DRUG NAME: Raltitrexed

SYNONYM(S): Raltitrexed disodium, ZD-1694

COMMON TRADE NAME(S): TOMUDEX® (notice of compliance,[1] September 1996; patent expires[2] July 2008)

CLASSIFICATION: Antimetabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Raltitrexed is a quinazoline folate analogue that selectively inhibits thymidylate synthase (TS).[3] Thymidylate synthase is a key enzyme in the *de novo* synthesis of thymidine triphosphate (TTP), a nucleotide required exclusively for deoxyribonucleic acid (DNA) synthesis. Inhibition of TS leads to DNA fragmentation and cell death.[3] Intracellular retention of polyglutamated forms of raltitrexed leads to prolonged inhibitory effects.[4] This permits a convenient dosing schedule of a single IV injection once every 3 weeks.[5] Raltitrexed is a radiation-sensitizing agent.[6] It is cell cycle phase-specific (S-phase).[7]

PHARMACOKINETICS:

Interpatient variability	considerable interpatient variability[4]	
Distribution	actively transported into cells[4]; long half life probably due to a slow return of raltitrexed to the plasma from a deep tissue compartment or binding site	
	cross blood brain barrier?	no information found
	volume of distribution	548 L
	plasma protein binding	93%
Metabolism	transported into cells via a reduced folate carrier and then extensively metabolized to polyglutamate forms[3] without metabolic degradation[4]	
	active metabolite(s)	polyglutamate forms
	inactive metabolite(s)	none
Excretion	active tubular secretion may contribute to the renal excretion	
	urine	50% excreted unchanged
	feces	15% excreted over 10 days
	terminal half life	198 h
	clearance	52 mL/min; 1 mL/min/kg; mild to moderate hepatic impairment leads to < 25% reduction in clearance[3]; mild to moderate renal impairment leads to 50% reduction in clearance[3,8]
Gender	no clinically significant difference	
Elderly	no clinically significant difference	
Children	no information found	
Race	no information found	

Adapted from reference[3] unless specified otherwise.

USES:

Primary uses:
* Colorectal cancer[9-11]

Other uses:
Breast cancer[12]
Gastroesophageal cancer[13]
Mesothelioma[14]

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindicated in patients with severe renal impairment, severe hepatic impairment[3] and/or clinically significant cardiac arrhythmias requiring drug therapy.[15]

Carcinogenicity: no information found.

Mutagenicity: Not mutagenic in Ames test or in mammalian *in vitro* mutation test. Raltitrexed is clastogenic in human lymphocytes *in vitro* and mammalian bone marrow *in vivo*.[3]

Fertility: animal studies showed impairment of male fertility. Fertility returned to normal three months after dosing ceased.[3]

Pregnancy: In pregnant rats, raltitrexed caused embryolethality and fetal abnormalities. If either partner is receiving raltitrexed, pregnancy should be excluded before treatment is commenced and avoided during and for at least 6 months after treatment.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk.[3]

SIDE EFFECTS:

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
blood/bone marrow febrile neutropenia	anemia (12-19%)		E	D	
	leukocytopenia (18-23%) nadir in the first or second week, recovery by the third week		E		
	thrombocytopenia (4%) nadir in the first or second week, recovery by the third week		E		
cardiovascular (arrhythmia)	cardiac rhythm abnormalities (3%)		E		
cardiovascular (general)	cardiac function abnormalities (2%)		E		
	edema (3-5%)		E		
constitutional symptoms	***asthenia*** (29-42%)		E	D	
	fever (20%)	I			
	malaise (2%)		E	D	
	sweating (2-3%)		E		
	weight loss (3-5%)		E	D	
dermatology/skin	*extravasation hazard:* none[3]				

