**Regimen Monograph**



## A - Regimen Name

# FOLFIRI+PNTM Regimen

**Folinic acid (leucovorin)-Fluorouracil-Irinotecan-Panitumumab**

**Disease Site**

Gastrointestinal
- Colorectal
- Small bowel and appendix

**Intent**

Palliative

**Regimen Category**

**Evidence-Informed :**

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

**Rationale and Uses**

- First-line* treatment for patients with wild-type RAS metastatic colorectal (mCRC), small bowel or appendiceal cancer, who have a contraindication or intolerance to bevacizumab and who would otherwise be treated with combination chemotherapy alone
- First-line* treatment for patients with wild-type RAS and BRAF left-sided mCRC

*Or second-line treatment for patients who received pembrolizumab as first-line

(Refer to NDFP eligibility forms for detailed funding criteria.)

| | |
|---|---|
| **Supplementary Public Funding** | **PANitumumab**<br>New Drug Funding Program (Panitumumab - In Combination with Chemotherapy for Metastatic Colorectal, Small Bowel, or Appendiceal Cancer) (NDFP Website )<br><br>**PANitumumab**<br>New Drug Funding Program (Panitumumab - First-Line Treatment for Left-Sided Metastatic Colorectal Cancer) (NDFP Website ) |

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## B - Drug Regimen

| | | | |
|---|---|---|---|
| **PANitumumab** | 6 mg /kg | IV | Day 1 |
| **irinotecan** | 180 mg /m² | IV over 90 minutes | Day 1 |
| **leucovorin** | 400 mg /m² | IV over 120 minutes concurrently with irinotecan | Day 1 |
| **fluorouracil**<br>***THEN*** | 400 mg /m² | IV bolus, after leucovorin | Day 1 |
| **fluorouracil** | 2400 mg /m² | IV continuous infusion over 46 hours only | Start on Day 1 |

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## C - Cycle Frequency

**REPEAT EVERY 2 WEEKS**

Until evidence of disease progression or unacceptable toxicity

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## D - Premedication and Supportive Measures

**Antiemetic Regimen:** Moderate

- Also refer to CCO Antiemetic Recommendations.

**Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.

**Other Supportive Care:**

Irinotecan:

- Unless contraindicated, atropine 0.25-1mg IV/SC may be used for cholinergic adverse effects (early diarrhea).
- Diarrhea (abdominal cramp = diarrhea) may be severe and delayed with Irinotecan; use Loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours.
- Patients with ileus, fever or febrile neutropenia should receive antibiotics.

5-fluorouracil:

- May advise patients to suck on ice chips during bolus injection of 5-FU to reduce stomatitis.

Panitumumab:

The following has been shown to be of benefit (in a randomized phase 2 study for prevention of rash) when used from day -1 to week 6:

- Skin moisturizer applied to the face, hands, feet, neck, back and chest in the morning
- Sunscreen to exposed areas (SPF 30; UVA and UVB) in the morning
- Hydrocortisone cream (1%) to the face, hands, feet, neck, back and chest at bedtime
- Doxycycline (or minocycline) PO

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## E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

**Dosage with toxicity**

Dose Levels:

| Regimen | Drug | Starting dose | Dose level -1 | Dose Level -2 |
|---|---|---|---|---|
| PNTM | Panitumumab | 6 mg/kg | 80% original dose | 60% original dose |
| FOLFIRI | Irinotecan | 180 mg/m$^2$ | 150 mg/m$^2$ | 120 mg/m$^2$ |
| | Leucovorin infusion | 400 mg/m$^2$ | No change | No change |
| | 5-FU bolus | 400 mg/m$^2$ | 320 mg/m$^2$ | 240 mg/m$^2$ |
| | 5-FU infusion (start day 1 over 46 h) | 2400 mg/m$^2$ | 2000 mg/m$^2$ | 1600 mg/m$^2$ |

Patients should not be re-treated with irinotecan until recovery from GI toxicity to baseline (without loperamide for at least 24 hours) has occurred, platelets ≥ 100 x $10^9$/L, and ANC ≥ 1.5 x $10^9$/L. All dose adjustments should be based on the worst preceding toxicity.

