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Pralym®

Pralatrexate

Solution for IV Injection

Read this leaflet carefully before you start taking this medication

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 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.

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 to10 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 and/or Hydrochloric Acid, Water for injection q.s to 1mL

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

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Manufacturing Authorization Holder & Manufacturing Site:
NanoAlvand Co.
Tehran, Iran

Pharmaceutical Incubation Center, Avicenna Tech. Park of Tehran University of Medical Sciences, No. 1462, North Kargar Ave., Tehran, Iran
P.O. Box: 1439955991
TEL: +9821-88020579
Fax: +9821-88020597
E-mail: info@nanoalvand.com
URL: www.nanoalvand.com

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Pralym®

Pralatrexate

Solution for IV Injection

Read all of this leaflet carefully for complete instruction

1. INDICATIONS AND USAGE

PRALATREXATE 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 PRALATREXATE. Continue folic acid during the full course of therapy and for 30 days

after the last dose of PRALATREXATE.

Vitamin B_{12}: Administer vitamin B_{12} 1 mg intramuscularly within 10 weeks prior to the first dose of PRALATREXATE and every 8-10 weeks thereafter. Subsequent vitamin B_{12} injections may be given the same day as treatment with PRALATREXATE.

Dosing and Administration

The recommended dose of PRALATREXATE is 30 mg/m^2 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 PRALATREXATE should be aseptically withdrawn into a syringe for immediate

use. Do not dilute PRALATREXATE.

For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), the recommended dose of PRALATREXATE is 15 mg/m^2.

PRALATREXATE 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 PRALATREXATE 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 PRALATREXATE:

- 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 m^2), the recommended starting dose of PRALATREXATE is 15 mg/m^2 with dose modification to 10 mg/m^2 for the toxicities specified in Tables 1, 2, and 3.

Table 1: PRALATREXATE 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: PRALATREXATE Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon Restart	Dos e 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/m^2	10 mg/m^2
	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/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		
G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor				

Table 3: PRALATREXATE 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)			

2.3. Special Handling Precautions

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

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

- PRALATREXATE vials should be refrigerated at 2-8°C (36-46°F) until use.
- PRALATREXATE vials should be stored in original carton to protect from light until use.
- PRALATREXATE 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

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

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

4. CONTRAINDICATIONS

Hypersensitivity to PRALATREXATE or any component of the formulation.

5. WARNINGS AND PRECAUTIONS

5.1. Bone Marrow Suppression

PRALATREXATE 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.

5.2. Mucositis

PRALATREXATE 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.

5.3. Dermatologic Reactions

PRALATREXATE 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 PRALATREXATE.

5.4. Tumor Lysis Syndrome

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

5.5. Hepatic Toxicity

PRALATREXATE 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.

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 PRALATREXATE therapy. Avoid PRALATREXATE 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 PRALATREXATE clearance.

5.7. Embryo-Fetal Toxicity

PRALATREXATE can cause fetal harm when administered to a pregnant woman. PRALATREXATE 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.

6. ADVERSE REACTIONS

>10%:

Cardiovascular: Edema (30%)

Central nervous system: Fatigue (36%)

Dermatologic: Skin rash (15%), pruritus (14%; grade 3: 2%), night sweats (11%)

Endocrine & metabolic: Hypokalemia (15%)

Gastrointestinal: Mucositis (70%; grade 3: 17%; grade 4: 4%), nausea (40%), constipation (33%), vomiting (25%), diarrhea (21%), anorexia (15%), abdominal pain (12%)

Hematologic & oncologic: Thrombocytopenia (41%; grade 3: 14%; grade 4: 19%), anemia (34%; grade 3: 15%; grade 4: 2%), neutropenia (24%; grade 3: 13%; grade 4: 7%), leukopenia (11%; grade 3: 3%; grade 4: 4%)

Hepatic: Increased serum transaminases (13%; grade 3: 5%)

Infection: Infection

Neuromuscular & skeletal: Limb pain (12%), back pain (11%)

Respiratory: Cough (28%), epistaxis (26%), dyspnea (19%), pharyngolaryngeal pain (14%)

Miscellaneous: Fever (32%)

1% to 10%:

Cardiovascular: Tachycardia (10%)

Endocrine & metabolic: Severe dehydration (>3%)

