Cyclophosphamide (oral)

Shared Care Guideline

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

This shared care guideline refers to the use of cyclophosphamide in the treatment of **NON-CANCER CONDITIONS ONLY.**

Unlicensed indications include: vasculitis and arteritis of any aetiology, end organ complications of connective tissue disease, pemphigus, dermatomyositis, polymyositis, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, inflammatory neuropathies.

Adult dosage and administration

Cyclophosphamide can be administered as pulse IV treatment (under which circumstance supply, administration and monitoring will be managed by secondary care) or as a daily oral dose, normally 2mg/kg/day. A typical dose may be 50 - 150mg orally daily as a single or divided dose. The dose is tailored according to the individual patient requirements with a maximum dosage of 200mg/day. Duration of treatment may be variable ranging from weeks to months depending on indication.
Use with caution if evidence of renal or hepatic dysfunction as dosage reduction may be required.
Available as: cyclophosphamide 50mg tablets.
In exceptional circumstances, a liquid preparation may be required. Cyclophosphamide **50mg/5ml** is the standard strength that must be used (available from special order manufacturers eg. Nova Laboratories).

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with cyclophosphamide.
- Agree shared care with the patient's GP.
- Varicella Zoster immune status: if non-immune, consider immunisation prior to starting treatment.
- Advise GP on dose of cyclophosphamide to be prescribed and intended duration of treatment.
- Provide patient/carer with relevant (preferably written) information on use, side-effects and need for monitoring of medication.
- Patients should be counselled regarding the recognised complication of infertility and cyclophosphamide treatment.
- If the liquid formulation is used, provide training on safe handling, storage, spillage and waste disposal (provide a cytotoxic spill kit and cytotoxic sharps box if necessary).
- Undertake baseline tests as indicated in monitoring table.
- Review results of safety monitoring and request additional tests as required.
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed.
- Provide any other advice or information for the GP if required.

<table>
<tr><th colspan="2">Monitoring table</th><th>Hospital specialist</th><th colspan="3">GP</th><th>Hospital specialist</th></tr>
<tr><th rowspan="2">Test</th><th rowspan="2">Indication</th><td rowspan="2">Pre-treatment baseline</td><td colspan="3">Stage of treatment</td><td rowspan="2">At review</td></tr>
<tr><td>First 4 Weeks</td><td>Week 5 - 12</td><td>After 12 weeks</td></tr>
<tr><td>FBC
LFTs
ESR / CRP
(Rheumatology only)
U&Es, eGFR*</td><td>Baseline assessment, disease activity scoring & dose adjustment</td><td>✓</td><td>Every week</td><td>Every 2 weeks</td><td>Every month</td><td>As part of the review or as clinically indicated</td></tr>
<tr><td>Chest x-ray
PFTs, TB screening if indicated</td><td>Baseline respiratory assessment and TB screening</td><td rowspan="2">✓</td><td colspan="3" rowspan="2">Not routinely required</td><td rowspan="4">If clinically indicated</td></tr>
<tr><td>Height, weight and blood pressure</td><td>Baseline assessment</td></tr>
<tr><td>Urinalysis</td><td>To detect adverse effects</td><td>✓</td><td colspan="3">Every month</td></tr>
<tr><td>Smear test</td><td></td><td>Ensure up to date</td><td colspan="3">Annually for the first 3 years and then as per the national screening programme</td></tr>
<tr><td colspan="2">Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding</td><td>✓</td><td colspan="3">At every consultation</td><td>✓</td></tr>
<tr><td colspan="7">* Report a drop of >20% in eGFR to the specialist but continue cyclophosphamide at the same dose.
If a further DMARD/JAK is added as combination therapy, or the dose is increased, the initial starting schedule should be reinstated.
There may be clinical circumstances where the frequency of monitoring may vary and this should be specified by the initiating specialist.</td></tr>
</table>

GP responsibilities

- Prescribe cyclophosphamide.
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly eg. asplenia), see BNF or Green Book.
- Provide COVID 19 and **inactivated** shingles (Shingrix®) vaccination as appropriate as per local arrangements and Green Book
- Post exposure prophylaxis (antivirals or VZIG if antivirals are contraindicated) should be considered in non-immune at risk patients if exposed to chickenpox or shingles. Contact the consultant virologists, Regional Virus Laboratory, Royal Group of Hospitals on 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green Book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals
- Ask about oral ulceration, sore throat, unexplained rash or unusual bruising/bleeding at every consultation.