Do not use in patients with ECOG PS of 3 or 4, nor in patients with moderate or severe increases in bilirubin.

Consider a reduction in the starting dose of irinotecan for elderly patients (≥ 70 years), patients with prior abdominal or pelvic irradiation, patients with a poor performance status (ECOG of 2), patients with mild increases in bilirubin (including Gilbert's syndrome), patients homozygous for UGT1A1*28 allele or patients with a history of myelosuppression with previous treatment.

Dose adjustments for FOLFIRI

| Toxicity Grade | Day 1 dose* of irinotecan and 5-fluorouracil |
|---|---|
| **Hematologic** | |
| ≤ Grade 2 | no change |
| Grade 3 | reduce by 1 dose level |
| Grade 4 or febrile neutropenia | reduce by 2 dose levels |
| **Diarrhea** | |
| ≤ Grade 2: 4-6/day > pre-treatment | no change |
| Grade 3: 7-9/day > pre-treatment | reduce by 1 dose level |
| Grade 4: ≥ 10/day > pre-treatment | reduce by 2 dose levels |
| **Other Non-hematologic toxicities (excludes alopecia, anorexia and fatigue)**<br><br>**For mucositis/stomatitis, decrease 5-FU only** | |
| ≤ Grade 2 | hold until ≤ grade 1, no change in dose |
| Grade 3 | hold until ≤ grade 2; reduce by 1 dose level |
| Grade 4 | hold until ≤ grade 2; reduce by 2 dose levels |
| *Relative to the starting dose used in the previous cycle. Patients should not be retreated until GI toxicity resolved to baseline (without loperamide for at least 24 h), platelets ≥ 100 x $10^9$/L, and ANC ≥ 1.5 x $10^9$/L. If no recovery after a 2-week delay, consider discontinuing treatment. | |

Dosage adjustments for panitumumab

| Toxicity | Action | Panitumumab dose (% previous dose) |
|---|---|---|
| ≥ grade 3 skin (1st occurrence) | Hold until ≤ grade 2* | Restart at 100% |
| ≥ grade 3 skin (2nd occurrence) | Hold until ≤ grade 2* | Restart at 80% |
| ≥ grade 3 skin (3rd occurrence) | Hold until ≤ grade 2* | Restart at 60% |
| ≥ grade 3 skin (4th occurrence) | Discontinue | n/a |
| Skin or soft tissue with severe or life-threatening inflammatory or infectious complications | Hold or discontinue, depending on severity | n/a |
| SJS/TEN | Discontinue | n/a |
| ≥ grade 3 diarrhea or dehydration | Hold until ≤ grade 2 | Consider dose reduction, if appropriate |
| ILD/pneumonitis | Hold and investigate | If confirmed, discontinue. |
| Mild to moderate hypersensitivity | ↓ Infusion rate by 50% | n/a |
| Severe hypersensitivity | Hold and consider discontinuing permanently | n/a |
| Keratitis or ulcerative keratitis | Hold or discontinue, depending on severity or persistence | n/a |
| *Hold for 1 to 2 doses until recovery. Discontinue if no recovery within 4 weeks. | | |

## Hepatic Impairment

No dosage adjustment is required for leucovorin. Omit leucovorin if 5-fluorouracil is omitted.

| **Bilirubin** [1] | | **Transaminases** | **Irinotecan** | **5-fluorouracil (% previous dose)** | **Panitumumab** |
|---|---|---|---|---|---|
| 1-1.5 x ULN or Gilbert's syndrome | | | monitor closely; may consider dose reduction | no change | no data |
| < 2 x ULN | AND | 3-5 x ULN* | monitor closely; may consider dose reduction | 75% | no data |
| 2-4 x ULN | OR | 5-10 x ULN | omit | 50-75% | no data |
| ≥ 4 x ULN | OR | > 10 x ULN | omit | omit | no data |

