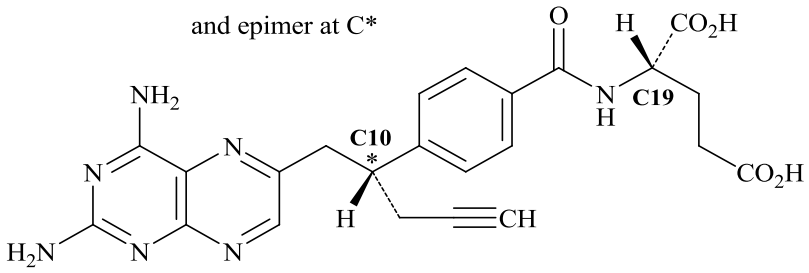
PRODUCT INFORMATION

FOLOTYN® solution for infusion
20 mg in 1 mL and 40 mg in 2 mL

NAME OF THE MEDICINE pralatrexate

Chemical name:
N-(4-{1-[(2,4-diaminopteridin-6-yl)methyl]but-3-yn-1-yl}benzoyl)-L-glutamic acid

Chemical Structure:



Molecular formula: $C_{23}H_{23}N_7O_5$ Molecular weight: 477.48

CAS Registry Number: 146464-95-1

DESCRIPTION

Pralatrexate is an off-white to yellow solid. It is soluble in aqueous solutions at pH 6.5 or higher, and practically insoluble in chloroform and ethanol. The aqueous solubility of pralatrexate is U-shaped over a pH range of 1-7, and is controlled by the neutral species within this range. The intrinsic solubility of the neutral species was calculated as 132 µM or 63 µg/mL. The lowest solubility is within the range of pH 3 to pH 6, which correlates with the measured pKa values of pralatrexate of 3.25 and 4.76 for the first two carboxylic acid groups, and 6.17 for the conjugate acid of the basic group. The partition coefficient (log P) is 0.025 (neutral) and 0.011 (monoanionic). Pralatrexate is a 1:1 mixture of *R*- and *S*-diastereomers at the C10 epimeric chiral centre, with a fixed chiral centre at C19.

Description of the product
Pralatrexate solution for infusion is a preservative-free, sterile, isotonic, non-pyrogenic clear yellow aqueous parenteral solution. It is supplied in a clear glass, single-use vial with a chlorobutyl stopper covered with an aluminium flip-off seal. Each 1 mL of solution contains 20 mg of pralatrexate, supplied as either 20 mg (1 mL) or 40 mg (2 mL) vials. The inactive ingredients in the solution for infusion are sodium chloride (approximately 6.3 mg in 1 mL of solution), a sufficient quantity of sodium hydroxide and hydrochloric acid if needed, to adjust and maintain the pH at 7.5-8.5, and water for injections.

PHARMACOLOGY

Actions

Pralatrexate is an antineoplastic folate analogue that is a substrate for reduced folate transporters, including reduced folate carrier 1 (RFC-1) and the enzyme folylpolyglutamyl synthetase (FPGS), resulting in internalisation and accumulation within tumour cells. Pralatrexate exerts anti-folate activity via the inhibition of dihydrofolate reductase (DHFR), resulting in a disruption of DNA synthesis and subsequent tumour cell death. *In vitro* testing indicates that pralatrexate exhibits cytotoxic activity across a number of human lymphoproliferative tumour cell types. Pralatrexate produced a significant reduction in tumour size in human tumour xenograft models.

The pharmacotherapeutic group for pralatrexate is "antineoplastic agents, antimetabolites, folic acid analogues". The ATC code is L01BA05.

Pharmacokinetics

Absorption

Pralatrexate is administered by intravenous infusion, therefore absorption is not applicable. Maximum pralatrexate serum concentrations (C_{max}) were generally observed at or shortly after the end of the infusion. The pharmacokinetics of pralatrexate administered as a single 30 mg/m^2 dose by intravenous infusion over 3-5 minutes once weekly for 6 weeks in 7-week cycles was evaluated in 10 patients with peripheral T-cell lymphoma (PTCL). The mean C_{max} value for pralatrexate was 5.8 μg/mL. The mean total systemic exposure ($AUC_{(0-\infty)}$) was 268 μg/mL·min.

