Aflibercept and FOLFIRI Therapy-14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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	N/A

*This is for post 2012 indications

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 systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Aflibercept	4mg/kg	IV infusion	100mL 0.9% NaCl over 60 minutes	Every 14 days
1	Irinotecan	180mg/m^2	IV infusion	250mL 0.9% NaCl over 90 minutes	Every 14 days
1	Folinic Acid (Calcium leucovorin)	[a]400mg/m^2	IV infusion	250mL 0.9% NaCl over 2 hours	Every 14 days
1	5-Fluorouracil	400mg/m^2	IV bolus	Slow push through side arm of fast flowing drip	Every 14 days
1	5-Fluorouracil[b]	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	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 dihydropyrimidine dehydrogenase (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 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase.					
Patients may suck on ice chips during the bolus injection of 5-Fluorouracil to reduce stomatitis.					

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

ELIGIBILITY:

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

CAUTION:

- 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, 5-Fluorouracil 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 dihydropyrimidine dehydrogenase (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
    - In patients with moderate or severe renal impairment, blood uracil levels used for 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.

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:

- Any dose modification should be discussed with a Consultant
- 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
- 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

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td>[a]Aflibercept</td><td colspan="2">No dose adjustment is needed

Haemodialysis: no need for dose adjustment is expected</td><td colspan="2">Mild/ Moderate</td><td colspan="2">No dose adjustment is needed</td></tr>
<tr><td></td><td colspan="2"></td><td colspan="2">Severe</td><td colspan="2">No need for dose adjustment is expected</td></tr>
<tr><td>[b]Irinotecan</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="4" rowspan="4">Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.</td></tr>
<tr><td>≥10</td><td>No need for dose adjustment is expected</td></tr>
<tr><td><10</td><td>Start with 50-66% of original dose, increase if tolerated</td></tr>
<tr><td>Haemodialysis</td><td>Start with 50-66% of original dose, increase if tolerated</td></tr>
<tr><td>[c]5-Fluorouracil</td><td colspan="2" rowspan="3">No need for dose adjustment is expected.</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td></td><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td></td><td>>85</td><td>or</td><td>>180</td><td>CI</td></tr>
</table>

	Haemodialysis: No need for dose adjustment is expected	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.
[a] Recommendations from Giraud et al 2023 [b]Renal recommendations from Giraud et al 2023, hepatic recommendations from SPC [c]Renal recommendations from Giraud et al 2023, hepatic recommendations from NLCN		

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/24 hours. Treatment suspended until < 2g/24 hours 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:

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

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

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

- 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:

Prophylactic atropine sulphate 250 micrograms subcutaneously.
Atropine should not be used in patients with glaucoma. **(See 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 are advised not to drive or operate machinery if these symptoms occur.

ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

- **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**.**

- **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 5-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.

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. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
5. NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting V6 2025. 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
6. 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
7. Irinotecan 20mg/mL Summary of Product Characteristics. Last updated: 15/10/24. Accessed November 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-044-

001_12042024135036.pdf
8. Fluorouracil 25mg/mL. Summary of Product Characteristics Accessed December 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-223-001_06122024145750.pdf
9. Aflibercept 40mg/mL (Eylea®) Summary of Product Characteristics. Accessed December 2024. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/eylea

Version	Date	Amendment	Approved By
1	10/01/2015	Initial draft	Prof Maccon Keane
2	13/04/2016	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	21/08/2020	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
5a	21/11/2023	Formatting changes and grammatical corrections.	NCCP
6	27/01/2025	Regimen reviewed. Updated diluent volume for Aflibercept. Updated baseline testing section. Updated dose modifications table to align with Giraud et al 2023. Updated regimen in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.