***Folotyn*® Solution for Infusion 20mg/ml**

INDICATIONS AND USAGE

Folotyn® is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate with the view to induce responses sufficient to allow patients to be eligible for stem cell transplant. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

In the pivotal open-label, single-arm, Phase II study, recruited patients were pre-treated with a median of 3 prior systemic therapies.

DOSAGE AND ADMINISTRATION

Folotyn® should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Peripheral T-cell Lymphoma

The recommended dose of ***Folotyn***® is 30 mg/m^2 administered as an intravenous (IV) push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity.

For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m2), the recommended dose of FOLOTYN is 15 mg/m2.

Pretreatment Vitamin Supplementation

Folic Acid

Instruct patients to take 1.0 to1.25 mg orally once daily beginning 10 days before the first dose of ***Folotyn***®. Continue folic acid during treatment with ***Folotyn***® and for 30 days after the last dose of ***Folotyn***®. [*see Warnings and Precautions*]

Vitamin B_{12}

Administer vitamin B_{12} (1 mg) intramuscular injection within 10 weeks prior to the first dose of ***Folotyn***® and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with ***Folotyn***® [*see Warnings and Precautions*].

Preparation and Administration Precautions

Folotyn® is a cytotoxic anticancer agent. Caution should be exercised in handling, preparing, and administering of the solution. The use of gloves and other protective clothing is recommended. If ***Folotyn***® comes in contact with the skin, immediately and thoroughly wash with soap and water. If ***Folotyn***® comes in contact with mucous membranes, flush thoroughly with water.

Preparation for Intravenous Push Administration

1. ***Folotyn***® vials should be refrigerated at 2-8°C (36-46°F) until use.

2. ***Folotyn***® vials should be stored in original carton to protect from light until use.

3. ***Folotyn***® is a clear, yellow solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use any vials exhibiting particulate matter or discoloration.

4. The calculated dose of ***Folotyn***® should be aseptically withdrawn into a syringe for immediate use.

5. Do not dilute ***Folotyn***®.

6. ***Folotyn***® vials contain no preservatives and are intended for single use only. After withdrawal of dose, discard vial including any unused portion.

7. Unopened vial(s) of ***Folotyn***® are stable if stored in the original carton at room temperature for 72 hours. Any vials left at room temperature for greater than 72 hours should be discarded.

Monitoring and Dose Modifications
Management of severe or intolerable adverse reactions may require dose omission, reduction, or interruption of ***Folotyn***® therapy.

Monitoring
Complete blood cell counts and severity of mucositis should be monitored weekly. Serum chemistry tests, including renal and hepatic function, should be performed prior to the start of the first and fourth dose of a given cycle.

Dose Modification Recommendations
Prior to administering any dose of:
- Mucositis should be ≤ Grade 1.
- Platelet count should be ≥ 100,000/μL for first dose and ≥ 50,000/μL for all subsequent doses.
- Absolute neutrophil count (ANC) should be ≥ 1,000/μL.

Doses may be omitted or reduced based on patient tolerance. Omitted doses will not be made up at the end of the cycle; once a dose reduction occurs for toxicity, do not re-escalate. For dose modifications and omissions, use the guidelines in Tables 1, 2, and 3.

For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m2), the recommended starting dose of FOLOTYN is 15 mg/m2 with dose modification to 10 mg/m2 for the toxicities specified in Tables 1, 2 and 3.

Table 1 *Folotyn*® Dose Modifications for Mucositis

Mucositis Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤ Grade 1	Dose Upon Recovery in Patients with Severe Renal Impairment
Grade 2	Omit dose	Continue prior dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2	10 mg/m^2
Grade 3	Omit dose	20 mg/m^2	10 mg/m^2
Grade 4	Stop therapy		

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

Table 2 *Folotyn*® Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart	Dose Upon Recovery in Patients with Severe Renal Impairment
Platelet < 50,000/μL	1 week	Omit dose	Continue prior dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2	10 mg/m^2
	3 weeks	Stop therapy		
ANC 500-1,000/μL and no fever	1 week	Omit dose	Continue prior dose	Continue prior dose
ANC 500-1,000/μL with fever or ANC < 500/μL	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support	10 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy		

