5-Fluorouracil 225mg/m^2/day and Radiotherapy (RT)- Continuous Infusion (7 day)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of locally advanced rectal cancer	C20	00421a	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.

5-fluorouracil is administered by continuous infusion with concurrent radiotherapy for 6 weeks.
The 5-fluorouracil infusor pump should be changed every 7 days.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1-7	*5-fluorouracil	225mg/m^2/day	Continuous IV infusion over 7 days	Infusor pump	For duration of radiotherapy (6 weeks)
* See dose modifications section for patients with identified partial DPD deficiency					

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to 5-fluorouracil 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.

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 (x 10^9/L) (on day of chemotherapy)		Platelets (x 10^9/L) (at any stage during cycle)	Dose Modification
≥1	and	≥100	100% Dose
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

Renal and Hepatic Impairment:

Table 2: Dose Modification in Renal and Hepatic Impairment

Renal impairment	Hepatic impairment			
Consider dose reduction in severe renal impairment only	**Bilirubin (micromol/L)**		**AST**	**Dose**
	<85		<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: Low **(Refer to local policy).**

PREMEDICATIONS: Not required

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details

- **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:** 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 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 fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Fluorouracil (5-FU) is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD). Current drug interaction databases should be consulted for more information.

REFERENCES:

1. O'Connell MJ, Martenson JA, Wie and HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N.Engl.J.Med. 1994. 331(8):502-507.
2. Smalley SR et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. J Clin Oncol 2006; 24:3542
3. Fluorouracil 50mg/ml infusion for injection HPRA. Last updated: 10May19. Accessed June 2021. Available at:https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_10052019144741.pdf
4. 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. Accessed Aug 2020 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

Version	Date	Amendment	Approved By
1	08/05/2017		Prof Maccon Keane
2	19/06/2019	Updated exclusions, hepatic dose modification table, drug interactions.	Prof Maccon Keane
3	09/10/2019	Update of exclusions	Prof Maccon Keane
4	19/08/2020	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
5	23/06/2021	Reviewed	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.