DRUG ADMINISTRATION

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td><strong>Bevacizumab</strong></td>
<td>5mg/kg</td>
<td>Infusion</td>
<td>100/250mls 0.9% Sodium Chloride (Rate see below)</td>
</tr>
<tr>
<td></td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Fast Running for Line Flush</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Calcium Leucovorin</strong></td>
<td>300mg</td>
<td>Infusion</td>
<td>250ml Glucose 5% over 2 hours concurrent with irinotecan</td>
</tr>
<tr>
<td></td>
<td>(folinic acid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Irinotecan</strong></td>
<td>180mg/ m²</td>
<td>Iv Infusion</td>
<td>250ml Glucose 5% over 2 hours concurrent with folinic acid</td>
</tr>
<tr>
<td></td>
<td>Dextrose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Line Flush</td>
</tr>
<tr>
<td></td>
<td><strong>5 Fluorouracil</strong></td>
<td>400mg/ m²</td>
<td>IV bolus</td>
<td>Over 5 minutes</td>
</tr>
<tr>
<td></td>
<td>5 Fluorouracil</td>
<td>2400mg/ m²</td>
<td>via infusor</td>
<td>Sodium Chloride 0.9% over 46 hours</td>
</tr>
<tr>
<td>Day 3</td>
<td>Attend ward/clinic for removal of 5-FU infusor device</td>
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</table>

DOSE FREQUENCY
Every 14 days

RATE
Bevacizumab must be given in combination with chemotherapy every three weekly. Intravenous infusion given over 90 minutes for initial dose; if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes. It can be given in 100ml Sodium Chloride provided the final solution stays within the range of 1.4-16.5 mg/ml.

EXCLUSION CRITERIA
Contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies
Caution in patients with:
- Untreated central nervous system metastases
- Uncontrolled hypertension
- History/ Risk factors for thromboembolic events e.g. history of arterial thromboembolic events
- Significant cardiac risk factors for development of CHF
- Patients with baseline renal function less than 30ml/min (Creatinine Clearance)
APPROVED INDICATIONS

Approved for use on the National Cancer drugs Fund List for patients who meet the following criteria:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. Advanced colorectal cancer
3. 1st line indication
4. Given in combination with (a) oxaliplatin based combination chemotherapy OR (b) Given in combination with irinotecan-based combination chemotherapy
5. No previous treatment with Bevacizumab

NOTE: If excessive toxicity with oxaliplatin or irinotecan, bevacizumab can be continued with a fluoropyrimidine alone until disease progression only.

NOTE: Bevacizumab is ONLY approved for use in combination with chemotherapy and is not for use as a single agent maintenance therapy.

No treatment breaks of more than 7 weeks are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

PREMEDICATION

- If acute cholinergic syndrome appears atropine sulphate should be administered unless clinically contraindicated. The irinotecan manufacturer recommends the use of prophylactic atropine sulphate with subsequent doses of Irinotecan
- Anti-emetics are not required for Bevacizumab treatment. Take home medications as per chemotherapy regimen.

RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days
Metoclopramide 10 to 20mg three to four times daily as required
Loperamide as required (4mg after first loose stool and 2mgs every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours.

INVESTIGATIONS / MONITORING REQUIRED

Pre treatment:
- Assessment of renal function, FBC, Cardiac history
- Cardiac assessment incl. history and physical exam

Prior to each cycle:
- FBC, U&E’s, LFT’s
- Tumour markers as appropriate, e.g. where CEA is elevated this should be measured before each cycle
• Monitor blood pressure every cycle and more frequently in patients who develop hypertension
• Proteinuria by dipstick analysis prior to treatment and before each dose. If protein present undertake quantitative measurement of protein in urine and if greater than 2g > 24hrs delay of bevacizumab.

ASSESSMENT OF RESPONSE
Assessed radiologically after 4th cycle.
Metastatic: Tumour size and patient symptomatic response

REVIEW BY CLINICIAN
Review at each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols

ADMINISTRATION NOTES
FOLFIRI
• Irinotecan must only be given in units where clear arrangements are made to manage possible toxicity related out of hour’s admissions. Patients must be made aware of the risk of delayed diarrhoea occurring 24 hours after the administration of irinotecan and at any time before the next cycle. This means supplying information sheets to the patient and if appropriate to their GP.
• Early onset diarrhoea (within the first 24 hours) can be a result of acute cholinergic syndrome and may occur in 9% of patients. Symptoms are short lasting and respond within minutes to administration of atropine (0.25-1mg subcutaneously)
• Delayed diarrhoea must be treated immediately with high dose loperamide (4mg after first loose stool and 2mgs every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours. Hospitalise if condition not resolved in 48 hours.
• For diarrhoea lasting greater than 24 hours add ciprofloxacin 250mg BD. Note many units give patient a supply of loperamide and ciprofloxacin at the start of treatment.
• *Note: A variety of calcium folinate doses have been used in clinical trials, e.g. 200mg/m² with max dose 350mg or 175mg Calcium LevoFolinate or 350mg Calcium Foline. To enable a convenient, cost effective single vial dose, 300mg is recommended.

