DRUG NAME: Pralatrexate

SYNONYM(S): PDX[1]

COMMON TRADE NAME(S): FOLOTYN®

CLASSIFICATION: antifolate antimetabolite

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

MECHANISM OF ACTION:

Pralatrexate is an analogue of methotrexate. It is a folate antagonist which selectively enters cells expressing reduced folate carrier type 1 (RFC-1). RFC-1 is a protein overexpressed on certain cancer cells. Intracellularly, pralatrexate competitively inhibits dihydrofolate reductase (DHFR), leading to interruption of RNA synthesis, DNA replication, and apoptosis. Compared to methotrexate, pralatrexate demonstrates a much higher intracellular concentration and prolonged retention within the cell. Pralatrexate is cell cycle phase-specific with arrested cell growth occurring in the S-phase. Pralatrexate is an immunosuppressive agent.[1-4]

PHARMACOKINETICS:

Distribution	dose-dependent increase in exposure and plasma concentration	
	cross blood brain barrier?	no information found
	volume of distribution	37-105 L
	plasma protein binding	67-84%
Metabolism	not significantly metabolized	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	10% of dose is excreted through exhalation over 24 h	
	urine	31-39% (parent drug)
	feces	34% (parent and metabolites)
	terminal half life	12-18 h
	clearance	191-417 mL/min

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

Lymphoma, non-Hodgkin's*

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***folic acid and vitamin B_{12} supplementation*** must be initiated prior to pralatrexate in all patients to minimize treatment-related toxicity[2]
- immune response to ***vaccines*** may be diminished by pralatrexate[3]
- ***live attenuated vaccines*** should not be administered during treatment and for at least three months after the last dose of pralatrexate due to risk of enhanced vaccine adverse effects[3]

Developed: 1 December 2019
Revised: 1 April 2020

Special populations:
- patients aged ***65 or older*** may experience a greater incidence of mucositis[4]
- patients with ***underlying*** moderate to severe ***renal impairment*** are at greater risk for increased pralatrexate toxicity; avoid pralatrexate in patients with end-stage renal disease, including those receiving dialysis[2,3]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Pralatrexate is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2,5]

Fertility: Irreversible effects on fertility were observed in animal studies.[2]

Pregnancy: In animal studies, pralatrexate demonstrated embryonic and fetal toxicity, including significant increases in early resorptions and post-implantation losses as well as significantly decreased fetal weights. Because of its mechanism of action and the fact that RFC-1 is overexpressed on fetal cells, pralatrexate is expected to be transmitted from mother to fetus. Females of reproductive potential should use effective contraception while on pralatrexate and for eight weeks after treatment has been discontinued. Male patients are advised to use condoms with spermicide (even after vasectomy) during sexual contact with a female of childbearing potential.[2,4]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (34%, severe 17%)
	febrile neutropenia (1-10%)
	leukopenia (11%, severe 7%)
	lymph node pain, lymphadenopathy (1-10%)
	lymphopenia (1-10%)
	neutropenia (24%, severe 20%)
	splenomegaly (1-10%)
	thrombocytopenia (41%, severe 33%)
cardiac	tachycardia (10%)
ear and labyrinth	ear pain, tinnitus, vertigo (1-10%)
eye	blurred vision, conjunctivitis, increased lacrimation, periorbital edema (1-10%)
gastrointestinal	*emetogenic potential:* low[7]
	abdominal pain (12%, severe 4%)
	constipation (33%)
	diarrhea (21%, severe 2%)