Table 3 *Folotyn*® Dose Modifications for All Other Treatment-related Toxicities

Toxicity Grade[a] on Day of Treatment	Action	Dose upon Recovery to ≤ Grade 2	Dose Upon Recovery in Patients with Severe Renal Impairment
Grade 3	Omit dose	20 mg/m^2	10 mg/m^2
Grade 4	Stop therapy		

[a] Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0)

DOSAGE FORMS AND STRENGTHS

Folotyn® is available in sterile, single-dose vials containing pralatrexate at a concentration of 20 mg/mL in the following presentations:
20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)
40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelosuppression

Folotyn® can cause myelosuppression, manifested by thrombocytopenia, neutropenia, and/or anemia. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of treatment-related myelosuppression. [*see Dosage and Administration]*

Monitor complete blood counts and omit and/or reduce the dose based on ANC and platelet count prior to each dose [*see Dosage and Administration and Adverse Reactions*].

Mucositis
Folotyn® can cause mucositis. [*see Adverse Reactions]*

Administer vitamin B12 and instruct patients to take folic acid to reduce the risk of mucositis. [*see Dosage and Administration*]

Monitor for mucositis weekly and omit and/ or reduce the dose for grade 2 or higher mucositis. [*see Dosage and Administration*]

Dermatologic Reactions
Folotyn® can cause severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (2.1% of 663 patients) and post marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). They may be progressive and increase in severity with further treatment and may involve skin and subcutaneous sites of known lymphoma.

Monitored closely for dermatologic reactions. Withhold or discontinue ***Folotyn***® based on severity. [*see Dosage and Administration*]

Tumor Lysis Syndrome
Folotyn® can cause tumor lysis syndrome (TLS). Monitor patients who are at increased risk of TLS and treat promptly.

Folic Acid and Vitamin B_{12} Supplementation
Patients should be instructed to take folic acid and receive vitamin B_{12} to potentially reduce treatment-related hematological toxicity and mucositis [*see Dosage and Administration*].

Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, ***Folotyn***® can cause fetal harm when administered to a pregnant woman. ***Folotyn***® was embryotoxic and fetotoxic in rats and rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ***Folotyn***® and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ***Folotyn***® and for 3 months after the last dose[*see Use in Specific Populations*].

Risk of Increased Toxicity with Renal Impairment
Patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m2 based on MDRD) may be at greater risk for increased exposure and adverse reactions. Reduce FOLOTYN dosage in patients with severe renal impairment [*see Dosage and Administration*]

Serious adverse reactions, including toxic epidermal necrolysis and mucositis were reported in patients with end stage renal disease (ESRD) undergoing dialysis who were administered ***Folotyn***® therapy. Avoid ***Folotyn***® use in patients with end stage renal disease with or without dialysis. If the potential benefit of administration justifies the potential risk, monitor renal function and reduce ***Folotyn***® dose based on adverse reactions. [*see Dosage and Administration*]

Hepatic Toxicity

Folotyn® can cause hepatic toxicity and liver function test abnormalities. Persistent liver function test abnormalities may be indicators of hepatic toxicity and require dose modification or discontinuation.

Monitor liver function tests. Omit dose until recovery, adjust or discontinue therapy based on the severity of the hepatic toxicity. [*see Dosage and Administration*].

ADVERSE REACTIONS

The most common adverse reactions (> 35%) observed in patients with peripheral T-cell lymphoma (PTCL) treated with ***Folotyn***® were mucositis, thrombocytopenia, nausea, and fatigue.

