

Panitumumab 6mg/kg and Modified FOLFOX-6 Therapy – 14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
First line treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC)	C18 C19 C20	00447a	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 patient's individual clinical circumstances.

Treatment is administered once every 14 days until disease progression or unacceptable toxicity occurs.

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

Admin Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	Panitumumab	6mg/kg	IV infusion	¹ 100ml 0.9% NaCl over 60min ² using a 0.22 micron in-line filter	Every 14 days
¹ In 150ml over 90min if dose > 1000mg Final concentration should not exceed 10mg/ml ² If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes Panitumumab is incompatible with glucose solutions, Ensure IV administration sets are flushed with sodium chloride 0.9% pre and post administration.						
2	1	Oxaliplatin	85mg/m ²	IV infusion	³ 500ml glucose 5% over 2hrs	Every 14 days
3	1	Folinic Acid (Calcium leucovorin)	400mg/m ²	IV infusion	250ml glucose 5% over 2hrs	Every 14 days
4	1	5-Fluorouracil	400mg/m ²	IV BOLUS		Every 14 days
5	1	5-Fluorouracil ⁴	2400mg/m ²	Continuous IV infusion	Over 46h in 0.9% NaCl.	Every 14 days
³ Oxaliplatin is incompatible with 0.9% NaCl. 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 Oxaliplatin may be given at the same time as Folinic Acid (Calcium Leucovorin) using a Y connector.						
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. 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.						
⁴ See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.						

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ELIGIBILITY:

- Indications as above
- Wild type RAS tumours verified by a validated test method
- ECOG 0-2
- Adequate marrow reserve
- Adequate renal and liver function

EXCLUSIONS:

- Hypersensitivity to panitumumab, oxaliplatin, folinic acid, 5-Fluorouracil or to any of the excipients
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Patients with interstitial pneumonitis or pulmonary fibrosis
- Renal impairment
- Hepatic impairment
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile prior to each treatment
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last panitumumab 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:

- 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

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- Panitumumab or Modified FOLFOX-6 therapy may be delayed independently of each other and dosing may continue with either component but consideration should be given to the timings of further treatment
- The following dose reductions should be used when calculating FOLFOX dose reductions for patients with toxicities (Table 1)

Table 1: Dose Reduction Levels of Modified FOLFOX-6 for All Toxicity

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Oxaliplatin	85 mg/m ²	65 mg/m ²	50 mg/m ²	Discontinue
Folinic Acid (Calcium Leucovorin)	400 mg/m ²	400 mg/m ²	400 mg/m ²	Discontinue
5-Fluorouracil bolus	400 mg/m ²	320 mg/m ²	260 mg/m ²	Discontinue
5-Fluorouracil infusion	2400 mg/m ²	1900 mg/m ²	1500 mg/m ²	Discontinue

Note: Folinic acid is delayed or omitted if bolus 5-Fluorouracil is delayed or omitted

Haematological:

Table 2: Dose Modifications of Modified FOLFOX-6 for Haematological Toxicity

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	ANC (x 10 ⁹ /L)	Oxaliplatin	5-Fluorouracil
<ul style="list-style-type: none"> • If ANC < 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks. • ANC ≥ 1.5 within 4 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment. 	1	≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	Maintain dose level
	4	<0.5	↓ 1 dose level	Omit bolus and ↓1 infusion dose level
	Grade	Platelets (x10 ⁹ /L)	Oxaliplatin	5-Fluorouracil
<ul style="list-style-type: none"> • If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 4 weeks. • Platelets ≥ 75 within 4 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remain <75 after 4 weeks discontinue treatment. 	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	Maintain dose level
	4	<10	↓ 2 dose levels	Maintain dose level

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Renal and Hepatic Impairment:

Table 3: Dose Modifications in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Panitumumab	No studies have been performed in patients with renal impairment.		No studies have been performed in patients with hepatic impairment.			
Oxaliplatin	CrCl (ml/min)	Dose	Little information available. Probably no dose reduction necessary: Clinical decision			
	≥30	Treat at normal dose and monitor renal function				
	<30	contraindicated				
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.			

Management of adverse events:

Table 4: Dose modification schedule of panitumumab based on skin reactions.

Occurrence of skin symptom(s): ≥ grade 3	Administration of panitumumab	Outcome	Dose regulation
Initial occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 100% original dose
		Not recovered	Discontinue
2 nd occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 80% of original dose
		Not recovered	Discontinue
3 rd occurrence	Hold 1 or 2 doses	Improved (< grade 3)	Continue infusion at 60% of original dose
		Not recovered	Discontinue
4 th occurrence	Discontinue		

Local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions should be instigated as appropriate.

