# Panitumumab 6mg/kg and FOLFIRI Therapy-14 day

## INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC)</td>
<td>C18</td>
<td>00448a</td>
<td></td>
</tr>
<tr>
<td>Second line treatment of adult patients with wild-type RAS mCRC who have received first-line fluoropyridine–based chemotherapy (excluding irinotecan)</td>
<td>C18</td>
<td>00448b</td>
<td></td>
</tr>
</tbody>
</table>

*If a reimbursement indicator (e.g. ODMS, CDS) is not defined, the drug and its detailed indication have not been assessed through the formal HSE reimbursement process.*

## 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 until disease progression or unacceptable toxicity develops.

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

<table>
<thead>
<tr>
<th>Admin. Order</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Panitumumab</td>
<td>6mg/kg</td>
<td>IV infusion</td>
<td>100ml 0.9% sodium chloride over 60min using a 0.22 micron in-line filter</td>
<td>Every 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>In 150ml over 90min if dose &gt; 1000mg. Final concentration should not exceed 10mg/ml</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Panitumumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Panitumumab is incompatible with glucose solutions.</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Ensure IV administration sets are flushed with sodium chloride 0.9% pre and post administration.</em></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Irinotecan</td>
<td>180mg/m²</td>
<td>IV infusion</td>
<td>500ml glucose 5% over 90mins</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Folinic Acid (Calcium leucovorin)</td>
<td>400mg/m²</td>
<td>IV infusion</td>
<td>250ml glucose 5% over 2hrs</td>
<td>Every 14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><em>Flush line with glucose 5% before administering S-FU</em></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Fluorouracil (S-FU)</td>
<td>400mg/m²</td>
<td>IV BOLUS</td>
<td>Slow push through side arm of fast flowing drip</td>
<td>Repeat every 14 days</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Fluorouracil</td>
<td>2400mg/m²</td>
<td>Continuous IV infusion</td>
<td>Over 46h in glucose 5% or 0.9% NaCl</td>
<td>Repeat every 14 days</td>
</tr>
</tbody>
</table>

*In 150ml over 90min if dose > 1000mg. Final concentration should not exceed 10mg/ml

*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.

*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.*

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NCCP Regimen: Panitumumab 6mg/kg and FOLFIRI Therapy-14 day
Published: 23/10/2017
Reviewed: 23/10/2019
Version number: 1

Tumour Group: Gastrointestinal
NCCP Regimen Code: 00448

ISMO Contributor: Prof Maccon Keane

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NCCP Chemotherapy Regimen

ELIGIBILITY:
- Indications as above
- Wild type RAS tumours verified by a validated test method
- 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 panitumumab, irinotecan or any of the excipients.
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Baseline neutrophils < 2 x 10^9/L and/or platelet count < 100 x 10^9/L.
- Renal impairment
- Hepatic impairment
- Patients with interstitial pneumonitis or pulmonary fibrosis
- Chronic bowel disease and/or bowel obstruction.
- Pregnancy and breast feeding

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).

Regular tests:
- FBC, liver and renal profile prior to each cycle
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last panitumumab treatment.
- 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
- Panitumumab or FOLFIRI 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.
- Irinotecan should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading and when treatment-related diarrhoea is fully resolved.
- At the start of a subsequent infusion of therapy, the dose of irinotecan and fluorouracil, should be decreased according to the worst grade of adverse events observed in the prior infusion.
- Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

The following dose reductions should be used when calculating FOLFIRI dose reductions for patients with toxicities

<table>
<thead>
<tr>
<th>Table 1: Dose Reduction Levels for All Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Level 0</strong></td>
</tr>
<tr>
<td>Irinotecan</td>
</tr>
<tr>
<td>Folinic Acid (Calcium Leucovorin)</td>
</tr>
<tr>
<td>Fluorouracil bolus</td>
</tr>
<tr>
<td>Fluorouracil infusion</td>
</tr>
</tbody>
</table>

Note: Folinic acid is delayed or omitted if bolus fluorouracil is delayed or omitted

NCCP Regimen: Panitumumab 6mg/kg and FOLFIRI Therapy -14 day
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Version number: 1
Table 2: Dose Modification of FOLFIRI for Haematological Toxicity