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of ***Folotyn***® was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

Most Frequent Adverse Reactions

Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥ 10% of patients)

	N=111					
	Total		Grade 3		Grade 4	
Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**
Any Adverse Event	111	100	48	43	34	31
Mucositis[a]	78	70	19	17	4	4
Thrombocytopenia[b]	45	41	15	14	21	19[b]
Nausea	44	40	4	4	0	0
Fatigue	40	36	5	5	2	2
Anemia	38	34	17	15	2	2
Constipation	37	33	0	0	0	0
Pyrexia	36	32	1	1	1	1
Edema	33	30	1	1	0	0
Cough	31	28	1	1	0	0
Epistaxis	29	26	0	0	0	0
Vomiting	28	25	2	2	0	0
Neutropenia	27	24	14	13	8	7
Diarrhea	23	21	2	2	0	0
Dyspnea	21	19	8	7	0	0
Anorexia	17	15	3	3	0	0
Hypokalemia	17	15	4	4	1	1
Rash	17	15	0	0	0	0
Pruritus	16	14	2	2	0	0
Pharyngolaryngeal pain	15	14	1	1	0	0
Liver function test abnormal[c]	14	13	6	5	0	0
Abdominal pain	13	12	4	4	0	0
Pain in extremity	13	12	0	0	0	0
Back pain	12	11	3	3	0	0
Leukopenia	12	11	3	3	4	4
Night sweats	12	11	0	0	0	0
Asthenia	11	10	1	1	0	0
Tachycardia	11	10	0	0	0	0
Upper respiratory tract infection	11	10	1	1	0	0

[a]Stomatitis or mucosal inflammation of the gastrointestinal and genitourinary tracts.

[b]Five patients with platelets < 10,000/μL

[c]Alanine aminotransferase, aspartate aminotransferase, and transaminases increased

Serious Adverse Events
Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days after their last dose of ***Folotyn***®. The most common serious adverse events (> 3%), regardless of causality, were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. One death from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial. Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all ***Folotyn***® trials at doses ranging from 30 to 325 mg/m^2.

Discontinuations
Twenty-three percent of patients (n = 25) discontinued treatment with ***Folotyn***® due to adverse reactions. The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis (6%, n = 7) and thrombocytopenia (5%, n = 5).

Dose Modifications
The target dose of ***Folotyn***® was 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The majority of patients (69%, n = 77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled doses were administered.

Post Marketing Experience
Toxic epidermal necrolysis, sometimes fatal, has been identified during post-marketing use of ***Folotyn***®. Fatal cases have been reported following the first dose of ***Folotyn***®, including when a reduced dose is given, and have been reported in patients with end-stage renal disease undergoing dialysis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure [*see Warnings and Precautions*].

DRUG INTERACTIONS

In vitro studies indicated that pralatrexate is not a substrate, inhibitor, or inducer of CYP450 isoenzymes and has low potential for drug-drug interactions at CYP450 isoenzymes [*see Clinical Pharmacology*]. *In vitro* transporter studies indicated that pralatrexate is not a significant substrate for P-gp, OCT2, OAT1, and OAT3, is a low to moderate substrate for BCRP, OATP1B1, MRP2, and MRP3, and is a substrate for OATP1B3. Pralatrexate does not significantly inhibit P-gp, BCRP, OCT2, OAT1, and OAT3 and OATP1B3, is a weak inhibitor of OATP1B1 and MRP2, and is a potent inhibitor of MRP3 [*see Clinical Pharmacology*]. MRP3 is a liver transporter implicated in the transport of etoposide, teniposide and methotrexate.

No formal clinical assessments of pharmacokinetic drug-drug interactions between ***Folotyn***® and other drugs have been conducted. The effect of co-administration of the uricosuric drug probenecid (an inhibitor of multiple transporter systems including the multidrug resistance-associated protein 2 (MRP2) efflux transporter) on pralatrexate pharmacokinetics was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in delayed clearance of pralatrexate and a commensurate increase in exposure [*see Clinical Pharmacology*]. Avoid coadministration of ***Folotyn***® with probenecid or nonsteroidal anti-inflammatory drugs. If coadministration is unavoidable, monitor for increased risk of adverse reactions. When administering ***Folotyn***® to patients receiving probenecid or other drugs that may affect relevant transporter systems (e.g. NSAIDs), monitor patients closely for signs of systemic toxicity due to increased drug exposure.

Due to the contribution of renal excretion (approximately 34%) to the overall clearance of pralatrexate, concomitant administration of drugs that are subject to substantial renal clearance (eg, NSAIDs, trimethoprim/ sulfamethotrexate) may result in delayed clearance of pralatrexate.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category D [*see Warnings and Precautions*].