The C_{max} and $AUC_{(0-\infty)}$ increased with the dose (dose range of 30-325 mg/m^2, including pharmacokinetic data from high-dose solid tumour clinical studies). The pharmacokinetics of pralatrexate did not change significantly over the course of a single treatment cycle (6 doses) in 5 patients, and no accumulation of pralatrexate was observed. The potential for accumulation beyond a single cycle of treatment has not been assessed.

Distribution

In the pivotal PDX-008 study in PTCL, pralatrexate diastereomers showed a steady-state volume of distribution of 105 L (*S*-diastereomer) and 37 L (*R*-diastereomer). *In vitro* studies indicated that pralatrexate is approximately 65% bound to human plasma proteins.

Metabolism

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

Excretion

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%). The mean fraction of unchanged pralatrexate diastereomers excreted in urine following a pralatrexate dose of 30 mg/m^2 administered as an IV infusion over 3-5 minutes was 31% (*S*-diastereomer) (CV = 47%) and 38% (*R*-diastereomer) (CV = 45%), respectively. Non-renal clearance accounts for the

elimination of the remainder (approximately two-thirds) of the administered pralatrexate. The exact mechanism of the non-renal clearance is unknown.

A mass-balance study has not been completed in humans.

Special populations

Renal impairment
Limited pharmacokinetic data are available for patients with moderate renal impairment (eGFR < 60 mL/min) and no data are available for patients with severe renal impairment (eGFR < 30 mL/min). Approximately 34% of pralatrexate was excreted unchanged into urine following a single dose of 30 mg/m^2 administered as an intravenous infusion over 3-5 minutes. Covariate analysis showed that pralatrexate clearance moderately decreased with decreasing creatinine clearance. 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. Avoid FOLOTYN use in patients with end stage renal disease including those undergoing dialysis unless the potential benefit justifies the potential risk.

Hepatic impairment
No pharmacokinetic data are available for patients with hepatic impairment. Approximately two-thirds of pralatrexate is eliminated by non-renal clearance that may be largely via hepatobiliary excretion. For this reason, a risk for increased exposure in patients with hepatic impairment cannot be excluded.

Elderly
Due to the contribution of renal excretion to overall clearance of pralatrexate, age-related decline in renal function may lead to a reduction in clearance and a commensurate increase in plasma exposure

CLINICAL TRIALS

The efficacy of FOLOTYN was evaluated in an open-label, single-arm, non-randomised, international study (PDX-008) 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 intravenous infusion over 3-5 minutes for 6 weeks in 7-week cycles until disease progression or unacceptable toxicity. If methylmalonic acid level was >200 nM and / or homocysteine >10 µM, vitamin supplementation was given for ≥10 days prior to first dose of pralatrexate; otherwise, patients received concurrent folic acid 1-1.25 mg PO daily) and vitamin B12 (1 mg IM every 8-10 weeks). Vitamin supplementation continued for at least 1 month after discontinuation of pralatrexate.

Of the 111 patients treated, 109 patients were evaluable for efficacy. Evaluable patients had histologically confirmed PTCL, as confirmed 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. Commoner subtypes included for study were PTCL-unspecified (n=59), primary systemic anaplastic

large cell lymphoma (n=17), angioimmunoblastic T cell lymphoma (n=13) and transformed mycosis fungoides (n=12).

The primary efficacy endpoint was response rate (complete response, complete response unconfirmed and partial response) as assessed by independent central review using International Workshop Criteria (IWC). 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 and by the local investigators. Overall survival and progression-free survival was estimated by the Kaplan-Meier method.

The median age of treated patients was 59.0 years (range 21-85); 68% were male and 32% were female. 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). In all treated evaluable patients (n = 109) the response rate was 29% (n = 32), with 12 of these patients achieving a complete response, as determined by independent central review using IWC.

