

FOLFIRINOX Therapy

INDICATIONS FOR USE:

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

* This is for post 2012 indications only.

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	500mLs 5% glucose over 2 hours immediately followed by:	Repeat every 14 days
1	Folinic Acid ^b (Calcium leucovorin)	400mg/m ²	IV infusion	250mL 0.9% NaCl 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 0.9% NaCl over 90mins 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 0.9% NaCl	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/m² 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.

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ELIGIBILITY:

- Indications as above
- ECOG 0-1
- 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
- Baseline neutrophils $< 2 \times 10^9/L$ and/or platelet count $< 100 \times 10^9/L$
- Severe renal impairment (creatinine clearance $< 30\text{mL/min}$)
- Bilirubin $> 3 \times \text{ULN}$
- Chronic bowel disease and/or bowel obstruction
- Pregnancy and lactation
- Severe bone marrow failure
- CNS metastases
- 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

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.

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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
- 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 $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$
- 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
1 st occurrence of ANC $< 1.5 \times 10^9/L$	Reduce dose to 150mg/m ²	Maintain full dose	Omit bolus 5-Fluorouracil
*2 nd occurrence of ANC $< 1.5 \times 10^9/L$	Maintain 150mg/m ² dose	Reduce to 60mg/m ²	
3 rd occurrence ANC $< 1.5 \times 10^9/L$	STOP TREATMENT		

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

	Irinotecan	Oxaliplatin	5-Fluorouracil
1 st occurrence of platelets $< 75 \times 10^9/L$	Maintain full dose	Reduce to 60mg/m ²	Reduce both the bolus and infusion to 75% of the original dose
2 nd occurrence of platelets $< 75 \times 10^9/L$	Reduce dose to 150mg/m ²	Maintain at 60mg/m ²	
3 rd occurrence of platelets $< 75 \times 10^9/L$	STOP TREATMENT		

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

	Irinotecan	Oxaliplatin	5-Fluorouracil
1 st occurrence of <ul style="list-style-type: none"> • Febrile neutropenia • ANC < 0.5 x 10⁹/L for > 7 days • Infection with concomitant ANC < 1 x 10⁹/L 	Reduce dose to 150mg/m ²	Maintain full dose	Omit bolus 5-Fluorouracil
2 nd occurrence of <ul style="list-style-type: none"> • Febrile neutropenia • ANC < 0.5 x 10⁹/L for > 7 days • Infection with concomitant ANC < 1 x 10⁹/L 	Maintain 150mg/m ² dose	Reduce to 60mg/m ²	
3 rd occurrence <ul style="list-style-type: none"> • Febrile neutropenia • ANC < 0.5 x 10⁹/L for > 7 days • Infection with concomitant ANC < 1 x 10⁹/L 	STOP TREATMENT		
1 st occurrence of Platelets < 50x 10 ⁹ /L	Maintain full dose	Reduce to 60mg/m ²	Reduce both the bolus and infusion to 75% of the original dose
2 nd occurrence of Platelets < 50x 10 ⁹ /L	Reduce dose to 150mg/m ²	Maintain at 60mg/m ²	Reduce infusional dose by an additional 25%
3 rd occurrence of Platelets < 50x 10 ⁹ /L	Discontinue treatment		

*For any febrile neutropenia or a 2nd episode of ANC < 1x10⁹/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				
Oxaliplatin	>30	Treat at normal dose and monitor renal function	Little information available. Probably no dose reduction necessary.			
	<30	Contraindicated				
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	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.			

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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			
1 st occurrence	↓ 1 dose level	↓ 1 dose level	Discontinue therapy
2 nd occurrence	↓ 1 dose level	↓ 1 dose level	
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 <ul style="list-style-type: none"> ≥ 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 <ul style="list-style-type: none"> ≥ 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.

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

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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.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.

Oxaliplatin

- **Platinum Hypersensitivity:** Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-Fluorouracil.
- **Extravasation:** Oxaliplatin causes irritation if extravasated (**Refer to local policy**).
- **Venous occlusive disease:** A rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with 5-Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should

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be instructed to report any jaundice, ascites or haematemesis immediately.

- **Haemolytic Uraemic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

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.
- **Diarrhoea** - Irinotecan induced diarrhoea can be life threatening and requires immediate management.
 - Diarrhoea (early onset) - see acute cholinergic syndrome above.
 - Diarrhoea (late onset):
 - Irinotecan induced diarrhoea can be life threatening and requires immediate management.
 - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.
 - Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥ 2 and women.
 - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles.
 - The SmPC (7) provides guidelines on when hospitalisation for the management of diarrhoea is recommended.
- **Extravasation:** Irinotecan causes pain and tissue necrosis if extravasated (**Refer to local extravasation guidelines**).
- **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients.
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.

5-Fluorouracil

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **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

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(TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.

- **Hand-foot syndrome (HFS)**, also known as palmar-plantar erythrodysesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

DRUG INTERACTIONS:

- 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 5-Fluorouracil regimens.
- Concurrent administration of 5-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 DPD. Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

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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	25/8/2020	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 erythrodysesthesia	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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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