Aflibercept and FOLFIRI Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Aflibercept is indicated as second line therapy in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.	C18	00238a	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.

Aflibercept is administered by IV infusion once every 14 days followed by the FOLFIRI regimen until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Aflibercept	4mg/kg	IV infusion	0.9% NaCl over 60 mins	Repeat every 14 days
1	Irinotecan	180mg/m^2	IV infusion	250ml 0.9% NaCl over 90 mins	Repeat every 14 days
1	Folinic Acid (Calcium leucovorin)	[a]400mg/m^2	IV infusion	250ml 0.9% NaCl over 2hrs	Repeat every 14 days
1	5-Fluorouracil (5-FU)	400mg/m^2	IV BOLUS	Slow push through side arm of fast flowing drip	Repeat every 14 days
1	5-Fluorouracil[b]	2400mg/m^2	Continuous IV infusion	Over 46h in r 0.9% NaCl	Repeat every 14 days
Final concentration of aflibercept for infusion should be within the range of 0.6 mg/ml to 8 mg/ml. PVC containing DEHP infusion bags or polyolefin infusion bags should be used. Diluted solutions of aflibercept should be administered using infusion sets containing a 0.2 micron polyethersulfone filter.					
[a]A dose of 200mg/m^2 of folinic acid may be considered.					
[b]See dose modifications section for patients with identified partial DPD deficiency					
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.					
Patients may suck on ice chips during the bolus injection of fluorouracil to reduce stomatitis.					

ELIGIBILITY:

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

CAUTION:

Use with caution in patients with

- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)

EXCLUSIONS:

- Hypersensitivity to aflibercept, irinotecan or any of the excipients
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- Impaired renal function
- Known complete DPD deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- Blood, liver and renal profile
- Proteinuria dipstick analysis
- Blood pressure
- ECG (if patient has compromised cardiac function)
- DPD testing prior to first treatment with 5-fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- Blood, liver and renal profile and proteinuria dipstick analysis prior to each cycle
- Patients with a UPCR > 1 should undergo a 24-hour urine collection
- INR tests if patient is on warfarin as clinically indicated

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
- Aflibercept should be temporarily suspended for at least 4 weeks prior to elective surgery.

Renal and Hepatic Impairment:

Table 1: Recommended dose modifications in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment	
Aflibercept	Mild	No dose modification required	Mild	No dose modification required
	Moderate		Moderate	
	Severe	Limited data –use with caution	Severe	No data available
Irinotecan	No dose reduction needed, however use with caution as no information in this setting.		Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.	
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 2: Dose modification of aflibercept/FOLFIRI, aflibercept and FOLFIRI based on adverse reaction

Adverse Reaction	Dose modification
Aflibercept/FOLFIRI	
Neutropenia or thrombocytopenia	Administration of aflibercept/FOLFIRI should be delayed until neutrophil count is ≥ 1.5 x 10^9/L or platelet count is ≥ 75 x 10^9/L.
Febrile neutropenia or neutropenic sepsis • 1st occurrence • 2nd occurrence • 3rd occurrence	• Irinotecan dose should be reduced by 15-20% in subsequent cycles. • 5-Fluorouracil bolus and infusion doses should additionally be reduced by 20% in subsequent cycles. Reduced dose of irinotecan should be maintained. • Reduction of aflibercept dose to 2 mg/kg could be considered. The use of granulocyte colony-stimulating factor (G-CSF) may be considered.

Mild to moderate hypersensitivity reactions to aflibercept	Temporarily suspend the infusion until the reaction resolves. Treatment with corticosteroids and/or antihistamines can be used as clinically indicated. Consider pre-treatment with corticosteroids and/or antihistamines in subsequent cycles.
Severe hypersensitivity reactions	Aflibercept/FOLFIRI should be discontinued.
Aflibercept	
Proteinuria • 1st occurrence • 2nd occurrence	 Aflibercept treatment should be suspended when proteinuria ≥ 2g/24 hours and resumed when proteinuria < 2g/24hours. Treatment suspended until < 2g/24hours and then the dose should be reduced permanently to 2mg/kg for subsequent cycles.
Hypertension Uncontrolled hypertension, hypertensive crisis or hypertensive encephalopathy	Withhold aflibercept treatment until hypertension is controlled. For recurrence of medically significant or severe hypertension, the treatment should be suspended until controlled and the dose permanently reduced to 2mg/kg for subsequent cycles. Discontinue aflibercept.
Severe haemorrhage	Discontinue aflibercept.
GI perforation	Discontinue aflibercept.
Fistula formation	Discontinue aflibercept.
Arterial thromboembolic events (ATE)	Discontinue aflibercept.
Grade 4 venous thromboembolic events (including pulmonary embolism)	Discontinue aflibercept.
Nephrotic syndrome or thrombotic microangiopathy (TMA)	Discontinue aflibercept.
Compromised wound healing requiring medical intervention	Discontinue aflibercept.
Posterior reversible encephalopathy syndrome (PRES)	Discontinue aflibercept.
FOLFIRI	
Severe stomatitis and PPE syndrome	Reduce 5-Fluorouracil bolus and infusion dose by 20%
Severe diarrhoea • 1st occurrence • 2nd occurrence	• Reduce irinotecan dose by 15-20%. • The 5-Fluorouracil bolus and infusion dose should also be reduced by 20%. • If severe diarrhoea persists with both dose reductions FOLFIRI should be discontinued. • Treatment with anti-diarrhoeal medicinal products and rehydration can be used as needed.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Aflibercept: Low risk (**Refer to local policy)**
Irinotecan: Moderate risk **(Refer to local policy).**
5-Fluorouracil: Low risk **(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.