Table 1: Response analysis

	Evaluable patients (N=109)			
	N (%)	**95% CI**	**Median duration of response**	**95% CI**
Primary assessment: Overall response per independent central review (IWC)				
CR+CRu+PR	32 (29)	21, 39	10.1 months	3.4 months – not estimable
CR/CRu	12 (11)			
PR	20 (18)			
Secondary assessment: Overall response per local investigator				
CR+CRu+PR	43 (39)	30, 49	8.1 months	5.1 – 12.5 months
CR/CRu	20 (18)			
PR	23 (21)			

CR = Complete response, CRu = Complete response unconfirmed, PR = Partial response

Of the responders, 63% responded within cycle 1. The median time to first response was 45 days (range 37 – 349 days). Approximately two-thirds of patients (63%, n = 69) did not have evidence of response to their most recent prior therapy before entering the study. Of these 69 patients, 17 patients (25%) responded to pralatrexate per IWC. Approximately one-fourth of patients (24%, n = 26) did not have evidence of response to any previous therapy. Of these 26 patients, 5 patients (19%) responded to pralatrexate per IWC review.
The median progression-free survival for the efficacy analysis set was 3.5 months (95% confidence interval (CI), 1.7 to 4.8 months). The median overall survival was 14.5 months (95% CI, 10.6 to 22.5 months). Forty-seven patients (43%) were censored for overall survival because they were still alive at the time of the data cut-off date.

Response rate by histopathology was similar among the subtypes, with the possible exception of angioblastic T-cell lymphoma in which there was only 1 responder out of a limited number of patients (n=13) with this histological subtype, for a responder rate

for that subtype of 8%. The study was not designed to assess tumour responsiveness by histological subtype.

Four patients in PDX-008 achieved a response following treatment with pralatrexate, confirmed by independent central review. These patients were able to proceed to transplant as their subsequent therapy, and have achieved a prolonged response.

INDICATIONS

FOLOTYN is indicated for the treatment of adult patients with peripheral T-cell lymphoma (nodal, extranodal, and leukaemic/disseminated) who have progressed after at least one prior therapy.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Pregnancy or breast-feeding (see **PRECAUTIONS**).

PRECAUTIONS

Folic acid and vitamin B_{12} supplementation

Patients should be instructed to take folic acid and vitamin B_{12} to potentially reduce treatment-related haematological toxicity and mucosal inflammation (see **DOSAGE AND ADMINISTRATION** section).

Bone marrow suppression

Pralatrexate can suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anaemia. Folic acid and vitamin B12 supplementation is recommended to reduce the risk of haematological toxicity. Dose modifications are based on absolute neutrophil count (ANC) and platelet count prior to each dose (see **DOSAGE AND ADMINISTRATION** section).

Mucosal inflammation

Treatment with pralatrexate can cause mucosal inflammation. Monitor for mucosal inflammation weekly and if ≥ Grade 2 mucosal inflammation is observed, omit and/or reduce the dose (see **DOSAGE AND ADMINISTRATION** section). Administer vitamin B12 and instruct the patient to take folic acid to reduce the risk of mucosal inflammation.

Dermatological reactions

FOLOTYN can cause severe dermatological reactions, which may result in death. Dermatological reactions with FOLOTYN have ranged from alopecia (reported in 12% of patients in Study PDX-008), pruritus (7%) and rash (7%), to serious or fatal skin exfoliation, ulceration, toxic epidermal necrolysis.

There have been a small number of fatal dermatological reactions both within the clinical trials and post-marketing setting with pralatrexate. In most cases the reaction occurred after the first dose. In 5/6 cases, there was extensive skin involvement by PTCL.

Such reactions involve skin and subcutaneous sites of known lymphoma. The majority of these reactions are mild and self-limiting; however serious and potentially life-threatening

events including skin exfoliation, ulceration and toxic epidermal necrolysis (TEN) have occurred, including fatal cases. Patients with extensive skin disease or a history of adverse skin reactions appear to be at highest risk of developing these severe reactions, with onset occurring early in the course of therapy in most cases. Skin reactions may be progressive and increase in severity with further treatment. Monitor patients with dermatological reactions closely, and if severe, discontinue FOLOTYN (see Table 3 under **DOSAGE AND ADMINISTRATION**).