[1]Consider investigating for reversible causes such as biliary obstruction and re-evaluate after stent.
*Or 5 x ULN with liver metastases

## Renal Impairment

Acute renal failure has been observed in patients experiencing severe diarrhea and dehydration (see dosage with toxicity table for management). No dosage adjustment is required for leucovorin.

| **Creatinine clearance (ml/min)** | **Irinotecan** | **5-fluorouracil** | **Panitumumab** |
|---|---|---|---|
| > 60 | no change | no change | no change |
| 30-60 | caution; no data | no change | no data |
| < 30 | caution; no data | caution; consider dose reduction | no data |

**Dosage in the Elderly**

Monitor patients ≥ 65 years closely for increased risk of diarrhea with irinotecan.

No overall differences in safety or efficacy with panitmumab were observed in patients aged 65 and older compared to younger patients. No dose modifications are required, however patients ≥ 65 years have more eye, skin, GI toxicities and fatigue, compared to younger patients when receiving panitumumab as a single agent or in combination with FOLFOX.

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## F - Adverse Effects

Refer to irinotecan, leucovorin, fluorouracil, fluorouracil, PANitumumab drug monograph(s) for additional details of adverse effects.

| Very common (≥ 50%) | Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|---|---|---|
| • Rash (may be severe)<br>• Increased LFTs (may be severe)<br>• Nausea, vomiting<br>• Fatigue<br>• Alopecia<br>• Abdominal pain<br>• Anorexia, weight loss<br>• Diarrhea (may be severe)<br>• EKG changes | • Abnormal electrolytes (hypomagnesemia)<br>• Paronychia<br>• Constipation<br>• Myelosuppression +/- infection, bleeding (may be severe) | • Skin fissures<br>• Cough, dyspnea<br>• Insomnia<br>• Headache<br>• Dizziness<br>• Musculoskeletal pain<br>• Mucositis<br>• Hand-foot syndrome<br>• Edema<br>• Abnormal eyelash growth | • GI obstruction / perforation<br>• Hemorrhage<br>• Hypersensitivity<br>• Renal failure<br>• Arterial / venous thromboembolism<br>• Cardiotoxicity<br>• Arrhythmia<br>• Pancreatitis<br>• Pneumonitis<br>• Hemolytic uremic syndrome<br>• Leukoencephalopathy<br>• Eye disorders<br>• Radiation recall<br>• Soft tissue necrosis<br>• Tumour lysis syndrome |

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## G - Interactions

Refer to irinotecan, leucovorin, fluorouracil, PANitumumab drug monograph(s) for additional details.

- Azole antifungals are contraindicated with irinotecan. Discontinue at least 1 week before starting irinotecan.
- Avoid concomitant use of CYP3A4 inhibitors with irinotecan; if must use, adjust irinotecan dose.
- Avoid concomitant use of CYP3A4 inducers with irinotecan. Switch to non-enzyme inducing anticonvulsants and discontinue St. John's wort at least 1 week prior to irinotecan.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during irinotecan treatment.
- Avoid concomitant use with laxatives, curcumin, neuromuscular blockers, prochlorperazine, atazanavir and other protease inhibitors with irinotecan.
- Monitor INR with warfarin and drug levels with phenytoin and adjust doses as needed.

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## H - Drug Administration and Special Precautions

Refer to irinotecan, leucovorin, fluorouracil, PANitumumab drug monograph(s) for additional details.