Folotyn® can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and fetotoxic in rats at IV doses of 0.06 mg/kg/day (0.36 mg/m^2/day or about 1.2% of the clinical dose on a mg/m^2 basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose-dependent decrease in fetal viability manifested as an increase in late, early, and total resorptions. There was also a dose-dependent increase in post-implantation loss. In rabbits, IV doses of 0.03 mg/kg/day (0.36 mg/m^2/day) or greater given on gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total resorptions, post-implantation loss, and a decrease in the total number of live fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers
It is not known whether pralatrexate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from this drug, a decision should be made whether to discontinue nursing or to discontinue ***Folotyn***®, taking into account the importance of ***Folotyn***® to the mother.

Pediatric Use

Pediatric patients were not included in clinical studies with ***Folotyn***®. The safety and effectiveness of ***Folotyn***® in pediatric patients have not been established.

Geriatric Use
In the PTCL efficacy study, 36% of patients (n = 40) were 65 years of age and over. No overall differences in efficacy and safety were observed in patients based on age (< 65 years compared with ≥ 65 years). Due to the contribution of renal excretion to overall clearance of pralatrexate (approximately 34%), age-related decline in renal function may lead to a reduction in clearance and a commensurate increase in plasma exposure. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Since elderly patients may be at higher risk, monitor more closely. Omit dose and subsequently adjust or discontinue therapy for exposure related toxicity.

Hepatic Impairment
Formal studies have not been performed with ***Folotyn***® in patients with hepatic impairment. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin > 1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN); and AST or ALT > 5 × ULN if documented hepatic involvement with lymphoma. Treatment with ***Folotyn***® can cause hepatic toxicity and liver function test abnormalities.

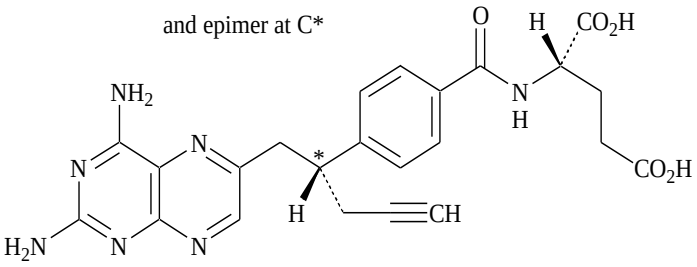
Renal Impairment
For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), the recommended dose of ***Folotyn***® is 15 mg/m^2. For patients with mild to moderate impairment, dose reduction is not necessary. Serious adverse drug reactions, including TEN and mucositis have been reported in patients with ESRD undergoing dialysis. Monitor patients for renal function and for systemic toxicity due to increased drug exposure and adjust dosing accordingly. Avoid the use of ***Folotyn***® in patients with end stage renal disease undergoing dialysis unless the potential benefit justifies the potential risk.

OVERDOSAGE

No specific information is available on the treatment of overdosage of ***Folotyn***®. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on ***Folotyn***®'s mechanism of action the prompt administration of leucovorin should be considered.

DESCRIPTION

Folotyn® (pralatrexate injection) contains pralatrexate, which is an antineoplastic folate analog. Pralatrexate has the chemical name (2*S*)-2-[[4-[(1*RS*)-1-[(2, 4-diaminopteridin-6-yl)methyl]but-3-ynyl]benzoyl]amino]pentanedioic acid. The structural formula is as follows:



Pralatrexate is a 1:1 racemic mixture of *S*- and *R*- diastereomers at the C10 position (indicated with *).

The molecular formula is $C_{23}H_{23}N_7O_5$ and the molecular weight is 477.48 g/mol.

Pralatrexate is an off-white to yellow solid. It is soluble in aqueous solutions at pH 6.5 or higher. Pralatrexate is practically insoluble in chloroform and ethanol. The pKa values are 3.25, 4.76, and 6.17.

