

1 ETHYOL[®]

2 (amifostine) for Injection

3 **Rx only**

4 DESCRIPTION

5 ETHYOL (amifostine) is an organic thiophosphate cytoprotective agent known
6 chemically as 2-[(3-aminopropyl)amino]ethanethiol dihydrogen phosphate (ester) and has
7 the following structural formula:



9 Amifostine is a white crystalline powder which is freely soluble in water. Its empirical
10 formula is C₅H₁₅N₂O₃PS and it has a molecular weight of 214.22.

11 ETHYOL is the trihydrate form of amifostine and is supplied as a sterile lyophilized
12 powder requiring reconstitution for intravenous infusion. Each single-use 10 mL vial
13 contains 500 mg of amifostine on the anhydrous basis.

14 CLINICAL PHARMACOLOGY

15 ETHYOL is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a
16 pharmacologically active free thiol metabolite. This metabolite is believed to be
17 responsible for the reduction of the cumulative renal toxicity of cisplatin and for the
18 reduction of the toxic effects of radiation on normal oral tissues. The ability of ETHYOL
19 to differentially protect normal tissues is attributed to the higher capillary alkaline
20 phosphatase activity, higher pH and better vascularity of normal tissues relative to tumor
21 tissue, which results in a more rapid generation of the active thiol metabolite as well as a
22 higher rate constant for uptake into cells. The higher concentration of the thiol metabolite
23 in normal tissues is available to bind to, and thereby detoxify, reactive metabolites of
24 cisplatin. This thiol metabolite can also scavenge reactive oxygen species generated by
25 exposure to either cisplatin or radiation.

26 **Pharmacokinetics:** Clinical pharmacokinetic studies show that ETHYOL is rapidly
27 cleared from the plasma with a distribution half-life of < 1 minute and an elimination
28 half-life of approximately 8 minutes. Less than 10% of ETHYOL remains in the plasma 6
29 minutes after drug administration. ETHYOL is rapidly metabolized to an active free thiol
30 metabolite. A disulfide metabolite is produced subsequently and is less active than the
31 free thiol. After a 10-second bolus dose of 150 mg/m² of ETHYOL, renal excretion of the
32 parent drug and its two metabolites was low during the hour following drug
33 administration, averaging 0.69%, 2.64% and 2.22% of the administered dose for the
34 parent, thiol and disulfide, respectively. Measurable levels of the free thiol metabolite
35 have been found in bone marrow cells 5-8 minutes after intravenous infusion of
36 ETHYOL. Pretreatment with dexamethasone or metoclopramide has no effect on
37 ETHYOL pharmacokinetics.

38 **Clinical Studies**

39 **Chemotherapy for Ovarian Cancer and Non-Small Cell Lung Cancer.** A randomized
40 controlled trial compared six cycles of cyclophosphamide 1000 mg/m², and cisplatin 100
41 mg/m² with or without ETHYOL pretreatment at 910 mg/m², in two successive cohorts of
42 121 patients with advanced ovarian cancer. In both cohorts, after multiple cycles of
43 chemotherapy, pretreatment with ETHYOL significantly reduced the cumulative renal
44 toxicity associated with cisplatin as assessed by the proportion of patients who had 40%
45 decrease in creatinine clearance from pretreatment values, protracted elevations in serum
46 creatinine (>1.5 mg/dL), or severe hypomagnesemia. Subgroup analyses suggested that
47 the effect of ETHYOL was present in patients who had received nephrotoxic antibiotics,
48 or who had preexisting diabetes or hypertension (and thus may have been at increased
49 risk for significant nephrotoxicity), as well as in patients who lacked these risks. Selected
50 analyses of the effects of ETHYOL in reducing the cumulative renal toxicity of cisplatin
51 in the randomized ovarian cancer study are provided in TABLES 1 and 2, below.

52 **TABLE 1**
53 **Proportion of Patients with 40% Reduction in Calculated Creatinine Clearance***

	ETHYOL+CP	CP	p-value (2-sided)
All Patients	16/122 (13%)	36/120 (30%)	0.001
First Cohort	10/63	20/58	0.018
Second Cohort	6/59	16/62	0.026

54 *Creatinine clearance values were calculated using the Cockcroft-Gault formula,
55 *Nephron* 1976; 16:31-41.