Withhold cyclophosphamide and contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- **Unexplained** eosinophilia > 0.5 x 10^9/L
- Platelets < 120 x 10^9/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 - 3 x ULN, continue cyclophosphamide, repeat bloods and seek specialist advice). Minor elevations of AST/ALT are common
- If renal impairment develops (not always appropriate to stop but may need dose adjustment)
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough
- If haematuria develops (on dipstick urinalysis).

Normal reference range may vary slightly between labs.
Please note an unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

Contraindicated in: pregnancy, patients with known hypersensitivity to cyclophosphamide, with acute infections, with bone-marrow aplasia, urinary tract infection or with acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy. Avoid in patients with cystitis from any cause until it has been treated.
Life threatening cutaneous reactions. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of cyclophosphamide.
General: malaise, dizziness, diarrhoea, rash, myalgia, arthralgia, thrombocytopenia, hair loss and anaemia can occur infrequently. If severe or persistent, refer to the specialist.
Nausea can occur initially, addition of anti-emetic medication may help.
Blood disorders: leucopenia, anaemia, and thrombocytopenia. GPs should be alert to any oral ulceration, sore throat, unexplained rash or abnormal bruising/bleeding.
Haemorrhagic cystitis. For those on oral cyclophosphamide a high oral fluid intake (3-4 litres per day) should be maintained to decrease risk (not always appropriate for renal patients). Withhold oral cyclophosphamide and contact the initiating consultant if haematuria develops on dipstick urinalysis.
Infection. Immunosuppressants can increase susceptibility to infection. Patients should be reviewed rapidly and appropriate therapy instituted should signs of infection develop. Normally cyclophosphamide would be withheld if anti-infective intervention is required. Please contact the initiating specialist if any doubt exists as patients on treatment with cyclophosphamide can develop septic shock rapidly. Patients receiving immunosuppressive therapy are at increased risk of fungal infections, consider prophylactic antifungal treatment. Pneumocystis carinii prophylaxis may be considered for patients who require steroids in addition to cyclophosphamide.
Abnormal liver function can occur early in treatment.
Amenorrhoea and azoospermia often occur during treatment with cyclophosphamide.
Pregnancy / contraception. Women of childbearing potential and men receiving cyclophosphamide should be advised to use effective contraception during and at least 6 to 12 months after stopping cyclophosphamide therapy. Patients who become pregnant should stop taking cyclophosphamide and be referred to the initiating specialist at the earliest opportunity. Patients planning to become pregnant should be referred to the initiating specialist.
Breastfeeding. Women being treated with cyclophosphamide should not breastfeed.
Cancer risk. Patients receiving cyclophosphamide are at increased risk of lymphomas and malignancies of the skin. Avoiding excessive exposure to the sun and use of high factor sunscreens are advised. Adherence to population screening programmes is particularly important in this population.
Live vaccines. Consult the Green Book and take additional advice from initiating specialist if required.

Common drug interactions

Substances that delay activation of cyclophosphamide altering its effectiveness include aprepitant, bupropion, busulfan, ciprofloxacin, chloramphenicol, fluconazole, itraconazole, prasugrel, sulfonamides, thiotepa.
An increase of the concentration of cytotoxic metabolites may occur with: allopurinol, chloral hydrate, protease inhibitors, disulfiram, ondansetron and Inducers of cytochrome P450 enzymes (e.g. rifampin, phenobarbital, carbamazepine, phenytoin, St. John's Wort, and corticosteroids).
Concomitant use with other agents, which have similar toxicities, can cause combined (increased) toxic effects. For example:

- Increased toxicity and/or immunosuppression with e.g: ACE inhibitors, natalizumab, paclitaxel, thiazide diuretics, zidovudine, clozapine.
- Increased cardiotoxicity with e.g: anthracyclines, cytarabine, pentostatin, trastuzumab.
- Increased pulmonary toxicity with e.g: amiodarone, granulocyte macrophage colony-stimulating factors.
- Increased nephrotoxicity with, e.g: amphotericin B, indomethacin.
- Increased risk of hepatotoxicity with e.g. azathioprine

Warfarin: both increased and decreased warfarin effects have been reported.
Ciclosporin: lower serum concentrations of cyclosporine have been reported.
Digoxin: concomitant cyclophosphamide decreases the absorption of digoxin.

Communication

For any queries relating to this patient's treatment with cyclophosphamide, please contact the specialist named at the top of this document.

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC at www.medicines.org.uk or the BNF

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