Folotyn® is supplied as a preservative-free, sterile, isotonic, non-pyrogenic clear yellow aqueous parenteral solution contained in a single-dose clear glass vial (Type I) for intravenous administration. Each 1 mL of solution contains 20 mg of pralatrexate, sufficient sodium chloride to achieve an isotonic (280-300 mOsm) solution, and sufficient sodium hydroxide, and hydrochloric acid if needed, to adjust and maintain the pH at 7.5-8.5. ***Folotyn***® is supplied as either 20 mg (1 mL) or 40 mg (2 mL) single-dose vials at a concentration of 20 mg/mL.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. It is also a competitive inhibitor for polyglutamylation by the enzyme folylpolyglutamyl synthetase. This inhibition results in the depletion of thymidine and other biological molecules the synthesis of which depends on single carbon transfer.

Pharmacokinetics

Absorption

The pharmacokinetics of pralatrexate administered as a single agent at a dose of 30 mg/m^2 administered as an intravenous push over 3-5 minutes once weekly for 6 weeks in 7-week cycles have been evaluated in 10 patients with PTCL. The total systemic clearance of pralatrexate diastereomers was 417 mL/min (*S*-diastereomer) and 191 mL/min (*R*-diastereomer). The terminal elimination half-life of pralatrexate was 12-18 hours (coefficient of variance [CV] = 62-120%). Pralatrexate total systemic exposure (AUC) and maximum plasma concentration

(C_{max}) increased proportionally with dose (dose range 30-325 mg/m^2, including pharmacokinetics data from high-dose solid tumor clinical studies). The pharmacokinetics of pralatrexate did not change significantly over multiple treatment cycles, and no accumulation of pralatrexate was observed.

Distribution

Pralatrexate diastereomers showed a steady-state volume of distribution of 105 L (*S*-diastereomer) and 37 L (*R*-diastereomer). *In vitro* studies indicate that pralatrexate is approximately 67% bound to plasma proteins. In *In vitro* transporter studies, pralatrexate was a low to moderate substrate for BCRP, OATP1B1, MRP2, and MRP3, and a substrate for OATP1B3. Pralatrexate was not a significant substrate for P-gp, OCT2, OAT1, and OAT3. Pralatrexate did not significantly inhibit P-gp, BCRP, OCT2, OAT1, OAT3 and OATP1B3. Pralatrexate was a weak inhibitor of OATP1B1 (35% inhibition at 100µM) and MRP2 (IC_{50} = 43.5 µM) and a potent inhibitor of MRP3 (IC_{50} < 0.3 µM).

Elimination

Metabolism

In vitro studies using human hepatocytes, liver microsomes and S9 fractions, and recombinant human CYP450 isozymes showed that pralatrexate is not significantly metabolized by the phase I hepatic CYP450 isozymes or phase II hepatic glucuronidases. *In vitro* studies indicated that pralatrexate has low potential to induce or inhibit the activity of CYP450 isozymes.

Excretion

The mean fraction of unchanged pralatrexate diastereomers excreted in urine following a pralatrexate dose of 30 mg/m^2 administered as an intravenous push over 3-5 minutes was 31% (*S*-diastereomer) (CV = 47%) and 38% (*R*-diastereomer) (CV = 45%), respectively. In a mass balance study conducted in patients with advanced cancer, an average of 39% (CV = 28%) of the administered radiolabeled pralatrexate dose was excreted in urine as parent, racemic pralatrexate (fe). An average of 34% (CV = 88%) of the administered dose was recovered in feces as total radiation (feTR) which included both parent pralatrexate and/or any metabolites. An average of 10% (CV = 95%) of total dose was exhaled as total radioactivity over 24 hours.

Pharmacokinetics in Specific Populations

Renal Impairment

34% of pralatrexate was excreted unchanged into urine following a single dose of 30 mg/m^2 administered as an intravenous push over 3-5 minutes. The pharmacokinetics of ***Folotyn***® was studied in patients with varying degrees of renal impairment. In patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), the ***Folotyn***® dose was 15 mg/m^2. Patients with normal renal clearance, mild renal impairment, and moderate renal impairment were all dosed with 30 mg/m^2. Mean exposures of the pralatrexate S-diastereomer and R-diastereomer were comparable across cohorts. The mean fraction of the administered dose excreted as unchanged diastereomers in urine (f_e) decreased with declining renal function. The non-renal clearance and volume of distribution of pralatrexate were unaffected by renal impairment [*see Warnings and Precautions*].

