

1 **NEUTREXIN® (trimetrexate glucuronate for injection)**

2

3 **Black Box**

4 **WARNINGS**

5 **NEUTREXIN (TRIMETREXATE GLUCURONATE FOR INJECTION) MUST BE USED**  
6 **WITH CONCURRENT LEUCOVORIN (LEUCOVORIN PROTECTION) TO AVOID**  
7 **POTENTIALLY SERIOUS OR LIFE-THREATENING TOXICITIES (SEE PRECAUTIONS**  
8 **AND DOSAGE AND ADMINISTRATION).**

9

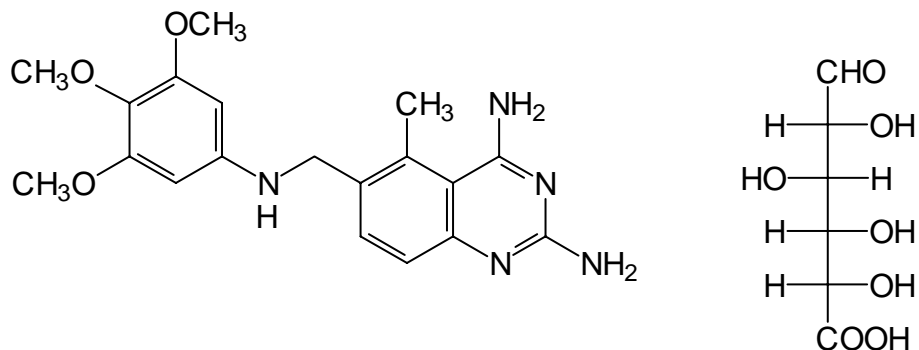
10 **DESCRIPTION**

11 Neutrexin is the brand name for trimetrexate glucuronate. Trimetrexate, a 2,4-diaminoquinazoline,  
12 non-classical folate antagonist, is a synthetic inhibitor of the enzyme dihydrofolate reductase  
13 (DHFR). Neutrexin is available as a sterile lyophilized powder, containing trimetrexate glucuronate  
14 equivalent to either 200mg or 25mg of trimetrexate without any preservatives or excipients. The  
15 powder is reconstituted prior to intravenous infusion (see **DOSAGE AND ADMINISTRATION,**  
16 **RECONSTITUTION AND DILUTION).**

17

18 Trimetrexate glucuronate is chemically known as 2,4-diamino-5-methyl-6-[(3,4,5-  
19 trimethoxyanilino)methyl] quinazoline mono-D-glucuronate, and has the following structure:

20



21

22

23 The empirical formula for trimetrexate glucuronate is  $C_{19}H_{23}N_5O_3 \cdot C_6H_{10}O_7$  with a molecular  
24 weight of 563.56. The active ingredient, trimetrexate free base, has an empirical formula of  
25  $C_{19}H_{23}N_5O_3$  with a molecular weight of 369.42. Trimetrexate glucuronate for injection is a pale  
26 greenish-yellow powder or cake. Trimetrexate glucuronate is soluble in water (>50 mg/mL),  
27 whereas trimetrexate free base is practically insoluble in water (<0.1 mg/mL). The pKa of  
28 trimetrexate free base in 50% methanol/water is 8.0. The logarithm<sub>10</sub> of the partition coefficient of  
29 trimetrexate free base between octanol and water is 1.63.

30

## 31 **CLINICAL PHARMACOLOGY**

### 32 **Mechanism of Action**

33 *In vitro* studies have shown that trimetrexate is a competitive inhibitor of dihydrofolate reductase  
34 (DHFR) from bacterial, protozoan, and mammalian sources. DHFR catalyzes the reduction of  
35 intracellular dihydrofolate to the active coenzyme tetrahydrofolate. Inhibition of DHFR results in the  
36 depletion of this coenzyme, leading directly to interference with thymidylate biosynthesis, as well as

37 inhibition of folate-dependent formyltransferases, and indirectly to inhibition of purine biosynthesis.  
38 The end result is disruption of DNA, RNA, and protein synthesis, with consequent cell death.  
39 Leucovorin (folinic acid) is readily transported into mammalian cells by an active, carrier-mediated  
40 process and can be assimilated into cellular folate pools following its metabolism. *In vitro* studies  
41 have shown that leucovorin provides a source of reduced folates necessary for normal cellular  
42 biosynthetic processes. Because the *Pneumocystis carinii* organism lacks the reduced folate carrier-  
43 mediated transport system, leucovorin is prevented from entering the organism. Therefore, at  
44 concentrations achieved with therapeutic doses of trimetrexate plus leucovorin, the selective  
45 transport of trimetrexate, but not leucovorin, into the *Pneumocystis carinii* organism allows the  
46 concurrent administration of leucovorin to protect normal host cells from the cytotoxicity of  
47 trimetrexate without inhibiting the antifolate's inhibition of *Pneumocystis carinii*. It is not known if  
48 considerably higher doses of leucovorin would affect trimetrexate's effect on *Pneumocystis carinii*.

