Cyclophosphamide (IV) Methotrexate and 5-Fluorouracil (CMF) 21 Day Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment for breast carcinoma in patients who are considered unsuitable for anthracycline therapy	C50	00381a	Hospital
Metastatic breast carcinoma	C50	00381b	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Cyclophosphamide, methotrexate and 5-Fluorouracil are administered on day 1 of a 21 day cycle.
Adjuvant treatment: Treatment is administered for 8 cycles
Metastatic: Treatment is administered until disease progression or unacceptable toxicity develops

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	5-fluorouracil[a]	600mg/m^2	IV bolus	n/a	Every 21 days
2	1	Methotrexate	40mg/m^2	IV bolus	n/a	Every 21 days
3	1	Cyclophosphamide[b]	600mg/m^2	IV	250 mL 0.9% NaCl over 30 min	Every 21 days
[a]See dose modifications section for patients with identified partial DPD deficiency						
[b]Cyclophosphamide may also be administered as an IV bolus over 5-10 mins						

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to cyclophosphamide, methotrexate, fluorouracil or any of the excipients.
- Known complete DPD deficiency
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile prior to each cycle

Disease monitoring:

- Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
  - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification of CMF in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Recommended Dose
>1.5	or	>90	100%
1-1.49	or	70-89	75%
<1	or	<70	delay

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Cyclophosphamide	**Cr Cl (ml/min)**	**Dose**	**Severe impairment: Clinical Decision**			
	>20	100%				
	10-20	75%				
	<10	50%				
Methotrexate	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>80	100%	<50	and	<180	100%
	60-80	65%	51-85	or	≥180	75%
	45-60	50%	>85		Contraindicated	
	30-45	Clinical Decision				
	<30	contraindicated				
5-Fluorouracil	**Consider dose reduction in severe renal impairment only**		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85	Or	<180	100%
			>85	or	>180	Contraindicated
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS:
Not usually required

OTHER SUPPORTIVE CARE:
Patients should have an increased fluid intake of 2-3 litres on day 1 and day 8 to prevent haemorrhagic cystitis associated with cyclophosphamide

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Pleural effusion or ascites**: Methotrexate should be used with caution in patients with pleural effusion or ascites, as methotrexate may accumulate in third space fluid compartments.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.
- **Myocardial ischaemia and angina**: Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.

DRUG INTERACTIONS:

- CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites
- NSAIDs may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
- Sulphonamides and penicillins may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
- Concomitant administration of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
- Ciprofloxacin may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.

- Probenecid may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
- Fluorouracil significantly reduces the metabolism of warfarin. INR and signs of bleeding should be monitored regularly and dose of warfarin adjusted as required.
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Cyclophosphamide	L01AA01
Methotrexate	L01BA01
5-Fluoruracil	L01BC02

REFERENCES:

1. Molterni et al. Cyclophosphamide, methotrexate, and fluorouracil with and without doxorubicin in the adjuvant treatment of resectable breast cancer with one to three positive axillary nodes. J Clin Oncol 1991; 9: 1124-1130.
2. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
3. Endoxana Injection 500 mg Powder for Solution for Injection Summary of Product Characteristics. Accessed November 2018. Available at https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0167-134-003_01022018163050.pdf
4. Methotrexate Summary of Product Characteristics Accessed Nov 2018 Available at https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-051-001_26072018152154.pdf
5. Fluorouracil 25mg.ml Solution for Injection or Infusion Summary of Product Characteristics Accessed Nov 2018. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-223-001_25092018155533.pdf

Version	Date	Amendment	Approved By
1	1/12/2016		Prof Maccon Keane
2	26/11/2018	Updated to new NCCP template. Standardised administration of cyclophosphamide and dosing in renal and hepatic impairment	Prof Maccon Keane
3	27/12/2019	Updated exclusions, dose recommendation for hepatic impairment and drug interactions.	Prof Maccon Keane
4	25/8/2020	Reviewed. Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.