Regimen Monograph

A - Regimen Name

RALT Regimen

Raltitrexed

Disease Site

Gastrointestinal
- Colorectal
- Esophagus
- Gastric / Stomach
- Small bowel and appendix

Intent

Adjuvant
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

- For adjuvant or palliative treatment of colorectal, small bowel, appendiceal, esophageal, gastroesophageal junction, or gastric cancer
- Funded by NDFP for patients who have complete dihydropyrimidine dehydrogenase (DPD) deficiency, have experienced unacceptable toxicity with 5-FU chemotherapy, live more than 60 km from the treatment centre/hospital, or have special transportation needs

Supplementary Public Funding	**raltitrexed** New Drug Funding Program (Raltitrexed - Metastatic Colorectal Small Bowel or Appendiceal Cancer) (NDFP Website) **raltitrexed** New Drug Funding Program (Raltitrexed - Metastatic Esophageal, Gastroesophageal Junction, or Gastric Cancer) (NDFP Website) **raltitrexed** New Drug Funding Program (Raltitrexed - Adjuvant Colorectal, Small Bowel, or Appendiceal Cancer) (NDFP Website) **raltitrexed** New Drug Funding Program (Raltitrexed - Adjuvant Esophageal, Gastroesophageal Junction, or Gastric Cancer) (NDFP Website)

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B - Drug Regimen

raltitrexed	3 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Adjuvant: Until disease progression, unacceptable toxicity, or up to a maximum of 8 cycles, whichever comes first

Palliative: Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- 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.

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E - Dose Modifications

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

Dosage with toxicity

Dosage in Myelosuppression ± Gastrointestinal Toxicity:

The dose of raltitrexed should be reduced based upon the worst hematologic and GI toxicity experienced in the previous cycle. Doses should not be re-escalated if reduced for toxicity.

Worst Toxicity in previous cycle			Action[1]	Dose (% previous dose)
grade 3 neutropenia / thrombocytopenia	**OR**	grade 2 GI toxicity	Hold until complete recovery	75%
grade 4 neutropenia / thrombocytopenia	**OR**	grade 3 GI toxicity		50%
grade 3 or 4 ↑ LFTs			Hold until ≤ grade 2	100%; if recurs consider ↓ to 75%.
grade 4 GI toxicity			Discontinue treatment	N/A
grade 4 neutropenia / thrombocytopenia	**AND**	grade 3 GI toxicity		
[1] Retreat only when GI toxicity resolved, platelets are ≥ 100 x 10^9/L, ANC ≥ 2 x 10^9/L, and WBC ≥ 4 x 10^9/L.				

Hepatic Impairment

Hepatic Impairment	Starting Dose
Mild to moderate	No dose adjustment recommended. Use with caution.
Severe	Contraindicated.

Renal Impairment

Raltitrexed is contraindicated in severe renal impairment.

Mild to moderate renal impairment results in a significant reduction in raltitrexed clearance and doses must be modified for renal impairment. Patients with renal impairment should be monitored carefully.

Creatinine Clearance mL/min	Dose as % of 3 mg/m^2	Dosing Interval
> 65	100	q3w
55-65	75	q4w
25-54	% equivalent to mL/min*	q4w
< 25	Contraindicated	Not applicable
*(e.g. if 30mL/min, give 30% of full dose.)		

Dosage in the Elderly

Use with extreme caution as the elderly are more susceptible to toxicity (especially GI).

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F - Adverse Effects

Refer to raltitrexed 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
• Nausea, vomiting	• Fatigue • Diarrhea (may be severe) • Anorexia, weight loss	• Myelosuppression ± infection, bleeding (may be severe) • Increased LFTs (may be severe) • Constipation • Rash • Mucositis	• Arrhythmia

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G - Interactions

Refer to raltitrexed drug monograph(s) for additional details.

- Avoid folinic or folic acid preparations immediately before or during raltitrexed administration, as these may interfere with raltitrexed action.

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H - Drug Administration and Special Precautions

Refer to raltitrexed drug monograph(s) for additional details.

Administration:

- Mix in 50-250 mL (NS, D5W); infuse IV over 15 minutes.
- Do not admix with other drugs.
- Store unopened vials at 2 to 25°C protected from light.
- Reconstituted and diluted solutions do not need to be protected from light.

Contraindications:

- Patients with hypersensitivity to the drug or any of its components
- Patients with severe renal and/or hepatic impairment
- Children < 18 years of age

Other Warnings/Precautions:

- Caution is necessary in patients with depressed bone marrow function, poor general condition, prior radiotherapy, mild to moderate hepatic impairment and in elderly patients.

Pregnancy/Lactation:

- This regimen is **contraindicated** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is **contraindicated** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Yes (especially in males)

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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 at each visit
- CBC, for patients who develop signs of GI toxicity; weekly
- Liver function tests; baseline and at each visit
- Renal function tests; baseline and at each visit
- Clinical assessment of GI toxicity, rash, infection and bleeding; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	18.6 minutes
Nursing Workload (average time per visit)	36.667 minutes

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K - References

Cocconi G, Cunningham D, Van Cutsem E. et al. Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. J Clin Oncol 1998;16(9):2943-52.

Cunningham D. Mature results from three large controlled studies with raltitrexed ('Tomudex'). Br J Cancer. 1998;77 Suppl 2(Suppl 2):15-21.

Cunningham D, Zalcberg JR, Rath U, et al. Final results of a randomised trial comparing 'Tomudex' (raltitrexed) with Fluorouracil plus leucovorin in advanced colorectal cancer. "Tomudex" Colorectal Cancer Study Group. Ann Oncol 1996;7(9):961-5.

Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency: Guidance for Clinicians. Ontario Health (Cancer Care Ontario), April 2023.

GI Drug Advisory Committee consensus, Ontario Health (Cancer Care Ontario).

Maughan TS, James RD, Kerr DJ, et al. Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. Lancet 2002;359(9317):1555-63.

Popov I , Carrato A, Sobrero A, et al. Raltitrexed (Tomudex) versus standard leucovorin modulated bolus 5-fluorouracil: Results from the randomised phase III PanEuropean trial in Adjuvant Colon Cancer 01 (PETACC1). Eur J Cancer 2008;44(15):220411.

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

Wilson KS , Fitzgerald CA, Barnett JB, et al. Adjuvant therapy with raltitrexed in patients with colorectal cancer intolerant of 5-fluorouracil: British Columbia Cancer Agency experience. Cancer Invest 2007;25(8):7114.

June 2024 Modified Dosage in Hepatic Impairment, Contraindications, Pregnancy/lactation, and Interactions sections

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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.

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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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