Hematologic & oncologic: Febrile neutropenia (serious: >3%)

Infection: Sepsis (serious: >3%)

Neuromuscular & skeletal: Weakness (10%)

Respiratory: Upper respiratory tract infection (10%)

<1%, postmarketing, and/or case reports: Dermal ulcer, desquamation, intestinal obstruction, lymphocytopenia, odynophagia, pancytopenia, toxic epidermal necrolysis, tumor lysis syndrome

7. DRUG INTERACTIONS

7.1. Risk X (Avoid Combination)

BCG (Intravesical), Cladribine, Natalizumab, Pimecrolimus, Tacrolimus (Topical), Vaccines (Live)

Exceptions: Smallpox and Monkeypox Vaccine (Live), Upadacitinib

7.2. Risk D (Consider therapy modification)

Baricitinib, Echinacea, Fingolimod, Leflunomide, Lenograstim, Lipegfilgrastim, Nivolumab, Palifermin, Roflumilast, Salicylates, Sipuleucel-T, Tofacitinib, Vaccines (Inactivated)

7.3. Risk C (Monitor therapy)

Coccidioides immitis Skin Test, Denosumab, Nonsteroidal Anti-Inflammatory Agents, Ocrelizumab, Pidotimod, Probenecid, Pyrimethamine, Sapropterin, Siponimod, Sulfamethoxazole, Tertomotide, Trastuzumab, Trimethoprim, Smallpox and Monkeypox Vaccine (Live)

8.USE IN SPECIAL POPULATIONS

8.1. Pregnancy

Pregnancy Risk Factor: **D**

PRALATREXATE can cause fetal harm when administered to a pregnant woman. 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 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

PRALATREXATE, taking into account the importance of PRALATREXATE to the mother.

8.3. Pediatric use

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

8.4. Geriatric Use

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.

8.5. Hepatic Impairment

The safety, efficacy and pharmacokinetics of PRALATREXATE have not been evaluated in patients with hepatic impairment. Treatment with PRALATREXATE can cause hepatic toxicity and liver function test abnormalities.

8.6. Renal Impairment

For patients with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), the recommended dose of PRALATREXATE is 15 mg/m^2. 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.

9. OVERDOSAGE

No specific information is available on the treatment of overdosage of PRALATREXATE. If an overdose occurs, general supportive measures

should be instituted as deemed necessary by the treating physician. Based on PRALATREXATE's mechanism of action, consider the prompt administration of leucovorin.

10. DESCRIPTION

PRALYM® (PRALATREXATE injection) contains Pralatrexate and is a sterile, clear, yellow aqueous parenteral solution in a clear glass vial, PRALYM® is available as 20mg/1mL 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

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.

11.2. Pharmacokinetic

Distribution: S-diastereomer: 105 L; R-diastereomer: 37 L

Protein binding: ~67%

Metabolism: Not significantly metabolized by phase

I hepatic isoenzymes or phase II glucuronidases.

Half-life elimination: 12 to 18 hours

Excretion: Urine (~34% as unchanged drug; parent drug [racemic pralatrexate]: ~39%); Feces (34%); Respiratory (10% [exhaled])

12.HOW SUPPLIED / STORAGE AND HANDLING

12.1. How supplied

PRALYM® is available in single-dose 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)

12.2. Storage Conditions

Store in refrigerator (2-8 °C). Keep vial in outer carton to protect from light.

12.3. Handling and Disposal

Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact. Several guidelines on this subject have been published. References for some of these guidelines are as below:

- NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and

Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

- OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
- American Society of Health-System Pharmacists. (2006) ASHP Guidelines on Handling Hazardous Drugs. Am J Health-Syst Pharm. 2006; 63:1172-1193.

Disclaimer: This leaflet was last approved in December 2019. This content should not be considered complete and may not include all the information needed to use PRALATREXATE for injection safely and effectively.

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

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Manufacturing Authorization Holder & Manufacturing Site:
NanoAlvand Co.
Tehran, Iran

Pharmaceutical Incubation Center, Avicenna Tech. Park of Tehran University of Medical Sciences, No. 1462, North Kargar Ave., Tehran, Iran
P.O. Box: 1439955991
TEL: +9821-88020579
Fax: +9821-88020597
E-mail: info@nanoalvand.com
URL: www.nanoalvand.com

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