56

57

58

59

TABLE 2
NCI Toxicity Grades of Serum Magnesium Levels
for Each Patient's Last Cycle of Therapy

NCI-CTC Grade: (mEq/L)	0 >1.4	1 1.4->1.1	2 1.1->0.8	3 0.8->0.5	4 0.5	p-value*
All Patients						
ETHYOL +CP	92	13	3	0	0	0.001
CP	73	18	7	5	1	
First Cohort						
ETHYOL+CP	49	10	3	0	0	0.017
CP	35	8	6	3	1	
Second Cohort						
ETHYOL+CP	43	3	0	0	0	0.012
CP	38	10	1	2	0	

60 * Based on 2-sided Mantel-Haenszel Chi-Square statistic.

61 In the randomized ovarian cancer study, ETHYOL had no detectable effect on the
62 antitumor efficacy of cisplatin-cyclophosphamide chemotherapy. Objective response
63 rates (including pathologically confirmed complete remission rates), time to progression,
64 and survival duration were all similar in the ETHYOL and control study groups. The
65 table below summarizes the principal efficacy findings of the randomized ovarian cancer
66 study.

67

68

TABLE 3
Comparison of Principal Efficacy Findings

	ETHYOL +CP	CP
Complete pathologic tumor response rate	21.3%	15.8%
Time to progression (months)		
Median (\pm 95% CI)	15.8 (13.2, 25.1)	18.1 (12.5, 20.4)
Mean (\pm Std error)	19.8 (\pm 1.04)	19.1 (\pm 1.58)
Hazard ratio (95% Confidence Interval)	.98 (.64, 1.4)	
Survival (months)		
Median (\pm 95% CI)	31.3 (28.3, 38.2)	31.8 (26.3, 39.8)
Mean (\pm Std error)	33.7 (\pm 2.03)	34.3 (\pm 2.04)
Hazard ratio (95% Confidence Interval)	.97 (.69, 1.32)	

69 A Phase II trial of ETHYOL, 740-910 mg/m², and cisplatin, 120 mg/m², administered on
 70 day 1 and vinblastine, 5mg/m², administered on days 1, 8, 15 and 22 of each monthly
 71 cycle was conducted in 25 patients with Stage IV non-small cell lung cancer. This
 72 regimen was repeated until disease progression or unacceptable toxicity occurred, or a
 73 maximum of six cycles had been administered. Among 13 patients who received 4 or
 74 more cycles of this intensive cisplatin regimen, 1 had a 40% reduction in creatinine
 75 clearance. These results are consistent with the randomized ovarian cancer trial.

76 Sixteen of the 25 patients treated demonstrated a partial response to chemotherapy. With
 77 a median follow-up of 19 months, the median survival was 17 months. At one year, 64%
 78 of the patients were alive. These results indicate that ETHYOL may not adversely affect
 79 the efficacy of this chemotherapy for non-small cell lung cancer.

80 **Radiotherapy for Head and Neck Cancer.** A randomized controlled trial of standard
 81 fractionated radiation (1.8 Gy - 2.0 Gy/day for 5 days/week for 5-7 weeks) with or
 82 without ETHYOL, administered at 200 mg/m² as a 3 minute i.v. infusion 15-30 minutes
 83 prior to each fraction of radiation, was conducted in 315 patients with head and neck
 84 cancer. Patients were required to have at least 75% of both parotid glands in the radiation
 85 field. The incidence of Grade 2 or higher acute (90 days or less from start of radiation)
 86 and late xerostomia (9-12 months following radiation) as assessed by RTOG Acute and
 87 Late Morbidity Scoring Criteria, was significantly reduced in patients receiving
 88 ETHYOL (TABLE 4).

89 **TABLE 4**
 90 **Incidence of Grade 2 or Higher Xerostomia**
 91 **(RTOG criteria)**

	ETHYOL +RT	RT	p-value
Acute (90 days from start of radiation)	51% (75/148)	78% (120/153)	p<0.0001
Late^a (9-12 months post radiation)	35% (36/103)	57% (63/111)	p=0.0016

92 ^aBased on the number of patients for whom actual data were available.

