Pralym®
Pralatrexate

PATIENT INFORMATION

PRALYM® (pralatrexate injection)

Read the Patient Information that comes with PRALYM® before you start treatment and each time you get treated with PRALYM®. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about PRALYM®.

What is PRALYM®?

PRALYM® is a prescription anti-cancer (chemotherapy) medicine. PRALYM® is used to treat people with a type of cancer called Peripheral T-cell Lymphoma (PTCL) that does not go away, gets worse, or comes back after use of another cancer treatment.

What should I tell my doctor before receiving PRALYM®?

Before you receive PRALYM®, tell your doctor if you:

- have liver problems.
- have kidney problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. PRALYM® can harm your unborn baby. Talk to your doctor about the best way to prevent pregnancy while taking PRALYM®. Tell your doctor right away if you become pregnant while taking PRALYM®.
- are breast-feeding or plan to breast-feed. It is not known if PRALYM® passes into breast milk. You and your doctor should decide if you will take PRALYM® or breast-feed. You should not do both. Talk to your doctor about the best way to feed your baby while you are being treated with PRALYM®.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may affect how PRALYM® works, and PRALYM® may affect how other medicines work. Especially tell your doctor if you take:

- sulfamethoxazole trimethoprim
- non-steroidal anti-inflammatory drugs (NSAIDs)
- probenecid

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them and show it to your doctor or pharmacist each time you start a new medicine.

How will I receive PRALYM®?

- PRALYM® will be given to you as directed by your doctor, as an intravenous (IV) injection into your vein over 3 to 5 minutes.
- PRALYM® is usually given in cycles, one time each week for 6 weeks, with no treatment on the 7th week. Treatment with PRALYM® may be continued as long as it is helpful to you.

To lower your chances of harmful side effects, it is important that you take folic acid and vitamin B_{12} during your treatment with PRALYM®. Your doctor will give you specific instructions for vitamin supplementation.

- You will take folic acid by mouth for 10 days before your first dose of PRALYM®. Do not take more or less folic acid than your doctor tells you to take. Continue taking folic acid every day until your doctor tells you to stop.
- Your doctor will give you a vitamin B_{12} injection into your muscle (intramuscular) before your first dose of PRALYM® and about every 8 to 10 weeks during treatment with PRALYM®.

You should have regular blood tests before and during your treatment with PRALYM®. Your doctor may change your dose of PRALYM® or delay treatment based on the results of your blood tests and on your general condition.

What are the possible side effects of PRALYM®?

PRALYM® may cause serious side effects, including:

- **Low Blood Cell Counts:** PRALYM® can affect your bone marrow and cause you to have low blood cell counts. Your doctor will do blood tests as needed to check your blood cell counts.
- **Low Platelet Count (thrombocytopenia):** Tell your doctor right away if you have any unusual bleeding, such as nosebleeds, or bruising under your skin.
- **Low White Blood Cell Count (neutropenia):** A low white blood cell count can cause you to get infections, which may be serious. Serious illness or death can happen if an infection is not treated right away when white blood cell counts are very low. Tell your doctor right away if you have any of the following signs or symptoms of an infection:
  - fever
  - chills
  - cough
  - shortness of breath
  - pain or burning on urination
- **Low Red Blood Cell Count (anemia):** Tell your doctor if you have any of these symptoms of anemia during treatment with PRALYM®:
  - feeling weak, tired, or you get tired easily
  - you look pale
  - you feel short of breath
- **Redness and sores of the mucous membrane lining of the mouth, lips, throat, digestive tract, and genitals (mucositis).** Discomfort or pain due to mucositis may happen as early as a few days after treatment with PRALYM®. Your doctor should tell you about ways to reduce your risk of getting mucositis, and how to maintain nutrition and control the discomfort from mucositis.
- **Severe skin reactions.** Severe skin reactions may happen after treatment with PRALYM®, especially if you have lymphoma in or under your skin. If your skin reactions are severe, they may lead to serious illness or death. Tell your doctor right away if you have any of the following skin reactions:
  - rash
  - peeling and loss of skin
  - sores
  - blisters
- **Tumor Lysis Syndrome (TLS).** PRALYM® can cause the fast breakdown of certain types of cancer cells. This can lead to TLS. Your doctor may do blood tests to check you for TLS and treat you for TLS if needed.
- **Harm to an unborn baby.** Females should avoid becoming pregnant while being treated with PRALYM®. Talk to your doctor about how to avoid pregnancy while taking PRALYM®.
- **Fever.** Fever is often one of the most common and earliest signs of infection. Follow your doctor's instructions about how often to take your temperature, especially during the days after treatment with PRALYM®. If you have a fever, tell your doctor or nurse right away.
- **Loss of too much fluid from the body (dehydration).** If you feel tired and weak this could be a sign of dehydration. Follow your doctor's instructions for what to do to help prevent or treat dehydration.
- **Shortness of breath.** Tell your doctor if this is a problem for you.