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
	alopecia (4-5%)		E	D	
	pruritus (2%)		E		
	rash (13%)		E		
	desquamation (rare)		E		
gastrointestinal	*emetogenic potential:* low moderate[3]				
	anorexia (18-24%)		E		
	constipation (6%)		E		
	dehydration (3-4%)		E		
	diarrhea (30-34%)		E		
	dyspepsia (2-6%)		E		
	mouth ulceration (2%)		E		
	nausea (47-54%)	I	E		
	stomatitis (9%)		E		
	taste disturbance (2-3%)		E		
	vomiting (29-32%)	I	E		
hepatic	fatal liver failure (rare)[16]			D	
	transient increase of alkaline phosphatase (2%)		E		
	transient increase of ALT (12-15%)		E		
	transient increase of AST (14-19%)		E		
infection	sepsis (2-3%)		E		
musculoskeletal	arthralgia (2%)		E		
	cellulitis (2-3%)		E		
	hypertonia (2%)		E		
ocular/visual	conjunctivitis (2%)		E		
pain	abdominal pain (6-8%)		E		
	headache (2-3%)		E		
	pain (2-3%)		E		
pulmonary	cough (2%)		E		
syndromes	flu-like symptoms (5-11%)	I	E		

Adapted from reference[3] unless specified otherwise.

Drug-related deaths in clinical trials: A similar incidence of drug-related death was found with single agent raltitrexed compared to the combination of fluorouracil plus leucovorin regimens in phase III trials in advanced colorectal cancer. There were 26 deaths in 684 raltitrexed patients (3.5%). However, 17 of these deaths were in patients who did not receive appropriate dosage modifications following toxicity/impaired renal function during a previous cycle of raltitrexed.[4] More recently, the drug manufacturer prematurely stopped the Pan European Trial in Adjuvant Colon Cancer-1 (PETACC-1). The interim safety review found that the number of drug-related deaths in the raltitrexed group (17 of 911 patients, 1.9%) was double that in the fluorouracil plus leucovorin group (7 of 927 patients, 0.8%). Eleven of the 17 drug-related deaths in the raltitrexed group were linked with serious deviations from the dose modification instructions in the protocol.[17] Health care providers are cautioned to follow dose modifications for impaired renal function.[3]

Fatal liver failure: Transient increases of hepatic transaminases are generally considered to be of no clinical significance. Recently, acute fatal liver failure has been reported in two patients. In both patients, toxicity occurred after repeated administration and was not preceded by a transient increase in transaminases during earlier cycles. Histologic findings showed acute necrosis of approximately 50% of the liver without concurrent changes suggestive of preexisting chronic conditions.[16]

Nausea and vomiting typically occurs after 2-3 days, rather than immediately after treatment. Most symptoms are managed with antiemetics such as oral metoclopramide.[18]

Cardiovascular system: A number of cardiac rhythm or cardiac function abnormalities have been reported in clinical trials in advanced colorectal cancer. These included sinus tachycardia, supraventricular tachycardia, atrial fibrillation and congestive heart failure. The incidence of disorders of rhythm and function in patients treated with raltitrexed was 2.8% and 1.8% respectively, compared to 1.9% and 1.4% for patients on the comparator treatment (fluorouracil and leucovorin). A causal relationship could not be established since many of the abnormalities were concurrent with the underlying conditions such as sepsis and dehydration and more than one third of the patients reported cardiovascular abnormalities prior to treatment.[3] The safe use of raltitrexed in two patients with fluorouracil-associated cardiotoxicity has been reported. The authors speculated that the mechanism of fluorouracil cardiotoxicity is not due to the direct cytotoxic effect on DNA synthesis caused by thymidylate synthase inhibition.[19]

Use in elderly patients: Recent reports have concluded that raltitrexed is suitable for use in elderly patients. In 90 patients greater than 70 years of age with advanced colorectal cancer, severe toxicity was reported as nausea and vomiting 7%, diarrhea 3%, liver toxicity 6%, neutropenia 3% and anemia 2%. There were 3 drug-related deaths.[20] In 51 patients greater than 70 years of age with metastatic colorectal cancer, severe toxicity was reported as increase in transaminases 20%, nausea/vomiting 8%, anemia 6%, diarrhea 10%, and infectious disease 2%. There were no drug-related deaths.[21]

