Bevacizumab 5mg/kg and FOLFOXIRI Therapy - 14 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of metastatic colorectal cancer	C18	00783a	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.

Treatment is administered every 14 days until disease progression or unacceptable toxicity develops. 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	Bevacizumab	5mg/kg	IV infusion	100mL 0.9% NaCl over 90 minutes [a]	Every 14 days
2	1	Irinotecan	165mg/m^2	IV infusion	250mL 0.9% NaCl over 90 minutes	Every 14 days
3	1	Oxaliplatin	85 mg/m^2	IV infusion	500mL 5% glucose over 2 hours [b]	Every 14 days
4	1	Folinic Acid [c] (Calcium leucovorin)	200mg/m^2	IV infusion	250mL 5% glucose over 2 hours Administer concurrently with oxaliplatin in separate bags via y-line connection	Every 14 days
5	1	5-Fluorouracil [d]	3200mg/m^2	Continuous IV infusion	Over 48 hours in 0.9% NaCl (equivalent to 1600mg/m^2/day)	Every 14 days

[a] The initial dose of bevacizumab should be delivered over 90 minutes as an intravenous infusion.
If the first infusion is well tolerated, the second infusion may be administered over 60 minutes.
If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.
Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance Available on the NCCP website .
Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.
It should not be administered as an intravenous push or bolus.

[b] Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with 0.9% NaCl.
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.

[c] 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.

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

ELIGIBILITY:

- Indications as above
- ECOG ≤2 (adults under 70 years)
- ECOG <1 (adults 71-75)
- Adequate haematological, renal and liver status

USE WITH CAUTION:

Use with caution in patients with:

- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness
- In patients known to be homozygous for UGT1A1*28 consideration may be given to a reduced irinotecan starting dose
- 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 bevacizumab, irinotecan, oxaliplatin, 5-Fluorouracil or any of the excipients
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Baseline neutrophils < 1.5 x 10^9/L and/or platelet count < 100 x 10^9/L
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- CNS metastases
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam
- ECG (where clinically relevant)
- ECHO should be considered in patients who have had chest wall radiation or prior treatment with an anthracycline
- INR if clinically indicated*
- 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

*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle)

Regular tests:

- FBC, liver, renal profile, dipstick analysis for protein prior to each cycle
- Blood pressure prior to each cycle and post treatment
- INR if clinically indicated*
- Evaluate for peripheral neuropathy every cycle prior to proceeding with treatment

*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle)

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:

- **Bevacizumab:**
  Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated, bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 6 and Table 7).
- **FOLFOXIRI:**
  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.

Haematological

- Treatment is not administered unless ANC ≥1.5 x 10^9L and platelets ≥75 x 10^9/L.
- If levels are below this at Day 1 treatment may be delayed for 1-2 weeks.
- If no recovery in 2 weeks consideration should be given to discontinuing the treatment.

Table 1: Dose modification of FOLFOXIRI based on Day 1 Absolute Neutrophil Count (ANC)

ANC < 1.5 x 10^9/L	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence	Reduce dose to 150mg/m^2	Maintain full dose	Reduce to 75% of the original dose
2nd occurrence	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	Reduce to 50% of the original dose
3rd occurrence	DISCONTINUE TREATMENT		

Table 2: Dose modification of FOLFOXIRI based on Day 1 Platelet Count

Platelets < 75 x10^9/L	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence	Maintain full dose	Reduce to 60mg/m^2	Reduce to 75% of the original dose
2nd occurrence	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	
3rd occurrence	DISCONTINUE TREATMENT		

Table 3: Dose modification of FOLFOXIRI based on low nadir blood counts or in case of infection

Platelets < 50 x10^9/L	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence	Maintain full dose	Reduce to 60mg/m^2	Reduce to 75% of the original dose
2nd occurrence	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	Reduce to 50% of the original dose
3rd occurrence	DISCONTINUE TREATMENT		

Renal and Hepatic Impairment:

Table 4: Recommended dose modifications for patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Bevacizumab [a]	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		No need for dose adjustment is expected			
Oxaliplatin [b]	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed			
	≥30	No dose adjustment is needed				
	<30	Consider 50% of the original dose				
	Haemodialysis:	Consider 50% of the original dose, haemodialysis within 90 minutes after administration.				
Irinotecan [c]	**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 the original dose, increase if tolerated				
	Haemodialysis:	Start with 50-66% of the original dose, increase if tolerated				
5-Fluorouracil [d]	No need for dose adjustment is expected. Haemodialysis: No need for dose adjustment is expected.		**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.			

