

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-468

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FOLOTYN™ safely and effectively. See full prescribing information for FOLOTYN.

FOLOTYN (pralatrexate injection)
Solution for intravenous injection
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

FOLOTYN is a folate analogue metabolic inhibitor 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. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of FOLOTYN is 30 mg/m² administered as an intravenous push over 3 to 5 minutes once weekly for 6 weeks in 7-week cycles. (2.1)
- Supplement patients with vitamin B₁₂ 1 mg intramuscularly every 8-10 weeks and folic acid 1.0-1.25 mg orally on a daily basis. (2.2)
- Treatment interruption or dose reduction to 20 mg/m² may be needed to manage adverse drug reactions. (2.5)

DOSAGE FORMS AND STRENGTHS

- Sterile, single-use vials containing pralatrexate at a concentration of 20 mg/mL in the following presentations:
 - 20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)
 - 40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL) (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Thrombocytopenia, neutropenia, and anemia may occur. Monitor blood counts and omit or modify dose for hematologic toxicities. (2.5, 5.1)
- Mucositis may occur. If ≥ Grade 2 mucositis is observed, omit or modify dose. (2.5, 5.2)
- FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN, and pregnant women should be informed of the potential harm to the fetus. (5.4, 8.1)
- Use caution in patients with moderate to severe renal function impairment. (5.5)
- Elevated liver function test abnormalities may occur. If liver function test abnormalities are ≥ Grade 3, omit or modify dose. (2.5, 5.6)

ADVERSE REACTIONS

Most common adverse reactions are mucositis, thrombocytopenia, nausea, and fatigue. Most common serious adverse reactions are pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Allos Therapeutics, Inc at 1-888-ALLOS88 (1-888-255-6788) or www.FOLOTYN.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Co-administration with probenecid, NSAIDs, and trimethoprim/sulfamethaxazole may result in delayed renal clearance. (7)

USE IN SPECIFIC POPULATIONS

- Women should be advised against breastfeeding while being treated with FOLOTYN. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 09/2009

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

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

6 2 DOSAGE AND ADMINISTRATION

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

10 2.1 Peripheral T-cell Lymphoma

11 The recommended dose of FOLOTYN is 30 mg/m² administered as an intravenous (IV) push over 3-5 minutes
12 via the side port of a free flowing 0.9% Sodium Chloride Injection, USP IV line once weekly for 6 weeks in 7-
13 week cycles until progressive disease or unacceptable toxicity.

14 2.2 Vitamin Supplementation

15 Patients should take low-dose (1.0-1.25 mg) oral folic acid on a daily basis. Folic acid should be initiated during
16 the 10-day period preceding the first dose of FOLOTYN, and dosing should continue during the full course of
17 therapy and for 30 days after the last dose of FOLOTYN. Patients should also receive a vitamin B₁₂ (1 mg)
18 intramuscular injection no more than 10 weeks prior to the first dose of FOLOTYN and every 8-10 weeks
19 thereafter. Subsequent vitamin B₁₂ injections may be given the same day as treatment with FOLOTYN
20 [see *Warnings and Precautions* (5.3)].

21 2.3 Preparation and Administration Precautions

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

26 Several published guidelines for handling and disposal of anticancer agents are available. [see *References* (15)].

27 2.4 Preparation for Intravenous Push Administration

- 28 1. FOLOTYN vials should be refrigerated at 2-8°C (36-46°F) until use.
- 29 2. FOLOTYN vials should be stored in original carton to protect from light until use.
- 30 3. FOLOTYN is a clear, yellow solution. Parenteral drug products should be inspected visually for
31 particulate matter and discoloration prior to administration, whenever solution and container permit.
32 Do not use any vials exhibiting particulate matter or discoloration.
- 33 4. The calculated dose of FOLOTYN should be aseptically withdrawn into a syringe for immediate use.
- 34 5. Do not dilute FOLOTYN.
- 35 6. FOLOTYN vials contain no preservatives and are intended for single use only. After withdrawal of
36 dose, discard vial including any unused portion.
- 37 7. Unopened vial(s) of FOLOTYN are stable if stored in the original carton at room temperature for
38 72 hours. Any vials left at room temperature for greater than 72 hours should be discarded.