The information below deals specifically with aflibercept.
Please refer to NCCP FOLFIRI regimen 00227 for detailed information on adverse effects/regimen specific complications.

- **Haemorrhage:** An increased risk of haemorrhage, including severe and sometimes fatal haemorrhagic events has been reported in patients treated with aflibercept. Patients should be monitored for signs and symptoms of GI bleeding and other severe bleeding. Aflibercept should not be administered to patients with severe haemorrhage.
- **Hypertension:** An increased risk of grade 3-4 hypertension has been observed in patients treated with aflibercept/FOLFIRI regimen. Pre-existing hypertension must be adequately controlled before starting aflibercept. If hypertension cannot be adequately controlled, treatment with

aflibercept should not be initiated. It is recommended to monitor blood pressure every 2 weeks including before each administration or as clinically indicated during treatment with aflibercept. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as coronary artery disease or CHF with aflibercept.

- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating aflibercept, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.
- **Cardiac failure and ejection fraction decreased**: Cardiac failure and ejection fraction decreased have been reported in patients treated with aflibercept. Baseline and periodic evaluations of left ventricular function should be considered while the patient is receiving aflibercept. Patients should be monitored for signs and symptoms of cardiac failure and ejection fraction decreased. Discontinue aflibercept in patients who experience cardiac failure and ejection fraction decreased.
- **Thrombotic and embolic events.**
  - Aflibercept treatment should be discontinued in patients who experience an ATE.
  - Aflibercept should be discontinued in patients with life-threatening (Grade 4) thromboembolic events. Patients with Grade 3 DVT should be treated with anticoagulation as clinically indicated and aflibercept therapy should be continued. In the event of recurrence, despite appropriate anticoagulation, aflibercept treatment should be discontinued. Patients with thromboembolic events of Grade 3 or lower need to be closely monitored.
- **Proteinuria:** Severe proteinuria, nephrotic syndrome, and thrombotic microangiopathy (TMA) have been observed in patients treated with aflibercept.
  Proteinuria should be monitored by urine dipstick analysis and urinary protein creatinine ratio (UPCR) for the development or worsening of proteinuria before each aflibercept administration. Patients with a UPCR >1 should undergo a 24-hour urine collection. Reference table 1 above for dose modifications for proteinuria. Aflibercept treatment should be discontinued in patients who develop nephrotic syndrome or TMA.
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Administration of aflibercept/FOLFIRI should be delayed until neutrophil count is ≥1.5 x 10^9/L. Therapeutic use of G-CSF at first occurrence of grade ≥3 neutropenia and secondary prophylaxis may be considered in patients who may be at increased risk for neutropenia complications.
- **Compromised wound healing**: Aflibercept impaired wound healing in animal models. Treatment should be suspended for at least 4 weeks prior to elective surgery. It is recommended that aflibercept not be initiated for at least 4 weeks following major surgery and not until the surgical wound is fully healed. For minor surgery such as central venous access port placement, biopsy, and tooth extraction, aflibercept may be initiated/restarted once the surgical wound is fully healed. Aflibercept should be discontinued in patients with compromised wound healing requiring medical intervention.
- **Diarrhoea:** A higher incidence of severe diarrhoea has been observed in patients treated with the aflibercept/FOLFIRI regimens.
- **Osteonecrosis of the jaw (ONJ):** Aflibercept treatment may be an additional risk factor for the development of ONJ. This risk should be considered, particularly when aflibercept and intravenous bisphosphonates are administered concomitantly or sequentially. A dental examination and appropriate dentistry should be considered before treatment with aflibercept.

Invasive dental procedures should, if possible be avoided in patients treated with aflibercept and who have previously received or are receiving IV bisphosphonates.

DRUG INTERACTIONS:

- Drug interaction studies have not been performed with aflibercept. Risk of interactions with other concomitant medication cannot be excluded.
- 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.
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimens.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-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 dihydroprimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Aflibercept	-	L01XX44
Irinotecan	-	L01XX19
5-Fluorouracil	-	L01BC02
Folinic acid	-	V03AF03

REFERENCES:

1. Van Cutsem E, Tabernero J, Lakomy R et al: Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomised trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012;30:3499-3506.
2. HPRA Safety notice 16th March 2016. ZALTRAP (aflibercept); Information on the risk of osteonecrosis of the jaw. Available at https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information---zaltrap-(aflibercept).pdf?sfvrsn=0
3. ZALTRAP® Summary of Product Characteristics. Accessed April 2020. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002532/WC500139484.pdf
4. Irinotecan® Summary of Product Characteristics. Accessed April 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-044-001_18042019115425.pdf
5. Fluorouracil. Summary of Product Characteristics Accessed April 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-223-001_10102019120038.pdf

6. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
7. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network . Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
8. 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
9. NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting V2 2019 Available at www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version control

Version	Date	Amendment	Approved By
1	10/1/2015	Initial draft	Prof Maccon Keane
2	13/4/2016	Updated Adverse Events /Regimen specific complications with information on risk of ONJ based on safety notice March 2016	Prof Maccon Keane
3	18/04/2018	Updated Title, new NCCP Regimen Template and Updated dosing modification for adverse events as per SmPC	Prof Maccon Keane
4	12/05/2020	Regimen review Updated infusion fluids in treatment table Amended exclusion criteria. Updated exclusion criteria in regards to Fluorouracil Amended emetogenic potential Updated adverse events/regimen specific complications as per SmPC update for aflibercept. Updated drug interactions to include information regarding 5-Fluorouracil	Prof Maccon Keane
5	21/8/2020	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.