**Administration**

**Irinotecan:**

- Mix in 500mL bag (D5W-preferred or NS) in a concentration range between 0.12 to 3 mg/mL; infuse IV over 90 minutes
- Do not refrigerate admixtures in NS (may result in precipitation)
- Avoid freezing irinotecan and its admixtures since this may result in drug precipitation.
- Do not admix with other drugs
- Protect from light
- Prior to the initial irinotecan treatment, patients should be given a sufficient supply of loperamide and instructed on its appropriate use.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during irinotecan treatment
- Irinotecan and leucovorin may be infused at the same time by using a y-connector, but not in the same bag, then fluorouracil.

**Leucovorin:**

- May be mixed in 50mL Normal Saline or 5% Dextrose minibag (doses up to 500mg) or 100mL minibag (doses >500mg) or in 100mL fluid in graduated administration set (5% Dextrose, Normal Saline or 2/3-1/3); Give over 15 minutes.
- Continuous infusion using CADD pump or similar device.
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

**Fluorouracil:**

IV PUSH OR INTERMITTENT INFUSION:

- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline)
- May be mixed in 50mL minibag (NS or D5W); infuse over 15 min.
- Protect from light.

IV CONTINUOUS INFUSION:

- Continuous infusion using CADD infusion pump, or similar device
- Infuse through central venous access device, if available
- Infusion volume and duration depend on protocol.
- Protect from light
- Infuse through patent peripheral venous catheter, if infusion for only 3-5 days; Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed between administrations of fluorouracil and these agents

**PANitumumab:**

- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS; MUST be administered using an IV infusion pump.
- Diluted with 0.9% sodium chloride only. Do not mix with other drugs or IV solutions.
- Dilute in a total volume of 100mL in sodium chloride 0.9% (Final concentration must be less than 10mg/mL). Infuse IV over 60 minutes. May give via peripheral line or in-dwelling catheter. If the first infusion is tolerated, subsequent infusions may be given over 30 to 60 minutes.
- Doses higher than 1000mg should be diluted in 150mL 0.9% sodium chloride injection, and infused IV over 90 minutes.
- Compatible with 0.9% sodium chloride in PVC bags or polyolefin bags
- Administer using a low-protein binding 0.2 micron or 0.22 micron in-line filter.
- Solution may contain a small amount of visible, amorphous, panitumumab particulates that will be removed by the low protein binding in-line filter during infusion.
- Do not shake. Mix diluted solution by gentle inversion.
- Flush line before and after administration with 0.9% sodium chloride.
- Keep vials refrigerated in the original carton. Protect from direct sunlight and do not freeze.

- The manufacturer recommends diluted solutions to be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C.

**Contraindications:**

- Patients with a known hypersensitivity to any drug in this regimen, or any excipients
- Patients with ECOG performance status of 3 or 4
- Patients with moderate to severe hepatic dysfunction
- Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Irinotecan should not be co-administered with azole antifungals (see Interactions section)
- Avoid in patients with hereditary fructose intolerance as irinotecan contains sorbitol
- Leucovorin is not to be administered for the treatment of pernicious anemia or other megaloblastic anemias where vitamin $B_{12}$ is deficient. Hematologic remission may occur while neurologic manifestations continue to progress. It is contraindicated for intrathecal use.
- Do not use panitumumab in combination with bevacizumab.

**Warnings / precautions:**

- Avoid the use of live or live attenuated vaccines
- Use with extreme caution in patients who are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- In a phase III panitumumab trial, patients with ECOG 2 had increased toxicity and shortened survival compared to those with ECOG 0-1. Assess risk vs. benefit prior to treatment in patients with ECOG 2.
- Elderly patients, patients with limited marrow reserve, 3rd space accumulation, Gilbert's syndrome and patients with reduced UGT1A1 activity may be more susceptible to the toxic effects of irinotecan; they should be carefully monitored and dose reduction considered.
- The concurrent administration of irinotecan with irradiation is not recommended. Patients with prior pelvic or abdominal irradiation are at an increased risk of severe myelosuppression following irinotecan therapy.
- Use with caution in patients with serious infections, poor nutritional state, those who have undergone recent major surgery, with renal or hepatic impairment, or widespread bone marrow involvement.
- Use with caution in patients with a history of pulmonary fibrosis or ILD.
- Use with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.
- If patients experience treatment-related effects on vision and/or ability to concentrate and react, they should not drive or operate machinery until the effect subsides.
- The panitumumab formulation contains 0.15 mmol sodium (= 3.45 mg sodium) per mL of concentrate. This sodium content should be taken into consideration in patients on sodium restriction.

