Bevacizumab 5mg/kg, 5-Fluorouracil and Folinic Acid Therapy-14 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of metastatic colorectal cancer	C18	00791a	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 NaCl 0.9% over 90 minutes[a]	Every 14 days
1	1	Folinic Acid[b] (Calcium leucovorin)	400mg/m^2	IV infusion	250mL 0.9% NaCl over 2 hours	Every 14 days
2	1	5-Fluorouracil[c]	400mg/m^2	IV bolus		Every 14 days
3	1	5-Fluorouracil[c]	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	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.
[ii]Alternatively, the unlicensed use of shorter infusion times is described in the NCCP Bevacizumab Rapid Infusion Rate Guidance- Available on the NCCP website .
It should not be administered as an intravenous push or bolus.

[b]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

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

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

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

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CAUTION:

- Recent MI
- Pre-existing uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- Baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Previous pelvic radiotherapy
- 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
- Surgical procedure or complications that could lead to increased risk of fistulation or perforation
- Underlying condition that could lead to increased risk of fistulation or perforation

EXCLUSIONS:

- Hypersensitivity to bevacizumab , 5-Fluorouracil, folinic acid or any of the excipients
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- Pregnancy and lactation
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG (as 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.
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam.

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- ECHO should be considered in patients who have had chest wall radiation or prior treatment with an anthracycline.
- INR if clinically indicated*
  *(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)

Regular tests:

- FBC, renal and liver profile prior to each cycle, dipstick urinalysis for protein.
- 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:

- 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).
- **DPD deficiency:**
  - Consider a reduced starting dose of 5-Fluorouracil 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
- The following dose reductions should be used when calculating dose reductions for patients with toxicities:

Table 1: Dose Reduction Levels for Folinic Acid and 5-Fluorouracil for All Toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
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	240 mg/m^2	Discontinue
5-Fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue

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

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Haematological:

Table 2: Dose Modifications for 5-Fluorouracil for Haematological Toxicity

Prior to a Cycle (DAY 1)	TOXICITY Grade	ANC (x 10^9/L)	Dose level of 5-Fluorouracil for subsequent cycles
• If ANC < 1.0 on Day 1 of cycle, hold treatment. Perform weekly FBC, maximum of 2 times. • ANC ≥ 1.0 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). • If ANC remains <1.0 after 2 weeks, discontinue treatment	1	≥ 1.5	Maintain dose level
	2	1.0-1.49	Maintain dose level
	3	0.5-0.99	↓1 dose level
	4	< 0.5	↓1 dose level
	Grade 4 neutropenia & greater than or equal to **Grade 2 fever**		↓1 dose level
	Grade	**Platelets (x10^9/L)**	**5-Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment. Perform weekly FBC, maximum of 2 times. • If platelets ≥ 75 within 2 weeks of initial treatment delay, 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	1	≥ 75	Maintain dose level
	2	50-74.9	Maintain dose level
	3	10-49.9	Maintain dose level
	4	<10	Maintain dose level

Renal and Hepatic Impairment:

Table 3: Dose Modifications in renal and hepatic impairment

Drug	Renal impairment	Hepatic impairment			
Bevacizumab	No need for dose adjustment is expected. Haemodialysis: no need for dose adjustment is expected.	No need for dose adjustment is expected.			
5-Fluorouracil	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.			

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Management of adverse events:

Table 4: 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 5: 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		

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Table 6: Dose modification schedule of 5-Flourouracil based on Adverse Events

Prior to a Cycle (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles
	Grade	**Diarrhoea**	**5-Fluorouracil**
• If diarrhoea ≥ Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum of 2 times. • If diarrhoea < Grade 2 within 2 weeks of treatment delay, proceed with treatment at the dose level noted across from the **highest** Grade experienced. • If diarrhoea remains ≥ Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓1 dose level
	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
Prior to a Cycle (DAY 1)	**TOXICITY**		**Dose Level for Subsequent Cycles**
	Grade	**Stomatitis**	**5-Fluorouracil**
• If stomatitis ≥ Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum of 2 times. • If stomatitis < Grade 2 within 2 weeks of initial treatment delay, proceed with treatment at the dose level noted across from the **highest** Grade experienced. • If stomatitis remains ≥ Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, oedema or ulcers, but can eat	Maintain dose level
	3	Painful erythema, oedema, ulcers, and cannot eat	↓1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration.	↓2 dose levels

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

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

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Anti-diarrhoeal treatment **(Refer to local policy).**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information

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Version	Date	Amendment	Approved By
1	10/09/2024		Prof Maccon Keane
1a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed regimen for the use of bevacizumab in Ireland. Patients 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.

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[ii] The rapid infusion is an unlicensed means of administration of bevacizumab for the indications described above, in Ireland. Patients 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" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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