[a] Bevacizumab (renal and hepatic - Giraud et al 2023);
[b] Oxaliplatin (renal and hepatic – Giraud et al 2023);
[c] Irinotecan (renal – Giraud et al 2023; SPC);
[d] 5-Fluorouracil (renal – Giraud et al 2023; hepatic – NLCN 2009)

Management of adverse events:

Table 5: Recommended dose modification schedule for FOLFOXIRI based on non-haematological, non-neurological toxicities

Prior to a Cycle (DAY 1)	Irinotecan	Dose Level for Subsequent Cycles	
		Oxaliplatin	5-Fluorouracil
Diarrhoea			
• **1st occurrence** ○ Grade 3 or 4 ○ With fever and/or Grade 3 or 4 neutropenia	Reduce dose to 150mg/m^2		Reduce to 75% of original dose
• **2nd occurrence**		Reduce dose to 60mg/m^2	Reduce to 50% of the original dose
• **3rd occurrence**	DISCONTINUE TREATMENT		
Mucositis or hand-foot syndrome Grade 3 or 4			Reduce to 75% of original dose
Other toxicity • ≥ Grade 2 (except alopecia and anaemia)	Consider dose reduction		
• Transient grade 3 paresthesias/dysesthesias or transient grade 2 symptoms lasting > 7 days		Decrease oxaliplatin by 25%	
• Grade 4 or persistent grade 3		Discontinue oxaliplatin	
Laryngo-pharyngeal dysaesthesia		Increase infusion time from 2 to 6 hours	

Proteinurea:

Table 6: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	Action
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled.
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below.
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection.
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour.
greater than 4	Discontinue Therapy

Table 7: Dose modifications of bevacizumab for adverse events

Adverse reactions		Recommended dose modification
Hypertension	Uncontrolled* or symptomatic hypertension on Day 1	Withhold bevacizumab treatment and start antihypertensive therapy or adjust pre-existing medication.
	Grade 2-3 hypertension	Initiate antihypertensive therapy and consider interruption of bevacizumab until controlled
	Grade 4 hypertension or persisting grade 3 hypertension	Discontinue bevacizumab
Grade 4 Proteinuria		Discontinue bevacizumab
Tracheoesophageal (TE) fistula or any Grade 4 fistula		Discontinue bevacizumab
Grade 4 Thromboembolic events		Discontinue bevacizumab
Haemorrhagic event ≥ Grade 3		Discontinue bevacizumab
Gastrointestinal Perforation		Discontinue bevacizumab

*Uncontrolled hypertension for initiating bevacizumab is defined as sustained BP>150/100mmHg while receiving anti-hypertensive medication

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

This regimen poses an overall high risk of emesis.

Bevacizumab: Minimal **(Refer to local policy)**

Irinotecan: Moderate **(Refer to local policy)**

Oxaliplatin: Moderate **(Refer to local policy)**

5-Fluorouracil: Low **(Refer to local policy)**

PREMEDICATIONS:

Bevacizumab: Not usually required unless the patient has had a previous hypersensitivity.

FOLFOXIRI: 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).

OTHER SUPPORTIVE CARE:

Bevacizumab: Anti-diarrhoeal treatment may be required **(Refer to local policy)**.

FOLFOXIRI: 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.

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

Bevacizumab:

- **Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.
- **Wound healing complications:** Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for major elective surgery for 28 days and for 7 days for minor surgery or as directed by the prescribing Consultant. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.
- **Hypertension:** An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.
    - Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician's discretion.
    - Patients should have their blood pressure measured before each dose or more frequently if hypertension develops/worsens.
    - Any patient who develops hypertension (>150/100 mmHg) should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension (>200/110 mm Hg) that is not controlled with medication should have

bevacizumab discontinued.
  - It should be permanently discontinued if the patient develops hypertensive crisis or hypertensive encephalopathy.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating therapy in patients previously experiencing PRES is not known.
- **Proteinuria:** Patients with a history of hypertension may be at increased risk for the development of proteinuria.
- **Thromboembolism:** Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism or age > 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
- **Haemorrhage:** Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage. Bevacizumab should be used with caution in patients at risk of bleeding.
- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

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 dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia 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.
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-Fluorouracil.
- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complication 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 Uraemic 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.

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 (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 ≥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
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.

5-Fluorouracil

- **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.
- **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 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): 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 (see Table 5 for dose modifications).

DRUG INTERACTIONS:

- The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established.
- No interaction studies have been performed between EGFR antibodies and bevacizumab. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.
- Concurrent use of bevacizumab and SUNItinib can increase the risk of microangiopathic haemolytic anaemia (MAHA).
- 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 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 dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	12/12/2022		Prof Maccon Keane
2	17/01/2024	Reviewed. Updated treatment table (footnotes), Updated exclusion criteria, Updated dose modifications for renal and hepatic impairment in line with Giraud et al 2023 recommendations, Table 7 and emetogenic potential.	Prof Maccon Keane
2a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.