49

## 50 **Microbiology**

51 Trimetrexate inhibits, in a dose-related manner, *in vitro* growth of the trophozoite stage of rat  
52 *Pneumocystis carinii* cultured on human embryonic lung fibroblast cells. Trimetrexate  
53 concentrations between 3 and 54.1  $\mu\text{M}$  were shown to inhibit the growth of trophozoites.  
54 Leucovorin alone at a concentration of 10  $\mu\text{M}$  did not alter either the growth of the trophozoites or  
55 the anti-pneumocystis activity of trimetrexate. Resistance to trimetrexate's antimicrobial activity  
56 against *Pneumocystis carinii* has not been studied.

57 **Pharmacokinetics**

58 Trimetrexate pharmacokinetics were assessed in six patients with acquired immunodeficiency  
59 syndrome (AIDS) who had *Pneumocystis carinii* pneumonia (4 patients) or toxoplasmosis (2  
60 patients). Trimetrexate was administered intravenously as a bolus injection at a dose of  
61  $30 \text{ mg/m}^2/\text{day}$  along with leucovorin  $20 \text{ mg/m}^2$  every 6 hours for 21 days. Trimetrexate clearance  
62 (mean  $\pm$  SD) was  $38 \pm 15 \text{ mL/min/m}^2$  and volume of distribution at steady state ( $V_{d_{ss}}$ ) was  $20 \pm 8$   
63  $\text{L/m}^2$ . The plasma concentration time profile declined in a biphasic manner over 24 hours with a  
64 terminal half-life of  $11 \pm 4$  hours.

65  
66 The pharmacokinetics of trimetrexate without the concomitant administration of leucovorin have  
67 been evaluated in cancer patients with advanced solid tumors using various dosage regimens. The  
68 decline in plasma concentrations over time has been described by either biexponential or  
69 triexponential equations. Following the single-dose administration of 10 to  $130 \text{ mg/m}^2$  to 37  
70 patients, plasma concentrations were obtained for 72 hours. Nine plasma concentration time profiles  
71 were described as biexponential. The alpha phase half-life was  $57 \pm 28$  minutes, followed by a  
72 terminal phase with a half-life of  $16 \pm 3$  hours. The plasma concentrations in the remaining patients  
73 exhibited a triphasic decline with half-lives of  $8.6 \pm 6.5$  minutes,  $2.4 \pm 1.3$  hours, and  $17.8 \pm 8.2$   
74 hours.

75  
76 Trimetrexate clearance in cancer patients has been reported as  $53 \pm 41 \text{ mL/min}$  (14 patients) and  $32$   
77  $\pm 18 \text{ mL/min/m}^2$  (23 patients) following single-dose administration. After a five-day infusion of  
78 trimetrexate to 16 patients, plasma clearance was  $30 \pm 8 \text{ mL/min/m}^2$ .

79 Renal clearance of trimetrexate in cancer patients has varied from about  $4 \pm 2$  mL/min/m<sup>2</sup> to  $10 \pm 6$   
80 mL/min/m<sup>2</sup>. Ten to 30% of the administered dose is excreted unchanged in the urine. Considering  
81 the free fraction of trimetrexate, active tubular secretion may possibly contribute to the renal  
82 clearance of trimetrexate. Renal clearance has been associated with urine flow, suggesting the  
83 possibility of tubular reabsorption as well.

84

85 The  $V_{d_{ss}}$  of trimetrexate in cancer patients after single-dose administration and for whom plasma  
86 concentrations were obtained for 72 hours was  $36.9 \pm 17.6$  L/m<sup>2</sup> (n=23) and  $0.62 \pm 0.24$  L/kg  
87 (n=14). Following a constant infusion of trimetrexate for five days,  $V_{d_{ss}}$  was  $32.8 \pm 16.6$  L/m<sup>2</sup>. The  
88 volume of the central compartment has been estimated as  $0.17 \pm 0.08$  L/kg and  $4.0 \pm 2.9$  L/m<sup>2</sup>.

89

90 There have been inconsistencies in the reporting of trimetrexate protein binding. The *in vitro* plasma  
91 protein binding of trimetrexate using ultrafiltration is approximately 95% over the concentration  
92 range of 18.75 to 1000 ng/mL. There is a suggestion of capacity limited binding (saturable binding)  
93 at concentrations greater than about 1000 ng/mL, with free fraction progressively increasing to about  
94 9.3% as concentration is increased to 15 µg/mL. Other reports have declared trimetrexate to be  
95 greater than 98% bound at concentrations of 0.1 to 10 µg/mL; however, specific free fractions were  
96 not stated. The free fraction of trimetrexate also has been reported to be about 15 to 16% at a  
97 concentration of 60 ng/mL, increasing to about 20% at a trimetrexate concentration of 6 µg/mL.