Developed: 1 December 2019
Revised: 1 April 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dry lips, dry mouth, oral pain (1-10%)
	dyspepsia, gastritis, gastrointestinal reflux (1-10%)
	dysphagia, esophagitis (1-10%)
	flatulence (1-10%)
	hemorrhoids (1-10%)
	mucositis (70%, severe 21%); see paragraph following **Side Effects** table
	nausea (40%, severe 4%)
	vomiting (25%, severe 2%)
general disorders and administration site conditions	*extravasation hazard:* none[5,8]
	asthenia (10%, severe 1%)
	axillary pain (1-10%)
	chest pain, sensation of pressure (1-10%)
	chills, flu-like symptoms (1-10%)
	edema (30%, severe 1%)
	fatigue (36%, severe 7%)
	infusion related reactions (1-10%)
	pyrexia (32%, severe 2%)
infections and infestations	candidiasis, oral candidiasis (5%)
	cellulitis, folliculitis (5%)
	ear infection (1-10%)
	herpes simplex, oral (6%); herpes simplex, genital (1-10%)
	herpes zoster (5%)
	influenza (1-10%)
	nasopharyngitis (7%); sinusitis (8%); upper respiratory tract infection (10%, severe 1%)
	pneumonia (1-10%)
	sepsis (5%)
	urinary tract infection (5%)
investigations	alkaline phosphatase increase (1-10%)
	ALT increase (9%, severe 4%)
	AST increase (5%, severe 2%)
	bilirubin increase (1-10%)
	creatinine increase (1-10%)
	weight loss (1-10%)
metabolism and nutrition	anorexia (15%, severe 3%)
	dehydration (1-10%, severe >3%)[2,3]

Developed: 1 December 2019
Revised: 1 April 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypercalcemia, hypocalcemia (1-10%)
	hyperglycemia, hypoglycemia (1-10%)
	hyperkalemia (1-10%); hypokalemia (15%, severe 5%)
	hyperuricemia (1-10%); tumour lysis syndrome (<1%)
	hypoalbuminemia (1-10%)
	hypomagnesemia (1-10%)
	hypophosphatemia (1-10%)
musculoskeletal and connective tissue	arthralgia, joint stiffness (1-10%)
	back pain (11%, severe 3%)
	muscle spasms, muscle stiffness, myalgia (1-10%)
	neck pain (1-10%)
	pain in extremities (12%)
	weakness (10%)[3]
nervous system	cerebral infarction (1-10%)
	dizziness, syncope (1-10%)
	headache (1-10%)
	hypoesthesia (1-10%)
	memory impairment (1-10%)
	neuropathy, peripheral and sensory; paresthesia (1-10%)
psychiatric	anxiety (1-10%)
	confusion (1-10%)
	depression (1-10%)
	excoriation (1-10%)
	insomnia (1-10%)
renal and urinary	renal failure, acute renal failure (1-10%)
reproductive system and breast disorders	balanoposthitis, testicular pain (1-10%)
	vaginal inflammation; including itching, discharge, pain, odour, and bleeding
	vulvovaginal pruritus (<1%)
respiratory, thoracic and mediastinal	atelectasis (1-10%)
	cough (28%, severe 1%)
	dry throat, dysphonia (1-10%)
	dyspnea (19%, severe 7%); hypoxia (1-10%)
	epistaxis (26%)
	hiccups (1-10%)
	pharyngeal inflammation (1-10%)

Developed: 1 December 2019
Revised: 1 April 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pharyngeal pain (14%, severe 1%)
	pleural effusion, pleuritic pain (1-10%)
	pneumonitis (1%)
	respiratory failure, acute respiratory distress syndrome (<1%)
	rhinorrhea, sinus congestion (1-10%)
skin and subcutaneous tissue	alopecia (1-10%)
	blisters (1-10%)
	dry skin (1-10%)
	erythema (1-10%)
	night sweats (11%)
	petechiae (1-10%)
	pruritus (14%, severe 2%)
	rash (15%); see paragraph following **Side Effects** table
	skin exfoliation, toxic epidermal necrolysis (<1%); see paragraph following **Side Effects** table
	skin ulceration (1-10%); see paragraph following **Side Effects** table
	urticaria (1-10%)
vascular	deep vein thrombosis, subclavian vein thrombosis (1-10%)
	flushing (1-10%)
	hypertension, hypotension (1-10%)

Adapted from standard reference[2] unless specified otherwise.