39 **2.5 Monitoring and Dose Modifications**

40 Management of severe or intolerable adverse reactions may require dose omission, reduction or interruption of
 41 FOLOTYN therapy.

42 **Monitoring**

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

46 **Dose Modification Recommendations**

47 Prior to administering any dose of FOLOTYN:

- 48 • Mucositis should be \leq Grade 1.
- 49 • Platelet count should be \geq 100,000/ μ L for first dose and \geq 50,000/ μ L for all subsequent doses.
- 50 • Absolute neutrophil count (ANC) should be \geq 1,000/ μ L.

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

54

Table 1 FOLOTYN Dose Modifications for Mucositis

Mucositis Grade ^a on Day of Treatment	Action	Dose upon recovery to \leq 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	

55

56

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

57

58

Table 2 FOLOTYN Dose Modifications for Hematologic Toxicities

Blood Count on Day of Treatment	Duration of Toxicity	Action	Dose upon restart
Platelet < 50,000/ μ L	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m ²
	3 weeks	Stop therapy	
ANC 500-1,000/ μ L and no fever	1 week	Omit dose	Continue prior dose
ANC 500-1,000/ μ L with fever or ANC < 500/ μ L	1 week	Omit dose, give 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
	3 weeks or 2 nd recurrence	Stop therapy	

59
60

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

Toxicity Grade ^a on Day of Treatment	Action	Dose upon recovery to ≤ Grade 2
Grade 3	Omit dose	20 mg/m ²
Grade 4	Stop therapy	

61
62

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

63 **3 DOSAGE FORMS AND STRENGTHS**

64 FOLOTYN is available in sterile, single-use vials containing pralatrexate at a concentration of 20 mg/mL in the
65 following presentations:

66 20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)

67 40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

68 **4 CONTRAINDICATIONS**

69 None.

70 **5 WARNINGS AND PRECAUTIONS**

71 **5.1 Bone Marrow Suppression**

72 FOLOTYN can suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia.
73 Dose modifications are based on ANC and platelet count prior to each dose [*see Dosage and Administration*
74 (2.5) and *Adverse Reactions* (6)].

75 **5.2 Mucositis**

76 Treatment with FOLOTYN may cause mucositis. If ≥ Grade 2 mucositis is observed, dose should be modified
77 [*see Dosage and Administration* (2.5)].

78 **5.3 Folic Acid and Vitamin B₁₂ Supplementation**

79 Patients should be instructed to take folic acid and receive vitamin B₁₂ to potentially reduce treatment-related
80 hematological toxicity and mucositis [*see Dosage and Administration* (2.2)].

81 **5.4 Pregnancy Category D**

82 FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN was embryotoxic and
83 fetotoxic in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while
84 taking this drug, the patient should be apprised of the potential hazard to the fetus. [*see Use in Specific*
85 *Populations* (8.1)].

86 **5.5 Decreased Renal Function**

87 Although FOLOTYN has not been formally tested in patients with renal impairment, caution is advised when
88 administering FOLOTYN to patients with moderate to severe impairment. Monitor patients for renal function
89 and systemic toxicity due to increased drug exposure [*see Clinical Pharmacology* (12.3)].

90 **5.6 Elevated Liver Enzymes**

91 Liver function test abnormalities have been observed after FOLOTYN administration. Persistent liver function
92 test abnormalities may be indicators of liver toxicity and require dose modification. Monitor patients for liver
93 function [*see Dosage and Administration* (2.6)].

94 **6 ADVERSE REACTIONS**

95 The most common adverse reactions observed in patients with peripheral t-cell lymphoma (PTCL) treated with
96 FOLOTYN were mucositis, thrombocytopenia, nausea, and fatigue.

97 **6.1 Clinical Trials Experience**

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

101 The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients
102 received a starting dose of 30 mg/m² once weekly for 6 weeks in 7-week cycles. The median duration of
103 treatment was 70 days (range 1-540 days).

