**FOLFIRI Therapy-14 day**

**INDICATIONS FOR USE:**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of patients with advanced colorectal cancer.</td>
<td>C18</td>
<td>00227a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Treatment of patients with metastatic oesophageal carcinoma</td>
<td>C15</td>
<td>00227b</td>
<td>Hospital</td>
</tr>
<tr>
<td>Second Line Treatment of patients with locally advanced metastatic pancreas carcinoma¹</td>
<td>C25</td>
<td>00227c</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

¹If the reimbursement status is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.

**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 patient's 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.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Irinotecan</td>
<td>180mg/m²</td>
<td>IV infusion</td>
<td>500ml glucose 5% over 90mins</td>
<td>Repeat every 14 days</td>
</tr>
<tr>
<td>1</td>
<td>Folinic Acid (Calcium leucovorin)</td>
<td>*400mg/m²</td>
<td>IV infusion</td>
<td>250ml glucose 5% over 2hrs</td>
<td>Repeat every 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Flush line with glucose 5% before administering 5-FU</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5-Fluorouracil</td>
<td>400mg/m²</td>
<td>IV BOLUS</td>
<td>Slow push through side arm of fast flowing drip</td>
<td>Repeat every 14 days</td>
</tr>
<tr>
<td>1</td>
<td>5-Fluorouracil</td>
<td>2400mg/m²</td>
<td>Continuous IV infusion</td>
<td>Over 46h in 0.9% NaCl</td>
<td>Repeat every 14 days</td>
</tr>
</tbody>
</table>

*A dose of 200mg/m² 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.

Patients may suck on ice chips during the bolus injection of 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).

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

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose Level 0</th>
<th>Dose Level -1</th>
<th>Dose Level -2</th>
<th>Dose Level -3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Folinic Acid (Calcium Leucovorin)</td>
<td>400 mg/m²</td>
<td>400 mg/m²</td>
<td>400 mg/m²</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Fluorouracil bolus</td>
<td>400 mg/m²</td>
<td>320 mg/m²</td>
<td>260 mg/m²</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Fluorouracil infusion</td>
<td>2400 mg/m²</td>
<td>1900 mg/m²</td>
<td>1500 mg/m²</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

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

### Table 2: Dose Modifications for Haematological Toxicity

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ANC (x 10⁹/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>≥ 1.5</td>
<td>Maintain dose level</td>
<td>Maintain</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1.0-1.49</td>
<td>Maintain dose level</td>
<td>Maintain</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5-0.99</td>
<td>1 dose level</td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&lt;0.5</td>
<td>2 dose levels</td>
<td>2 dose</td>
<td></td>
</tr>
<tr>
<td>Grade 4 neutropenia and grade≥2 fever</td>
<td>2 dose levels</td>
<td>2 dose levels</td>
<td>2 dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If platelets &lt; 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks</td>
<td>Maintain dose level</td>
<td>Maintain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets ≥ 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks</td>
<td>Maintain dose level</td>
<td>Maintain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets ≥ 75 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s).</td>
<td>Maintain dose level</td>
<td>Maintain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If platelets remains &lt;1.5 after 4 weeks, discontinue treatment</td>
<td>Maintain dose level</td>
<td>Maintain</td>
<td></td>
</tr>
</tbody>
</table>

The use of granulocyte colony-stimulating factor (G-CSF) may be considered.

NCCP Regimen: FOLFIRI Therapy - 14 day
Published: 10/01/2015
Review: 21/09/2020
Version number: 5

Tumour Group: Gastrointestinal
NCCP Regimen Code: 00227
ISMO Contributor: Prof Maccon Keane

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer)

This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoregimens](http://www.hse.ie/NCCPchemoregimens)
Renal and Hepatic Impairment:

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>No dose reduction needed, however use with caution as no information in this setting.</td>
<td>Irinotecan is contraindicated in patients with bilirubin levels &gt; 3 x ULN.</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Grade of Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td>1 and 2</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>≥ Grade 2, hold treatment max of 2 weeks</td>
<td></td>
<td></td>
<td>3</td>
<td>↓1 dose level</td>
</tr>
<tr>
<td>&lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the highest grade experienced</td>
<td></td>
<td></td>
<td>4</td>
<td>↓2 dose levels</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td></td>
<td>1 and 2</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>≥ Grade 2, hold treatment max of 2 weeks</td>
<td></td>
<td></td>
<td>3</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>&lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the highest grade experienced</td>
<td></td>
<td></td>
<td>4</td>
<td>Maintain dose level</td>
</tr>
</tbody>
</table>

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-Fluouracil - L01BC02
- Folinic acid - V03AF03

**REFERENCES:**

7. Cereda S, Reni M et al. XELIRI or FOLFIRI as Salvage Therapy in Advanced Pancreatic Cancer Anticancer Res 2010; 30: 4785-4790
9. BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Leucovorin GIFOLFIRI

Version control

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10/1/2015</td>
<td>Initial draft</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>24/2/2015</td>
<td>Infusor table update</td>
<td>Prof Maccon Keane</td>
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<tr>
<td>3</td>
<td>01/03/2017</td>
<td>Reviewed</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>4</td>
<td>27/09/2017</td>
<td>Updated with new NCCP template, updated dose reductions for all toxicities</td>
<td>Prof Maccon Keane</td>
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<tr>
<td></td>
<td></td>
<td>and dosing in renal and hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19/09/2018</td>
<td>Updated with new indications for oesophageal and second line pancreatic</td>
<td>Prof Maccon Keane</td>
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<tr>
<td></td>
<td></td>
<td>cancer. Standardisation of treatment table</td>
<td></td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
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.

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/proinfo/medonc/cdmp/