

## Cetuximab (14 days)<sup>i</sup> and FOLFIRI (14 days) Therapy

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with RAS wild type metastatic colorectal cancer.	C18	00585a	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 FOLFIRI are administered once every 14 days 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	Cetuximab	500mg/m <sup>2</sup>	IV infusion Observe post infusion <sup>1</sup>	<sup>2</sup> Over 2 hours (Consideration should be given to the maximum infusion rate of 5mg/min for the first infusion)	Every 14 days
1	Irinotecan	180mg/m <sup>2</sup>	IV infusion	250ml 0.9% NaCl over 90mins	Every 14 days
1	Folinic Acid (Calcium leucovorin)	<sup>3</sup> 400mg/m <sup>2</sup>	IV infusion	250ml 0.9% NaCl over 2hrs	Every 14 days
1	Fluorouracil (5-FU)	400mg/m <sup>2</sup>	IV BOLUS	Slow push through side arm of fast flowing drip	Every 14 days
1	Fluorouracil <sup>4</sup>	2400mg/m <sup>2</sup>	Continuous IV infusion	Over 46h in 0.9% NaCl	Every 14 days

<sup>1</sup>Obtain vital signs pre-infusion, at 1 hr and post-infusion. 1hr observation period following end of 1<sup>st</sup> and 2<sup>nd</sup> cetuximab infusions. If no infusion reactions occur for 2 consecutive doses, then may discontinue observation period and vital signs.

<sup>2</sup>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.

<sup>3</sup>A dose of 200mg/m<sup>2</sup> 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.

Folinic Acid (*Calcium Leucovorin*) must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.

<sup>4</sup>See dose modifications section for patients with identified partial DPD deficiency

Patients may suck on ice chips during the bolus injection of fluorouracil to reduce stomatitis.

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## ELIGIBILITY:

- Indications as above
- Wild type RAS tumours verified by a validated test method
- 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 cetuximab, irinotecan, fluorouracil or any of the excipients.
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Baseline neutrophils  $<2 \times 10^9/L$  and/or platelet count  $<100 \times 10^9/L$ .
- Severe renal impairment (creatinine clearance  $<30 \text{ml/min}$ ).
- Bilirubin  $>3 \times \text{ULN}$ .
- Chronic bowel disease and/or bowel obstruction.
- Pregnancy and breast feeding
- Known complete DPD deficiency

## PRESCRIPTIVE AUTHORITY:

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

## TESTS:

### Baseline tests:

- FBC, liver and renal profile
- ECG (if patient has compromised cardiac function)
- 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.
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

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### Regular tests:

- FBC, liver and renal profile prior to each cycle
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last cetuximab treatment.
- INR tests if patient is on warfarin as clinically indicated.

### 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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
  - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant.
- Cetuximab or FOLFIRI therapy may be delayed independently of each other and dosing may continue with either component but consideration should be given to the timings of further treatment.
- 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).

**Table 1: Dose Reduction Levels for All Toxicities**

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Irinotecan	180 mg/m <sup>2</sup>	150 mg/m <sup>2</sup>	120 mg/m <sup>2</sup>	Discontinue
Folinic Acid ( <i>Calcium Leucovorin</i> )	400 mg/m <sup>2</sup>	400 mg/m <sup>2</sup>	400 mg/m <sup>2</sup>	Discontinue
Fluorouracil bolus	400 mg/m <sup>2</sup>	320 mg/m <sup>2</sup>	260 mg/m <sup>2</sup>	Discontinue
Fluorouracil infusion	2400 mg/m <sup>2</sup>	1900 mg/m <sup>2</sup>	1500mg/m <sup>2</sup>	Discontinue

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

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**Table 2: Dose Modification of FOLFIRI for Haematological Toxicity**

Prior to a Cycle (DAY 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade	ANC ( $\times 10^9/L$ )	Irinotecan	Fluorouracil
<ul style="list-style-type: none"> <li>If ANC &lt; 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks</li> <li>ANC <math>\geq</math> 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the <b>lowest ANC</b> result of the delayed week(s).</li> <li>If ANC remains &lt;1.5 after 4 weeks discontinue treatment</li> </ul>	1	$\geq$ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	↓ 1 dose level
	4	<0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia and grade $\geq$ 2 fever		↓ 2 dose levels	↓ 2 dose levels
	Grade	Platelets ( $\times 10^9/L$ )	Irinotecan	Fluorouracil
<ul style="list-style-type: none"> <li>If platelets &lt; 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks</li> <li>Platelets <math>\geq</math> 75 within 2 weeks, proceed with treatment at the dose level noted across from the <b>lowest platelets</b> result of the delayed week(s).</li> <li>If platelets remains &lt;75 after 2 weeks, discontinue treatment</li> </ul>	1	$\geq$ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	↓ 1 dose level
	4	<10	↓ 2 dose levels	↓ 2 dose levels
The use of granulocyte colony-stimulating factor (G-CSF) may be considered.				

