Cyclophosphamide (IV) Methotrexate and 5-Fluorouracil (CMF) 28 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	00378a	Hospital
Metastatic breast carcinoma	C50	00378b	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.

Adjuvant treatment: Treatment is administered for 6 cycles
Metastatic: Treatment is administered until disease progression or unacceptable toxicity develops

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,8	5-Fluourouracil	600mg/m^2	IV bolus	NA	Every 28 days
2	1,8	Methotrexate	40mg/m^2	IV Bolus	NA	Every 28 days
3	1,8	Cyclophosphamide	600mg/m^2	IV*	250 ml 0.9% NaCl over 30 mins	Every 28 days
* Cyclophosphamide may also be administered as an IV bolus over 5-10mins						

ELIGIBILTY:

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

EXCLUSIONS:

- Hypersensitivity to cyclophosphamide, methotrexate, fluorouracil or any of the excipients.
- Fluorouracil should not be given to patients who are known to be homozygotic for dihydropyrimidine dehydrogenase (DPD) or with known complete absence of DPD activity
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile

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:

- 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)	Dose
>1.5	or	>90	100%
1-1.49	or	70-89	75%
<1	or	<70	Delay

Renal and Hepatic Impairment:

Table 2: Dose modification of CMF (IV) 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 (micromole/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 (micromole/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.
- **DPD deficiency**: This may result in severe and unexpected toxicity to fluorouracil – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea
- **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 counseled 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.

- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- 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 dihydroprimidine dehydrogenase activity
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- Current drug interaction databases should be consulted for more information

ATC CODE:

Cyclophosphamide	L01AA01
Methotrexate	L01BA01
5-Fluorouracil	L01BC02

REFERENCES:

1. Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in nodepositive breast cancer: 20 yr followup. N.Engl.J.Med. 1995;332(14):901906.
2. Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study. BMJ 2005;330(7485):217.
3. Endoxana Injection 500 mg Powder for Solution for Injection Summary of Product Characteristics. Accessed October 2018. Available at https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0167-134-003_01022018163050.pdf
4. Methotrexate Summary of Product Characteristics Accessed Oct 2018 Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-206-002_24092018155405.pdf
5. Fluorouracil 25mgml Solution for Injection or Infusion Summary of Product Characteristics Accessed Oct 8 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 modifications for hepatic impairment and drug interactions.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.