98 Trimetrexate metabolism in man has not been characterized. Preclinical data strongly suggest that  
99 the major metabolic pathway is oxidative O-demethylation, followed by conjugation to either  
100 glucuronide or the sulfate. N-demethylation and oxidation is a related minor pathway. Preliminary  
101 findings in humans indicate the presence of a glucuronide conjugate with DHFR inhibition and a  
102 demethylated metabolite in urine.

103

104 The presence of metabolite(s) in human plasma following the administration of trimetrexate is  
105 suggested by the differences seen in trimetrexate plasma concentrations when measured by HPLC  
106 and a nonspecific DHFR inhibition assay. The profiles are similar initially, but diverge with time;  
107 concentrations determined by DHFR being higher than those determined by HPLC. This suggests  
108 the presence of one or more metabolites with DHFR inhibition activity. After intravenous  
109 administration of trimetrexate to humans, urinary recovery averaged about 40%, using a DHFR  
110 assay, in comparison to 10% urinary recovery as determined by HPLC, suggesting the presence of  
111 one or more metabolites that retain inhibitory activity against DHFR. Fecal recovery of trimetrexate  
112 over 48 hours after intravenous administration ranged from 0.09 to 7.6% of the dose as determined  
113 by DHFR inhibition and 0.02 to 5.2% of the dose as determined by HPLC.

114

115 The pharmacokinetics of trimetrexate have not been determined in patients with renal insufficiency  
116 or hepatic dysfunction.

117 **INDICATIONS AND USAGE**

118 Neutrexin (trimetrexate glucuronate for injection) with concurrent leucovorin administration  
119 (leucovorin protection) is indicated as an alternative therapy for the treatment of moderate-to-severe  
120 *Pneumocystis carinii* pneumonia (PCP) in immunocompromised patients, including patients with the  
121 acquired immunodeficiency syndrome (AIDS), who are intolerant of, or are refractory to,  
122 trimethoprim-sulfamethoxazole therapy or for whom trimethoprim-sulfamethoxazole is  
123 contraindicated.

124

125 This indication is based on the results of a randomized, controlled double-blind trial comparing  
126 Neutrexin with concurrent leucovorin protection (TMTX/LV) to trimethoprim-sulfamethoxazole  
127 (TMP/SMX) in patients with moderate-to-severe *Pneumocystis carinii* pneumonia, as well as results  
128 of a Treatment IND. These studies are summarized below:

129

130 **Neutrexin Comparative Study with TMP/SMX:** This double-blind, randomized trial initiated by  
131 the AIDS Clinical Trials Group (ACTG) in 1988 was designed to compare the safety and efficacy of  
132 TMTX/LV to that of TMP/SMX for the treatment of histologically confirmed, moderate-to-severe  
133 PCP, defined as (A-a) baseline gradient >30 mmHg, in patients with AIDS.

134

135 Of the 220 patients with histologically confirmed PCP, 109 were randomized to receive TMTX/LV  
136 and 111 to TMP/SMX. Study patients randomized to TMTX/LV treatment were to receive 45  
137 mg/m<sup>2</sup> of TMTX daily for 21 days plus 20 mg/m<sup>2</sup> of LV every 6 hours for 24 days. Those  
138 randomized to TMP/SMX were to receive 5 mg/kg TMP plus 25 mg/kg SMX four times daily for 21  
139 days.

140 Response to therapy, defined as alive and off ventilatory support at completion of therapy, with no  
141 change in anti-pneumocystis therapy, or addition of supraphysiologic doses of steroids, occurred in  
142 fifty percent of patients in each treatment group.

143

144 The observed mortality in the TMTX/LV treatment group was approximately twice that in the  
145 TMP/SMX treatment group (95% CI: 0.99 - 4.11). Thirty of 109 (27%) patients treated with  
146 TMTX/LV and 18 of 111 (16%) patients receiving TMP/SMX died during the 21-day treatment  
147 course or 4-week follow-up period. Twenty-seven of 30 deaths in the TMTX/LV arm were  
148 attributed to PCP; all 18 deaths in the TMP/SMX arm were attributed to PCP.

149 A significantly smaller proportion of patients who received TMTX/LV compared to TMP/SMX  
150 failed therapy due to toxicity (10% vs. 25%), and a significantly greater proportion of patients failed  
151 due to lack of efficacy (40% vs. 24%). Six patients (12%) who responded to TMTX/LV relapsed  
152 during the one-month follow-up period; no patient responding to TMP/SMX relapsed during this  
153 period. Information is not available as to whether these patients received prophylaxis therapy for  
154 PCP.

155

156 **Treatment IND:** The FDA granted a Treatment IND for Neutrexin with leucovorin protection in  
157 February 1988 to make Neutrexin therapy available to HIV-infected patients with histologically  
158 confirmed PCP who had disease refractory to or who were intolerant of TMP/SMX and/or  
159 intravenous pentamidine.