Pneumonitis

Pneumonitis has been reported in patients treated with FOLOTYN. Across clinical studies, pneumonitis was reported in 9 patients (1.3%), including 7 patients with PTCL. Most cases were considered causally related to pralatrexate. In one case, it was considered to be an acute hypersensitivity reaction to pralatrexate.

Tumour lysis syndrome

Tumour lysis syndrome has been reported in patients with lymphoma receiving pralatrexate. Patients should be monitored closely and treated for complications.

Hepatic impairment

Administration of pralatrexate to patients with hepatic impairment should only be done with caution and close monitoring of liver function and adverse events (see **DOSAGE AND ADMINISTRATION** and **Pharmacokinetics**).

Renal impairment

Administration of pralatrexate to patients with moderate to severe renal function impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min) should only be done with caution and close monitoring of renal function and adverse events (see **ADVERSE EFFECTS**, **DOSAGE AND ADMINISTRATION** and **Pharmacokinetics**).

Sodium content

FOLOTYN contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

Driving and operating dangerous machinery

There have been no studies relating to effects of pralatrexate treatment on the ability to drive or operate machinery. However, patients should be advised that they may experience fatigue, blurred vision or dizziness during treatment with FOLOTYN and should be advised against driving or operating machinery, if they experience any of these side effects.

Effects on fertility

There are no human data on the effect of pralatrexate on fertility. No fertility studies have been performed in animals. Due to the potential of antifolates to irreversibly affect fertility, patients should be offered appropriate counselling

Use in pregnancy - Category D.

There are no data from the use of pralatrexate in pregnant women. In pregnant rats and rabbits, pralatrexate administered IV during the period of organogenesis had a negative effect on fetal viability, manifested as an increase in post-implantation loss and a reduced number of live fetuses at greater than or equal to 0.06 mg/kg in rats and 1 mg/kg in rabbits. Total litter loss was seen at greater than or equal to 0.1 mg/kg in rats and 1 mg/kg in rabbits.

Estimated exposures at these doses were below or slightly higher than the clinical exposure based on AUC. Retardation of fetal growth was also seen in rats at greater than or equal to 0.006 mg/kg. One rat fetus in the 0.06 mg/kg group had a syndactyly hindlimb or brachydactyly forelimbs.

FOLOTYN is not recommended during pregnancy or in women of childbearing potential, unless they are using reliable contraception. If pralatrexate is used during pregnancy or if the patient becomes pregnant while receiving pralatrexate, the possible risks to the foetus should be discussed with the patient.

Women of childbearing potential must use effective contraception during treatment with pralatrexate. Pralatrexate may have genetically damaging effects. Sexually mature males are advised not to father a child during treatment or up to six months thereafter. Barrier contraceptive measures or abstinence are recommended.

Use in lactation
FOLOTYN is contraindicated during breast-feeding (see **CONTRAINDICATIONS**).

Paediatric use
No data are available in children aged 0 to 18 years, and the safety and efficacy of FOLOTYN has not yet been established in these patients.

Use in the elderly
No overall differences in efficacy and safety were observed in patients based on age (under 65 years compared with 65 years and over). No dose adjustment is required in elderly patients with normal renal function (see **DOSAGE AND ADMINISTRATION** and **Pharmacokinetics**). However, the decision whether to administer FOLOTYN to elderly patients should be made in the context of: concomitant disease, concomitant drug therapy or signs and symptoms of systemic toxicity.

Genotoxicity
Pralatrexate was not mutagenic in the standard *in vitro* and *in vivo* mutagenicity assays, including Ames test, Chinese hamster ovary (CHO) cell chromosome aberration assay and mouse micronucleus assay. However, these tests may not reliably predict genotoxicity for this class of compound. Based on experience with other antifolates, an increased risk for genotoxicity from pralatrexate treatment cannot be excluded.

Carcinogenicity
Carcinogenicity studies have not been performed with pralatrexate.

Effects on laboratory tests
Liver function test abnormalities have been observed after FOLOTYN administration and are usually not cause for modification of FOLOTYN treatment. Persistent liver function test abnormalities may be indicators of liver toxicity and require evaluation. Caution is advised when administering pralatrexate to patients with hepatic impairment. It is recommended that patients are monitored for liver function (see **PRECAUTIONS**).

