5-Fluorouracil (5 day) and mitoMYcin Chemoradiation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved Reimbursement Status*
Treatment of muscle invasive bladder cancer in patients	C67	00450a	N/A

*This applies to post 2012 indications only

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.

mitoMYcin is administered at a dose of 12mg/m^2 on day 1 only.
5-Fluorouracil is administered at a dose of 500mg/m^2/day on days 1–5 (week 1) and days 22-26 (week 4) corresponding to fractions 1-5 and 16-20 of radiotherapy for 1 cycle.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	mitoMYcin	12mg/m^2	IV Bolus	Via fast running NaCl 0.9% infusion
1-5, 22-26	5-Fluorouracil[a]	500mg/m^2/day (Total dose = 2500mg/m^2 over 120 hours)	Continuous IV infusion over 5 days	Infusor pump
[a]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency				

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to 5-Fluorouracil, mitoMYcin or any of the excipients
- Pregnancy
- Breast Feeding
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

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
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, renal and liver profile weekly throughout treatment

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 for Haematological toxicity

ANC (x 10^9/L) (on day of chemotherapy)		Platelets (x 10^9/L) (at any stage during cycle)	Dose Modification
≥1	and	≥ 100	100%
0.5-0.99	or	50-99	Delay treatment until recovery
<0.5	or	<50	Delay treatment until recovery and consider reducing 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

Renal and Hepatic Impairment:

Table 2: Dose Modification in Renal and Hepatic Impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="5">5-Fluorouracil</td><td colspan="2" rowspan="5">Consider dose reduction in severe renal impairment only</td><td>Bilirubin</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>CI</td></tr>
<tr><td colspan="4" rowspan="2">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.</td></tr>
<tr><td></td></tr>
<tr><td rowspan="4">mitoMYcin</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="4" rowspan="4">Dose reductions probably not necessary – clinical decision when AST levels > 2 x ULN.</td></tr>
<tr><td>>10</td><td>100%</td></tr>
<tr><td><10</td><td>75%</td></tr>
<tr><td colspan="2">Consider a dose reduction for high doses of mitoMYcin when CrCl 10-60mL/min.</td></tr>
</table>

Non-Haematological Toxicity:

Table 3: Dose modification of 5-Fluorouracil for adverse events

Adverse Event	Dose modification of 5-Fluorouracil
Diarrhoea or Mucositis Grade 2 Grade ≥ 3	 Delay treatment until toxicity has resolved to Grade 1 or less Delay treatment until toxicity has resolved to Grade 1 or less and reduce 5-Fluorouracil by 50% for subsequent cycles.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

5-Fluorouracil Low **(Refer to local policy).**
mitoMYcin Low **(Refer to local policy).**

PREMEDICATIONS: Not required

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(Refer to local policy).**
Mouth Care **(Refer to local policy).**

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.

mitoMYcin

- **Extravasation:** mitoMYcin causes pain and tissue necrosis if extravasated **(Refer to local policy).**

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated

with 5-Fluorouracil, should be carefully monitored during therapy.

- **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 5-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.

DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil metabolising enzyme DPD.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network
3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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
5. 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. 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
6. mitoMYcin-C Kyowa 10 mg. SmPC HPRA. Last updated: 20/02/2019. Accessed: Nov 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Final_PA2288-002-001_20022019120937.pdf
7. Fluorouracil 50 mg/ml Solution for Injection or Infusion SmPC HPRA. Last updated: 08/12/2020. Accessed Nov 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_16042021165722.pdf

Version	Date	Amendment	Approved By
1	15/11/2017		Prof Maccon Keane
2	06/11/2019	Reviewed. Updated exclusions, emetogenic potential and drug interactions.	Prof Maccon Keane
3	01/09/2020	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
4	21/12/2021	Reviewed.	Prof Maccon Keane
4b	23/11/2023	Formatting changes and grammatical corrections.	NCCP
4c	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.