Roswell Park Modified (5-Fluorouracil 500mg/m^2 and Folinic Acid 50mg weekly x 6) Regimen

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of metastatic colorectal cancer	C18	00427a	N/A
Adjuvant treatment of colorectal cancer	C18	00427b	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.

Metastatic: Folinic Acid and 5-Fluorouracil are administered once weekly for 6 weeks followed by a 2 week break (1 cycle = 8weeks) until disease progression or unacceptable toxicity develops.

Adjuvant: Folinic Acid and 5-Fluorouracil are administered once weekly for 6 weeks followed by a 2 week break (1 cycle = 8weeks) for 3 cycles or until disease progression or unacceptable toxicity develops.

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

Order of Admin	Day	Drug	Dose	Route and Method of Administration	Cycle
1	**1, 8, 15, 22, 29, 36**	Folinic Acid (Calcium folinate)	50mg	IV bolus	Every 56 days
2	**1, 8, 15, 22, 29, 36**	5-Fluorouracil[a]	500mg/m^2	IV bolus	Every 56 days
Note: Treatment may be administered once weekly for 4 weeks followed by a 2 week break at the discretion of the prescribing Consultant.					
[a]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.					

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to 5-Fluorouracil, folinic acid or any of the excipients
- Pregnancy
- Breast Feeding
- Severe liver impairment
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, liver and renal profile.
- 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:

- FBC, liver and renal profile prior to each 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
- The dose of folinic acid remains fixed at 50mg and is delayed or omitted if 5-Fluorouracil bolus is delayed or omitted

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 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

***Missed doses will not be made up**

Renal and Hepatic Impairment:

Table 2. Dose modification for 5-Fluorouracil in patients with renal or 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.			

Management of adverse events:

Table 3: Dose modification schedule based on adverse events

Adverse Reaction		Dose Modification
Mucositis or Stomatitis **Diarrhoea**	Grade 2 • First occurrence • Second occurrence • Third occurrence • Fourth occurrence	Delay treatment until resolved to Grade ≤1 and reduce the dose for subsequent cycles as follows: • No dose reduction • Reduce 5-Fluorouracil by 25% • Reduce 5-Fluorouracil by 50% • Omit 5-Fluorouracil
Hand and foot syndrome (Palmar-plantar erythrodysaesthesia syndrome)	Grade 3 or 4 • First occurrence • Second occurrence	Delay treatment until resolved to Grade ≤1 and reduce the dose for subsequent cycles as follows: • Reduce 5-Fluorouracil by 50% • Omit 5-Fluorouracil

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low **(Refer to local policy)**

PREMEDICATIONS: None

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.

- **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.

- **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.
- **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 (see Table 3 for dose modifications).

DRUG INTERACTIONS:

- Marked elevations of prothrombin time and INR have been reported in patients stabilised on warfarin therapy following initiation of 5-Fluorouracil regimes.
- 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 DPD.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. 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 Jun 2021. 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
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7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	14/06/2017		Prof Maccon Keane
2	10/07/2019	Update of exclusion criteria. Removal of INR testing. Update of drug interactions.	Prof Maccon Keane
3	09/10/2019	Update of exclusions	Prof Maccon Keane
4	26/8/2020	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. Updated eligibility, exclusion criteria and adverse effects	Prof Maccon Keane
5a	23/08/2022	Amended title and anti-emetic document version.	NCCP
5b	21/11/2023	Formatting changes and grammaticalcorrections.	NCCP
5c	03/03/2025	Additional wording added to baseline testing section	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.