BEVACIZUMAB
• Hypertension is commonly observed, may be dose-related and should be managed with antihypertensives, e.g. calcium channel blockers.
• Units administering bevacizumab must have facilities available for the treatment of anaphylaxis and resuscitation.
• May not need to stop treatment for minor hypersensitivity e.g. reactions, flushing, localised rash. Must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.
• Paracetamol can be used to treat reactions.
• Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. If elective surgery is planned, bevacizumab should be withheld and the long half-life considered.

No treatment breaks of more than 7 weeks from the start of the previous cycle are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

**EXTRAVASATION** Follow Network and Local Trust Guidelines

**MAIN TOXICITIES**

**FOLFIRI**
• Acute cholinergic syndrome (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation
• Diarrhoea – risk of severe delayed diarrhoea – can be life threatening
• Myelosuppression
• Alopecia
• Dizziness during treatment
• Anaphylaxis
• Nausea and Vomiting
• Allergic reaction
• Diarrhoea
• Stomatitis
• Palmar/Plantar Erythrodysesthesia
• Darkening/discoloration of veins
• Cardiotoxicity - Occasionally patients may experience coronary artery spasm
• Laryngopharyngeal dysethesia

**BEVACIZUMAB**
• Fatigue Hypertension Proteinuria Headache
• Infusion-associated symptoms / acute hypersensitivity reactions (anaphylaxis, chills and fever, nausea, vomiting, pain, rigors, headache, asthenia etc.)
• Diarrhoea
• Abdominal pain
• Nausea and vomiting

*Less Common Toxicities that may be severe or life-threatening include:*  
• Arterial/venous thromboembolism
• GI perforation, fistulas, wound dehiscence
• Haemorrhage
• Cardiac failure
• Pneumonitis
DOSE MODIFICATIONS

Haematological toxicity:
- Delay 1 week if ANC < 1.5 and Platelets < 75 to 100
- No dose reduction for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered, then proceed at 20% 5FU and Irinotecan dose reduction
- If delay > 1 week or delay 2 weeks or greater occurs, reduce the 5FU dose (bolus & infusional) and Irinotecan by 20%. Continue at the reduced dose for subsequent cycles unless other toxicity occurs.
- If further delay(s) for bone marrow suppression occur despite a 20% dose reduction, consider a further 20% dose reduction.

Note: In the case of asymptomatic dose delay of chemotherapy for haematological toxicity the bevacizumab may still be given if the clinician decides it is appropriate as bevacizumab does not cause significant haematological toxicity.

Non –Haematological toxicity:
- Diarrhoea grade 2 during course of treatment → delay until recovered and give full dose
- Diarrhoea grade 3/4 during a course of treatment → delay until recovered and resume treatment at 20% reduced dose of Irinotecan and 5FU
- Hepatic - bilirubin rising consider 50% chemotherapy dose reduction.
- Omit if bilirubin 3 x ULN
- Renal - rising creatinine and GFR < 30ml/min, consider 50% chemotherapy dose reduction.
- The kidneys and liver are not major organs for bevacizumab metabolism or excretion.

Note CTC grading for Diarrhoea toxicity
- CTC Grade 1 = Diarrhoea (watery stool 2-3 times/day) OR mild increase in ostomy output compared to baseline
- CTC Grade 2 = Diarrhoea (watery stool 4-6 times/day) OR moderate increase in ostomy output compared to baseline
- CTC Grade 3/4 = Diarrhoea (watery stool >7 times/day OR severe increase in ostomy output compared to baseline

Bevacizumab dose reduction for toxicity is not recommended, but dosing with bevacizumab should be omitted or discontinued for the following adverse events:
- Uncontrollable hypertension, delayed wound healing, surgery, grade 3 proteinuria (>3g in 24hrs ref. CTCv4).

TREATMENT LOCATION
Cancer Centre or Cancer Unit where there is an oncologist with a specialisation in Colorectal cancer patients as appropriate.
REFERENCES

- Bevacizumab summary of product characteristics (SPC) available at https://www.medicines.org.uk/emc/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/

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<tr>
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<td>Mandy Nagra, NHS England CNTW Area</td>
</tr>
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<td>Checked By:</td>
<td>Steve Williamson, Area Team Cancer Pharmacist</td>
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