93

94 At one year following radiation, whole saliva collection following radiation showed that
 95 more patients given ETHYOL produced >0.1 gm of saliva (72% vs. 49%). In addition,
 96 the median saliva production at one year was higher in those patients who received
 97 ETHYOL (0.26 gm vs. 0.1 gm). Stimulated saliva collections did not show a difference
 98 between treatment arms. These improvements in saliva production were supported by the
 99 patients' subjective responses to a questionnaire regarding oral dryness.
 100 In the randomized head and neck cancer study, locoregional control, disease-free survival
 101 and overall survival were all comparable in the two treatment groups after one year of
 102 follow-up (see TABLE 5).

103
104

TABLE 5
Comparison of Principal Efficacy Findings at 1 Year

	ETHYOL +RT	RT
Locoregional Control Rate^a	76.1%	75.0%
Hazard Ratio ^b	1.013	
95% Confidence Interval	(0.671, 1.530)	
Disease-Free Survival Rate^a	74.6%	
Hazard Ratio ^b	70.4%	
95% Confidence Interval	1.035 (0.702, 1.528)	
Overall Survival Rate^a	89.4%	
Hazard Ratio ^b	82.4%	
95% Confidence Interval	1.585 (0.961, 2.613)	

105 ^a1 year rates estimated using Kaplan-Meier method
 106 ^bHazard ratio >1.0 is in favor of the ETHYOL + RT arm

107 **INDICATIONS AND USAGE**

108 **ETHYOL (amifostine) is indicated to reduce the cumulative renal toxicity associated**
 109 **with repeated administration of cisplatin in patients with advanced ovarian cancer**
 110 **or non-small cell lung cancer.**

111
 112 **ETHYOL is indicated to reduce the incidence of moderate to severe xerostomia in**
 113 **patients undergoing post-operative radiation treatment for head and neck cancer,**
 114 **where the radiation port includes a substantial portion of the parotid glands (see**
 115 **Clinical Studies).**

116
 117 For the approved indications, the clinical data do not suggest that the effectiveness of
 118 cisplatin based chemotherapy regimens or radiation therapy is altered by ETHYOL.

119 There are at present only limited data on the effects of ETHYOL on the efficacy of
120 chemotherapy or radiotherapy in other settings. ETHYOL should not be administered to
121 patients in other settings where chemotherapy can produce a significant survival benefit
122 or cure, or in patients receiving definitive radiotherapy, except in the context of a clinical
123 study (see WARNINGS).

124 **CONTRAINDICATIONS**

125 ETHYOL is contraindicated in patients with known sensitivity to aminothiols compounds.

126 **WARNINGS**

127 1. Effectiveness of the Cytotoxic Regimen

128 Limited data are currently available regarding the preservation of antitumor efficacy
129 when ETHYOL is administered prior to cisplatin therapy in settings other than advanced
130 ovarian cancer or non-small cell lung cancer. Although some animal data suggest
131 interference is possible, in most tumor models the antitumor effects of chemotherapy are
132 not altered by amifostine. ETHYOL should not be used in patients receiving
133 chemotherapy for other malignancies in which chemotherapy can produce a significant
134 survival benefit or cure (e.g., certain malignancies of germ cell origin), except in the
135 context of a clinical study.

136

137 2. Effectiveness of Radiotherapy

138 ETHYOL should not be administered in patients receiving definitive radiotherapy, except
139 in the context of a clinical trial, since there are at present insufficient data to exclude a
140 tumor-protective effect in this setting. ETHYOL was studied only with standard
141 fractionated radiotherapy and only when 75% of both parotid glands were exposed to
142 radiation. The effects of ETHYOL on the incidence of xerostomia and on toxicity in the
143 setting of combined chemotherapy and radiotherapy and in the setting of accelerated and
144 hyperfractionated therapy have not been systematically studied.