Common side effects of PRALYM® include:

- nausea
- vomiting
- tiredness
- constipation
- swelling
- cough
- nosebleed
- diarrhea

These are not all the possible side effects of PRALYM®. For more information, ask your doctor or pharmacist.

General information about PRALYM®

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. This patient information leaflet summarizes the most important information about PRALYM®. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about PRALYM® that is written for health professionals.

What are the ingredients in PRALYM®?

Active ingredient: pralatrexate

Inactive ingredients: sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

What is PTCL?

PTCL is a rare type of non-Hodgkin's lymphoma, a cancer of the lymphatic system. It happens when a type of T-cell (a kind of white blood cell) grows too much. PTCL may be found in different parts of the body, such as the lymph nodes, skin, bone marrow, liver, or spleen.

To access the latest revision of this prescribing information, please visit our website: www.nanoalvand.com

Pralym®
Pralatrexate

PRALYM® SOLUTION FOR IV INJECTION

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

PRALYM® is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

2. DOSAGE AND ADMINISTRATION

2.1. General Dosing and Administration

Pretreatment Vitamin Supplementation

Folic Acid: Patients should take folic acid 1.0-1.25 mg orally once daily beginning 10 days before the first dose of PRALYM®. Continue folic acid during the full course of therapy and for 30 days after the last dose of PRALYM® *[see Warnings and Precautions (5.1)(5.2)]*

Vitamin B_{12} : Administer vitamin B_{12} 1 mg intramuscularly within 10 weeks prior to the first dose of PRALYM® and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with PRALYM® *[see Warnings and Precautions (5.1)(5.2)]*

Dosing and Administration

The recommended dose of PRALYM® is 30 mg/m² administered as an intravenous push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, intravenous line once weekly for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity. The calculated dose of PRALYM® should be aseptically withdrawn into a syringe for immediate use. Do not dilute PRALYM®.

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

PRALYM® 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.

2.2. Monitoring and Dose Modifications

Management of severe or intolerable adverse reactions may require dose omission, reduction, or discontinuation of PRALYM® therapy.

Monitoring

Monitor complete blood cell counts and severity of mucositis at baseline and weekly. Perform serum chemistry tests, including renal and hepatic function, prior to the start of the first and fourth dose of each cycle.

Dose Modification Recommendations

Prior to administering any dose of PRALYM®:

- Mucositis should be ≤ Grade 1.
- Platelet count should be ≥ 100,000/mcL for first dose and ≥ 50,000/mcL for all subsequent doses.
- Absolute neutrophil count (ANC) should be ≥ 1,000/mcL.

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 PRALYM® is 15 mg/m² with dose modification to 10 mg/m² for the toxicities specified in Tables-1, 2, and 3.