Hepatic Impairment

Pralatrexate has not been studied in patients with hepatic impairment.

There was no significant effect of gender on pharmacokinetics.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies have not been performed with pralatrexate.

Mutagenesis
Pralatrexate did not cause mutations in the Ames test or the Chinese hamster ovary cell chromosome aberration assay. Nevertheless, these tests do not reliably predict genotoxicity for this class of compounds. Pralatrexate did not cause mutations in the mouse micronucleus assay. Based on the pharmacology of pralatrexate and experience with other folate analogs, an increased risk for genotoxicity from pralatrexate treatment cannot be excluded.

Impairment of Fertility
No fertility studies have been performed.

CLINICAL STUDIES

Peripheral T-cell Lymphoma (PTCL)
The safety and efficacy of ***Folotyn***® was evaluated in an open-label, single-arm, multi-center, international trial that enrolled 115 patients with relapsed or refractory PTCL. One hundred and eleven patients were treated with ***Folotyn***® at 30 mg/m^2 once weekly by IV push over 3-5 minutes for 6 weeks in 7-week cycles until disease progression or unacceptable toxicity. Of the 111 patients treated, 109 patients were evaluable for efficacy. Evaluable patients had histologically confirmed PTCL by independent central review using the Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification, and relapsed or refractory disease after at least one prior treatment.

The primary efficacy endpoint was overall response rate (complete response, complete response unconfirmed, and partial response) as assessed by International Workshop Criteria (IWC). The key secondary efficacy endpoint was duration of response. Response assessments were scheduled at the end of cycle 1 and then every other cycle (every 14 weeks). Duration of response was measured from the first day of documented response to disease progression or death. Response and disease progression were evaluated by independent central review using the IWC.

The median age of treated patients was 59.0 years (range 21-85); 68% were male and 32% were female. Most patients were White (72%) and other racial origins included: Black (13%), Hispanic (8%), Asian (5%), other and unknown (<1% each). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status at study entry of 0 (39%), 1 (44%), or 2 (17%). The median time from initial diagnosis to study entry was 15.6 months (range 0.8 – 322.3).

The median number of prior systemic therapies was 3 (range 1-12). Approximately one-fourth of patients (24%, n = 27) did not have evidence of response to any previous therapy. Approximately two-thirds of patients (63%, n = 70) did not have evidence of response to their most recent prior therapy before entering the study.

In all evaluable patients (n = 109) treated with ***Folotyn***®, the response rate, as determined by independent central review by IWC, was 27% (n = 29) (Table 5).

Table 5 Response Analysis per Independent Central Review (IWC)

	Evaluable Patients (N=109)			
	N (%)	**95% CI**	**Median Duration of Response**	**Range of Duration of Response**
Overall Response				
CR+CRu+PR	29 (27)	19, 36	287 days (9.4 months)	1-503 days
CR/CRu	9 (8)			
PR	20 (18)			
Responses ≥ 14 weeks				
CR+CRu+PR	13 (12)	7, 20	Not Reached	98-503 days
CR/CRu	7 (6)			
PR	6 (6)			

Fourteen patients went off treatment in cycle 1; 2 patients were unevaluable for response by IWC due to insufficient materials provided to central review.
CR = Complete Response, CRu = Complete Response unconfirmed, PR = Partial Response

The initial response assessment was scheduled at the end of cycle 1. Of the responders, 66% responded within cycle 1. The median time to first response was 45 days (range 37-349 days).

PRESENTATIONS

Folotyn® is available in single-use clear glass vials containing pralatrexate at a concentration of 20 mg/mL as a preservative-free, sterile, clear yellow solution individually packaged for intravenous use in the following presentations:

20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)
40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

Not all presentations may be available locally.

STORAGE AND HANDLING

Vials must be stored refrigerated at 2-8°C (36-46°F) in original carton to protect from light.

Handle and dispose of ***Folotyn***® according to guidelines issued for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact.

Each vial of ***Folotyn***® is intended for single use only. Any unused drug remaining after injection must be discarded.

Keep out of reach and sight of children.

SHELF LIFE

Refer to the manufacture and expiry date printed on the packaging.

MANUFACTURER

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