Drug Monograph

A - Drug Name

raltitrexed

SYNONYM(S): Raltitrexed disodium; ZD 1694

COMMON TRADE NAME(S): Tomudex® (Pfizer)

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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. Ralitrexed is transported into cells via the reduced folate carrier and is then extensively polyglutamated by enzyme folyl polyglutamate synthetase to polyglutamate forms. These are retained in cells and are even more potent inhibitors of thymidylate synthase, which may both increase antitumour activity as well as toxicity.

Absorption	Oral absorption: No information found	
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	Not metabolized. Active metabolites include polyglutamates.	
	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 t½)

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C - Indications and Status

Health Canada Approvals:

- Advanced colorectal cancer

Other Uses:

- Pleural mesothelioma (in combination with cisplatin)

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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 (28%)	E
	Constipation (15%)	E
	Diarrhea (38%) (may be severe)	E
	Dyspepsia (6%)	E
	Mucositis (12%)	E
	Nausea, vomiting (58%)	I E
General	Edema (10%)	E

	Fatigue (49%)	E
Hematological	Myelosuppression ± infection, bleeding (13%) (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.
Dose-limiting side effects are underlined.

** 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 adverse events associated with raltitrexed in phase III trials were gastrointestinal and hematological in nature. **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. Numerous dosing schedules exist depending on disease, response and concomitant therapy.

Adults:

Dose: 3 mg/m^2 IV as a 15 minute infusion.
In the absence of toxicity, treatment may be repeated every 3 weeks. Dose escalation is not recommended.

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.

<table>
<tr><th colspan="3">Worst Toxicity in previous cycle</th><th>Action[1]</th><th>Dose
(% previous dose)</th></tr>
<tr><td>grade 3 neutropenia / thrombocytopenia</td><td>OR</td><td>grade 2 GI toxicity</td><td rowspan="2">Hold until complete recovery</td><td>75%</td></tr>
<tr><td>grade 4 neutropenia / thrombocytopenia</td><td>OR</td><td>grade 3 GI toxicity</td><td>50%</td></tr>
<tr><td colspan="3">grade 3 or 4 ↑ LFTs</td><td>Hold until ≤ grade 2</td><td>100%; if recurs consider ↓ to 75%.</td></tr>
<tr><td colspan="3">grade 4 GI toxicity</td><td rowspan="2">Discontinue treatment</td><td rowspan="2">N/A</td></tr>
<tr><td>grade 4 neutropenia / thrombocytopenia</td><td>AND</td><td>grade 3 GI toxicity</td></tr>
<tr><td colspan="5">[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.</td></tr>
</table>

Dosage with Hepatic Impairment:

Grade	Initial Dose (baseline values)
1	100%
2	100%, watch carefully
3	Extreme caution (no data)
4	Do not treat (no data)

Dosage with 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. (Continued on next page)

Creatinine Clearance mL/min	*Dose as % of 3mg/m^2*	*Dosing Interval*
>65	100	q3w
55-65	75	q4w
25-54	% equivalent to mL/min*	q4w
<25	Discontinue	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.

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
- 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

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.
- Raltitrexed results in asthenia and malaise; it may impair ability to drive and to operate machinery.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Raltitrexed is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- 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 ralitrexed action	Theoretical competition for the enzyme folyl polyglutamate synthetase and also competition for the binding of TS	Avoid

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	Ralitrexed may displace protein bound drugs thus increasing plasma concentrations	Caution (no evidence)

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and at each visit
Renal function tests	Baseline and at each visit
CBC	Baseline and at each visit
CBC, for patients who develop signs of GI toxicity	weekly
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

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K - References

Product Monograph: Tomudex® (raltitrexed). Hospira Healthcare Corp., April 23, 2008.

November 2017 updated public funding form title

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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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