FOLFIRI Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with advanced colorectal cancer.	C18	00227a	Hospital
Treatment of patients with metastatic oesophageal carcinoma.	C15	00227b	Hospital
Second Line Treatment of patients with locally advanced metastatic pancreatic carcinoma[i].	C25	00227c	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.

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 90mins	Repeat every 14 days
1	Folinic Acid (Calcium leucovorin)	[a]400mg/m^2	IV infusion	250ml 0.9% NaCl over 2hrs	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 46h 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.					

ELIGIBILITY:

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

CAUTION:

Use with caution in patients with

- 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

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:

- 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
- 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**	**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			
Irinotecan	No dose reduction needed, however use with caution as no information in this setting.	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.			
5-Fluorouracil	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 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:

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

PREMEDICATIONS:

Prophylactic atropine sulphate 250micrograms subcutaneously – see adverse effects below.
Atropine should not be used in patients with glaucoma.
(See Adverse Effects/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 / REGIMEN SPECIFIC COMPLICATIONS

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

- **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**.**
- **Diarrhoea -** Irinotecan induced diarrhoea can be life threatening and requires immediate management.
    - Diarrhoea (early onset) - see acute cholinergic syndrome above
    - Diarrhoea (late onset):
    - Irinotecan induced diarrhoea can be life threatening and requires immediate management
    - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan
    - Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women
    - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles
    - The SmPC (12) provides guidelines on when hospitalisation for the management of diarrhoea is recommended
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated

appropriately.

- **Extravasation:** Irinotecan causes pain and tissue necrosis if extravasated **(Refer to local extravasation guidelines).**
- **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients.
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.
- **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.

DRUG INTERACTIONS:

- Risk of drug interactions causing decreased concentrations of irinotecan with CYP3A inducers.
- Risk of drug interactions causing increased concentrations of irinotecan with CYP3A inhibitors
- Patients should also be counselled with regard to consumption of grapefruit juice.
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized 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 d 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.

REFERENCES:

1. André T, Boni C et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. N Engl J Med 2004;350:2343-2351
2. Tournigand C, André T et al. FOLFIRI followed by FOLFOX6 or the reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study. J Clin Oncol 2004; Vol 22 No.2: 229-237.
3. Douillard JY et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000;355:1041-1047.
4. Andre T et al. CPT-11 (irinotecan) addition to bimonthly, high dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer. 1999;35(9):1343-7.
5. Tournigand C, André T et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004; 22(2): 229-37.
6. Guimbarud R, Louvet C et al. Prospective, Randomized Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: a French Intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) Study J Clin Oncol 2014; 32: 3520-3526
7. Cereda S, Reni M et al. XELIRI or FOLFIRI as Salvage Therapy in Advanced Pancreatic Cancer Anticancer Res 2010; 30: 4785-4790
8. Neuzillet C, Hentic O et al. FOLFIRI Regimen in Metastatic Pancreatic Adenocarcinoma Resistant to Gemcitabine and Plantinum-Salts. World J Gastroenterol 2012; 18;4533-4541
9. BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Leucovorin GIFOLFIRI
10. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
11. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network .
12. Irinotecan Summary of Product Characteristics. Accessed May 2020 Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-044-001_18042019115425.pdf
13. Fluorouracil. Summary of Product Characteristics Accessed May 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-223-001_10102019120038.pdf
14. 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
15. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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 control

NCCP Regimen: FOLFIRI Therapy - 14 day	Published: 10/01/2015 Review: 12/05/2025	Version number: 8a
Tumour Group: Gastrointestinal NCCP Regimen Code: 00227	ISMO Contributor: Prof Maccon Keane	Page 7 of 8

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

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.