## Renal and Hepatic Impairment:

**Table 3: Dose modification of cetuximab, irinotecan and 5-fluorouracil in renal or 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 >3xULN.		
5-fluorouracil	Consider dose reduction in severe renal impairment only	Bilirubin (micromol/L)	AST	Dose
		<85	<180	100%
		>85	or >180	Contraindicated
		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		

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## Management of adverse events:

**Table 4: Dose modification of cetuximab based on adverse events**

Adverse reaction	Recommended dose modification
<b>Infusion Reaction</b>	
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
<b>Interstitial lung disease</b>	Discontinue
<b>Skin reaction grade 1 or 2</b>	No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions.
Severe skin reaction $\geq$ grade 3*	
First occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at <b>500mg/m<sup>2</sup></b>
Second occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at <b>400mg/m<sup>2</sup></b>
Third occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at <b>300mg/m<sup>2</sup></b>
Fourth occurrence	Discontinue

\* See other supportive care section below

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**Table 5: Dose modification of FOLFIRI based on adverse events**

Prior to a Cycle (DAY 1)	Grade of Toxicity	Dose Level for Subsequent Cycles	
		Irinotecan	Fluorouracil
<b>Diarrhoea</b> <ul style="list-style-type: none"> <li>• ≥ Grade 2, hold treatment max of 2 weeks</li> <li>• &lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the <b>highest</b> grade experienced</li> <li>• Remains ≥ Grade 2 after 2 weeks, discontinue treatment</li> </ul>	1 and 2	Maintain dose level	Maintain dose level
	3	↓1 dose level	↓ 1 dose level
	4	↓2 dose levels	↓2 dose levels
<b>Stomatitis</b> <ul style="list-style-type: none"> <li>• ≥ Grade 2, hold treatment max of 2 weeks</li> <li>• &lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the <b>highest</b> grade experienced.</li> <li>• Remains ≥ Grade 2 after 2 weeks, discontinue treatment</li> </ul>	1 and 2	Maintain dose level	Maintain dose level
	3	Maintain dose level	↓1 dose level
	4	Maintain dose level	↓2 dose levels

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

Cetuximab	- Low	<b>( Refer to local policy).</b>
Irinotecan	-Moderate	<b>( Refer to local policy).</b>
Fluorouracil (5-FU)	- Low	<b>( Refer to local policy).</b>

### PREMEDICATIONS:

- **Cetuximab**  
Patients must receive premedication with an antihistamine and a corticosteroid at least one hour 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
- **Irinotecan**  
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).

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## OTHER SUPPORTIVE CARE:

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 (4mg 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.*

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately
- **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.

### Cetuximab

- **Infusion-related reactions (IRR):**
  - The first dose of cetuximab should be administered slowly and the speed must not exceed 5mg/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.
  - 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

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- 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 4 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.

## **FOLFIRI**

- **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  $\geq 2$  and women.
  - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles.
  - The SmPC provides guidelines on when hospitalisation for the management of diarrhoea is recommended.
- **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.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients

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with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.

- **Hand-foot syndrome (HFS)**, also known as palmar-plantar erythrodysesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.

## DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Cetuximab when use in combination with fluoropyrimidines, the frequency of palmar-plantar erythrodysesthesia and of cardiac ischaemia including myocardial infarction and congestive heart failure were increased.
- 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.
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-fluorouracil -metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.

## REFERENCES:

1. Hubbard JM, Alberts SR. Alternate dosing of cetuximab for patients with metastatic colorectal cancer. *Gastrointest Cancer Res.* 2013 Mar; 6(2):47-55.
2. Tabernero J et al. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. *Ann Oncol* 2010.; 21:1537–1545
3. Tabernero J et al. Pharmacogenomic and pharmacoproteomic studies of cetuximab in metastatic colorectal cancer: biomarker analysis of a phase I dose-escalation study. *J Clin Oncol* 2010; 28:1181–1189
4. Colorectal metastatic FOLFIRI (modified) (fluorouracil leucovorin irinotecan) with cetuximab (two weekly) EVIQ ID: 1682 v3. Last reviewed: October 2020  
<https://www.eviq.org.au/medical-oncology/colorectal/metastatic/1682-colorectal-metastatic-folfiri-modified-flu>

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5. Van Cutsem E et al. Cetuximab and Chemotherapy as Initial Treatment for Metastatic Colorectal Cancer. *New Eng J Med* 2009;360:1408
6. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
7. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
8. 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>
9. [HPRA](#) Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Oct 2021 Available at:  
[https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-\(i-v\)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0](https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0)
10. Cetuximab (Erbix<sup>®</sup>) Summary of Product Characteristics. EMA Last updated: 30/01/2020. Accessed May 2022 . Available at [https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf)
11. Irinotecan 20mg/ml Summary of Product Characteristics. HPRA last updated: July 2021 . Accessed May 2022 Available at  
[https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA2059-044-001\\_28072021081627.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-044-001_28072021081627.pdf)
12. Fluorouracil 50 mg/ml solution. Summary of Product Characteristics. HPRA last updated: September 2020 . Accessed: May 2022 . Available at  
<http://www.hpra.ie/img/uploaded/swedocuments/4b83796e-7f00-4163-aeb9-6593504c5a1f.pdf>

Version	Date	Amendment	Approved By
1	11/09/2019		Prof Maccon Keane
2	09/10/2019	Update of exclusions	Prof Maccon Keane
3	13/05/2020	Update of cetuximab infusion rate for subsequent doses.	Prof Maccon Keane
4	3/9/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysesthesia.	Prof Maccon Keane
5	18/05/2022	Reviewed. Updated references, adverse effects and drug interactions sections. Updated emetogenic potential.	Prof Maccon Keane

NCCP Regimen: Cetuximab (14 days) and FOLFIRI (14 days) Therapy	Published: 25/09/2019 Review: 18/05/2027	Version number: 5
Tumour Group: Gastrointestinal NCCP Regimen Code: 00585	ISMO Contributor: Prof Maccon Keane	Page 10 of 11
<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 <a href="http://www.hse.ie/eng/Disclaimer">http://www.hse.ie/eng/Disclaimer</a></p> <p><i>This information is valid only on the day of printing, for any updates please check <a href="http://www.hse.ie/NCCPchemoregimens">www.hse.ie/NCCPchemoregimens</a></i></p>		

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

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<sup>i</sup> The biweekly (every 14 days) administration is an unlicensed method of administration of cetuximab for the indications described above, 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.

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