Methotrexate 8 day Charing Cross Regimen

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of low risk gestational trophoblastic neoplasia (GTN) (FIGO score ≤ 6)	D39	00246a	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.

- Methotrexate is administered once daily on **day 1, 3, 5 and 7** of a **14 day** cycle.
- Treatment is administered continuously until hCG values fall below upper limit of normal or unacceptable toxicity develops.

Treatment should be continued for 3 cycles of maintenance treatment after hCG normalization

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 3, 5 and 7	Methotrexate	50mg	IM	n/a	Every 14 days (see note above)
2	2,4, 6 and 8	Folinic Acid (24 hours post methotrexate)	15mg	PO	n/a	Every 14 days (see note above)

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to methotrexate or any of the excipients.
- Bilirubin > 50micrograms/ml (85.5micromol/L)
- Creatinine clearance <30ml/min

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- human chorionic gonadotropin (hCG)

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Serum hCG/blood levels should be done on day one of each cycle or more frequently if required.
- After remission is achieved, serum hCG should be measured fortnightly for six months after consolidation therapy then monthly for a further six months and then every two months for two years

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:

- Due to the curative aim of treatment, dose modifications should be avoided and made only after discussion with the Consultant in charge of treatment.
- G-CSF support may be considered to mitigate haematological toxicities.

Renal and Hepatic Impairment:

Table 1: Dose modification of methotrexate in renal and hepatic impairment

Renal Impairment		Hepatic Impairment			
Cr Cl (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				

Management of adverse events:

Table 2: Dose Modification of methotrexate for Adverse Events

Adverse reactions	Recommended dose modification
Third space fluids (ascites, pleural effusions, very large ovarian cysts)	Hold methotrexate until recovery.
Malignant lymphoma	Discontinue

SUPPORTIVE CARE:

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

PREMEDICATIONS: Not usually required.

OTHER SUPPORTIVE CARE: G-CSF may be used to mitigate the risk of haematological toxicities

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.
- **Respiratory system:** Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.
- **Hepatotoxicity:** Methotrexate-induced hepatotoxicity can be seen with both high and low-dose methotrexate, and can be life threatening. Increased serum aminotransferases and less commonly hyperbilirubinemia is seen more often in high-dose methotrexate. The liver enzymes can increase with each cycle, and usually return to pre- treatment levels once methotrexate has been discontinued for 1 month. Cirrhosis and fibrosis are more often seen with chronic low-dose methotrexate. Patients should be warned to avoid alcohol, prescription medications or herbal supplements that may increase risk of hepatotoxicity.
- **Malignant lymphomas:** These may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued.
- **Pleural effusions and ascites:** These should be drained prior to initiation of methotrexate treatment.

DRUG INTERACTIONS:

- 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.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Methotrexate L01BA01
Folinic Acid V03AF03

REFERENCES:

1. McNeish IA, Strickland S et al. Low-Risk Persistent Gestational Trophoblastic Disease: Outcome After Initial Treatment with Low-Dose Methotrexate and Folinic Acid From 1992 to 2000. J Clin Oncol. 2002; 20 (7):1838-1844.
2. https://doi.org/10.1016/j.ygyno.2019.07.024
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
5. Methotrexate 1g/10ml Summary of Product Characteristics. Accessed October 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-206-006_23092020105544.pdf
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	01/02/2016		Dr Maccon Keane
2	07/02/2018	Updated with new NCCP regimen template, clarified dosing in renal and hepatic impairment and updated emetogenic status	Prof Maccon Keane
3	06/01/2021	Updated exclusion criteria, updated hCG monitoring requirements, renal dose modifications, emetogenic potential and adverse effects section	Prof Seamus O'Reilly

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.