Bevacizumab 5mg/kg and FOLFIRI 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	00449a	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.

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.						
2	1	Irinotecan	180mg/m^2	IV infusion	250ml 0.9% NaCl over 90mins	Every 14 days
3	1	Folinic Acid (Calcium leucovorin)	[2]400mg/m^2	IV infusion	250ml 0.9% NaCl over 2hrs	Every 14 days
4	1	Fluorouracil (5-FU)	400mg/m^2	IV BOLUS	Slow push through side arm of fast flowing drip	Every 14 days
5	1	[3]Fluorouracil	2400mg/m^2	Continuous IV infusion	Over 46h in 0.9% NaCl	Every 14 days
[2]A dose of 200mg/m^2 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.						
[3]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.						

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to bevacizumab, irinotecan or to any of the excipients
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Bilirubin > 3 x ULN
- 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

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
- 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 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.
- 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^2	150 mg/m^2	120 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	1500mg/m^2	Discontinue

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

Haematological:

Table 2: Dose Modifications of FOLFIRI for Haematological Toxicity

Prior to a Cycle (DAY 1)	Toxicity Grade	ANC (x 10^9/L)	Dose Level for Subsequent Cycles: Irinotecan	Fluorouracil
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • ANC ≥ 1.5 within 2 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	↓ 1 dose level
	4	<0.5	↓2 dose levels	↓2 dose levels
	Grade 4 neutropenia and grade≥2 fever		↓2 dose levels	↓2 dose levels
	Grade	**Platelets (x10^9/L)**	**Irinotecan**	**Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • Platelets ≥ 75 within 2 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 2 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	↓ 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 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.			
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	CI
		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			

Management of adverse events:

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 of bevacizumab for adverse events

Adverse reactions	**Recommended dose modification**
Hypertension Uncontrolled or symptomatic hypertension on Day 1 Grade 4 hypertension or persisting grade 3 hypertension	 Withhold bevacizumab treatment, start antihypertensive therapy or adjust pre-existing medication 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

Table 6: Dose modification of FOLFIRI for adverse events

Prior to a Cycle (DAY 1)	Grade of Toxicity	Dose Level for Subsequent Cycles	
		Irinotecan	Fluorouracil
Diarrhoea • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	Maintain dose level
	3	↓1 dose level	↓ 1 dose level
	4	↓2 dose levels	↓2 dose levels
Stomatitis • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced. • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	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:

Irinotecan – Moderate **(Refer to local policy).**
5-fluorouracil – Low **(Refer to local policy).**
Bevacizumab – Minimal **(Refer to local policy).**

PREMEDICATIONS:

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:

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 (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.

Bevacizumab

- **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 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.

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 ≥2 and women.
  - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles.
  - The SmPC (6) provides guidelines on when hospitalisation for the management of diarrhoea is recommended.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.
- **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, 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 erythrodysaesthesia (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).
- 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.
- 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
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Bevacizumab	-	L01XC07
Irinotecan	-	L01XX19
5-Fluorouracil	-	L01BC02
Folinic acid	-	V03AF03

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Version	Date	Amendment	Approved By
1	23/10/2017		Prof Maccon Keane
2	21/11/2018	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, emetogenic potential.	Prof Maccon Keane
4	12/02/2020	Updated exclusions. Clarification of dose modifications of bevacizumab for proteinuria	Prof Maccon Keane
5	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 erythrodysaesthesia	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.