104 ***Most Frequent Adverse Reactions***

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

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

Preferred Term	N=111					
	Total		Grade 3		Grade 4	
	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/ μ L

^c Alanine Aminotransferase, Aspartate Aminotransferase, and Transaminases Increased

111 ***Serious Adverse Events***

112 Forty-four percent of patients (n = 49) experienced a serious adverse event while on study or within 30 days
113 after their last dose of FOLOTYN. The most common serious adverse events (> 3%), regardless of causality,
114 were pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea and thrombocytopenia. One death
115 from cardiopulmonary arrest in a patient with mucositis and febrile neutropenia was reported in this trial.
116 Deaths from mucositis, febrile neutropenia, sepsis, and pancytopenia occurred in 1.2% of patients treated on all
117 FOLOTYN trials at doses ranging from 30 to 325 mg/m².

118 ***Discontinuations***

119 Twenty-three percent of patients (n = 25) discontinued treatment with FOLOTYN due to adverse reactions.
120 The adverse reactions reported most frequently as the reason for discontinuation of treatment were mucositis
121 (6%, n = 7) and thrombocytopenia (5%, n = 5).

122 ***Dose Modifications***

123 The target dose of FOLOTYN was 30 mg/m² once weekly for 6 weeks in 7-week cycles. The majority of
124 patients (69%, n = 77) remained at the target dose for the duration of treatment. Overall, 85% of scheduled
125 doses were administered.

126 **7 DRUG INTERACTIONS**

127 *In vitro* studies indicate that pralatrexate is not a substrate, inhibitor, or inducer of CYP450 isoenzymes and has
128 low potential for drug-drug interactions at CYP450 isoenzymes [see *Clinical Pharmacology (12.3)*]. No formal
129 clinical assessments of pharmacokinetic drug-drug interactions between FOLOTYN and other drugs have been
130 conducted. The effect of co-administration of the uricosuric drug probenecid on pralatrexate pharmacokinetics
131 was investigated in a Phase 1 clinical study. Co-administration of increasing doses of probenecid resulted in
132 delayed clearance of pralatrexate and a commensurate increase in exposure.

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

136 **8 USE IN SPECIFIC POPULATIONS**

137 **8.1 Pregnancy**

138 Pregnancy Category D [see *Warnings and Precautions (5.4)*].

139 FOLOTYN can cause fetal harm when administered to a pregnant woman. Pralatrexate was embryotoxic and
140 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
141 basis) given on gestation days 7 through 20. Treatment with pralatrexate caused a dose dependant decrease in
142 fetal viability manifested as an increase in late, early and total resorptions. There was also a dose dependant
143 increase in post implantation loss. In rabbits, IV doses of 0.03 mg/kg/day (0.36 mg/m²/day) or greater given on
144 gestation days 8 through 21 also caused abortion and fetal lethality. This toxicity manifested as early and total
145 resorptions, post implantation loss and a decrease in the total number of live fetuses. If this drug is used during
146 pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the
147 potential hazard to the fetus.

148 **8.3 Nursing Mothers**

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

153 **8.4 Pediatric Use**

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

156 **8.5 Geriatric Use**

157 In the PTCL efficacy study, 36% of patients (n = 40) were 65 years of age and over. No overall differences in
158 efficacy and safety were observed in patients based on age (< 65 years compared with ≥ 65 years).

159 No dosage adjustment is required in elderly patients with normal renal function [*see Clinical Pharmacology*
160 (12.3)]

161 **8.6 Hepatic Impairment**

162 Formal studies have not been performed with FOLOTYN in patients with hepatic impairment. Patients with the
163 following laboratory values were excluded from the pralatrexate lymphoma clinical trials: total bilirubin
164 > 1.5 mg/dL; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of
165 normal (ULN); and AST or ALT > 5 × ULN if documented hepatic involvement with lymphoma.

166 **8.7 Renal Impairment**

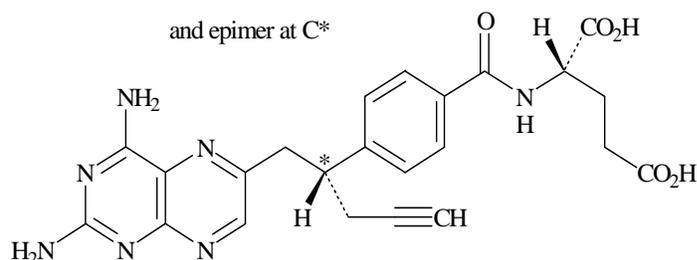
167 [*see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)*].

