

Bevacizumab 5mg/kg and Modified FOLFOX- 6 Therapy – 14 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of adult patients with metastatic carcinoma of the colon or rectum.	C18 C19 C20	00446a	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 patient's individual clinical circumstances.

Treatment is administered once every 14 days until disease progression or unacceptable toxicity occurs. Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Bevacizumab	5mg/kg	IV infusion	100ml 0.9% NaCl over 90mins ¹	Every 14 days
¹ 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. It should not be administered as an intravenous push or bolus.						
Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.						
2	1	Oxaliplatin	85mg/m ²	IV infusion	² 500ml glucose 5% over 2hrs	Every 14 days
3	1	Folinic Acid (Calcium leucovorin)	400mg/m ²	IV infusion	250ml glucose 5% over 2hrs	Every 14 days
4	1	Fluorouracil	400mg/m ²	IV BOLUS		Every 14 days
5	1	Fluorouracil ³	2400mg/m ²	Continuous IV infusion	Over 46h in 0.9% NaCl.	Every 14 days
² 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-FU. Oxaliplatin may be given at the same time as Folinic Acid (Calcium Leucovorin) using a Y connector. 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. 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 fluorouracil.						
³ See dose modifications section for patients with identified partial DPD deficiency						

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 1 of 10
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 This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens		

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to bevacizumab, oxaliplatin or to any of the excipients
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Severe renal impairment (creatinine clearance < 30ml/min)
- Peripheral neuropathy with functional impairment prior to first cycle.
- Pregnancy
- Breast Feeding
- Known complete DPD deficiency

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

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Dipstick urinalysis for protein
- Blood pressure measurement
- Cardiac assessment including history and physical exam.
 - ECG (if patient has compromised cardiac function)
- 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

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 2 of 10
<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>		

Regular tests:

- FBC, liver and renal profile prior to each cycle
- Dipstick urinalysis for protein prior to each cycle
- Blood pressure prior to each cycle and post treatment
- Evaluate for peripheral neuropathy every 2 cycles
- INR if clinically indicated*

*(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:

- 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
- 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 4 and Table 5).
- Bevacizumab or Modified 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 dose reductions for patients with toxicities.

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
Fluorouracil bolus	400 mg/m ²	320 mg/m ²	260 mg/m ²	Discontinue
Fluorouracil infusion	2400 mg/m ²	1900 mg/m ²	1500 mg/m ²	Discontinue

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

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 3 of 10
<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>		

Haematological:

Table 2. Dose Modifications of Modified FOLFOX-6 for Haematological Toxicity

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	ANC (x 10 ⁹ /L)	Oxaliplatin	Fluorouracil
<ul style="list-style-type: none"> 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	Fluorouracil
<ul style="list-style-type: none"> 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 remains < 75 after 4 weeks discontinue treatment 	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	Maintain dose level
	4	<10	↓ 2 dose levels	Maintain dose level

Renal and Hepatic Impairment:

Table 3: Dose Modifications in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment				
Bevacizumab	No studies have been performed in patients with renal impairment.		No studies have been performed in patients with hepatic impairment.				
Oxaliplatin	CrCl(ml/min)	Dose	Little information available. Probably no dose reduction necessary Clinical decision				
	>30	Treat at normal dose and monitor renal function					
	<30	Contraindicated					
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				

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 4 of 10
<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>		

Management of adverse events:

Proteinuria :

Table 4: Dose modifications of bevacizumab for proteinuria

≥2+ proteinuria (dipstick)	24 hour urine collection for total protein
≥2+ proteinuria (dipstick) and 24 hour proteinuria ≤ 2g	Continue with normal dose.
≥2+ proteinuria (dipstick) and 24 hour proteinuria > 2g	Withhold treatment until proteinuria < 2g at discretion of prescribing consultant. Re-check 24 hour urine protein every 2-4 weeks or as clinically indicated.
Nephrotic syndrome	Discontinue bevacizumab.

Table 5: Dose modification for adverse events

Adverse reactions	Recommended dose modification
Hypertension Uncontrolled or symptomatic hypertension on Day 1	Withhold bevacizumab treatment, start antihypertensive therapy or adjust pre-existing medication
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
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 <ul style="list-style-type: none"> • First occurrence • 2nd occurrence • Persistent Grade 4	Reduce oxaliplatin by 1 dose level ↓ 1 dose level ↓ 1 dose level Discontinue oxaliplatin Discontinue oxaliplatin
Laryngo-pharyngeal dysaesthesia	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.

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 5 of 10
<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 This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</p>		

Table 6: Dose modification of FOLFOX-6 for diarrhoea

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	Diarrhoea	Oxaliplatin	Fluorouracil
<ul style="list-style-type: none"> 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 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 fluorouracil

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

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

OTHER SUPPORTIVE CARE: Anti-diarrhoeal treatment may be required **(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.

- Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. 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.
- Hypertension:** An increased incidence of hypertension has been observed in patients treated with

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 6 of 10
<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 <i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		

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.
- **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.
- **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:** Patients treated with fluorouracil should be closely monitored for diarrhea and managed appropriately.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- **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.
- **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,

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 7 of 10
<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>		

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 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:

- 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).
- 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-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Bevacizumab	-	L01XC07
Oxaliplatin	-	L01XA03
5-Fluorouracil	-	L01BC02
Folinic acid	-	V03AF03

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 8 of 10
<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>		

REFERENCES:

1. Saltz LB, Clarke S et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first line therapy in metastatic colorectal cancer: a randomized phase III study. et al. J Clin Oncol 2008; 26: 2013-2019
2. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019;20:e201-08.
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019 Available at:
<https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf>
4. 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 Aug 2020 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)
5. Bevacizumab (Avastin[®]) Summary of product characteristics. Last updated: 27/09/2019 Accessed August 2019. Available at https://www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf
6. Eloxatin[®] Summary of Product Characteristics Accessed 20 /9/2013 Available at: http://www.imb.ie/images/uploaded/swedocuments/LicenseSPC_PA0540-148-001_04092012155136.pdf
7. Oxaliplatin (Eloxatin[®]) Summary of Product Characteristics Accessed September 2019. Last updated: 23/04/2019. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0540-148-001_23042019151332.pdf
8. Fluorouracil 50 mg/ml solution. Summary of Product Characteristics. HPRA last updated: 10/05/2019. Accessed: Sept 2019. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_10052019144741.pdf

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 9 of 10
<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>		

Version	Date	Amendment	Approved By
1	23/10/2017		Prof Maccon Keane
2	22/11/2018	Update of dose modifications of bevacizumab for proteinuria	Prof Maccon Keane
3	09/10/2019	Reviewed. Standardisation of treatment table. Update of exclusion criteria, drug interactions, dose modifications, emetogenic potential.	Prof Maccon Keane
4	12/02/2020	Standardisation of treatment table. Updated exclusions and dose modifications for oxaliplatin in renal impairment. Clarified dose modifications of bevacizumab for proteinuria.	Prof Maccon Keane
5	26/02/2020	Standardisation of treatment table.	Prof Maccon Keane
6	1/9/2020	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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

NCCP Regimen: Bevacizumab 5mg/kg and Modified FOLFOX-6 Therapy– 14day	Published: 23/10/2017 Review: 09/10/2021	Version number: 6
Tumour Group: Gastrointestinal NCCP Regimen Code: 00446	ISMO Contributor: Prof Maccon Keane	Page 10 of 10
<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>		