Cetuximab (14 days) and Irinotecan (14 days) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Second line therapy for metastatic colorectal cancer with non-mutated (wild type) *RAS* after failure of or contraindication to oxaliplatin based therapy	C18	00331a	N/A

*This is for post 2012 indications only

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.

Cetuximab and irinotecan are administered once every **14 days** until disease progression or unacceptable toxicity.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cetuximab	500mg/m^2	IV infusion Observe post infusion[a]	See footnote [b] below	Repeat every 14 days
1	Irinotecan	180mg/m^2	IV infusion	250mL 0.9% NaCl over 90 minutes	Repeat every 14 days
[a]Obtain vital signs pre-infusion, at 1 hour and post-infusion. 1 hour observation period following end of 1st and 2nd cetuximab infusions. If no infusion reactions occur for 2 consecutive doses, then may discontinue observation period and vital signs.					
[b]The initial dose should be given slowly and speed of infusion must not exceed 5 mg/minute. For subsequent doses, the maximum infusion rate must not exceed 10 mg/minute if no adverse reaction to first infusion. May be administered diluted in 0.9% NaCl or undiluted. Flush the line with 0.9% NaCl at the end of the cetuximab infusion.					

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

- Indications as above
- Wild type RAS tumours verified by a validated test method
- ECOG 0-2
- Adequate marrow reserve
- Adequate renal and liver function

CAUTION:

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

EXCLUSIONS:

- Hypersensitivity to cetuximab, irinotecan or to any of the excipients.
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Bilirubin > 3 x ULN

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Complete medical history specifically asking about any previous infusion related reactions (IRR) to another antibody, allergy to red meat or tick bites, or any results of tests for IgE antibodies against cetuximab

Regular tests:

- FBC, renal and liver profile
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last cetuximab treatment

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 modifications for haematological toxicity

ANC (x 10^9/L		Platelets (x 10^9/L)	Cetuximab Dose	Irinotecan Dose
≥ 1.5	and	≥ 75	500mg/m^2	180mg/m^2
1-1.4	or	50 - 74	Delay until ANC ≥ 1.5 and platelets ≥ 75 then resume at the same dose.	
< 1	or	<50	Delay until ANC ≥ 1.5 and platelets ≥ 75 then resume cetuximab at same dose and irinotecan at 150mg/m^2.	
<0.5*	or	<10	Delay until ANC ≥ 1.5 and platelets ≥ 75 then resume cetuximab at same dose and irinotecan at 120mg/m^2.	
*If ANC remains < 0.5 after 2 weeks, discontinue irinotecan. May continue cetuximab at oncologist's discretion, if evidence of non-progression. Fever or other evidence of infection must be assessed promptly and treated aggressively.				

Renal and Hepatic Impairment:

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

Drug	Renal Impairment		Hepatic Impairment
Cetuximab	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		No need for dose adjustment is expected
Irinotecan	**CrCl (mL/min)**	**Dose**	Irinotecan is contraindicated in patients with bilirubin levels >3 x ULN
	≥10	No need for dose adjustment is expected	
	<10	Start with 50-66% of original dose, increase if tolerated	
	Haemodialysis	Start with 50-66% of original dose, increase if tolerated	
Cetuximab: Renal and hepatic dose modifications from Giraud et al 2023. Irinotecan: Renal dose modifications from Giraud et al 2023; Hepatic dose modifications from SmPC.			

Management of adverse events:

Diarrhoea:

Table 3: Dose Modification of cetuximab and irinotecan based on Grade diarrhoea experienced

Grade	Cetuximab Dose	Irinotecan Dose
Grade 1-2	500mg/m^2	180mg/m^2
Grade 3	Delay until grade 2 or less within 2 weeks then resume at cetuximab 400mg/m^2 and irinotecan 150mg/m^2	
Grade 4	Delay until grade 2 or less within 2 weeks then resume at cetuximab 300mg/m^2 and irinotecan 120mg/m^2	
If diarrhoea remains greater than grade 2 for greater than 2 weeks, discontinue irinotecan.		

Table 4: Dose modification schedule for cetuximab based on adverse events

Adverse reaction	Recommended dose modification
Infusion Reaction Grade 1	Continue slow infusion under close supervision.
Grade 2	Continue slow infusion and immediately administer treatment for symptoms.
Grade 3 and 4	Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab
Interstitial lung disease	Discontinue
Skin reaction **Grade 1 or 2**	No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions.
Severe skin reaction **≥ grade 3*** First occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at **500**mg/m^2
Second occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at **400**mg/m^2
Third occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at **300**mg/m^2
Fourth occurrence	Discontinue

* See other supportive care section below

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting- Available on the NCCP website

Cetuximab Low **(Refer to local policy).**
Irinotecan Moderate **(Refer to local policy).**

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS:

- Patients must receive premedication with an antihistamine and a corticosteroid before receiving cetuximab infusion. This premedication is recommended prior to all subsequent infusions. Patient should be educated about the possibility of delayed infusion-related symptoms.

- Prophylactic atropine sulphate 250 micrograms subcutaneously prior to irinotecan infusion. Atropine should not be used in patients with glaucoma.

Table 5: Suggested pre-medications prior to cetuximab infusion:

Drugs	Dose	Route
Chlorphenamine	10mg	IV bolus 60 minutes prior to cetuximab infusion
dexAMETHasone	8mg	IV bolus 60 minutes prior to cetuximab infusion

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.
- **See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions**

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details

REGIMEN SPECIFIC COMPLICATIONS:

- **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**.**

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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2. Pfeiffer P, Nielsen D et al. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Annals Oncol 2008; 19:1141-1145.
3. Martin-Martorell, P, Roselle S et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008; 99:455-458
4. Taberno J, Ciardiello F et al. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. Annals Oncol 2010; 21:1537-1545
5. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
7. Cetuximab 5mg/mL (Erbitux®) Summary of Product Characteristics. Last updated: 16/08/2024. Accessed November 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf
8. Irinotecan 20mg/mL Summary of Product Characteristics. Last updated: 20/06/24. Accessed November 2024. Available at: https://assets.hpra.ie/products/Human/27707/Licence_PA2315-108-001_05122023164035.pdf

Version	Date	Amendment	Approved By
1	03/06/2016		Prof Maccon Keane
2	20/06/2018	Updated with new NCCP regimen template. Standardisation of treatment table and dosing in renal and hepatic impairment	Prof Maccon Keane
3	12/02/2019	Updated dosing in hepatic impairment for irinotecan in combination therapy regimens	Prof Maccon Keane
4	10/04/2019	Updated dose modification schedule for adverse events	Prof Maccon Keane
5	10/06/2020	Regimen reviewed. Update of renal and hepatic dose modifications and emetogenic potential.	Prof Maccon Keane
6	17/01/2022	Added caution for patients known to be homozygous for UGT1A1*28 . Removed ATC Codes. Updated references	Prof Maccon Keane
7	27/01/2025	Regimen reviewed. Update to renal and hepatic dose modifications table.	Prof Maccon Keane

		Addition of Table 5 pre medications. Regimen updated in line with NCCP standardisation (emetogenic potential, adverse effects, regimen specific complications and drug interactions).	

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this regimen 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