168 **10 OVERDOSAGE**

169 No specific information is available on the treatment of overdose of FOLOTYN. If an overdose occurs,
170 general supportive measures should be instituted as deemed necessary by the treating physician. Based on
171 FOLOTYN'S mechanism of action the prompt administration of leucovorin should be considered.

172 **11 DESCRIPTION**

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



176

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

178 The molecular formula is C₂₃H₂₃N₇O₅ and the molecular weight is 477.48 g/mol.

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

181 FOLOTYN is supplied as a preservative free, sterile, isotonic, non-pyrogenic clear yellow aqueous parenteral
182 solution contained in a single-use clear glass vial (Type I) for intravenous administration. Each 1 mL of
183 solution contains 20 mg of pralatrexate, sufficient sodium chloride to achieve an isotonic (280-300 mOsm)
184 solution, and sufficient sodium hydroxide, and hydrochloric acid if needed, to adjust and maintain the pH at
185 7.5-8.5. FOLOTYN is supplied as either 20 mg (1 mL) or 40 mg (2 mL) single-use vials at a concentration of
186 20 mg/mL.

187 **12 CLINICAL PHARMACOLOGY**

188 **12.1 Mechanism of Action**

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

193 **12.3 Pharmacokinetics**

194 ***Absorption***

195 The pharmacokinetics of pralatrexate administered as a single agent at a dose of 30 mg/m² administered as an
196 intravenous push over 3-5 minutes once weekly for 6 weeks in 7-week cycles have been evaluated in 10 patients
197 with PTCL. The total systemic clearance of pralatrexate diastereomers was 417 mL/min (*S*-diastereomer) and
198 191 mL/min (*R*-diastereomer). The terminal elimination half-life of pralatrexate was 12-18 hours (coefficient
199 of variance (CV) = 62-120%). Pralatrexate total systemic exposure (AUC) and maximum plasma concentration
200 (C_{max}) increased proportionally with dose (dose range 30-325 mg/m², including pharmacokinetics data from
201 high dose solid tumor clinical studies). The pharmacokinetics of pralatrexate did not change significantly over
202 multiple treatment cycles, and no accumulation of pralatrexate was observed.

203 ***Distribution***

204 Pralatrexate diastereomers showed a steady-state volume of distribution of 105 L (*S*-diastereomer) and 37 L
205 (*R*-diastereomer). *In vitro* studies indicate that pralatrexate is approximately 67% bound to plasma proteins. In
206 *in vitro* studies using MDR1-MDCK and Caco-2 cell systems, pralatrexate was not a substrate for
207 P-glycoprotein (Pgp)-mediated transport nor did it inhibit Pgp-mediated transport.

208 ***Metabolism***

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

213 ***Excretion***

214 A mass balance study has not been performed. The mean fraction of unchanged pralatrexate diastereomers
215 excreted in urine following a pralatrexate dose of 30 mg/m² administered as an intravenous push over
216 3-5 minutes was 31% (*S*-diastereomer) (CV = 47%) and 38% (*R*-diastereomer) (CV = 45%), respectively.

217 ***Patients with Renal Impairment***

218 Approximately 34% of pralatrexate was excreted unchanged into urine following a single dose of 30 mg/m²
219 administered as an intravenous push over 3-5 minutes. In a population pharmacokinetic analysis drug clearance
220 decreased with decreasing creatinine clearance. [see *Warnings and Precautions (5.5)*]

221 ***Patients with Hepatic Impairment***

222 Pralatrexate has not been studied in patients with hepatic impairment.

223 *Effects of Age and Gender*

224 Due to the contribution of renal excretion to overall clearance of pralatrexate, age-related decline in renal
225 function may lead to a reduction in clearance and a commensurate increase in plasma exposure. There was no
226 significant effect of gender on pharmacokinetics.

227 **13 NONCLINICAL TOXICOLOGY**

228 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

229 *Carcinogenesis*

230 Carcinogenicity studies have not been performed with pralatrexate.

231 *Mutagenesis*

232 Pralatrexate did not cause mutations in the Ames test or the Chinese hamster ovary cell chromosome aberration
233 assay. Nevertheless, these tests do not reliably predict genotoxicity for this class of compounds. Pralatrexate
234 did not cause mutations in the mouse micronucleus assay.