Table 1: PRALYM® 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/m²	10 mg/m²
Grade 3	Omit dose	20 mg/m²	10 mg/m²
Grade 4	Stop therapy		

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

Table 2: PRALYM® 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/mcL	1 week	Omit dose	Continue prior dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m²	10 mg/m²
	3 weeks	Stop therapy		
ANC 500-1,000/mcL and no fever	1 week	Omit dose	Continue prior dose	Continue prior dose
ANC 500-1,000/mcL with fever or ANC < 500/mcL	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/m² with G-CSF or GM-CSF support	10 mg/m² with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Stop therapy		

G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor

Table 3: PRALYM® 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/m²	10 mg/m²
Grade 4	Stop therapy		

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

2.3. Special Handling Precautions

PRALYM® 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 PRALYM® comes in contact with the skin, immediately and thoroughly wash with soap and water.

If PRALYM® comes in contact with mucous membranes, flush thoroughly with water.

- PRALYM® vials should be refrigerated at 2-8°C (36-46°F) until use.
- PRALYM® vials should be stored in original carton to protect from light until use.
- PRALYM® vials contain no preservatives and are intended for single use only. After withdrawal of dose, discard vial including any unused portion.

3. DOSAGE FORMS AND STRENGTHS

PRALYM® is available as a clear yellow solution in sterile, single-dose vials containing PRALYM® at a concentration of 20 mg/mL in the following presentation:

20 mg of PRALYM® in 1 mL solution in a vial (20 mg/1 mL)

4. CONTRAINDICATIONS

Hypersensitivity to PRALYM® or any component of the formulation.

5. WARNINGS AND PRECAUTIONS:

5.1. Bone Marrow Suppression

PRALYM® can cause bone marrow suppression, manifested by thrombocytopenia, neutropenia, and/or anemia. Monitor complete blood counts and omit and/or reduce the dose based on ANC and platelet count prior to each dose as outlined in Table 2. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of treatment-related hematological toxicity *[see Dosage and Administration (2.1)(2.2) and Adverse Reactions (6.1)]*.

5.2. Mucositis

PRALYM® can cause mucositis. Monitor for mucositis weekly and if ≥ Grade 2 mucositis is observed, omit and/or reduce the dose as outlined in Table-1. Administer vitamin B_{12} and instruct patients to take folic acid to reduce the risk of mucositis *[see Dosage and Administration (2.1)(2.2) and Adverse Reactions (6.1)]*.

5.3. Dermatologic Reactions

PRALYM® can cause severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies 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. Monitor patients with dermatologic reactions closely, and if severe, withhold or discontinue PRALYM® *[see Adverse Reactions (6.2) and Use in Specific Populations (8.6)]*.

5.4. Tumor Lysis Syndrome

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

5.5. Hepatic Toxicity

PRALYM® 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 (2.2) and Use in Specific Populations (8.5)]*.

5.6. Risk of Increased Toxicity in the Presence of Impaired Renal Function

Patients with moderate to severe renal function impairment may be at greater risk for increased exposure and toxicity. Monitor patients for renal function and systemic toxicity and adjust dosing accordingly.

Serious adverse drug reactions including toxic epidermal necrolysis and mucositis were reported in patients with end stage renal disease (ESRD) undergoing dialysis who were administered PRALYM® therapy. Avoid PRALYM® use in patients with end stage renal disease including those undergoing dialysis unless the potential benefit justifies the potential risk. Concurrent use with drugs with substantial renal clearance (eg, NSAIDs, sulfamethoxazole/trimethoprim) may result in delayed PRALYM® clearance *[see Dosage and Administration (2.2), Adverse Reactions (6.2), Use in Specific Populations (8.6), and Clinical Pharmacology (11.2)]*.

5.7. Embryo-Fetal Toxicity

PRALYM® can cause fetal harm when administered to a pregnant woman. PRALYM® was embryotoxic and fetotoxic in rats and rabbits. 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 *[see Use in Specific Populations (8.1)]*.

6. ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*
- Mucositis *[see Warnings and Precautions (5.2)]*
- Dermatologic Reactions *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Hepatic Toxicity *[see Warnings and Precautions (5.5)]*

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

6.1. Clinical Trials Experience

The safety of Pralatrexate was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m² 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/mcL

[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 Pralatrexate. 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 Pralatrexate trials at doses ranging from 30 to 325 mg/m².

Discontinuations

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

Dose Modifications

The target dose of Pralatrexate was 30 mg/m² 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.

6.2. Post Marketing Experience

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.

Dermatologic Reactions

Toxic epidermal necrolysis, sometimes fatal, has been reported during post-marketing use of Pralatrexate. Fatal cases have been reported following the first dose of Pralatrexate, including when a reduced dose is given, and have been reported in patients with end-stage renal disease undergoing dialysis *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Pharmacology (11.2)].*

7. DRUG INTERACTIONS

No formal clinical assessments of pharmacokinetic drug-drug interactions between Pralatrexate 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 (11.2)].*

When administering PRALYM® to patients receiving probenecid or other drugs that may affect relevant transporter systems (eg, NSAIDs), monitor patients closely for signs of systemic toxicity due to increased drug exposure.

8. USE IN SPECIAL POPULATIONS

8.1. Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.7)]*

Embryo-Fetal Toxicity

PRALYM® 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/m²/day or about 1.2% of the clinical dose on a mg/m² 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/m²/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.

8.2. Nursing Mothers

It is not known whether PRALYM® 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 PRALYM®, taking into account the importance of PRALYM® to the mother.

8.3. Pediatric Use

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

8.4. 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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.5)(5.6), Use in Specific Populations (8.5)(8.6), and Clinical Pharmacology (11.2)].*

8.5. Hepatic Impairment

The safety, efficacy and pharmacokinetics of Pralatrexate have not been evaluated 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 x upper limit of normal (ULN); and AST or ALT > 5 x ULN if documented hepatic involvement with lymphoma. Treatment with PRALYM® can cause hepatic toxicity and liver function test abnormalities *[see Dosage and Administration (2.2) and Warnings and Precautions (5.6)].*

8.6. Renal Impairment

For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m²), the recommended dose of Pralatrexate is 15 mg/m². For patients with mild to moderate renal 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 Pralatrexate in patients with end stage renal disease undergoing dialysis unless the potential benefit justifies the potential risk *[see Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.3, 5.6), Adverse Reactions (6.2), and Clinical Pharmacology (11.2)].*

9. OVERDOSAGE

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

10. DESCRIPTION

PRALYM® (PRALYM® injection) contains Pralatrexate and is a sterile, clear, yellow aqueous parenteral solution in a clear glass vial, PRALYM® is available as 20 mg/1 mL single-use vials. PRALYM® contains Pralatrexate as active ingredient , sodium chloride and water for injection as inactive ingredients. Sodium hydroxide and/or hydrochloric acid may be used to adjust the pH.

11. CLINICAL PHARMACOLOGY

11.1. Mechanism of Action

PRALYM® 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.

11.2. Pharmacokinetic:

Absorption

The pharmacokinetics of Pralatrexate administered as a single agent at a dose of 30 mg/m² 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 (Cmax) increased proportionally with dose (dose range 30-325 mg/m², 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.

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.

Excretion

The mean fraction of unchanged Pralatrexate diastereomers excreted in urine following a Pralatrexate dose of 30 mg/m² 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 (fe^{TR}) 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

In patients with cancer without renal impairment, approximately 34% of Pralatrexate was excreted unchanged into urine following a single dose of 30 mg/m² administered as an intravenous push over 3-5 minutes. The pharmacokinetics of Pralatrexate was studied in patients with varying degrees of renal impairment. In patients with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m²), the Pralatrexate dose was 15 mg/m². Patients with normal renal clearance, mild renal impairment, and moderate renal impairment were all dosed with 30 mg/m². 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 (fe) decreased with declining renal function. The non-renal clearance and volume of distribution of Pralatrexate were unaffected by renal impairment *[see Use in Specific Populations (8.6)].*

Hepatic Impairment

Pralatrexate has not been studied in patients with hepatic impairment.

