5-Fluorouracil and Folinic Acid Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Adjuvant treatment of colorectal carcinoma	C18	00660a	N/A
Locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation	C18	00660b	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.

Adjuvant treatment is administered every 14 days for a maximum of 12 cycles or until disease progression or unacceptable toxicity develops.

For **metastatic colon carcinoma,** treatment is administered continuously or until disease progression or unacceptable toxicity develops.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Folinic Acid (Calcium leucovorin)	400mg/m^2	IV infusion	250mL 0.9% NaCl over 30 mins	Every 14 days
2	1	*5-Fluorouracil	400mg/m^2	IV bolus		Every 14 days
3	1	*5-Fluorouracil	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	Every 14 days
Folinic Acid *(Calcium Leucovorin)* must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase.						
*See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.						

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:

Use with caution in patients with:

- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- Baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)

EXCLUSIONS:

- Hypersensitivity to 5-Fluorouracil, folinic acid or any of the excipients
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- Pregnancy and lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- Blood, renal and liver profile
- ECG (if patient has compromised cardiac function)
- 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:

- Blood, liver and renal profile prior to each cycle

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:

- **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
- Any dose modification should be discussed with a Consultant
- The following dose reductions should be used when calculating dose reductions for patients with toxicities**:**

Table 1: Dose Reduction Levels for All Toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Folinic Acid *(Calcium Leucovorin)*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
5-Fluorouracil bolus	400 mg/m^2	320 mg/m^2	240 mg/m^2	Discontinue
5-Fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus 5-Fluorouracil is delayed or omitted

Haematological:

Table 2: Dose Modifications for Haematological Toxicity

<table>
<tr><th rowspan="2">Prior to a Cycle (DAY 1)</th><th colspan="2">TOXICITY</th><th></th></tr>
<tr><th>Grade</th><th>ANC (x 10^9/L)</th><th>Dose level of 5-Fluorouracil for subsequent cycles</th></tr>
<tr><td rowspan="5">• If ANC < 1.0 on Day 1 of cycle, hold treatment. Perform weekly FBC, maximum of 2 times.
• ANC ≥ 1.0 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s).
• If ANC remains <1.0 after 2 weeks, discontinue treatment.</td><td>1</td><td>≥ 1.5</td><td>Maintain dose level</td></tr>
<tr><td>2</td><td>1.0-1.49</td><td>Maintain dose level</td></tr>
<tr><td>3</td><td>0.5-0.99</td><td>↓1 dose level</td></tr>
<tr><td>4</td><td>< 0.5</td><td>↓1 dose level</td></tr>
<tr><td colspan="2">Grade 4 neutropenia & greater than or equal to Grade 2 fever</td><td>↓1 dose level</td></tr>
<tr><td></td><td>Grade</td><td>Platelets (x10^9/L)</td><td>5-Fluorouracil</td></tr>
<tr><td rowspan="4">• If platelets < 75 on Day 1 of cycle, hold treatment. Perform weekly FBC, maximum of 2 times.
• If platelets ≥ 75 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s).
• If platelets remain <75 after 4 weeks, discontinue treatment.</td><td>1</td><td>≥ 75</td><td>Maintain dose level</td></tr>
<tr><td>2</td><td>50-74.9</td><td>Maintain dose level</td></tr>
<tr><td>3</td><td>10-49.9</td><td>Maintain dose level</td></tr>
<tr><td>4</td><td><10</td><td>Maintain dose level</td></tr>
</table>

Renal and Hepatic Impairment:

Table 3: Dose modifications in patients with renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment			
5-Fluorouracil	Consider dose reduction in severe renal impairment only.	**Bilirubin (micromole/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.			

Management of adverse events:

Table 4: Dose modification schedule based on Adverse Events

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles
	Grade	**Diarrhoea**	**5-Fluorouracil**
• If diarrhoea ≥ Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum of 2 times. • If diarrhoea < Grade 2 within 2 weeks of treatment delay, proceed with treatment at the dose level noted across from the **highest** Grade experienced. • If diarrhoea remains ≥ Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓1 dose level
Prior to a Cycle (DAY 1)	**TOXICITY**		**Dose Level for Subsequent Cycles**
	Grade	**Stomatitis**	**5-Fluorouracil**
• If stomatitis ≥ Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum of 2 times. • If stomatitis < Grade 2 within 2 weeks of initial treatment delay, proceed with	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, oedema or ulcers, but can eat	Maintain dose level

treatment at the dose level noted across from the **highest** Grade experienced. • If stomatitis remains ≥ Grade 2 after 2 weeks, discontinue treatment.	3	Painful erythema, oedema, ulcers, and cannot eat	↓1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration.	↓2 dose levels

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: 5-Fluorouracil: Low **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(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 aggressively.
- **Gastrointestinal toxicity:** Patients treated with 5-Fluorouracil should be closely monitored for diarrhoea and managed appropriately.
- **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.
- **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.
- **Stomatitis:** Sucking ice chips may be considered for patients experiencing stomatitis. Remove dentures and place ice chips in mouth five minutes before chemotherapy. Continuously swish in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches, which subside quickly.

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-Fluorouracilmetabolising 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.

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Version	Date	Amendment	Approved By
1	21/06/2021		Prof Maccon Keane
2	08/08/2023	Regimen review. Infusion time for folinic acid reduced to 30 mins.	Prof Maccon Keane
2a	15/11/2023	Formatting changes and grammatical corrections.	NCCP
2b	13/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.