160



161 Over 500 physicians in the United States participated in the Treatment IND. Of the first 753 patients  
162 enrolled, 577 were evaluable for efficacy. Of these, 227 patients were intolerant of both TMP/SMX  
163 and pentamidine (IST - patients intolerant of both standard therapies), 146 were intolerant of one  
164 therapy and refractory to the other (RIST - patients refractory to one therapy and intolerant of the  
165 other) and 204 were refractory to both therapies (RST - refractory to both standard therapies). This  
166 was a very ill patient population; 38% required ventilatory support at entry (Table 1). These studies  
167 did not have concurrent control groups.

168 **TABLE 1**

169 **TREATMENT IND**

170 **Baseline Characteristics**

	<b>IST</b> <b>(n = 227)</b>		<b>RIST</b> <b>(n = 146)</b>		<b>RST</b> <b>(n = 204)</b>		<b>TOTAL</b> <b>(n = 577)</b>	
Ventilatory Support Required n (%)	39	(17)	50	(34)	129	(63)	218	(38)
Median Days on Standard Therapy	10		12		16		14	
First Episode of PCP n (%)	104	(46)	103	(71)	190	(93)	397	(69)

174  
175

176 The overall survival rate one month after completion of TMTX/LV as salvage therapy was 48%.  
177 Patients who had not responded to treatment with both TMP/SMX and pentamidine, of whom 63%  
178 required mechanical ventilation at entry, achieved a survival rate of 25% following treatment with  
179 TMTX/LV. Survival was 67% in patients who were intolerant to both TMP/SMX and pentamidine  
180 (Table 2).

181 **TABLE 2**

182 **TREATMENT IND**

183 **Survival Rate One Month After Completion of Neutrexin**  
184 **Therapy**

185

186

	<b>IST</b>		<b>RIST</b>		<b>RST</b>	
All Patients	153/227	(67%)	73/146	(50%)	50/204	(25%)
Baseline Ventilatory Support	9/39	(23%)	15/50	(30%)	18/129	(14%)
No Baseline Ventilatory Support	144/188	(77%)	58/96	(60%)	32/75	(43%)

187

188

189

190

191 In the Treatment IND, 12% of the patients discontinued Neutrexin therapy (with leucovorin  
192 protection) for toxicity.

193

194 **CONTRAINDICATIONS**

195 Neutrexin (trimetrexate glucuronate for injection) is contraindicated in patients with clinically  
196 significant sensitivity to trimetrexate, leucovorin, or methotrexate.

197

198 **WARNINGS**

199 Neutrexin (trimetrexate glucuronate for injection) must be used with concurrent leucovorin to avoid  
200 potentially serious or life-threatening complications including bone marrow suppression, oral and  
201 gastrointestinal mucosal ulceration, and renal and hepatic dysfunction. Leucovorin therapy must  
202 extend for 72 hours past the last dose of Neutrexin. Patients should be informed that failure to take  
203 the recommended dose and duration of leucovorin can lead to fatal toxicity. Patients should be  
204 closely monitored for the development of serious hematologic adverse reactions (see  
205 **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

206

207 Neutrexin can cause fetal harm when administered to a pregnant woman. Trimetrexate has been  
208 shown to be fetotoxic and teratogenic in rats and rabbits. Rats administered 1.5 and 2.5 mg/kg/day  
209 intravenously on gestational days 6-15 showed substantial postimplantation loss and severe  
210 inhibition of maternal weight gain. Trimetrexate administered intravenously to rats at 0.5 and 1.0  
211 mg/kg/day on gestational days 6-15 retarded normal fetal development and was teratogenic. Rabbits  
212 administered trimetrexate intravenously at daily doses of 2.5 and 5.0 mg/kg/day on gestational days  
213 6-18 resulted in significant maternal and fetal toxicity. In rabbits, trimetrexate at 0.1 mg/kg/day was  
214 teratogenic in the absence of significant maternal toxicity. These effects were observed using doses  
215 1/20 to 1/2 the equivalent human therapeutic dose based on a mg/m<sup>2</sup> basis. Teratogenic effects  
216 included skeletal, visceral, ocular, and cardiovascular abnormalities. If Neutrexin is used during  
217 pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised  
218 of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid  
219 becoming pregnant.

220 **PRECAUTIONS**

221 **General**

222 Patients receiving Neutrexin (trimetrexate glucuronate for injection) may experience severe  
223 hematologic, hepatic, renal, and gastrointestinal toxicities. Caution should be used in treating  
224 patients with impaired hematologic, renal, or hepatic function. Patients who require concomitant  
225 therapy with nephrotoxic, myelosuppressive, or hepatotoxic drugs should be treated with Neutrexin  
226 at the discretion of the physician and monitored carefully. To allow for full therapeutic doses of  
227 Neutrexin, treatment with zidovudine should be discontinued during Neutrexin therapy.