Gender

There was no significant effect of gender on pharmacokinetics.

Drug Interactions

In vitro studies indicated that Pralatrexate does not induce or inhibit the activity of CYP450 isozymes at concentrations of Pralatrexate that can be reasonably expected clinically.

In vitro, Pralatrexate is a substrate for the breast cancer resistance protein (BCRP), MRP2, multidrug resistance-associated protein 3 (MRP3), and organic anion transport protein 1B3 (OATP1B3) transporter systems at concentrations of Pralatrexate that can be reasonably expected clinically. Pralatrexate is not a substrate of the P glycoprotein (P-gp), organic anion transport protein 1B1 (OATP1B1), organic cation transporter 2 (OCT2), organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3) transporter systems.

In vitro, Pralatrexate inhibits MRP2 and MRP3 transporter systems ([I]/IC50 > 0.1) at concentrations of Pralatrexate that can be reasonably expected clinically. MRP3 is a transporter that may affect the transport of etoposide and teniposide.

In vitro, Pralatrexate did not significantly inhibit the P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3 transporter systems at concentrations of Pralatrexate that can be reasonably expected clinically.

12. NONCLINICAL TOXICOLOGY

12.1. 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.

Impairment of Fertility

No fertility studies have been performed.

13. CLINICAL STUDIES

Peripheral T-cell Lymphoma (PTCL)

The safety and efficacy of Pralatrexate 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 Pralatrexate at 30 mg/m² 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 Pralatrexate, 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)			

14. HOW SUPPLIED / STORAGE AND HANDLING

14.1. How supplied:

PRALYM® is available in single-dose clear glass vials containing PRALYM® 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 PRALYM® in 1 mL solution in a vial (20 mg / 1 mL)

Vials must be stored in refrigerator (2-8 °C). Keep vial in outer carton to protect from light.

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

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

15. PATIENT COUNSELING INFORMATION

Patients should be instructed to read the Patient Information carefully.

15.1. Need for Folic Acid and Vitamin B_{12}

Advise patients treated with PRALYM® to take folic acid and vitamin B_{12} as a prophylactic measure to reduce the risk of possible side effects *[see Dosage and Administration (2.1)].*

15.2. Low Blood Cell Counts

Inform patients of the risk of low blood cell counts and to immediately contact their physician should any signs of infection develop, including fever. Inform patients to contact their physician if bleeding or symptoms of anemia occur.

15.3. Mucositis

Inform patients of the signs and symptoms of mucositis. Instruct patients on ways to reduce the risk of its development, and on ways to maintain nutrition and control discomfort from mucositis if it occurs.

15.4. Fatal Dermatologic Reactions

Advise patients about the risks for and the signs and symptoms of dermatologic reactions. Instruct patients to immediately notify their physician if any skin reactions occur *[see Warnings and Precautions (5.3)].*

15.5. Tumor Lysis Syndrome

Inform patients about the risk of and the signs and symptoms of tumor lysis syndrome. Patients should be instructed to notify their physician if they experience these symptoms *[see Warnings and Precautions (5.4)].*

15.6. Concomitant Medications

Patients should be instructed to inform their physician if they are taking any concomitant medications including prescription drugs (such as trimethoprim/sulfamethoxazole) and nonprescription drugs (such as nonsteroidal anti-inflammatory drugs) *[see Drug Interactions (7)].*

15.7. Pregnancy/Nursing

Patients should be instructed to tell their physician if they are pregnant or plan to become pregnant due to the risk of fetal harm. Patients should be instructed to tell their physician if they are nursing.

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