Irinotecan 150mg/m^2 Monotherapy – 28 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Second line therapy for advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum	C16	00654a	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 on days 1 and 15 of a 28 day treatment cycle until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 15	Irinotecan	150mg/m^2	IV infusion	250ml 0.9% NaCl over 90 mins	Every 28 days

ELIGIBILITY:

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

CAUTION:

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

EXCLUSIONS:

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

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 administration

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 in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	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	Irinotecan is contraindicated in patients with bilirubin levels >3 x ULN

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 effect	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 experience 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:

- CYP3A4 enzyme inducers may increase the clearance of irinotecan thus decreasing its efficacy.
- CYP3A4 enzyme inhibitors may decrease the clearance of irinotecan.
- Yellow fever vaccine and live attenuated vaccines – concomitant use is contraindicated.

- St. John's wort should not be administered with irinotecan as the interaction may result in a decrease in the active metabolite of irinotecan, SN-38.
- Vitamin K antagonists: If taken concomitantly with irinotecan, there is an increased risk of haemorrhage and thrombotic events – an increased frequency in INR monitoring is required.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
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5. 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
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Version	Date	Amendment	Approved By
1	24/03/2021		Prof Maccon Keane
2	29/04/2022	Added caution for patients known to be homozygous for UGT1A1*28. Reviewed.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of irinotecan in Ireland. Patient's should be informed of this 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 fully aware of their responsibility in communicating any relevant information to the patient and also 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.