228

229 Neutrexin-associated myelosuppression, stomatitis, and gastrointestinal toxicities generally can be  
230 ameliorated by adjusting the dose of leucovorin. Mild elevations in transaminases and alkaline  
231 phosphatase have been observed with Neutrexin administration and are usually not cause for  
232 modification of Neutrexin therapy (see **DOSAGE AND ADMINISTRATION**). Seizures have  
233 been reported rarely (< 1%) in AIDS patients receiving Neutrexin; however, a causal relationship  
234 has not been established. Trimetrexate is a known inhibitor of histamine metabolism.  
235 Hypersensitivity/allergic type reactions including but not limited to rash, chills/rigors, fever,  
236 diaphoresis and dyspnea have occurred with trimetrexate primarily when it is administered as a bolus  
237 infusion or at doses higher than those recommended for PCP, and most frequently in combination  
238 with 5FU and leucovorin. In rare cases, anaphylactoid reactions, including acute hypotension and  
239 loss of consciousness have occurred. Neutrexin infusion should be permanently discontinued in all  
240 patients with severe hypersensitivity reactions. Epinephrine should be available for treatment of  
241 acute allergic symptoms.

242

243 Neutrexin has not been evaluated clinically for the treatment of concurrent pulmonary conditions  
244 such as bacterial, viral, or fungal pneumonia or mycobacterial diseases. *In vitro* activity has been  
245 observed against *Toxoplasma gondii*, *Mycobacterium avium* complex, gram positive cocci, and gram  
246 negative rods. If clinical deterioration is observed in patients, they should be carefully evaluated for  
247 other possible causes of pulmonary disease and treated with additional agents as appropriate.

248 **Laboratory Tests**

249 Patients receiving Neutrexin with leucovorin protection should be seen frequently by a physician.  
250 Blood tests to assess the following parameters should be performed at least twice a week during  
251 therapy: hematology (absolute neutrophil counts [ANC], platelets), renal function (serum creatinine,  
252 BUN), and hepatic function (AST, ALT, alkaline phosphatase).

253

254 **Drug Interactions**

255 Since trimetrexate is metabolized by a P450 enzyme system, drugs that induce or inhibit this drug  
256 metabolizing enzyme system may elicit important drug-drug interactions that may alter trimetrexate  
257 plasma concentrations. Agents that might be coadministered with trimetrexate in AIDS patients for  
258 other indications that could elicit this activity include erythromycin, rifampin, rifabutin,  
259 ketoconazole, and fluconazole. *In vitro* perfusion of isolated rat liver has shown that cimetidine  
260 caused a significant reduction in trimetrexate metabolism and that acetaminophen altered the relative  
261 concentration of trimetrexate metabolites possibly by competing for sulfate metabolites. Based on  
262 an *in vitro* rat liver model, nitrogen substituted imidazole drugs (clotrimazole, ketoconazole,  
263 miconazole) were potent, non-competitive inhibitors of trimetrexate metabolism. Patients medicated  
264 with these drugs and trimetrexate should be carefully monitored.

265

266 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

267 Carcinogenesis: Long term studies in animals to evaluate the carcinogenic potential of trimetrexate  
268 have not been performed.

269 Mutagenesis: Trimetrexate was not mutagenic when tested using the standard Ames *Salmonella*  
270 mutagenicity assay with and without metabolic activation. Trimetrexate did not induce mutations in  
271 Chinese hamster lung cells or sister-chromatid exchange in Chinese hamster ovary cells.  
272 Trimetrexate did induce an increase in the chromosomal aberration frequency of cultured Chinese  
273 hamster lung cells; however, trimetrexate showed no clastogenic activity in a mouse micronucleus  
274 assay.

275

276 Impairment of fertility: No studies have been conducted to evaluate the potential of trimetrexate to  
277 impair fertility. However, during standard toxicity studies conducted in mice and rats, degeneration  
278 of the testes and spermatocytes including the arrest of spermatogenesis was observed.

279

#### 280 **Pregnancy, Teratogenic Effects**

281 See **WARNINGS**.

#### 282 **Pregnancy Category D**

#### 283 **Nursing Mothers**

284 It is not known if trimetrexate is excreted in human milk. Because many drugs are excreted in  
285 human milk and because of the potential for serious adverse reactions in nursing infants from  
286 trimetrexate, it is recommended that breast feeding be discontinued if the mother is treated with  
287 Neutrexin.

288 **Pediatric Use**

289 The safety and effectiveness of Neutrexin for the treatment of histologically confirmed PCP has not  
290 been established for patients under 18 years of age. Two children, ages 15 months and 9 months,  
291 were treated with trimetrexate and leucovorin using a dose of 45 mg/m<sup>2</sup> of trimetrexate per day for  
292 21 days and 20 mg/m<sup>2</sup> of leucovorin every 6 hours for 24 days. There were no serious or unexpected  
293 adverse effects.