145

146 3. Hypotension

147 Patients who are hypotensive or in a state of dehydration should not receive ETHYOL.
148 Patients receiving ETHYOL at doses recommended for chemotherapy should have
149 antihypertensive therapy interrupted 24 hours preceding administration of ETHYOL.
150 Patients receiving ETHYOL at doses recommended for chemotherapy who are taking
151 antihypertensive therapy that cannot be stopped for 24 hours preceding ETHYOL
152 treatment, should not receive ETHYOL.

153 Prior to ETHYOL infusion patients should be adequately hydrated. During ETHYOL
154 infusion patients should be kept in a supine position. Blood pressure should be
155 monitored every 5 minutes during the infusion, and thereafter as clinically indicated. It is
156 important that the duration of the 910 mg/m² infusion not exceed 15 minutes, as
157 administration of ETHYOL as a longer infusion is associated with a higher incidence of
158 side effects. For infusion durations less than 5 minutes, blood pressure should be
159 monitored at least before and immediately after the infusion, and thereafter as clinically
160 indicated. If hypotension occurs, patients should be placed in the Trendelenburg position
161 and be given an infusion of normal saline using a separate i.v. line. During and after
162 ETHYOL infusion, care should be taken to monitor the blood pressure of patients whose

163 antihypertensive medication has been interrupted since hypertension may be exacerbated
164 by discontinuation of antihypertensive medication and other causes such as IV hydration.

165 Guidelines for interrupting and restarting ETHYOL infusion if a decrease in systolic
166 blood pressure should occur are provided in the DOSAGE AND ADMINISTRATION
167 section. Hypotension may occur during or shortly after ETHYOL infusion, despite
168 adequate hydration and positioning of the patient (see ADVERSE REACTIONS and
169 PRECAUTIONS). Hypotension has been reported to be associated with dyspnea, apnea,
170 hypoxia, and in rare cases seizures, unconsciousness, respiratory arrest and renal failure.

171

172 4. Hypersensitivity

173 Allergic manifestations including anaphylaxis and severe cutaneous reactions have been
174 associated rarely with ETHYOL administration. Serious cutaneous hypersensitivity
175 reactions have included erythema multiforme, Stevens-Johnson syndrome, toxic
176 epidermal necrolysis, toxoderma and exfoliative dermatitis, which have been reported
177 more frequently when ETHYOL is used as a radioprotectant (see ADVERSE
178 REACTIONS). Some of these reactions have been fatal or have required hospitalization
179 and/or discontinuance of therapy. Patients should be carefully monitored prior to, during
180 and after ETHYOL administration (see PRECAUTIONS).

181

182 5. Nausea and Vomiting

183 Antiemetic medication should be administered prior to and in conjunction with ETHYOL
184 (see DOSAGE AND ADMINISTRATION). When ETHYOL is administered with highly
185 emetogenic chemotherapy, the fluid balance of the patient should be carefully monitored.

186

187 6. Hypocalcemia

188 Serum calcium levels should be monitored in patients at risk of hypocalcemia, such as
189 those with nephrotic syndrome or patients receiving multiple doses of ETHYOL (see
190 ADVERSE REACTIONS). If necessary, calcium supplements can be administered.

191 **PRECAUTIONS**

192 **General**

193 Patients should be adequately hydrated prior to the ETHYOL infusion and blood pressure
194 should be monitored (see DOSAGE AND ADMINISTRATION).

195 The safety of ETHYOL administration has not been established in elderly patients, or in
196 patients with preexisting cardiovascular or cerebrovascular conditions such as ischemic
197 heart disease, arrhythmias, congestive heart failure, or history of stroke or transient
198 ischemic attacks. ETHYOL should be used with particular care in these and other patients
199 in whom the common ETHYOL adverse effects of nausea/vomiting and hypotension may
200 be more likely to have serious consequences.

201 Prior to chemotherapy, ETHYOL should be administered as a 15-minute infusion (see
202 DOSAGE AND ADMINISTRATION). Blood pressure should be monitored every 5
203 minutes during the infusion, and thereafter as clinically indicated.

204 Prior to radiation therapy, ETHYOL should be administered as a 3-minute infusion (see
205 DOSAGE AND ADMINISTRATION). Blood pressure should be monitored at least
206 before and immediately after the infusion, and thereafter as clinically indicated.