INTERACTIONS WITH OTHER MEDICINES
No formal interaction studies have been performed.

Cytochrome P450 interactions
In vitro studies indicated that pralatrexate is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP450) isoenzymes, and thus it has low potential for drug-drug interactions at CYP450 isoenzymes.

Uricosurics
Concomitant use with probenecid should be avoided. The effect of co-administration of the uricosuric probenecid on pralatrexate pharmacokinetics was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in reduced clearance of pralatrexate and a commensurate increase in systemic exposure and reduced tolerability of pralatrexate. Monitor patients closely for systemic toxicity due to increased drug exposure.

Renal interactions
Caution should be used in the concomitant administration of drugs that affect glomerular filtration and/or renal tubular secretion, because of the significant contribution of renal excretion to the overall clearance of pralatrexate (approximately 34% of unchanged pralatrexate is excreted renally). Such drugs include nonsteroidal anti-inflammatory drugs (NSAIDs), penicillins, omeprazole or pantoprazole, as they may result in reduced clearance of pralatrexate. Monitor patients closely for systemic toxicity due to increased drug exposure.

In addition, concomitant administration of nephrotoxic drugs (e.g. aminoglycosides, loop diuretics, platinum compounds, cyclosporine) could also potentially result in reduced clearance of pralatrexate and should be avoided in patients being treated with FOLOTYN.

Transporters
In *in vitro* transporter studies, pralatrexate was a substrate for BCRP, OATP1B1, MRP2, MRP3 and OATP1B3. Pralatrexate was not a significant substrate for P-gp, OCT2, OAT1 or OAT3. Pralatrexate did not significantly inhibit P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3. Pralatrexate was a weak inhibitor of MRP2 (IC_{50} = 43.5 µM), and a potent inhibitor of MRP3 (IC_{50} < 0.3 µM). Since pralatrexate was found to be a potent inhibitor of MRP3, a liver transporter implicated in transport of etoposide, teniposide, and methotrexate, caution is advised with concomitant use of these agents with pralatrexate.

Trimethoprim/sulfamethoxazole
Trimethoprim/sulfamethoxazole has been reported in rare cases to increase bone marrow suppression in patients treated with methotrexate, presumably because of the increased antifolate effect. Caution should be exercised in the concomitant use of these agents with pralatrexate.

ADVERSE EFFECTS
The safety of pralatrexate was evaluated in 111 peripheral T-cell lymphoma (PTCL) patients in one single-arm pivotal clinical study, PDX-008, in which patients received 30 mg/m^2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days, with a range of 1 - 696 days.

The most frequently reported adverse reactions included mucosal inflammation, myelosuppression (thrombocytopenia, neutropenia and anaemia), gastrointestinal symptoms (nausea, vomiting and constipation), fatigue, and epistaxis. The most serious adverse reactions included bone marrow suppression (thrombocytopenia, neutropenia and anaemia), mucosal inflammation, dermatological reactions (skin exfoliation and toxic epidermal necrolysis) and tumour lysis syndrome. Deaths, regardless of causality, 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.

Adverse reactions reported in the trial that were at least possibly related to FOLOTYN are listed below by system organ class and frequency. The frequency key was as follows:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100).
Adverse effects are shown in order of decreasing seriousness within each frequency grouping.

Adverse Drug Reactions (from Study PDX-008 in 111 PTCL patients)

Infections and infestations

Common	Sepsis, pneumonia[1], bronchitis, urinary tract infection, cellulitis, herpes zoster, abscess[1], infection[1], herpes virus infection[1], upper respiratory infection[1], fungal infection[1], folliculitis
Uncommon	Clostridium difficile colitis, cytomegalovirus colitis

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon	Tumour lysis syndrome

Blood and lymphatic system disorders

Very common	Neutropenia[1], leukopenia[1], thrombocytopenia[1], anaemia[1]
Common	Febrile neutropenia, pancytopenia, lymphopenia
Uncommon	Haemolytic anaemia

Metabolism and nutrition disorders

Very common	Anorexia[1]
Common	Hyperkalaemia, hypokalaemia[1], dehydration, hyperuricaemia[1], hyperglycaemia[1], hypomagnesaemia, hypophosphataemia
Uncommon	Hypercalcaemia