294 **ADVERSE REACTIONS**

295 Because many patients who participated in clinical trials of Neutrexin (trimetrexate glucuronate for  
296 injection) had complications of advanced HIV disease, it is difficult to distinguish adverse events  
297 caused by Neutrexin from those resulting from underlying medical conditions.

298

299 Table 3 lists the adverse events that occurred in  $\geq 1\%$  of the patients who participated in the  
300 Comparative Study of Neutrexin plus leucovorin versus TMP/SMX.

**TABLE 3**  
**NEUTREXIN COMPARATIVE TRIAL**  
**Comparison of Adverse Events Reported for ≥ 1% of Patients**

Adverse Events	Number and Percent (%) of Patients with Adverse Events			
	TMTX/LV (n = 109)		TMP/SMX (n = 111)	
<b>Non-Laboratory Adverse Events:</b>				
Fever	9	(8.3)	14	(12.6)
Rash/Pruritus	6	(5.5)	14	(12.6)
Nausea/Vomiting	5	(4.6) <sup>a</sup>	15	(13.5) <sup>a</sup>
Confusion	3	(2.8)	3	(2.7)
Fatigue	2	(1.8)	0	(0.0)
<b>Hematologic Toxicity:</b>				
Neutropenia ( $\leq 1000/\text{mm}^3$ )	33	(30.3)	37	(33.3)
Thrombocytopenia ( $\leq 75,000/\text{mm}^3$ )	11	(10.1)	17	(15.3)
Anemia (Hgb $< 8$ g/dL)	8	(7.3)	10	(9.0)
<b>Hepatotoxicity:</b>				
Increased AST ( $> 5$ x ULN <sup>b</sup> )	15	(13.8)	10	(9.0)
Increased ALT ( $> 5$ x ULN)	12	(11.0)	13	(11.7)
Increased Alkaline Phosphatase ( $> 5$ x ULN)	5	(4.6)	3	(2.7)
Increased Bilirubin (2.5 x ULN)	2	(1.8)	1	(0.9)
<b>Renal:</b>				
Increased Serum Creatinine ( $> 3$ x ULN)	1	(0.9)	2	(1.8)
<b>Electrolyte Imbalance:</b>				
Hyponatremia	5	(4.6)	10	(9.0)
Hypocalcemia	2	(1.8)	0	(0.0)
<b>No. of Patients With at Least one Adverse Event<sup>c</sup></b>	<b>58</b>	<b>(53.2)</b>	<b>60</b>	<b>(54.1)</b>

<sup>a</sup> Statistically significant difference between treatment groups (Chi-square:  $p=0.022$ )

<sup>b</sup> ULN = Upper limit of normal range

<sup>c</sup> Patients could have reported more than one adverse event; therefore, the sum of adverse events exceeds the number of patients

301

302 Laboratory toxicities were generally manageable with dose modification of

303 trimetrexate/leucovorin (see **DOSAGE AND ADMINISTRATION**).

304 Table 4 lists the adverse events resulting in discontinuation of study therapy in the Neutrexin

305 Comparative Study with TMP/SMX. Twenty-nine percent of the patients on the TMP/SMX arm

306 discontinued therapy due to adverse events compared to 10% of the patients treated with  
 307 TMTX/LV (p < 0.001).

308

**TABLE 4**  
**NEUTREXIN COMPARATIVE TRIAL**  
**Adverse Events Resulting in Discontinuation of Therapy**

Adverse Events	Number and Percent (%) of Patients Discontinued for Adverse Events <sup>b</sup>			
	TMTX/LV (n = 109)		TMP/SMX (n = 111)	
<b>Non-Laboratory Adverse Events:</b>				
Rash/Pruritus	3	(2.8)	5	(4.5)
Fever	2	(1.8)	4	(3.6)
Nausea/Vomiting	1	(0.9)	8	(7.2)
Neurologic Toxicity	1	(0.9) <sup>c</sup>	2	(1.8)
<b>Hematologic Toxicity:</b>				
Neutropenia ( $\leq 1000/\text{mm}^3$ )	4	(3.7)	6	(5.4)
Thrombocytopenia ( $\leq 75,000/\text{mm}^3$ )	0	(0.0)	4	(3.6)
Anemia (Hgb <8 g/dL)	0	(0.0)	4	(3.6)
<b>Hepatotoxicity:</b>				
Increased AST (>5 x ULN <sup>a</sup> )	3	(2.8)	9	(8.1)
Increased ALT (>5 x ULN)	1	(0.9)	4	(3.6)
Increased Alkaline Phosphatase (>5 x ULN)	0	(0.0)	1	(0.9)
<b>Electrolyte Imbalance:</b>				
Hyponatremia	0	(0.0)	3	(2.7)
<b>No. of Patients Discontinuing Therapy Due to an Adverse Event<sup>b</sup></b>	<b>11</b>	<b>(10.1)<sup>d</sup></b>	<b>32</b>	<b>(28.8)<sup>d</sup></b>

<sup>a</sup> ULN = Upper limit of normal range

<sup>b</sup> Patients could discontinue therapy due to more than one toxicity; therefore the sum exceeds number of patients who discontinued due to toxicity

<sup>c</sup> Patient discontinued TMTX/LV due to seizure, though causal relationship could not be established.

