FOLFIRINOX Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Metastatic pancreatic cancer	C25	00329a	N/A

* This applies to post 2012 indications.

The Modified FOLFIRINOX 00515 regimen includes an indication for the metastatic setting also.

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 patient's individual clinical circumstances.

Treatment is administered every 14 days or until disease progression or unacceptable toxicity develops to a maximum of 12 cycles.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Oxaliplatin[a]	85 mg/m^2	IV	500mL 5% glucose over 2 hours immediately followed by:	Repeat every 14 days
1	Folinic Acid[b] (Calcium leucovorin)	400mg/m^2	IV infusion	250mL NaCl 0.9% over 2 hours with the addition after 30 minutes of irinotecan as below	Repeat every 14 days
1	Irinotecan	180mg/m^2	IV infusion	250mL NaCl 0.9% over 90 minutes given through a Y connector placed immediately before the injection site Immediately followed by:	Repeat every 14 days
1	5-Fluorouracil	400mg/m^2	IV Bolus	Slow push through side arm of fast flowing drip	Repeat every 14 days
1	5-Fluorouracil[c]	2400mg/m^2	Continuous IV infusion	Over 46 hours in NaCl 0.9%	Repeat every 14 days
[a] Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline. For oxaliplatin doses ≤ 104mg use 250mL glucose 5%. Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction Oxaliplatin administration must always precede the administration of 5-Fluorouracil.					
[b] A dose of 200mg/m^2 of folinic acid may be considered. 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.					
[c] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency					
Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of 5-Fluorouracil.					

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)
- Symptomatic peripheral neuropathy
- In patients known to be homozygous for UGT1A1* consideration may be given to a reduced irinotecan starting dose

EXCLUSIONS:

- Hypersensitivity to irinotecan, oxaliplatin, 5-Fluorouracil or any of the excipients
- Severe renal impairment (creatinine clearance < 30mL/min)
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and breastfeeding
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, liver and renal profile
- 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-FU or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every cycle prior to proceeding with treatment

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 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.
- The following dose reductions should be used when calculating FOLFIRINOX dose reductions for patients with toxicities

Table 1: Dose Reduction Levels for All Toxicities

	Dose Level 0	Dose Level -1	Dose Level -2*
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
5-Fluorouracil bolus	400 mg/m^2	320 mg/m^2	200 mg/m^2
5-Fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600mg/m^2
Folinic acid is delayed or omitted if bolus 5-Fluorouracil is delayed or omitted *For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.			

Haematological

- Treatment is not administered unless ANC ≥1.5 x 10^{9}L and platelets ≥75 x 10^9/L
- If levels are below this at Day 1 treatment may be delayed for 1-2 weeks
- If no recovery in 2 weeks consideration should be given to discontinuing the treatment

Table 2: Dose modification of FOLFIRINOX based on Day 1 Absolute Neutrophil Count (ANC)

	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of ANC < 1.5 x 10^9/L	Reduce dose to 150mg/m^2	Maintain full dose	Omit bolus 5-Fluorouracil
*2nd occurrence of ANC < 1.5 x 10^9/L	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	
3rd occurrence ANC < 1.5 x 10^9/L	STOP TREATMENT		

Table 3: Dose modification of FOLFIRINOX based on Day 1 Platelet Count

	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of platelets < 75 x10^9/L	Maintain full dose	Reduce to 60mg/m^2	Reduce both the bolus and infusion to 75% of the original dose
2nd occurrence of platelets < 75 x10^9/L	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	
3rd occurrence of platelets < 75 x10^9/L	STOP TREATMENT		

Table 4: Dose modification of FOLFIRINOX based on low nadir blood counts or in case of infection

	Irinotecan	Oxaliplatin	5-Fluorouracil
1st occurrence of • Febrile neutropenia	Reduce dose to 150mg/m^2	Maintain full dose	Omit bolus 5-Fluorouracil

• ANC < 0.5 x 10^9L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L			
2nd occurrence of • Febrile neutropenia • ANC < 0.5 x 10^9L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	Maintain 150mg/m^2 dose	Reduce to 60mg/m^2	
3rd occurrence • Febrile neutropenia • ANC < 0.5 x 10^9L for > 7 days • Infection with concomitant ANC < 1 x 10^9/L	STOP TREATMENT		
1st occurrence of Platelets < 50 x 10^9/L	Maintain full dose	Reduce to 60mg/m^2	Reduce both the bolus and infusion to 75% of the original dose
2nd occurrence of Platelets < 50 x 10^9/L	Reduce dose to 150mg/m^2	Maintain at 60mg/m^2	Reduce infusional dose by an additional 25%
3rd occurrence of Platelets < 50 x 10^9/L	Discontinue treatment		

*For any febrile neutropenia or a 2nd episode of ANC < 1x10^9/L. G-SCF prophylaxis should be considered for subsequent cycles.

