Drug Monograph

A - Drug Name

PRALAtrexate

COMMON TRADE NAME(S): Folotyn®

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B - Mechanism of Action and Pharmacokinetics

Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase (DHFR) and polyglutamylation by the enzyme folylpolyglutamyl synthetase (FPGS) in cells expressing reduced folate carrier type 1 (RFC-1). This inhibition results in the inhibition of RNA synthesis, DNA replication and cancer growth and apoptosis.

Absorption	Following IV injection (30 mg/m^2 over 3–5 minutes) once weekly for 6 weeks in 7-week cycles, C_{max} and AUC increased proportionally with dose. PK was stable over multiple cycles and no accumulation of pralatrexate was observed.	
Distribution	PPB	67% - 84%
Metabolism	Pralatrexate is not significantly metabolized by the phase I hepatic CYP450 isozymes or phase II hepatic glucuronidases.	
Elimination	Half-life	12-18 hours
	Feces	34%
	Urine	39% parent drug (racemic pralatrexate)

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C - Indications and Status

Health Canada Approvals:

- Peripheral T-cell lymphoma (PTCL)

(Includes conditional approvals)
Refer to the product monograph for a full list of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

The following table lists adverse effects that occurred in ≥10% of patients in the single arm phase II trial in relapsed or refractory peripheral T-cell lymphoma (PTCL). Severe, life-threatening or post-marketing adverse events are also included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (<1%)	E
	Tachycardia (10%)	E
Dermatological	Other (11%) - night sweats	E
	Rash, pruritus (15%) (may be severe - TEN)	I E
Gastrointestinal	Abdominal pain (12%)	E
	Anorexia, weight loss (15%)	E
	Constipation (33%)	E
	Dehydration (4%) (severe)	E D
	Diarrhea (21%)	E
	Dyspepsia (10%)	E
	Mucositis (70%) (may be severe)	E
	Nausea, vomiting (40%)	E
General	Edema (30%)	E
	Fatigue (36%)	E

	Fever, chills (32%)	E
Hematological	Anemia (34%)	E
	Myelosuppression (41%) (including bleeding; may be severe)	E
Hepatobiliary	↑ LFTs (13%) (may be severe)	E
Hypersensitivity	Infusion related reaction (<10%)	E
Infection	Infection (54%) (may be severe)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (15%) (↓ K)	E
	Tumor lysis syndrome (1%)	E
Musculoskeletal	Musculoskeletal pain (14%) (including pharyngolaryngeal pain)	E
Nervous System	Headache (12%)	E
Renal	Renal failure (<10%)	E
Respiratory	Cough, dyspnea (28%)	E
	Epistaxis (26%)	E
	Pneumonitis (1%) (including ARDS)	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 pralatrexate include mucositis, infection, myelosuppression, nausea, vomiting, fatigue, anemia, constipation, fever, chills, edema, cough and dyspnea.

Pralatrexate may cause severe and life-threatening **mucositis** including stomatitis or mucosal inflammation of gastrointestinal and genitourinary tracts. The median time to onset for ≥ grade 3 mucosal inflammation was 15 days with a median duration of 13 days.

Fatal cases of hematologic toxicity (**thrombocytopenia**, **neutropenia** and/or **anemia**) have been reported. The median time to onset of ≥ grade 3 thrombocytopenia was 15 days with a median duration of 16 days. None of the thrombocytopenic events were associated with ≥ grade 3 bleeding events. The median time to onset of ≥ grade 3 neutropenia was 22 days with a median duration of 8 days.

Severe **infections** including pneumonia, sepsis, septic shock, and herpes zoster have been reported and may be fatal.

Severe and potentially life-threatening **dermatologic reactions**, including skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN), have been reported. Skin reaction may be

progressive and increase in severity with continued treatment and may also involve skin and subcutaneous tissues which are affected by lymphoma.

Severe and potentially life-threatening cases of **pulmonary toxicity** have been reported.

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E - Dosing

Refer to protocol by which patient is being treated.

Adults:

Premedications:

- Folic acid 1 to 1.25 mg PO daily: start 10 days prior to first pralatrexate dose; continue during treatment and for 30 days after last pralatrexate dose.
- Vitamin B_{12} 1 mg IM: administer within 10 weeks prior to first pralatrexate dose and every 8 to 10 weeks thereafter (after first dose, subsequent B_{12} doses may be administered on the same day as pralatrexate)

Prior to administering any pralatrexate dose:

- Mucositis should be ≤ grade 1.
- Absolute neutrophil count (ANC) should be ≥ 1×10^9/L.
- Platelet count should be ≥ 100×10^9/L for first dose and ≥ 50×10^9/L for all subsequent doses.

Intravenous: 30 mg/m² once weekly for 6 weeks of a 7-week treatment cycle.

Continue until disease progression or unacceptable toxicity.

Refer to the PRAL regimen monograph for details on an alternate schedule (doses given weekly x 3, with 1 week rest).

Dosage with Toxicity:

Do not make up omitted doses at the end of a cycle.

Refer to the PRAL regimen monograph for dose modifications of doses given in the alternate schedule.

Standard Schedule (6 weeks on, 1 week off):

Dose Levels:

Dose Level	Pralatrexate dose (mg/m^2)	Pralatrexate dose in Patients with Severe Renal Impairment (mg/m^2)
0	30	15
-1	20	10
-2	Discontinue	

Non-Hematologic toxicities:

Toxicity on Day of Treatment	Grade	Action†
Mucositis	2	Hold until recovery to ≤ grade 1; restart at same dose
	2 recurrence or grade 3	Hold until recovery to ≤ grade 1; restart at 1 dose level ↓
	4	Discontinue
All other non-Hematologic toxicities	3	Hold until recovery to ≤ grade 2; restart at 1 dose level ↓
	4	Discontinue

† Do not re-escalate dose after a reduction due to toxicity.