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade</td>
<td>ANC (x 10^9/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If ANC&lt; 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks</td>
<td>1</td>
<td>≥ 1.5</td>
</tr>
<tr>
<td>• ANC ≥ 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s).</td>
<td>2</td>
<td>1.0-1.49</td>
</tr>
<tr>
<td>• If ANC remains &lt;1.5 after 4 weeks discontinue treatment</td>
<td>3</td>
<td>0.5-0.99</td>
</tr>
<tr>
<td>• Grade 4 neutropenia and grade≥2 fever</td>
<td>4</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

The use of granulocyte colony-stimulating factor (G-CSF) may be considered.

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in patients with renal or hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab</td>
<td>No studies have been performed in patients with renal impairment.</td>
<td>No studies have been performed in patients with hepatic impairment.</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>No dose reduction needed, however use with caution as no information in this setting.</td>
<td>Irinotecan is contraindicated in patients with bilirubin levels &gt; 3 x ULN.</td>
</tr>
<tr>
<td>5-FU</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td>&lt;85</td>
<td>&lt;180</td>
</tr>
<tr>
<td></td>
<td>&gt;85 or &gt;180</td>
<td>CI</td>
</tr>
</tbody>
</table>

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 for FOLFIRI based on adverse events

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Grade of Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irinotecan</td>
<td>Fluorouracil</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ Grade 2, hold treatment max of 2 weeks</td>
<td>1 and 2</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>• &lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the highest grade experienced</td>
<td>3</td>
<td>↓ 1 dose level</td>
</tr>
<tr>
<td>• Remains ≥ Grade 2 after 2 weeks, discontinue treatment</td>
<td>4</td>
<td>↓ 2 dose levels</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥ Grade 2, hold treatment max of 2 weeks</td>
<td>1 and 2</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>• &lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the highest grade experienced.</td>
<td>3</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>• Remains ≥ Grade 2 after 2 weeks, discontinue treatment</td>
<td>4</td>
<td>Maintain dose level</td>
</tr>
</tbody>
</table>

Table 5: Dose modification schedule of panitumumab based on skin reactions.
Local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions should be instigated as appropriate.

<table>
<thead>
<tr>
<th>Occurrence of skin symptom(s): ≥ grade 3</th>
<th>Administration of panitumumab</th>
<th>Outcome</th>
<th>Dose regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial occurrence</td>
<td>Hold 1 or 2 doses</td>
<td>Improved (&lt; grade 3)</td>
<td>Continue infusion at 100% original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recovered</td>
<td>Discontinue</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Hold 1 or 2 doses</td>
<td>Improved (&lt; grade 3)</td>
<td>Continue infusion at 80% of original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recovered</td>
<td>Discontinue</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Hold 1 or 2 doses</td>
<td>Improved (&lt; grade 3)</td>
<td>Continue infusion at 60% of original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recovered</td>
<td>Discontinue</td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6: Dose modification schedule for panitumumab based on adverse events

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>Decrease infusion rate of panitumumab and maintain lower rate for subsequent infusions</td>
</tr>
<tr>
<td>Severe infusion reaction</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (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:
See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse
Oral pyridoxine 50mg three times a day when required for the relief of palmar- plantar erythrodysesthesia.
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.

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

**FOLFIRI**

- **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 (4) provides guidelines on when hospitalisation for the management of diarrhoea is recommended.
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **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.
- **Myocardial ischaemia and angina**: Cardiotoxicity is a serious complication during treatment with

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flourouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.

- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.
- **Palmar Plantar Erythrodysesthesia (PPE):** This has been reported as an unusual complication of high dose bolus or protracted continuous therapy with 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.
- 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 regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 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:**

- Panitumumab - L01XC07
- Irinotecan - L01XX19
- 5-Fluourouracil - L01BC02
- Folinic acid - V03AF03

**COMPANY SUPPORT RESOURCES/Useful Links:**

*Please note that this is for information only and does not constitute endorsement by the NCCP*


**REFERENCES:**

2. BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Leucovorin GIFOFLIRI
NCCP Chemotherapy Regimen


Version control

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23/10/2017</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/proinfo/medonc/cdmp/

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