Drug Monograph

A - Drug Name

raltitrexed

COMMON TRADE NAME(S): Tomudex®

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B - Mechanism of Action and Pharmacokinetics

Raltitrexed is a quinazoline folate analogue that selectively inhibits thymidylate synthase (TS). TS is a key enzyme in the de novo synthesis of thymidine triphosphate (TTP), a nucleotide required exclusively for DNA synthesis. Inhibition of TS leads to DNA fragmentation and cell death. Raltitrexed is transported into cells and is then extensively polyglutamated. These polyglutamate forms are retained in cells and are even more potent inhibitors of TS, which may both increase antitumour activity as well as toxicity.

Distribution	Following intravenous administration, peak concentrations are reached at the end of the infusion, followed by a rapid initial decline in concentration and then a slow elimination phase. Pharmacokinetics are linear.	
	Cross blood brain barrier?	no information found
	PPB	93 %
Metabolism	Apart from intracellular polyglutamination, raltitrexed is not extensively metabolized.	
	Active metabolites	Yes
	Inactive metabolites	None

Elimination	Excreted unchanged in the urine (approximately 50%) and in the feces (approximately 15%). About 50% of dose retained in tissues.	
	Half-life	198 hours (terminal)

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C - Indications and Status

Health Canada Approvals:

- Colorectal cancer

Refer to the product monograph for a full list of approved indications.

Other Uses:

- Pleural mesothelioma
- Gastric cancer
- Esophageal cancer

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (3%)	E
Dermatological	Alopecia (6%)	E
	Rash (14%)	I E
Gastrointestinal	Abdominal pain (18%)	E
	Anorexia, weight loss (26%)	E
	Constipation (15%)	E
	Diarrhea (37%) (11% severe)	E

	Dyspepsia (6%)	E
	Mucositis (11%)	E
	Nausea, vomiting (57%)	I E
General	Edema (10%)	E
	Fatigue (46%)	E
Hematological	Myelosuppression ± infection, bleeding (20%) (12% severe)	E
Hepatobiliary	↑ LFTs (18%) (may be severe)	E
Metabolic / Endocrine	↓ K (2%)	E
Musculoskeletal	Musculoskeletal pain (3%)	E
Nervous System	Depression (3%)	E
	Dizziness (5%)	E
	Dysgeusia (6%)	E
	Headache (6%)	E
	Insomnia (4%)	E
	Paresthesia (3%)	E
Ophthalmic	Conjunctivitis (3%)	E
Renal	Creatinine increased (3%)	E
Respiratory	Cough, dyspnea (5%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for raltitrexed include nausea, vomiting, fatigue, diarrhea, anorexia, weight loss, myelosuppression ± infection, bleeding, ↑ LFTs, abdominal pain, rash and mucositis.

Diarrhea, nausea and **vomiting** are usually mild to moderate; however, severe diarrhea can occur, and may be associated with concurrent hematological suppression.

Myelosuppression is common and may be severe. The use of leucovorin as a rescue agent should be considered with severe toxicity.

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E - Dosing

Refer to protocol by which patient is being treated.

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

Adults:

Dose: 3 mg/m^2 IV every 3 weeks

Patients should not receive subsequent courses of raltitrexed until they have recovered from prior toxicity including GI, neutropenia, thrombocytopenia, and transaminase elevations (if present) show reversibility.

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.				

Dosage with Hepatic Impairment:

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

Dosage with 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).

Children:

Use is not recommended as safety and effectiveness in children have not been established.

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F - Administration Guidelines

- 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.

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G - Special Precautions

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.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Raltitrexed is **contraindicated** in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **6 months** after the last dose.
- Breastfeeding:
  Breastfeeding is **contraindicated**.
- Fertility effects: Yes
  (especially in males)

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Folinic acid, folic acid or vitamin preparation containing these agents	May interfere with raltitrexed action	Theoretical competition for the enzyme folyl polyglutamate synthetase and also competition for the binding of TS	Avoid immediately before or during raltitrexed administration.
Renally secreted drugs (e.g. NSAID's)	Potential competition interaction with actively secreted drugs	Raltitrexed may compete for active tubular secretory sites	Caution (no evidence)
Highly protein bound drugs (e.g. warfarin)	Potential displacement	Raltitrexed may displace protein bound drugs thus increasing plasma concentrations	Caution (no evidence)

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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

Monitor Type	Monitor Frequency
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 - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Raltitrexed - Advanced Malignant Pleural Mesothelioma (MPM)
- Raltitrexed - Metastatic Colorectal Small Bowel or Appendiceal Cancer
- Raltitrexed - Metastatic Esophageal, Gastroesophageal Junction, or Gastric Cancer
- Raltitrexed - Adjuvant Colorectal, Small Bowel, or Appendiceal Cancer
- Raltitrexed - Adjuvant Esophageal, Gastroesophageal Junction, or Gastric Cancer

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K - References

Blair EY, Rivory LP, Clarke SJ, McLachlan AJ. Population pharmacokinetics of raltitrexed in patients with advanced solid tumours. Br J Clin Pharmacol. 2004 Apr;57(4):416-26.

Product Monograph: Tomudex® (raltitrexed). Hospira Healthcare Corp., December 7, 2021.

Summary or Product Characteristics: Tomudex® (raltitrexed). Hospira UK Ltd., March 2024.

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

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L - Disclaimer

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

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