Immunosuppressive Therapy in Lupus Nephritis: The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide. Arthritis & Rheumatism, August 2002, Volume 46, Issue 8, 2121-31.</i> 9. <i>Fine, D., Pharmacological Therapy of Lupus Nephritis. Journal of the American Medical Association, 2005. Volume 293, Issue 24: 3053-60.</i> 10. <i>Cyclophosphamide infusion (fixed low dose regimen). Canberra Health Services, issued 4 May 2021, accessed 23 Oct 2024.</i> 11. SGH-TSH CBR: Cytotoxic Medication including Staff Training, Administration, Extravasation and Post Administration (SGH-TSH BR 201). 12. SESLHD Procedure: Health Monitoring for Occupational Exposures other than Infectious Diseases (SESLHDP/378)
<p>Groups consulted in development of this guideline</p>	<p>POWH Nephrology Department POWH Neurology Department POWH Immunology Department POWH Rheumatology Department</p>

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