Irinotecan Monotherapy- 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with advanced colorectal cancer as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.	C18	00213a	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.

Irinotecan is administered once every 21 days until disease progression or unacceptable toxicity develops.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Irinotecan	350mg/m^2	IV infusion	250ml NaCl 0.9% over 90 minutes	Every 21 days

ELIGIBILITY:

- Indications as above
- ECOG 0-2

CAUTION:

- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose

EXCLUSIONS:

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

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PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile

Regular tests:

- FBC weekly
- Renal and liver 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.

Haematological:

Table 1: Dose modification of irinotecan for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Recommended dose
≥ 1.5	And	≥75	100% dose
<1.5	Or	<75	Delay until ANC ≥ 1.5 and platelets ≥ 75 then resume at the same dose
<0.5	And	<25	Dose reduction of 15 to 20%
Febrile neutropenia			
Grade 4* thrombocytopenia and leucopenia (<1.0 x 10^9/L)			

*NCI CTCAE grading

Renal and Hepatic Impairment:

Table 2: Dose modification of irinotecan in renal and hepatic impairment

Renal Impairment	Hepatic Impairment	
No dose reduction needed, however use with caution as no information in this setting.	In monotherapy: Blood bilirubin levels (up to 3 times ULN) in patients with performance status 2, should determine the starting dose of irinotecan. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased and therefore the risk of hematotoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.	
	Bilirubin	**Recommended dose**
	≤ 1.5 x ULN	350mg/m^2
	1.5-3 x ULN	200mg/m^2
	> 3 x ULN	Discontinue

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Management of adverse events:

Table 3: Dose Modification of irinotecan for Adverse Events

Adverse reactions*	Recommended dose modification
Non Haematological Toxicity ≥ Grade 3	Dose reduction of 15 to 20%
Any Adverse Event	At the start of a subsequent infusion of therapy, the dose of irinotecan, should be decreased according to the worst grade of adverse events observed in the prior infusion.
	Treatment should be delayed by 1-2 weeks to allow recovery from treatment-related adverse events. If not recovered after 2 weeks, consider discontinuing treatment.
	Treatment should be administered after appropriate recovery of all adverse events to grade 0 or 1 and when treatment-related diarrhoea is fully resolved.

*NCI-CTCAE grading

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (**Refer to local policy).**

PREMEDICATIONS:

Prophylactic atropine sulphate – see adverse effects below.
Atropine should not be used in patients with glaucoma. **(See Adverse Effects/Regimen specific complications below)**

OTHER SUPPORTIVE CARE:

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 (0.25mg subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced

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an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan. The dose of atropine sulphate may be repeated if required.

- **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.
    - A prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 0.5 x 10^9/L).
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.
- **Cardiac disorders:** Myocardial ischaemic events have been observed predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy.
- **Other:** Since this medicinal product contains sorbitol, it is unsuitable in hereditary fructose intolerance.

DRUG INTERACTIONS:

- CYP enzyme inducers may increase the clearance of irinotecan thus decreasing its efficacy.
- CYP enzyme inhibitors may decrease the clearance of irinotecan.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	05/04/14		Prof Maccon Keane
2	25/03/2016	Insertion of standard text re treatment	Prof Maccon Keane
3	18/04/2018	Updated with new NCCP regimen template. Standardisation of treatment table	Prof Maccon Keane
4	01/05/2019	Inclusion of dose modification of irinotecan for haematological toxicity table Updated dose management of irinotecan for adverse events table	Prof Maccon Keane
5	28/04/2021	Reviewed	Prof Maccon Keane
6	13/01/2022	Added caution for patients known to be homozygous for UGT1A1*28	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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