Psychiatric disorders

Common	Insomnia, anxiety

Nervous system disorders

Common	Neuropathy peripheral[1], headache, dizziness, paraesthesia[1], hypoaesthesia
Uncommon	Syncope, memory impairment

Eye disorders

Common	Vision blurred, eye irritation[1], lacrimation increased, ocular hyperaemia[1], eye pruritus[1]
Uncommon	Visual acuity reduced, uveitis, photopsia, eyelid ptosis, conjunctivitis

Ear and labyrinth disorders

Common	Tinnitus

Uncommon	Deafness, vertigo, hypoacusis

Cardiac disorders

Common	Tachycardia[1]
Uncommon	Cardio-respiratory arrest, cardiomegaly

Vascular disorders

Common	Hypotension
Uncommon	Venous thrombosis[1]

Respiratory, thoracic and mediastinal disorders

Very common	Epistaxis
Common	Pleural effusion, dyspnoea, cough[1], pharyngolaryngeal pain, dysphonia
Uncommon	Pneumonitis, pulmonary embolism, hypoxia, pulmonary congestion, pleuritic pain

Gastrointestinal disorders

Very common	Mucosal inflammation[1], vomiting, diarrhoea, nausea[1], constipation
Common	Abdominal pain[1], odynophagia[1], oral pain, dyspepsia[1], rectal haemorrhage[1], dry mouth[1]
Uncommon	Pancreatitis

Hepatobiliary disorders

Common	Hepatosplenomegaly[1], hyperbilirubinaemia[1]
Uncommon	Cholangitis

Skin and subcutaneous tissue disorders

Very common	Rash[1]
Common	Skin ulcer[1], skin lesion[1], urticaria, pruritus[1], skin haemorrhage[1], periorbital oedema, erythema[1], alopecia, blisters, dry skin
Uncommon	Skin exfoliation, skin toxicity, night sweats

Musculoskeletal and connective tissue disorders

Very Common	Musculoskeletal pain[1]
Common	Back pain, neck pain, arthralgia[1], myalgia, muscle spasms, pain in extremity
Uncommon	Costochondritis, joint swelling

Renal and urinary disorders

Uncommon	Renal failure

General disorders and administration site conditions

Very common	Pyrexia, peripheral oedema[1], fatigue
Common	Influenza-like illness, chest pain, chills, pain[1], asthenia, face oedema
Uncommon	Infusion-related reaction

Investigations

Very common	Liver function test abnormal[1] (elevated AST, ALT)
Common	Blood creatinine increased[1], weight decreased

Uncommon	Ejection fraction decreased

Injury, poisoning, and procedural complications

Common	Contusion

[1] Closely-related adverse event terms were coded to the same lowest-level term in order to present the event in a uniform manner

Description of selected adverse reactions

Gastrointestinal Disorders

Mucosal inflammation occurred in 68% of patients,18% with Grade 3 and 4% with Grade 4 reactions, classified in accordance with the National Cancer Institute-Common Terminology Criteria (NCI-CTC). Most patients for whom the dose was modified recovered to mucosal inflammation equal to, or below, Grade 1 (see **DOSAGE AND ADMINISTRATION**, Table 2, below).

Blood Disorders

Myelosuppression was a very commonly observed adverse reaction.

Thrombocytopenia occurred in 40% of patients, 14% with Grade 3 and 17% with Grade 4 reactions. Platelet count recovery usually occurred after treatment was omitted or ceased. Bleeding complications (coincident with low platelet counts) were generally mild and predominantly presented clinically as epistaxis.

Neutropenia occurred in 24% of patients, 14% with Grade 3 reactions and 7% with Grade 4 reactions. Infection complications (coincident with low neutrophil counts) were mostly Grade 1-2 in severity.

Anaemia occurred in 32% of patients, 14% with Grade 3 and 2% with Grade 4 reactions. Other common hematologic Grade 3 and 4 haematologic reactions included febrile neutropenia, pancytopenia and leucopenia.

Other Grade 3 and 4 adverse reactions

Other common Grade 3 and 4 adverse reactions included skin ulcers, infections, anorexia, dyspnoea, vomiting, nausea, pain, and fatigue.