235 *Impairment of Fertility*

236 No fertility studies have been performed.

237 **14 CLINICAL STUDIES**

238 *Peripheral T-cell Lymphoma (PTCL)*

239 The safety and efficacy of FOLOTYN was evaluated in an open-label, single-arm, multicenter, international
240 trial that enrolled 115 patients with relapsed or refractory PTCL. One hundred and eleven patients were treated
241 with FOLOTYN at 30 mg/m² once weekly by IV push over 3-5 minutes for 6 weeks in 7-week cycles until
242 disease progression or unacceptable toxicity. Of the 111 patients treated, 109 patients were evaluable for
243 efficacy. Evaluable patients had histologically confirmed PTCL by independent central review using the
244 Revised European American Lymphoma (REAL) World Health Organization (WHO) disease classification, and
245 relapsed or refractory disease after at least one prior treatment.

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

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

257 The median number of prior systemic therapies was 3 (range 1-12). Approximately one-fourth of patients
258 (24%, n = 27) did not have evidence of response to any previous therapy. Approximately two-thirds of patients
259 (63%, n = 70) did not have evidence of response to their most recent prior therapy before entering the study.

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

Table 5 Response Analysis per Independent Central Review (IWC)

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

Fourteen patients went off treatment in cycle 1; 2 patients were unevaluable for response by IWC due to insufficient materials provided to central review.

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

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264
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266 The initial response assessment was scheduled at the end of cycle 1. Of the responders, 66% responded within
267 cycle 1. The median time to first response was 45 days (range 37-349 days).

268 15 REFERENCES

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- 271 2 OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to
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- 273 3 American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. Am J
274 Health-Syst Pharm. 2006;63:1172-1193.
- 275 4 Polovich, M., White, J. M., & Kelleher, L. O. (eds.) 2005. Chemotherapy and biotherapy guidelines and
276 recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

277 16 HOW SUPPLIED/STORAGE AND HANDLING

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

281 **NDC 48818-001-01:** 20 mg of pralatrexate in 1 mL solution in a vial (20 mg / 1 mL)

282 **NDC 48818-001-02:** 40 mg of pralatrexate in 2 mL solution in a vial (40 mg / 2 mL)

283 Vials must be stored refrigerated at 2-8°C (36-46°F) (*see* USP Controlled Cold Temperature) in original carton
284 to protect from light.

285 Handle and dispose of FOLOTYN according to guidelines issued for cytotoxic drugs, including the use of
286 gloves and other protective clothing to prevent skin contact [*see References (15)*].

287 Each vial of FOLOTYN is intended for single use only. Any unused drug remaining after injection must be
288 discarded.

289 **Rx only**

290 **17 PATIENT COUNSELING INFORMATION**

291 **17.1 Need for Folic Acid and Vitamin B₁₂**

292 Patients treated with FOLOTYN must be instructed to take folic acid and Vitamin B₁₂ as a prophylactic
293 measure to potentially reduce possible side effects [*see Dosage and Administration (2.2)*].

294 **17.2 Mucositis**

295 Physicians should discuss with patients the signs and symptoms of mucositis. Patients should be instructed on
296 ways to reduce the risk of its development, and/or ways to maintain nutrition and control discomfort from
297 mucositis if it occurs.

298 **17.3 Low Blood Cell Counts**

299 Patients should be adequately informed of the risk of low blood cell counts and instructed to immediately
300 contact their physician should any signs of infection develop including fever. Patients should also be instructed
301 to contact their physician if bleeding or symptoms of anemia occur.

302 **17.4 Concomitant Medications**

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

306 **17.5 Pregnancy/Nursing**

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



309 **ALLOS™**
THERAPEUTICS

310 Manufactured for:

311 Allos Therapeutics, Inc.

312 Westminster, CO 80020

313 1-888-ALLOS88 (1-888-255-6788)

314 FOLOTYN is a trademark of Allos Therapeutics, Inc.

315 U.S. Patent: 6,028,071

316 Issued: (Date)

317 Rev. 1: (Date)

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