Mucositis, including inflammation of the gastrointestinal, respiratory, and genitourinary tracts, is reported in up to 70% of patients receiving pralatrexate. Up to 21% of patients experience severe reactions. Fatalities have been reported. Mucositis may occur more frequently in patients aged 65 and older. Onset is usually within 2 to 15 days of treatment initiation, with a median duration of 13 days. To reduce the risk of mucosal inflammation, vitamin B_{12} and folic acid supplementation is required for all patients and should begin prior to pralatrexate treatment (folic acid beginning10 days prior and vitamin B_{12} beginning within 10 weeks of pralatrexate initiation). Omit pralatrexate dose for grade two or three mucositis. Treatment may be resumed following resolution of symptoms to grade one or less; however, dose reduction may be required for subsequent doses. Permanently discontinue pralatrexate for grade four mucositis.[2-4]

Severe dermatologic reactions, such as skin exfoliation, ulceration, and toxic epidermal necrolysis are reported with pralatrexate. Skin and subcutaneous sites of lymphoma may be involved. Fatalities have occurred after the first dose of pralatrexate, even when a reduced dose was administered. Patients with extensive skin involvement may be at greater risk of developing severe skin reactions. Onset of dermatologic reactions is usually early in the course of therapy and the severity of the reaction may progress with further treatment. Hold or permanently discontinue pralatrexate therapy for severe reactions.[2]

Developed: 1 December 2019
Revised: 1 April 2020

INTERACTIONS:

Pralatrexate is a *substrate* of breast cancer resistance protein (BCRP), multidrug resistance-associated proteins 2 and 3 (MRP2 and MRP3), and organic anion transport protein 1B3 (OATP1B3) transporters *in vitro*. Increased pralatrexate exposure may result following coadministration with drugs utilizing these transporters; monitor for symptoms of pralatrexate toxicity.[2]

In vitro, pralatrexate is an *inhibitor* of MRP2 and MRP3 transporter systems.[2] Clinical significance is unknown.

SUPPLY AND STORAGE:

***Injection*:** Servier Canada Inc. supplies pralatrexate as 20 mg and 40 mg single-use, preservative-free vials in a concentration of 20 mg/mL. Refrigerate. Protect from light.[2]

Additional information: Unopened vials stored in the original carton are stable for 72 hours at room temperature.[2]

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

SOLUTION PREPARATION AND COMPATIBILITY:

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

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[2,9]	***over 3-5 minutes***
Intermittent infusion	no information found
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 with other toxicities.

Developed: 1 December 2019
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***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Intravenous:	Cycle Length:	
	4 weeks[1,9]:	cycle 1: ***10 mg/m^2 IV for one dose on day 1***, followed by ***20 mg/m^2 IV for one dose on day 8***, and ***30 mg/m^2 IV for one dose on day 15*** (total dose per cycle 1 = 60 mg/m^2) cycle 2 onwards: ***30 mg/m^2 IV for one dose on days 1, 8, and 15*** (total dose per cycle 90 mg/m^2)
	7 weeks[1,2,10]:	30 mg/m^2 IV for one dose on days 1, 8, 15, 22, 29, and 36 (total dose per cycle 180 mg/m^2)
	4 weeks[1,3]:	15 mg/m^2 IV for one dose on days 1, 8, and 15 (total dose per cycle 45 mg/m^2)

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure[2,3]:

CrCl ≥30 mL/min: no adjustment required
CrCl 15-29 mL/min: 15 mg/m^2
CrCl <15 mL/min: no information found; however, risk of serious adverse reactions may be increased

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: no information found

Dosage in dialysis[2]: no information found; risk of serious adverse reactions may be increased

Children: no information found

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Developed: 1 December 2019
Revised: 1 April 2020

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Developed: 1 December 2019
Revised: 1 April 2020