5-Fluorouracil (5 day) and mitoMYcin Chemoradiation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Treatment of muscle invasive bladder cancer in patients	C67	00450a	

**If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not gone been assessed through the formal HSE reimbursement process.*

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 (5-FU) is administered at a dose of 500 mg/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.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	mitoMYcin	12mg/m^2	IV Bolus	
1-5, 22-26	5-Fluorouracil	500mg/m^2 /day (Total dose = 2500mg/m^2 over 120 hours)	Continuous IV infusion over 5 days	Infusor pump

ELIGIBILTY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to 5- fluorouracil, mitoMYcin or any of the excipients
- Pregnancy
- Breast Feeding

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 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:

- 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 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.</td></tr>
<tr><td></td></tr>
<tr><td rowspan="4">mitoMYcin</td><td>GFR (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 GFR 10-60 ml/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 fluorouracil by 50% for subsequent cycles

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: 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

- **Extravasation:** mitoMYcin causes pain and tissue necrosis if extravasated **(Refer to local policy)**
- **Neutropenia :** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.

DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- 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 dihydroprimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

5-Fluorouracil	-	L01BC02
mitoMYcin	-	L01DC03

REFERENCES:

1. James ND, Hussain SA, Hall E. et al. Radiotherapy with or without Chemotherapy in Muscle-Invasive Bladder Cancer.N Engl J Med; 2012;366;16: 1477-88.
2. 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
3. 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
4. Fluorouracil 50mg/ml infusion for injection. Accessed Oct 2017. Available at

http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-015-001_19012017155040.pdf

Version	Date	Amendment	Approved By
1	15/11/2017		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/