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Table 5: Dose modification schedule based on adverse events

Adverse reaction	Recommended dose modification
Panitumumab	
Infusion reaction	Decrease infusion rate of panitumumab and maintain lower rate for subsequent infusions
Severe infusion reaction	Discontinue
Interstitial lung disease	Discontinue
Oxaliplatin	
*Peripheral neuropathy Grade 2 present at start of cycle Grade 3 <ul style="list-style-type: none"> • First occurrence • 2nd occurrence • Persistent Grade 4	Reduce oxaliplatin by 1 dose level ↓ 1 dose level ↓ 1 dose level Discontinue oxaliplatin Discontinue oxaliplatin
Laryngopharyngeal dysaesthesia	Increase infusion time from 2 to 6 hrs
Stomatitis	Delay treatment until stomatitis reaches level of grade 1 or less
Unexplained respiratory symptoms e.g. Non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates	Discontinue oxaliplatin until interstitial disease or pulmonary fibrosis excluded.

*Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re- challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed.

Table 6: Dose modification of mFOLFOX-6 for diarrhoea

Prior to a Cycles (DAY 1)	TOXICITY		Dose Level for Subsequent Cycles	
	Grade	Diarrhoea	Oxaliplatin	5-Fluorouracil
<ul style="list-style-type: none"> • If diarrhoea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 4 times. • If diarrhoea is less than Grade 2 within 4 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If diarrhoea remains greater than or equal to Grade 2 after 4 weeks, discontinue treatment. 	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level of IV push and infusional 5-Fluorouracil
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 1 dose level of IV push and infusional 5-Fluorouracil

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Oxaliplatin Moderate **(Refer to local policy).**
 5-Fluorouracil Low **(Refer to local policy).**
 Panitumumab Low **(Refer to local policy).**

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE:

See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions. Anti-diarrhoeal treatment may be required **(Refer to local policy).**

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 aggressively.

Panitumumab

- **Infusion-related reactions:**
 - In cases of mild or moderate infusion-related reaction, the infusion rate may be decreased and maintained at the lower rate in all subsequent infusions.
 - Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of panitumumab therapy and may necessitate emergency treatment.
 - Hypersensitivity reactions occurring more than 24 hours after infusion have been reported. Patients should be warned of the possibility of such a late onset and instructed to contact their physician if symptoms occur.
- **Respiratory disorders:** Interstitial lung disease (ILD) has been observed with EGRF inhibitors. Treatment should be withheld in the event of onset or worsening respiratory symptoms. If ILD is confirmed, treatment should be discontinued.
- **Acute renal failure:** This has been observed in patients who develop severe diarrhoea and dehydration.
- **Skin reactions:** This is the main adverse reaction of panitumumab. Refer to local policy for skin care regime and to Table 4 under Dose Modifications for management of treatment if patient experiences skin reactions.
- **Electrolyte disturbances:** Hypomagnesaemia, hypokalaemia or hypocalcaemia may occur. Electrolyte repletion is recommended, as appropriate.
- **Ocular toxicities:** Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is

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confirmed, treatment should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

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.
- **Haemolytic Uremic 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.
- **Extravasation:** Oxaliplatin causes irritation if extravasated (**Refer to local policy**).

5-Fluorouracil

- **Gastrointestinal toxicity:** Patients treated with 5-Fluorouracil should be closely monitored for diarrhea and managed appropriately.
- **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 (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome (HFS):** 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:

- No formal drug-drug interaction studies have been conducted with panitumumab.
- Panitumumab should not be administered in combination with IFL chemotherapy or with bevacizumab-containing chemotherapy.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimens.

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- 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	Date	Amendment	Approved By
1	23/10/2017		Prof Maccon Keane
2	09/10/2019	Reviewed. Standardisation of treatment table. Update of eligibility criteria, drug interactions, emetogenic potential. Removal of company support resources.	Prof Maccon Keane
3	12/02/2020	Standardisation of treatment table. Updated exclusions. Updated recommended dose modifications for oxaliplatin in renal impairment.	Prof Maccon Keane
4	26/02/2020	Standardisation of treatment table. Update of diluent of Folinic Acid to glucose 5%	Prof Maccon Keane
5	1/9/2020	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	21/12/2021	Reviewed. Added to exclusions and adverse effects.	Prof Maccon Keane
6a	21/11/2023	Formatting changes and grammatical corrections.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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