<sup>d</sup> Statistically significant difference between treatment groups (Chi-square: p < 0.001)

309

309 Hematologic toxicity was the principal dose-limiting side effect.

310

### 311 **OVERDOSAGE**

312 Neutrexin (trimetrexate glucuronate for injection) administered without concurrent  
313 leucovorin can cause lethal complications. There has been no extensive experience in humans  
314 receiving single intravenous doses of trimetrexate greater than 90 mg/m<sup>2</sup>/day with concurrent  
315 leucovorin. The toxicities seen at this dose were primarily hematologic. In the event of overdose,  
316 Neutrexin should be stopped and leucovorin should be administered at a dose of 40 mg/m<sup>2</sup> every 6  
317 hours for 3 days. The LD<sub>50</sub> of intravenous trimetrexate in mice is 62 mg/kg (186 mg/m<sup>2</sup>).

318

### 319 **DOSAGE AND ADMINISTRATION**

320 **Caution: Neutrexin (trimetrexate glucuronate for injection) must be administered with**  
321 **concurrent leucovorin (leucovorin protection) to avoid potentially serious or life-threatening**  
322 **toxicities. Leucovorin therapy must extend for 72 hours past the last dose of Neutrexin.**

323

324 Neutrexin (trimetrexate glucuronate for injection) is administered at a dose of 45 mg/m<sup>2</sup> once daily  
325 by intravenous infusion over 60 minutes. Leucovorin must be administered daily during treatment  
326 with Neutrexin and for 72 hours past the last dose of Neutrexin. Leucovorin may be administered  
327 intravenously at a dose of 20 mg/m<sup>2</sup> over 5 to 10 minutes every 6 hours for a total daily dose of 80  
328 mg/m<sup>2</sup>, or orally as 4 doses of 20 mg/m<sup>2</sup> spaced equally throughout the day. The oral dose should be  
329 rounded up to the next higher 25 mg increment. The recommended course of therapy is 21 days of  
330 Neutrexin and 24 days of leucovorin.

331 Neutrexin and leucovorin may alternatively be dosed on a mg/kg basis, depending on the patient's  
332 body weight, using the conversion factors shown in the table below:

333

Body Weight (kg)	Neutrexin Dose (mg/kg/day)	Leucovorin Dose (mg/kg/qid)
<50	1.5	0.6
50-80	1.2	0.5
>80	1.0	0.5

334

335 **Dosage Modifications**

336 Hematologic toxicity: Neutrexin (trimetrexate glucuronate for injection) and leucovorin doses  
337 should be modified based on the worst hematologic toxicity according to the following table. If  
338 leucovorin is given orally, doses should be rounded up to the next higher 25 mg increment.

339

**TABLE 5**

**DOSE MODIFICATIONS FOR HEMATOLOGIC TOXICITY**

Toxicity Grade	Neutrophils (Polys and Bands)	Platelets	Recommended Dosages of	
			Neutrexin	Leucovorin
1	>1000/mm <sup>3</sup>	>75,000/mm <sup>3</sup>	45 mg/m <sup>2</sup> once daily	20 mg/m <sup>2</sup> every 6 hours
2	750-1000/mm <sup>3</sup>	50,000-75,000/mm <sup>3</sup>	45 mg/m <sup>2</sup> once daily	40 mg/m <sup>2</sup> every 6 hours
3	500-749/mm <sup>3</sup>	25,000-49,999/mm <sup>3</sup>	22 mg/m <sup>2</sup> once daily	40 mg/m <sup>2</sup> every 6 hours
4	<500/mm <sup>3</sup>	<25,000/mm <sup>3</sup>	Day 1-9 Discontinue Day 10-21 Interrupt up to 96 hours <sup>a</sup>	40 mg/m <sup>2</sup> every 6 hours

<sup>a</sup> If Grade 4 hematologic toxicity occurs prior to Day 10, Neutrexin should be discontinued. Leucovorin (40 mg/m<sup>2</sup>, q6h) should be administered for an additional 72 hours. If Grade 4 hematologic toxicity occurs at Day 10 or later, Neutrexin may be held up to 96 hours to allow counts to recover. If counts recover to Grade 3 within 96 hours, Neutrexin should be administered at a dose of 22 mg/m<sup>2</sup> and leucovorin maintained at 40 mg/m<sup>2</sup>, q6h. When counts recover to Grade 2 toxicity, Neutrexin dose may be increased to 45 mg/m<sup>2</sup>, but the leucovorin dose should be maintained at 40 mg/m<sup>2</sup> for the duration of treatment. If counts do not improve to ≤ Grade 3 toxicity within 96 hours, Neutrexin should be discontinued. Leucovorin at a dose of 40 mg/m<sup>2</sup>, q6h should be administered for 72 hours following the last dose of

Neutrexin.