Hematologic Toxicities

Toxicity on Day of Treatment	Duration of toxicity	Action*†
Platelet < 50 x 10^9/L	1 week	Hold; restart at same dose
	2 weeks	Hold; restart at 1 dose level ↓
	3 weeks	Discontinue
ANC 0.5-1 x 10^9/L and no fever	1 week	Hold; restart at same dose
ANC 0.5-1 x 10^9/L with fever or ANC < 0.5 x 10^9/L	1 week	Hold, give G-CSF support; restart at same dose
	2 weeks or recurrence	Hold, give G-CSF support; restart at 1 dose level ↓
	3 weeks or 2nd recurrence	Discontinue
*Administer subsequent doses only when platelet count ≥ 50×10^9/L and ANC ≥ 1×10^9/L on day of treatment. † Do not re-escalate dose after a reduction due to toxicity.		

Dosage with Hepatic Impairment:

The safety, efficacy and pharmacokinetics of pralatrexate have not been evaluated in patients with hepatic impairment. Patients with total bilirubin > ULN, AST or ALT > 2.5 x ULN or AST or ALT > 5 x ULN if documented hepatic lymphoma involvement were excluded from clinical trials.

Dosage with Renal Impairment:

Renal Impairment	Pralatrexate Dose (% of Usual Dose)
Mild to moderate (CrCl ≥ 30 mL/min)	No dosage adjustment necessary
Severe (CrCl 15-29 mL/min)	50%
End-stage renal disease (ESRD), including dialysis	Avoid (unless the potential benefit outweighs risks*)

*Serious reactions, including fatal cases of TEN and severe mucositis have been reported in patients with end-stage renal disease undergoing dialysis

Dosage in the elderly:

No overall differences in efficacy and safety were observed in patients ≥65 years compared with patients <65 years. No dose adjustment required; however, close monitoring for toxicity is recommended.

Dosage based on gender:

There was no significant effect of gender on pharmacokinetics.

Dosage based on ethnicity:

No significant effect of ethnic origin on pharmacokinetics observed.

Children:

The safety and effectiveness of pralatrexate have not been established.

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F - Administration Guidelines

- Pralatrexate is for intravenous use only.
- Administered undiluted as an intravenous push over 3-5 minutes into the line of a free-flowing 0.9% sodium chloride Injection.
- Refrigerate at 2-8°C; protect from light.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitive to pralatrexate, any ingredient in the formulation or component of the container.

Other Warnings/Precautions:

- Patients should be cautioned not to drive cars, use machines or perform hazardous tasks if they experience fatigue.

Other Drug Properties:

- Carcinogenicity:
  No data

Pregnancy and Lactation:

- Mutagenicity:
  No data
- Embryotoxicity: Documented in animals
  Pralatrexate is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **8 weeks** after the last dose.
- Fetotoxicity: Documented in animals
- Breastfeeding: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Unknown
  Semen preservation prior to initiation of pralatrexate therapy could be considered.

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H - Interactions

No formal clinical drug interaction assessments have been conducted.

In vitro studies indicate that pralatrexate is not a substrate, inhibitor, or inducer of cytochrome P-450 (CYP) isoenzymes. Pralatrexate is a substrate for BCRP, MRP2, MRP3 and OATP1B3. It is not a substrate of P-gp, OATP1B1, OCT2, OAT1, and OAT3 transport systems. Pralatrexate is an inhibitor of MRP2 and MRP3 but is not an inhibitor of P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Probenecid	↑ pralatrexate concentration and/or toxicity	delayed clearance	Caution; monitor closely
NSAIDs	↑ pralatrexate concentration and/or toxicity	↓ renal excretion	Caution; monitor closely
Drugs eliminated by renal excretion (i.e. trimethoprim/sulfamethoxazole)	↑ pralatrexate concentration and/or toxicity	delayed clearance	Caution; monitor for systemic toxicity due to ↑ drug exposure with drugs that undergo substantial renal excretion

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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 PRAL regimen monograph for alternate schedule monitoring info.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and weekly
Liver function tests	Prior to the first and fourth doses in each cycle and as clinically indicated

Renal function tests	Prior to the first and fourth doses in each cycle and as clinically indicated
Mucosal inflammation	Baseline and weekly
Clinical toxicity assessment for signs of infection, electrolyte imbalances, TLS, cardiac, dermatologic, GI, pulmonary, and musculoskeletal effects.	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)

- Pralatrexate - Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)

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K - References

FOLOTYN ® (pralatrexate) Product Monograph. Servier Canada Inc, October 19, 2018.

Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood. 2012 May 3;119(18):4115-22. doi: 10.1182/blood-2011-11-390211

O'Connor OA, Amengual J, Colbourn D, et al. Pralatrexate: a comprehensive update on pharmacology, clinical activity and strategies to optimize use. Leuk Lymphoma. 2017 Nov;58(11):2548-2557. doi: 10.1080/10428194.2017.1306642

O'Connor OA, Pro B, Pinter-Brown L et al. Pralatrexate in patients with relapsed or refractory peripheral t-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 2011;29(9):1182-9.

December 2021 Added reference to alternate schedule in Dosing and Monitoring 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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