FOLFIRI Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with advanced colorectal cancer.	C18	00227a	N/A
Treatment of patients with metastatic oesophageal carcinoma.	C15	00227b	N/A
Second Line Treatment of patients with locally advanced metastatic pancreatic carcinoma[i].	C25	00227c	N/A

*This is for 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.

Treatment is administered every 14 days or until disease progression or unacceptable toxicity develops. Discontinue if no response after 2 cycles.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Irinotecan	180mg/m^2	IV infusion	250mL 0.9% NaCl over 90 minutes	Repeat every 14 days
1	Folinic Acid (Calcium leucovorin)	[a]400mg/m^2	IV infusion	250mL 0.9% NaCl over 2 hours	Repeat every 14 days
1	5-Fluorouracil	400mg/m^2	IV BOLUS	Slow push through side arm of fast flowing drip	Repeat every 14 days
1	5-Fluorouracil[b]	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	Repeat every 14 days
[a]A dose of 200mg/m^2 of folinic acid may be considered.					
[b]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency					
Irinotecan and leucovorin may be infused at the same time by using a y-connector placed immediately before the injection site. Irinotecan and leucovorin should not be combined in the same infusion bag.					
Patients may suck on ice chips during the bolus injection of 5-Fluorouracil to reduce stomatitis.					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

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

CAUTION:

- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose

EXCLUSIONS:

- Hypersensitivity to irinotecan, 5-Fluorouracil or any of the excipients
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- Impaired renal function
- 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
- 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 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 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:

- Any dose modification should be discussed with a Consultant
- Consider a reduced starting dose of 5-Fluorouracil 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
- Irinotecan should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading and when treatment-related diarrhoea is fully resolved
- At the start of a subsequent infusion of therapy, the dose of irinotecan and 5-Fluorouracil should be decreased according to the worst grade of adverse events observed in the prior infusion
- Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events

The following dose reductions should be used when calculating FOLFIRI dose reductions for patients with toxicities:

Table 1: Dose Reduction Levels for All Toxicities

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	Discontinue
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	260 mg/m^2	Discontinue
5-Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500mg/m^2	Discontinue

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

Table 2: Dose Modifications for Haematological Toxicity

Prior to a Cycle (DAY 1)	Toxicity Grade	ANC (x 10^9/L)	Dose Level for Subsequent Cycles: Irinotecan	5-Fluorouracil
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • ANC ≥ 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment	1	≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	↓ 1 dose level
	4	<0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia and grade ≥2 fever		↓ 2 dose levels	↓ 2 dose levels
	Grade	**Platelets (x10^9/L)**	**Irinotecan**	**5-Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • Platelets ≥ 75 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s). • If platelets remain <75 after 2 weeks, discontinue treatment	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	↓ 1 dose level
	4	<10	↓ 2 dose levels	↓ 2 dose levels
The use of granulocyte colony-stimulating factor (G-CSF) may be considered.				

Renal and Hepatic Impairment:

Table 3: Recommended dose modification for 5-Fluorouracil in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
[a]Irinotecan	**CrCl (mL/min)**	**Dose**	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.			
	≥10	No need for dose adjustment is expected				
	<10	Start with 50-66% of original dose, increase if tolerated				
	Haemodialysis	Start with 50-66% of original dose, increase if tolerated				
[b]5-Fluorouracil	No need for dose adjustment is expected. Haemodialysis: No need for dose adjustment is expected.		**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.			

[a]Renal recommendations from Giraud et al 2023, hepatic recommendations from SPC and as agreed with clinical reviewer
[b]Renal recommendations from Giraud et al 2023, hepatic recommendations from NLCN

Management of adverse events:

Table 4: Dose modification schedule based on adverse events

Prior to a Cycle (DAY 1)	Grade of Toxicity	Dose Level for Subsequent Cycles	
		Irinotecan	Fluorouracil
Diarrhoea • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	Maintain dose level
	3	↓ 1 dose level	↓ 1 dose level
	4	↓ 2 dose levels	↓ 2 dose levels
Stomatitis • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced. • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	Maintain dose level
	3	Maintain dose level	↓ 1 dose level
	4	Maintain dose level	↓ 2 dose levels

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website

Irinotecan: Moderate (**Refer to local policy).**
5-Fluorouracil: Low (**Refer to local policy)For information:**

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

Prophylactic atropine sulphate 250micrograms subcutaneously. Atropine should not be used in patients with glaucoma. (**See Regimen specific complications below).**

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(Refer to local policy).**
Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle.

- As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately
- The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours)
- This therapy should continue for 12 hours after the last liquid stool and should not be modified
- In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours

Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details

REGIMEN SPECIFIC COMPLICATIONS

- **Acute cholinergic syndrome:** If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation) atropine sulphate (250 micrograms subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who

experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan**.**

- **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.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

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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

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Version control

Version	Date	Amendment	Approved By
1	10/1/2015	Initial draft	Prof Maccon Keane
2	24/2/2015	Infusor table update	Prof Maccon Keane
3	01/03/2017	Reviewed	Prof Maccon Keane
4	27/09/2017	Updated with new NCCP template, updated dose reductions for all toxicities and dosing in renal and hepatic impairment	Prof Maccon Keane
5	19/09/2018	Updated with new indications for oesophageal and second line pancreatic cancer. Standardisation of treatment table	Prof Maccon Keane
6	12/05/2020	Regimen review Updated infusion fluids in treatment table Amended exclusion criteria. Updated exclusion criteria in regards to Fluorouracil Amended emetogenic potential Updated drug interactions to include information regarding 5-Fluorouracil	Prof Maccon Keane
7	28/08/2020	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

8	17/05/2022	Added caution for pts known to be homozygous for UGT1A1*28. Removed ATC codes.	Prof Maccon Keane
8a	21/11/2023	Formatting changes and grammatical corrections.	NCCP
9	27/01/2025	Updated baseline testing section. Updated renal and hepatic dose modifications table. Regimen updated in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This indication is outside the licensed indications for irinotecan in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.