

Cetuximab (14 days) and Irinotecan (14 days) Therapyⁱ

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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	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.

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

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cetuximab	500mg/m ²	IV infusion Observe post infusion ^a	Over 2 hours ^b (Consideration should be given to the maximum infusion rate of 5mg/min for the first infusion)	Repeat every 14 days
1	Irinotecan	180mg/m ²	IV infusion	250ml 0.9% NaCl over 90minutes	Repeat every 14 days
^a Obtain vital signs pre-infusion, at 1 hr and post-infusion. 1hr observation period following end of 1 st and 2 nd 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/min. The recommended infusion period is 120 minutes. For subsequent doses, the maximum infusion rate must not exceed 10 mg/min 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.					

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

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

NCCP Regimen: Cetuximab (14day) and Irinotecan (14 day) Therapy	Published: 20/06/2016 Review: 10/06/2025	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 1 of 7

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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
- 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.				

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Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 2 of 7
<p>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</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		

Renal and Hepatic Impairment:

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

Drug	Renal Impairment	Hepatic Impairment
Cetuximab	Clinical decision – unlikely to require a reduction.	Unlikely to require a reduction
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

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 Grade 2 Grade 3 and 4	Continue slow infusion under close supervision. Continue slow infusion and immediately administer treatment for symptoms. Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab
Interstitial lung disease	Discontinue
Skin reaction Grade 1 or 2 Severe skin reaction ≥ grade 3* First occurrence Second occurrence Third occurrence Fourth occurrence	No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions. Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at 500mg/m² Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at 400mg/m² Hold cetuximab treatment for a maximum of 2 weeks. Reinitate therapy only if reaction has resolved to grade 2 at 300mg/m² Discontinue

* See other supportive care section below

NCCP Regimen: Cetuximab (14day) and Irinotecan (14 day) Therapy	Published: 20/06/2016 Review: 10/06/2025	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 3 of 7

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>

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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 –250micrograms subcutaneously prior to irinotecan infusion 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.
- **See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Cetuximab

- **Infusion-related reactions:**
 - The first dose of cetuximab should be administered slowly and the speed must not exceed 5 mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have preformed IgE antibodies before a subsequent infusion is given.

NCCP Regimen: Cetuximab (14day) and Irinotecan (14 day) Therapy	Published: 20/06/2016 Review: 10/06/2025	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 4 of 7
<p>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</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		

- If an IRR develops later during the infusion or at a subsequent infusion further management will depend on its severity (Ref Table 4)
- In cases of mild or moderate infusion-related reaction, the infusion rate may be decreased and maintained at the lower rate in all subsequent infusions.
- Severe infusion-related reactions may occur with symptoms usually occurring during the first infusion and up to 1 hour after the end of the infusion. They may occur several hours after or with subsequent infusions. Patients should be warned of the possibility of such a late onset and instructed to contact their physician if symptoms occur
- Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment.
- Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.
- **Respiratory disorders:** Interstitial lung disease has been observed with EGFR inhibitors. Treatment should be withheld in the event of onset or worsening respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued.
- **Cardiovascular:** An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed. When prescribing cetuximab, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account.
- **Skin reactions:** This is the main adverse reaction of cetuximab. Refer to local policy for skin care regime and to Table 2 under Dose Modifications for management of treatment if patient experiences skin reactions.
- **Electrolyte disturbances:** Hypomagnesaemia, hypokalaemia or hypocalcaemia may occur. Electrolyte repletion is recommended, as appropriate.

Irinotecan

- **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 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 $< 0.5 \times 10^9/L$).

NCCP Regimen: Cetuximab (14day) and Irinotecan (14 day) Therapy	Published: 20/06/2016 Review: 10/06/2025	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 5 of 7

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- **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.

ATC CODE:

Cetuximab L01XC06
Irinotecan L01XX19

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NCCP Regimen: Cetuximab (14day) and Irinotecan (14 day) Therapy	Published: 20/06/2016 Review: 10/06/2025	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 6 of 7
<p>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</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		

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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	10/4/19	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

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

NCCP Regimen: Cetuximab (14day) and Irinotecan (14 day) Therapy	Published: 20/06/2016 Review: 10/06/2025	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00331	ISMO Contributor: Prof Maccon Keane	Page 7 of 7
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