340

341

342 Hepatic toxicity: Transient elevations of transaminases and alkaline phosphatase have been  
343 observed in patients treated with Neutrexin. Interruption of treatment is advisable if transaminase  
344 levels or alkaline phosphatase levels increase to >5 times the upper limit of normal range.

345

346 Renal toxicity: Interruption of Neutrexin is advisable if serum creatinine levels increase to > 2.5  
347 mg/dL and the elevation is considered to be secondary to Neutrexin.

348

349 Other toxicities: Interruption of treatment is advisable in patients who experience severe mucosal  
350 toxicity that interferes with oral intake. Treatment should be discontinued for fever (oral  
351 temperature  $\geq 105^{\circ}\text{F}/40.5^{\circ}\text{C}$ ) that cannot be controlled with antipyretics.

352 **Leucovorin therapy must extend for 72 hours past the last dose of Neutrexin.**

353

#### 354 **RECONSTITUTION AND DILUTION**

355 Each vial of Neutrexin (trimetrexate glucuronate for injection) should be reconstituted in accordance  
356 with labeled instructions with either 5% Dextrose Injection, USP, or Sterile Water for Injection,  
357 USP, to yield a concentration of 12.5 mg of trimetrexate per mL (complete dissolution should occur  
358 within 30 seconds). The reconstituted product will appear as a pale greenish-yellow solution and  
359 must be inspected visually prior to dilution. **Do not use if cloudiness or precipitate is observed.**

360 Neutrexin should not be reconstituted with solutions containing either chloride ion or leucovorin,  
361 since precipitation occurs instantly.

362

363 After reconstitution, the solution should be used immediately; however, the solution is stable for 6  
364 hours at room temperature (20 to 25°C), or 24 hours under refrigeration (2-8°C).

365

366 Prior to administration, the reconstituted solution should be further diluted with 5% Dextrose  
367 Injection, USP, to yield a final concentration of 0.25 to 2 mg of trimetrexate per mL. The diluted  
368 solution should be administered by intravenous infusion over 60 minutes. Neutrexin should not be  
369 mixed with solutions containing either chloride ion or leucovorin, since precipitation occurs  
370 instantly. The diluted solution is stable under refrigeration or at room temperature for up to 24  
371 hours. Do not freeze. Discard any unused portion after 24 hours. The intravenous line must be  
372 flushed thoroughly with at least 10 mL of 5% Dextrose Injection, USP, before and after  
373 administering Neutrexin.

374

375 Leucovorin protection may be administered prior to or following Neutrexin. In either case, the  
376 intravenous line must be flushed thoroughly with at least 10 mL of 5% Dextrose Injection, USP.  
377 Leucovorin calcium for injection should be diluted according to the instructions in the leucovorin  
378 package insert, and administered over 5 to 10 minutes every 6 hours.

379

380 **Caution: Parenteral products should be inspected visually for particulate matter and**  
381 **discoloration prior to administration, whenever solution and container permit. Neutrexin**  
382 **forms a precipitate instantly upon contact with chloride ion or leucovorin, therefore it should**  
383 **not be added to solutions containing sodium chloride or other anions. Neutrexin and**  
384 **leucovorin solutions must be administered separately. Intravenous lines should be flushed**  
385 **with at least 10 mL of 5% Dextrose Injection, USP, between Neutrexin and leucovorin**  
386 **infusions.**

387

388 **HANDLING AND DISPOSAL**

389 If Neutrexin (trimetrexate glucuronate for injection) contacts the skin or mucosa, immediately wash  
390 thoroughly with soap and water. Procedures for proper disposal of cytotoxic drugs should be  
391 considered. Several guidelines on this subject have been published (1-5).



392 **HOW SUPPLIED**

393 Neutrexin (trimetrexate glucuronate for injection) is supplied as a sterile lyophilized powder in  
394 either 5 mL or 30 mL vials. Each 5 mL vial contains trimetrexate glucuronate equivalent to 25 mg  
395 of trimetrexate. Each 30 mL vial contains trimetrexate glucuronate equivalent to 200 mg of  
396 trimetrexate. The 5 mL vials are packaged and available in two market presentations as listed below:

397 10 Pack - 10 vials in a white chip-board carton (NDC 58178-020-10)

398 50 Pack - 2 trays of 25 vials per shrink-wrapped tray (NDC 58178-020-50)

399 The 30 mL vials are packaged and available as listed below:

400 Single Pack - 1 vial (NDC 58178-021-01)

401 Store at controlled room temperature 20° to 25°C (68° to 77°F). **Protect from exposure to light.**

402 U.S. Patents 4,376,858; 4,694,007; 6,017,922

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419

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422 Ben Venue Laboratories, Inc.

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426 MedImmune Pharma B.V.

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