Cetuximab and FOLFOX-6 (modified) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of patients with *KRAS* wild type metastatic colorectal cancer	C18	00733a	N/A

* This applies to 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 FOLFOX-6 chemotherapy 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.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Cetuximab	500mg/m^2	IV infusion Observe post infusion [a]	See footnote [b] below	Every 14 days
2	1	Oxaliplatin [c]	85mg/m^2	IV infusion	500mL glucose 5% over 2 hours	Every 14 days
3	1	Folinic Acid [d] (Calcium leucovorin)	400mg/m^2	IV infusion	250mL glucose 5% over 2 hours	Every 14 days
4	1	5-Fluorouracil [e, f]	400mg/m^2	IV Bolus		Every 14 days
5	1	5-Fluorouracil [f]	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	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/min.
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.

[c] Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline.
For oxaliplatin doses ≤ 104mg use 250mL glucose 5%.
Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction.
Oxaliplatin administration must always precede the administration of 5-Fluorouracil.
Oxaliplatin may be given at the same time as Folinic Acid *(Calcium Leucovorin)* using a Y connector.

[d] Folinic Acid *(Calcium Leucovorin)* must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase. Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of 5-Fluorouracil.

[e] Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of 5-Fluorouracil.

[f] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.

ELIGIBILITY:

- Indications as above
- Wild type *KRAS* tumours verified by a validated test method
- ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:

- 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)
- Symptomatic peripheral neuropathy

EXCLUSIONS:

- Hypersensitivity to cetuximab, oxaliplatin, folinic acid, 5-Fluorouracil or any of the excipients
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Peripheral neuropathy with functional impairment prior to first cycle
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- Pregnancy
- Lactation

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
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every 2 cycles
- 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
- 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
- Cetuximab or FOLFOX-6 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
- The following dose reductions should be used when calculating FOLFOX-6 dose reductions for patients with toxicities (Table 1)

Table 1: Dose reduction levels for all toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	Discontinue
Folinic Acid *(Calcium Leucovorin)*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
5-Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
5-Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500 mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus 5-Fluorouracil is delayed or omitted

Haematological:

Table 2. Dose modifications for FOLFOX-6 for haematological toxicity

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	**ANC (x 10^9/L)**	**Oxaliplatin**	**5-Fluorouracil**
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks • ANC ≥ 1.5 within 4 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment	1	≥ 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	Maintain dose level
	4	<0.5	↓ 1 dose level	Omit bolus and ↓1 infusion dose level
	Grade	**Platelets (x10^9/L)**	**Oxaliplatin**	**5-Fluorouracil**
	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level

• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks. • Platelets ≥ 75 within 4 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remain <75 after 4 weeks discontinue treatment.	3	10-49.9	↓ 1 dose level	Maintain dose level
	4	<10	↓ 2 dose levels	Maintain dose level

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in renal and hepatic impairment

<table>
<tr><th>Drug</th><th>Renal impairment</th><th>Hepatic impairment</th></tr>
<tr><td>Cetuximab [a]</td><td>No need for dose adjustment is expected.

Haemodialysis: No need for dose adjustment is expected.</td><td>No need for dose adjustment is expected.</td></tr>
<tr><td>Oxaliplatin [b]</td><td><table><tr><th>CrCl (mL/min)</th><th>Dose</th></tr><tr><td>≥30</td><td>No dose adjustment is needed</td></tr><tr><td><30</td><td>Consider 50% of the original dose</td></tr></table>Haemodialysis: Consider 50% of the original dose.
Haemodialysis within 90 minutes after administration.</td><td>No dose adjustment is needed.</td></tr>
<tr><td>5-Fluorouracil [c]</td><td>No need for dose adjustment is expected.

Haemodialysis: No need for dose adjustment is expected.</td><td><table><tr><th>Bilirubin (micromol/L)</th><th></th><th>AST</th><th>Dose</th></tr><tr><td><85</td><td></td><td><180</td><td>100%</td></tr><tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr></table>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.</td></tr>
<tr><td colspan="3">[a] Cetuximab (renal and hepatic - Giraud et al 2023);
[b] Oxaliplatin (renal and hepatic – Giraud et al 2023);
[c] 5-Fluorouracil (renal – Giraud et al 2023; hepatic – NLCN 2009)</td></tr>
</table>

Management of adverse events:

Table 4: Dose modification of 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. Reinitiate 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. Reinitiate 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. Reinitiate therapy only if reaction has resolved to grade 2 at **300**mg/m^2.
Fourth occurrence	Discontinue

* See other supportive care section below

Table 5: Dose modification for FOLFOX-6 schedule based on adverse events

Adverse reactions	Recommended dose modification
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 • First occurrence • 2nd occurrence • Persistent Grade 4	Reduce oxaliplatin by 1 dose level ↓ 1 dose level ↓ 1 dose level Discontinue oxaliplatin Discontinue oxaliplatin
Laryngopharyngeal dysaethesia	Increase infusion time from 2 to 6 hrs
Stomatitis	Delay treatment until stomatitis reaches level of grade 1 or less
Unexplained respiratory symptoms e.g. Non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates	Discontinue oxaliplatin until interstitial disease or pulmonary fibrosis excluded.

*Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re- challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.

Table 6: Dose modification of Modified FOLFOX-6 for diarrhoea

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	**Diarrhoea**	**Oxaliplatin**	**5-Fluorouracil**
• If diarrhoea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. • If diarrhoea is less than Grade 2 within 4 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If diarrhoea remains greater than or equal to Grade 2 after 4 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level of IV push and infusional 5-Fluorouracil
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 1 dose level of IV push and infusional 5-Fluorouracil

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL

Cetuximab: Low **(Refer to local policy).**
Oxaliplatin: Moderate **(Refer to local policy).**
5-Fluorouracil: Low **(Refer to local policy).**

PREMEDICATIONS:

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.

Table 7: 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:

- See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions **(Refer to local policy).**
- Anti-diarrhoeal treatment **(Refer to local policy).**

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 aggressively.

Cetuximab:

- **Infusion-related reactions (IRR):**
  - The first dose 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.
  - 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 IRR , the infusion rate may be decreased and maintained at the lower rate in all subsequent infusions.
  - Severe IRR 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 IRR 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 EGRF 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.

Oxaliplatin:

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations, the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysesthesia:** An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1-2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly

reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.

- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with 5-Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
- **Haemolytic Ureamic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

5-Fluorouracil:

- **Gastrointestinal toxicity:** Patients treated with 5-Fluorouracil should be closely monitored for diarrhoea and managed appropriately.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **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 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 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome, HFS,** also known as palmar-plantar erythrodysaesthesia (PPE), has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

DRUG INTERACTIONS:

- When cetuximab is used in combination with platinum-based chemotherapy, it may result in increased frequency of severe leukopenia or severe neutropenia.
- When cetuximab is used in combination with fluoropyrimidines, the frequency of palmar-plantar erythrodysaesthesia and of cardiac ischaemia including myocardial infarction and congestive heart failure were increased.
- When cetuximab is used in combination with capecitabine and oxaliplatin, the frequency of severe diarrhoea may be increased.
- Marked elevations of prothrombin time and INR have been reported in patients stabilised on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil metabolising enzyme DPD.
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	08/09/2022		Prof Maccon Keane
2	17/01/2024	Reviewed. Updated treatment table footnotes; exclusion criteria; Added cetuximab pre-medication table; Updated Hepatic and Renal dose modifications in line with Giraud et al 2023.	Prof Maccon Keane
2a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed posology for the use of cetuximab 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.'