FOLFIRI Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Treatment of patients with advanced colorectal cancer.	C18	00227a	

If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not gone through the formal reimbursement process as legislated for in the Health (Pricing and Supply of Medical Goods) Act 2013.

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 the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Irinotecan	180mg/m^2	IV infusion	500ml glucose 5% over 90mins	Repeat every 14 days
1	Folinic Acid (Calcium leucovorin)	*400mg/m^2	IV infusion	250ml glucose 5% over 2hrs	Repeat every 14 days
Flush line with glucose 5% before administering 5-FU					
1	Fluorouracil (5-FU)	400mg/m^2	IV BOLUS	Slow push through side arm of fast flowing drip	Repeat every 14 days
1	Fluorouracil	2400mg/m^2	Continuous IV infusion	Over 46h in glucose 5% or 0.9% NaCl	Repeat every 14 days
*A dose of 200mg/m^2 of folinic acid may be considered.					
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.					
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.					
Patients may suck on ice chips during the bolus injection of fluorouracil to reduce stomatitis.					

ELIGIBILTY:

- 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).

EXCLUSIONS:

- Hypersensitivity to irinotecan or any of the excipients.
- Baseline neutrophils < 2 x 10^9/L and/or platelet count < 100 x 10^9/L.
- Severe renal impairment (creatinine clearance < 30ml/min).
- Bilirubin > 3 x ULN.
- Chronic bowel disease and/or bowel obstruction.
- Pregnancy and lactation.
- Severe bone marrow failure.
- Impaired renal function.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

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

Regular tests:

- Blood, liver and renal profile prior to each cycle
- INR tests if patient is on warfarin as clinically indicated.

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
- 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 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
Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus fluorouracil is delayed or omitted

Table 2:Dose Modifications for Haematological Toxicity

Prior to a Cycle (DAY 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade	**ANC (x 10^9/L)**	**Irinotecan**	**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 remains <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-FU 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-FU	Consider dose reduction in severe renal impairment only	**Bilirubin (micromol/L)**		**AST**	**Dose**
		<85		<180	100%
		>85	or	>180	CI
		Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduceinitial 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: Moderate (**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:

Oral pyridoxine 50mg three times a day when required for the relief of palmar- plantar erythrodysesthesia.

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 (9) 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 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:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.
- **Palmar Plantar Erythrodysesthesia (PPE):** This has been reported as an unusual complication of high dose bolus or protracted continuous therapy with 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 fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydroprimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Irinotecan	-	L01XX19
5-Fluorouracil	-	L01BC02
Folinic acid	-	V03AF03

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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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/