Overdose: For an overdose, consideration should be given to the administration of leucovorin. From clinical experience with other antifolates, leucovorin may be given at a dose of 25 mg/m² IV every 6 hours.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
folic acid	may reduce efficacy of raltitrexed	may interfere with action of raltitrexed	avoid immediately before or during raltitrexed administration
irinotecan[22]	no pharmacokinetic interactions observed		
leucovorin	may reduce efficacy of raltitrexed	may interfere with action of raltitrexed	avoid immediately before or during raltitrexed administration
nonsteroidal antiinflammatory drugs	no clinically significant interaction	interferes with active renal tubular secretion of raltitrexed	
vitamin preparations containing folic acid or leucovorin	may reduce efficacy of raltitrexed	may interfere with action of raltitrexed	avoid immediately before or during raltitrexed administration
warfarin	no clinically significant interaction	no displacement between raltitrexed and warfarin *in vitro*	

Adapted from reference[3] unless specified otherwise.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Injection: 2 mg vial (as the disodium salt). Store at room temperature. Protect from light.[3]

Reconstitute powder with 4 mL SWI to a final concentration of 0.5 mg/mL.[3]

***Reconstituted solution for injection*:** chemically stable for 24 hours at room temperature exposed to ambient light, however, it is recommended that raltitrexed be refrigerated to avoid bacterial contamination.[3]

***Diluted solution for infusion*:** Dilute in 50-250 mL NS or D5W. Chemically stable for 24 hours at room temperature exposed to ambient light. If not used promptly, it is recommended that raltitrexed be refrigerated to avoid bacterial contamination.[3]

***Compatibility*:** It is recommended that raltitrexed not be mixed with other drugs.[3]

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***in 50 mL NS over 15 min***
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or in patients with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 week:***	***3 mg/m²*** (range 0.75-3 mg/m²) ***IV for one dose on day 1*** once a dose reduction has been made, all subsequent doses should be given at the reduced dose level
Concurrent radiation:	5-6 weeks	investigational, 2.6 mg/m² IV for one dose on days 1 and 22 concurrent with radiation for 5-6 weeks (total dose per cycle 5.2 mg/m²)[6]

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in gastrointestinal toxicity[3]:

Toxicity		Dose
grade 2 diarrhea:	increase of 4-6 stools per day, or nocturnal stools	75%
grade 2 stomatitis:	painful erythema, edema, or ulcers, but can eat or swallow	75%
grade 3 diarrhea:	increase of greater than 6 stools per day or incontinence; or need for parenteral support for dehydration	50%
grade 3 stomatitis:	painful erythema, edema, or ulcers requiring IV hydration	50%
grade 3 diarrhea or stomatitis with grade 4 hematologic toxicity (neutrophils < 0.5 x 10^9/L or platelets < 10 x 10^9/L)		discontinue
grade 4 diarrhea (hemodynamic collapse or requires intensive care) or stomatitis (severe ulceration or requires parenteral or enteral nutrition or prophylactic intubation)		discontinue

Dosage in renal failure[3]: For patients with abnormal serum creatinine, CrCl should be performed or calculated. For patients with normal serum creatinine but the serum creatinine may not correlate well with CrCl due to age or weight loss, CrCl should be performed or calculated.[3]

$$\text{CrCl} = \frac{N \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/L})}$$

where N = 1.04 for females and 1.23 for males

CrCl (mL/min)	Dose	Dosing interval
>65	100%	3-weeks
55-65	75%	4-weeks
25-54	% equivalent to mL/min*	4-weeks
< 25	discontinue	

*eg, if CrCl = 30 mL/min, give 30% of full dose

Dosage in hepatic failure[3]:

Bilirubin	Dose
< 10 x upper limit of normal	100% (if preexisting hyperbilirubinemia)
suspected drug-related rise	delay until resolved
> 10 x upper limit of normal	has not been studied, use not recommended

Dosage in dialysis: no information found

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