Investigations

Elevated liver enzymes were the most frequently reported clinical chemistry laboratory abnormality. Clinically significant abnormalities were those ≥ Grade 2, per NI CTCAE and that represented a shift of ≥ 1 grade from the baseline value. Nineteen (17%) and 18 (16%) patients had increased AST and ALT values, respectively, that were considered clinically significant.

Post-marketing

Toxic epidermal necrolysis (TEN), a clinically significant adverse reaction, was reported during post-approval use.

Serious adverse drug reactions including TEN and mucosal inflammation were reported in patients with end-stage renal disease undergoing dialysis who were administered FOLOTYN. Fatal events of serious skin reactions have been reported in patients in dialysis who received a dose of less than 30 mg/m^2 per day.

DOSAGE AND ADMINISTRATION

Treatment should only be administered under the supervision of a physician experienced in the use of anticancer chemotherapy. FOLOTYN vials contain no antimicrobial preservative and are for use in one patient on one occasion only.

Premedication regimen

Patients should take low-dose (1.0-1.25 mg) oral folic acid on a daily basis. Folic acid should be initiated during the 10-day period preceding the first dose of FOLOTYN, and dosing should continue during the full course of therapy and for 30 days after the last dose of FOLOTYN. Patients should also receive a vitamin B12 (1 mg) intramuscular injection no more than 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks thereafter. Subsequent vitamin B12 injections may be given the same day as treatment with FOLOTYN. The premedication regimen should be strictly observed.

Dosage

Adults

The recommended starting dose of FOLOTYN is 30 mg/m^2 administered as an intravenous infusion over 3-5 minutes, once weekly for six (6) weeks, followed by a one (1) week rest period (7-week treatment cycle), until progressive disease or unacceptable toxicity.

Monitoring

Full blood cell counts and severity of mucositis should be monitored weekly for all patients receiving FOLOTYN. 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, or more often if required. Prior to initiating any dose of FOLOTYN, mucositis should be ≤ Grade 1, absolute neutrophil count (ANC) should be ≥ 1,000/µL, and platelet count should be ≥ 100,000/µL for the first dose and ≥ 50,000/µL for all subsequent doses.

Dose adjustments during treatment

Doses may be omitted or reduced, based on patient tolerance. Omitted doses should not be made up at the end of the cycle. Once a dosage reduction occurs for toxicity, the dosing should not be re-escalated. For dose modifications and omissions, use the guidelines in Tables 2, 3 and 4, below:

Table 2: FOLOTYN dose modifications for mucositis

Mucositis grade[a] on treatment day	**Action**	**Dose upon recovery to ≤ Grade 1**
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	-

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

Table 3: FOLOTYN dose modifications for haematological toxicities

Blood count on treatment day	**Duration of toxicity**	**Action**	**Dose upon restart**
Platelets < 50,000/µL	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Stop therapy	-

ANC 500-1,000/µL and no fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/µL with fever or ANC < 500/µL	1 week	Omit dose, administer G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, administer G-CSF or GM-CSF support	20 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 4: FOLOTYN dose modifications for all other treatment-related toxicities

Toxicity grade[a] on treatment day	**Action**	**Dose upon recovery to ≤ Grade 2**
Grade 3	Omit dose	20 mg/m^2
Grade 4	Stop therapy	

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

Patients with hepatic impairment
FOLOTYN has not been formally studied in patients with hepatic impairment, and caution is advised when administering pralatrexate to this patient group. Patients with the following laboratory values were excluded from the pralatrexate lymphoma clinical studies: 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. Liver function test abnormalities have been observed after FOLOTYN administration and are usually not cause for modification of treatment. Persistent liver function test abnormalities may be indicators of liver toxicity and require evaluation. Liver function monitoring during treatment is recommended.

Patients with renal impairment
FOLOTYN has not been formally studied in patients with moderate to severe renal impairment, and caution is advised when administering pralatrexate to patients with an estimated glomerular filtration rate [eGFR] of less than 60 mL/min. Avoid FOLOTYN use in patients with end stage renal disease, including those undergoing dialysis, unless the potential benefit justifies the risk. Approximately 34% of pralatrexate is excreted unchanged into urine. Renal function monitoring during treatment is recommended (see **PRECAUTIONS; Renal impairment** and **PHARMACOLOGY; Renal impairment**).

