5-Fluorouracil and Folinic Acid Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of colorectal carcinoma	C18	00660a	Hospital
Locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation	C18	00660b	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.

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 the chemotherapy 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 2 hrs	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 46hrs in 0.9% NaCl	Every 14 days
Folinic Acid *(Calcium Leucovorin)* must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.						
*See dose modifications section for patients with identified partial 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 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

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 fluorouracil is delayed or omitted

Haematological:

Table 2: Dose Modifications for Haematological Toxicity

Prior to a Cycle (DAY 1)	TOXICITY Grade	ANC (x 10^9/L)	Dose level of 5-Fluorouracil for subsequent cycles
• 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	1	≥ 1.5	Maintain dose level
	2	1.0-1.49	Maintain dose level
	3	0.5-0.99	↓1 dose level
	4	< 0.5	↓1 dose level
	Grade 4 neutropenia & greater than or equal to **Grade 2 fever**		↓1 dose level
	Grade	**Platelets (x10^9/L)**	**Fluorouracil**
• 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	1	≥ 75	Maintain dose level
	2	50-74.9	Maintain dose level
	3	10-49.9	Maintain dose level
	4	<10	Maintain dose level

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 treatment at the dose level noted across from the **highest** Grade experienced. • If stomatitis remains ≥ Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, oedema or ulcers, but can eat	Maintain dose level
	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 fluorouracil should be closely monitored for diarrhoea and managed appropriately.
- **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.
- **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.

- **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 fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using 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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1	21/06/2021		Prof Maccon Keane

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