Renal and Hepatic Impairment:

Table 5: Recommended dose modifications for patients with renal or hepatic impairment

Drug	Renal Impairment		Hepatic impairment
	CrCl (mL/min)	**Dose**	
[a]Oxaliplatin	>30	No dose adjustment is needed	No dose adjustment is needed.
	<30	Consider 50% of the original dose	
	Haemodialysis	Consider 50% of the original dose, Haemodialysis within 1·5 hour after administration.	
[b]Irinotecan	**CrCl (mL/min)**	**Dose**	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.
	≥10	No need for dose adjustment is expected	
	<10	Start with 50-66% of original dose, increase if tolerated	

	Haemodialysis	Start with 50-66% of original dose, increase if tolerated				
[c]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.			
[a]Renal and hepatic dose modifications from Giraud et al 2023 [b]Renal recommendations from Giraud et al 2023, hepatic recommendations from SPC and as agreed with clinical reviewer [c]Renal recommendations from Giraud et al 2023, hepatic recommendations from NLCN						

Management of adverse events:

Table 6: Dose Modifications for Oxaliplatin NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1-7 days	> 7 days	
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Maintain dose level	Maintain dose level	↓ 1 dose level
3 1st occurrence 2nd occurrence	 ↓ 1 dose level ↓ 1 dose level	 ↓ 1 dose level ↓ 1 dose level	Discontinue therapy
4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Laryngo-pharyngeal dysaesthesia	Maintain dose level	Increase infusion time from 2 to 6 hrs	Increase infusion time from 2 to 6 hrs

Table 7: Dose modification schedule based on non-haematological, non-neurological toxicities

Prior to a Cycle (DAY 1)	Grade of Toxicity	Dose Level for Subsequent Cycles	
		Irinotecan	5-Fluorouracil
Diarrhoea • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	
	3	↓ 1 dose level of irinotecan and infusional 5-Fluorouracil. Discontinue bolus 5-Fluorouracil and leucovorin	
	4	↓ 1 dose levels of oxaliplatin and infusional 5-Fluorouracil. Discontinue irinotecan, bolus 5-Fluorouracil and leucovorin	
Stomatitis • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced. • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	
	3	↓ 1 dose level of bolus and infusional 5-Fluorouracil	
	4	↓ 1 dose level of oxaliplatin, irinotecan and infusional 5-Fluorouracil.	

		Discontinue bolus 5- Fluorouracil and leucovorin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

This regimen poses an overall high risk of emesis.

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

Irinotecan: Moderate **(Refer to local policy)**
Oxaliplatin: 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 250micrograms 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 advised not to drive or operate machinery if these symptoms occur.

ADVERSE EFFECTS:

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

REGIMEN SPECIFIC COMPLICATIONS:

Irinotecan

- **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**.**

5-Fluorouracil

- **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. Conroy T, Desseigne F et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. NEJM 2011;364:1817-1825.
2. 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
3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting V6 2025. 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
5. HPRA Direct Healthcare Professional Communications. Medicines containing 5-fluorouracil (i.v.): In patients with moderate or severe renal impairment, phenotyping for dihydropyrimidine dehydrogenase (DPD) deficiency by measuring blood uracil levels should be interpreted with caution. Accessed February 2025. Available at: https://assets.hpra.ie/data/docs/default-source/product-updates/dhpc/human-medicines/label-for-dhpcs/medicines-containing-5-fluorouracil-(i-v-)---direct-healthcare-professional-communication-october-2024.pdf?sfvrsn=77aa96a6_1

6. Oxaliplatin 5mg/mL (Accord). Summary of Product Characteristics.Accessed February 2025. Available at: https://assets.hpra.ie/products/Human/27562/Licence_PA2315-114-001_13122024160914.pdf
7. Fluorouracil 25mg/mL. Summary of Product Characteristics Accessed February 2025 . Available at: https://assets.hpra.ie/products/Human/22124/Licence_PA0822-223-001_20012025121233.pdf
8. Irinotecan 20mg/mL Concentrate for solution for infusion. Summary of Product Characteristics Accessed February 2025.Available at: https://assets.hpra.ie/products/Human/29960/Licence_PA1986-068-001_21112022154139.pdf

Version control

Version	Date	Amendment	Approved By
1	03/06/2016		Prof Maccon Keane
2	30/05/2018	Updated with new NCCP template, standardization of treatment table, dosing in renal impairment and updated supportive care	Prof Maccon Keane
3	07/01/2020	Updated recommended dose modifications for oxaliplatin in renal impairment. Updated exclusions and drug interaction sections	Prof Maccon Keane
4	27/05/2020	Regimen reviewed	Prof Maccon Keane
5	25/08/2020	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
6	17/01/2022	Added caution for patients known to be homozygous for UGT1A1*28. Removed ATC codes.	Prof Maccon Keane
7	05/09/2022	Updated emetogenic potential	Prof Maccon Keane
7a	23/11/2023	Formatting changes and grammatical corrections.	NCCP
8	17/01/2024	Added note regarding addition of metastatic indication to NCCP Regimen 00515 modified FOLFIRINOX	Prof Maccon Keane
9	19/05/2025	Regimen reviewed. Updated eligibility and exclusions sections. Updated baseline testing section. Updated renal and hepatic dose modifications table. Regimen updated in line with NCCP standardisation.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.