Third space fluid accumulation
The effect of third space compartment fluid accumulation (e.g. pleural effusions, ascites, significant peripheral oedema) is unknown. In patients with clinically significant third space fluid, consideration should be given to draining the effusion prior to initiation of treatment with pralatrexate.

Elderly patients
No overall differences in efficacy and safety were observed in patients based on age (< 65 years compared with ≥ 65 years). No dose adjustment is required in elderly patients with normal renal function (see **PRECAUTIONS**). In patients with age-related renal impairment,

the dose should be reduced because of the possibility of increased pralatrexate plasma levels due to decreased renal clearance.

Paediatric patients
Not recommended for children below 18 years.

Method of administration
FOLOTYN is administered undiluted as an intravenous infusion over 3-5 minutes. The calculated dose of FOLOTYN should be aseptically withdrawn into a syringe and administered via the side port of a free flowing sodium chloride 9 mg/mL (0.9%) solution for injection intravenous line. FOLOTYN must not be administered by any other route of administration. A vial can be used in one patient on one occasion only as FOLOTYN contains no antimicrobial preservatives. Once the vial is opened, the solution should be used immediately.

Compatibility
In the absence of compatibility studies, FOLOTYN must not be mixed with other medicines.

Special precautions for handling and disposal
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.

FOLOTYN is a clear, yellow solution. The vials should be inspected visually for particulate matter and discolouration prior to administration, and the solution should be clear and yellow. Vials showing particulate matter or discolouration should not be used. FOLOTYN vials contain no antimicrobial preservatives and are for use in one patient on one occasion only. After withdrawal of the dose, discard any unused portion left in the vial. Unused portions should not be saved for later administration. Any unused product or waste materials should be disposed of in accordance with local hospital requirements for hazardous waste.

OVERDOSAGE

No specific information is available on the treatment of pralatrexate overdosage. General supportive measures should be instituted as deemed necessary. Based on the mechanism of action of pralatrexate, and clinical experience with other antifolates, prompt administration of leucovorin, adequate hydration and alkalinisation of the urine should be considered.

Experience with overdose of pralatrexate is very limited. However, doses of more than ten times the prescribed starting dose of pralatrexate for the indication of relapsed or refractory PTCL have been administered in solid tumour clinical studies with a similar adverse event profile. Anticipated symptoms of overdose might include increased severity and/or duration of mucosal inflammation and myelosuppression (primarily manifested by thrombocytopenia, leucopenia, neutropenia and anaemia).
For information on the management overdose, contact the Poisons Information Centre on 13 11 26 (Australia) for advice on managing overdose.

PRESENTATION AND STORAGE CONDITIONS

Presentation

FOLOTYN solution for infusion is a preservative-free, sterile, isotonic, non-pyrogenic clear yellow aqueous parenteral solution. FOLOTYN is supplied in a carton containing a clear glass, single-use 2 mL vial with a chlorobutyl stopper covered with an aluminium flip-off seal.

Each 1 mL of solution contains 20 mg of pralatrexate. Two vial presentations are registered:

20 mg in 1 mL: Each vial contains 20 mg of pralatrexate in 1 mL of solution. Pack size of 1 vial.
40 mg in 2 mL: Each vial contains 40 mg of pralatrexate in 2 mL of solution. Pack size of 1 vial.

Storage conditions

Store in a refrigerator (2ºC – 8ºC). Keep the vial in its outer carton to protect it from light. Unopened vials are stable if stored in the original carton for a single period at up to 30ºC for 120 hours. Any vials left at 30ºC for longer than 120 hours should be discarded. FOLOTYN should be used immediately after opening the vial and any unused portion should be discarded.

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited
ABN 87 081 322 509
88 Phillip Street
SYDNEY NSW 2000

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE ARTG

26 February 2015

DATE OF MOST RECENT AMENDMENT

17 October 2018

ORBIS RA-0167