**Pregnancy and lactation:**

- This regimen is CONTRAINDICATED in pregnancy as it may cause fetal harm. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- As maternal IgG is excreted in milk, discontinue breastfeeding during panitumumab therapy and for 2 months following the last dose.

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## I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and before each dose
- Liver and renal function tests; baseline and before each dose
- Electrolytes (including calcium, magnesium and potassium); baseline and at each visit, until 8 weeks after completion of therapy
- Clinical pulmonary exam; Baseline and clinically as indicated
- Clinical assessment and grading of GI, skin and respiratory effects, infusion reactions, infection, bleeding, cardiac and ophthalmic effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Blood glucose, especially in patients with diabetes; Baseline and regular
- Pulmonary function tests; Baseline

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## J - Administrative Information

| | |
|---|---|
| Approximate Patient Visit | 3.5 hours |
| Pharmacy Workload (average time per visit) | 37.403 minutes |
| Nursing Workload (average time per visit) | 61.667 minutes |

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## K - References

Bond MJG, Bolhuis K, Loosveld OJL, et al. First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group. Lancet Oncol. 2023 Jul;24(7):757-771.

CADTH Reimbursement Recommendation: Panitumumab Solution for IV Infusion. Canada's Drug and Health Technology Agency. April 2024.

Fluorouracil drug monograph, Ontario Health (Cancer Care Ontario).

Irinotecan drug monograph, Ontario Health (Cancer Care Ontario).

Leucovorin drug monograph, Ontario Health (Cancer Care Ontario).

Panitumumab drug monograph, Ontario Health (Cancer Care Ontario).

Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28(31):4706-13.

Shitara K, Yonesaka K, Denda T, et al. Randomized study of FOLFIRI plus either panitumumab or bevacizumab for wild-type KRAS colorectal cancer-WJOG 6210G. Cancer Sci. 2016 Dec;107(12):1843-1850.

### PEBC Advice Documents or Guidelines

- The Role of Primary Tumour Location in the Selection of Biologics for the Treatment of Unresectable Metastatic Colorectal Cancer

**January 2025** Updated Rationale and Uses section; added NDFP forms; updated DPD deficiency information in the Dose Modifications and Special Precautions sections; added fluorouracil antidote info to the Other Notes section

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## L - Other Notes

**Antidote for Fluorouracil Overdose:**

**Uridine triacetate** is a prodrug of uridine and is a specific antidote for treating fluorouracil overdose or severe early onset toxicities. If available, consider administering as soon as possible (i.e. within 96 hours) for suspected overdose. If not available, treatment is symptomatic and supportive.

For usage approval and supply, contact Health Canada's Special Access Program (SAP) (Phone: 613-941-2108. On-call service is available for emergencies).

The recommended dosing and administration for **uridine triacetate** in patients ≥18 years is:

- 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total, without regards to meals.
- Granules should not be chewed. They should be mixed with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt.
- The dose should be ingested within 30 minutes of preparation, followed by at least 4 ounces of water.
- Refer to the prescribing information on dose preparation for NG-tube or G-tube use.

Additional resources on the management of fluorouracil infusion overdose:

- Management of Fluorouracil Infusion Overdose Guideline (Alberta Health Services)
- Management of Fluorouracil Infusion Overdose at the BCCA - Interim Guidance (BC Cancer Agency)

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## M - Disclaimer

***Regimen Abstracts***

*A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.*

*Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.*

***Regimen Monographs***

*Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.*

*The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.*

*The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.*

*Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.*

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