5-Fluorouracil (4 day) and mitoMYcin Chemoradiation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of anal canal carcinoma	C21	00451a	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.

mitoMYcin is administered at a dose of 10mg/m^2 on day 1 and day 29.
5-Fluorouracil (5-FU) is administered at a dose of 1000 mg/m^2/day on days 1–4 (week 1) and 29–32 (week 5) by continuous 24 hr intravenous infusion with radiotherapy.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1, 29	mitoMYcin[1]	10mg/m^2 (Max single dose =20mg)	IV Bolus	
1-4 29-32	5-Fluorouracil[2]	1000mg/m^2 /day (Total dose = 4000mg/m^2 over 96hours)	Continuous IV infusion over 4 days	Infusor pump
[1]Alternative mitoMYcin schedule: 12 mg/m^2 IV on Day 1 ONLY				
[2] See dose modifications section for patients with identified partial 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 DPD deficiency

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

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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 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 ($x10^9$/L) (on day of chemotherapy)		Platelets ($x10^9$/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

Drug	Renal Impairment		Hepatic Impairment			
5-Fluorouracil	Consider dose reduction in severe renal impairment only		**Bilirubin**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	CI
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.			
mitoMYcin	**CrCl (ml/min)**	**Dose**	Dose reductions probably not necessary – clinical decision when AST levels > 2 x ULN.			
	>10	100%				
	<10	75%				
	Consider a dose reduction for high doses of mitoMYcin when CrCl 10-60 ml/min.					

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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	Delay treatment until toxicity has resolved to Grade 1 or less.
Grade ≥ 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce 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.
- **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 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome (HFS):** 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.

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DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimens.
- 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 dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	15/11/2017		Prof Maccon Keane
2	06/11/2019	Reviewed. Update of exclusions, emetogenic potential and drug interactions	Prof Maccon Keane
3	1/9/2020	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. Amended Table 2.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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