Bevacizumab 7.5mg/kg and Capecitabine 1250mg/m^2 Therapy - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of metastatic or unresectable colorectal cancer in patients not suitable for combination chemotherapy with irinotecan or oxaliplatin	C18	00623a	Bevacizumab – Hospital Capecitabine – CDS

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.

Bevacizumab is administered on day 1 and capecitabine is administered on days 1-14 of a 21 day cycle until disease progression or unacceptable toxicity occurs.

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	7.5mg/kg	IV infusion	100ml NaCl 0.9% over 90mins[a]	21 days
2	1-14	Capecitabine	1250mg/m^2 twice daily[b,c,d,e]	PO	n/a	21 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 here. It should not be administered as an intravenous push or bolus.

[b]The dose to be administered should consider the available tablet strengths.
Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine Here.
Tablets should be swallowed whole with plenty of water with food or within 30 minutes of eating. Tablets should not be crushed or cut.
[c](total daily dose = 2500mg/m^2)

[d]See dose modifications section for patients with identified partial DPD deficiency.

[e]Starting dose of 1000 mg/m^2 twice daily may be considered for elderly patients, patients with a poor performance status or extensively pretreated patients.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Patients unsuitable for treatment with oxaliplatin or irinotecan in first line setting

- Adequate haematological (ANC≥ 1.2 x 10^9/L , platelets >100 x 10^9/L) renal creatinine ≤1.5 x ULN and liver status (bilirubin ≤ 26 micromol/L; AST/ Alkaline Phosphatase ≤5 x ULN)

EXCLUSIONS:

- Hypersensitivity to bevacizumab, capecitabine or any of the excipients
- Pregnancy and lactation
- Capecitabine:
  - Known complete DPD deficiency
  - History of severe and unexpected reactions to fluoropyrimidine therapy
  - Severe hepatic or renal impairment
  - Recent or concomitant treatment with brivudine
- Bevacizumab:
  - Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies

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

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam.
- 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:

- 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 7 and Table 8)
- Capecitabine:
  - 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
  - Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction)
  - Once the dose has been reduced, it should not be increased at a later time
  - For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption
  - Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs
  - Doses of capecitabine omitted for toxicity are not replaced

Haematological:

- Initiation of treatment with capecitabine in patients with baseline neutrophil counts $<1.5x10^9$/L and/or thrombocyte counts of $<100 \times 10^9$/L should be undertaken with caution
- If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below $1x10^9$/L or that the platelet count drops below $75x10^9$/L, treatment with capecitabine should be interrupted

Table 1: Dose modification of Capecitabine in haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
≥ 1.5	and	≥ 75	100%	100%	100%	100%
1-1.49	or	50 – 74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25- 49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
< 0.5	or	< 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

*Delay until ANC ≥ 1.5x 10^9/L and platelets ≥ 75x10^9/L

Renal and Hepatic Impairment:

Table 2: Dose modification of capecitabine and bevacizumab in renal and hepatic impairment

<table>
<tr><td rowspan="4">Capecitabine</td><td colspan="2">Renal Impairment</td><td>Hepatic Impairment*</td></tr>
<tr><td>CrCl (ml/min)</td><td>Dose</td><td rowspan="3">In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.</td></tr>
<tr><td>≥30</td><td>100% dose</td></tr>
<tr><td><30</td><td>Discontinue treatment</td></tr>
<tr><td colspan="3">*Reference Table 6 - for dose modification of capecitabine in treatment related hepatotoxicity</td></tr>
<tr><td>Bevacizumab</td><td colspan="2">No studies have been performed in patients with renal impairment.</td><td>No studies have been performed in patients with hepatic impairment.</td></tr>
</table>

Management of adverse events:

Table 3 shows the recommended dose modifications of capecitabine for those toxicities which are not individually specified:

Table 3: capecitabine dose reduction schedule based on toxicity

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
• 1st appearance	Interrupt until resolved to grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue permanently	
Grade 3		
• 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4		
• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue permanently	
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy		

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 4: Dose Modification of capecitabine for diarrhoea

Grade	Diarrhoea	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
0-1	Increase of 2 to 3 stools/day or nocturnal stools	Maintain dose level	Maintain dose level
2	Increase of 4 to 6 stools/day or nocturnal stools		
	• 1st appearance	Interrupt until resolved to grade 0-1	100%
	• 2nd appearance		75%
	• 3rd appearance		50%
	• 4th appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence		
	• 1st appearance	Interrupt until resolved to grade 0-1	75%
	• 2nd appearance		50%
	• 3rd appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		

	• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
	• 2nd appearance	Discontinue permanently	
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy			

Hand foot syndrome:

Table 5: Dose modification of capecitabine in hand foot syndrome

Toxicity Grade		Dose Modification
Grade 1	Skin changes (e.g., numbness, dysesthesia, paraesthesia, tingling, erythema) with discomfort not disrupting normal activities	100% Dose
Grade 2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living	Withhold treatment until event resolves or decreases in intensity to grade 1.
Grade 3	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased

Treatment related hepatotoxicity:

Table 6: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3.0 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

Proteinuria:

Table 7: 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 8: Dose modification 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:
Bevacizumab: Minimal (**Refer to local policy).**
Capecitabine: Minimal to low (**Refer to local policy).**

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

OTHER SUPPORTIVE CARE: Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see 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.

Capecitabine:

- **Diarrhoea and dehydration:** This may be dose limiting. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.
- **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.
- **Hand-foot syndrome (HFS**): HFS, also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 5 for dose modification of capecitabine for HFS.)

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.

DRUG INTERACTIONS:

- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Brivudine must not be administered concomitantly with capecitabine. Fatal cases have been reported following this drug interaction.There must be at least a 4-week waiting period between end of treatment with brivudine and start of capecitabine therapy.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Concurrent use of bevacizumab and sunitinib can increase the risk of microangiopathic haemolytic anaemia (MAHA).
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. NCCP | Bevacizumab Rapid Infusion Rate Guidance V2 2021 .Available at https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/bevacizumab-rapid-infusion-rate-guidance.pdf
3. 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. https://doi.org/10.1016/S1470-2045(19)30145-7
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
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6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023 .Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
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8. Capecitabine (Xeloda®) tablets. Summary of Product Characteristics. Accessed Oct 2022. Last updated July 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	18/12/2020		Prof Maccon Keane
2	04/10/2022	Reviewed	Prof Maccon Keane
3	10/08/2023	Updated bevacizumab dose modifications for adverse events	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i]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.