207 **Allergic Reactions**

208 In case of severe acute allergic reactions ETHYOL should be immediately and
209 permanently discontinued. Epinephrine and other appropriate measures should be
210 available for treatment of serious allergic events such as anaphylaxis. ETHYOL should
211 also be permanently discontinued for serious or severe cutaneous reactions (see
212 WARNINGS and ADVERSE REACTIONS) or for cutaneous reactions associated with
213 fever or other constitutional symptoms not known to be due to another etiology.
214 ETHYOL should be withheld and dermatologic consultation and biopsy considered for
215 cutaneous reactions or mucosal lesions of unknown etiology appearing outside of the
216 injection site or radiation port and for erythematous, edematous or bullous lesions on the
217 palms of the hand or soles of the feet. Reinitiation of ETHYOL should be at the
218 physician's discretion based on medical judgment and appropriate dermatologic
219 evaluation.

220

221 **Drug Interactions**

222 Special consideration should be given to the administration of ETHYOL in patients
223 receiving antihypertensive medications or other drugs that could cause or potentiate
224 hypotension.

225 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

226 No long term animal studies have been performed to evaluate the carcinogenic potential
227 of ETHYOL. ETHYOL was negative in the Ames test and in the mouse micronucleus
228 test. The free thiol metabolite was positive in the Ames test with S9 microsomal fraction
229 in the TA1535 *Salmonella typhimurium* strain and at the TK locus in the mouse L5178Y
230 cell assay. The metabolite was negative in the mouse micronucleus test and negative for
231 clastogenicity in human lymphocytes.

232 **Pregnancy**

233 Pregnancy Category C. ETHYOL has been shown to be embryotoxic in rabbits at doses
234 of 50 mg/kg, approximately sixty percent of the recommended dose in humans on a body
235 surface area basis. There are no adequate and well-controlled studies in pregnant women.
236 ETHYOL should be used during pregnancy only if the potential benefit justifies the
237 potential risk to the fetus.

238 **Nursing Mothers**

239 No information is available on the excretion of ETHYOL or its metabolites into human
240 milk. Because many drugs are excreted in human milk and because of the potential for
241 adverse reactions in nursing infants, it is recommended that breast feeding be
242 discontinued if the mother is treated with ETHYOL.

243 **Pediatric Use**

244 The safety and effectiveness in pediatric patients have not been established.

245 **Geriatric Use**

246 The safety Clinical studies did not include sufficient number of subjects aged 65 and over
247 to determine whether they respond differently from younger subjects. Other reported
248 clinical experience has not identified differences in responses between elderly and

249 younger patients. In general, dose selection for an elderly patient should be cautious,
 250 reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of
 251 concomitant disease or other drug therapy in elderly patients.

252

253 **ADVERSE REACTIONS**

254 **Controlled Trials**

255 In the randomized study of patients with ovarian cancer given ETHYOL at a dose of 910
 256 mg/m² prior to chemotherapy, transient hypotension was observed in 62% of patients
 257 treated. The mean time of onset was 14 minutes into the 15-minute period of ETHYOL
 258 infusion, and the mean duration was 6 minutes. In some cases, the infusion had to be
 259 prematurely terminated due to a more pronounced drop in systolic blood pressure. In
 260 general, the blood pressure returned to normal within 5-15 minutes. Fewer than 3% of
 261 patients discontinued ETHYOL due to blood pressure reductions. In the randomized
 262 study of patients with head and neck cancer given ETHYOL at a dose of 200 mg/m² prior
 263 to radiotherapy, hypotension was observed in 15% of patients treated. (TABLE 6)

264
 265

TABLE 6
Incidence of Common Adverse Events in Patients Receiving ETHYOL

	Phase III Ovarian Cancer Trial (WR-1) 910 mg/m²		Phase III Head and Neck Cancer Trial (WR-38) 200 mg/m²	
	Per Patient	Per Infusion	Per Patient	Per Infusion
Nausea/Vomiting				
Grade 3	36/122 (30%)	53/592 (9%)	12/150 (8%)	13/4314 (<1%)
All Grades	117/122 (96%)	520/592 (88%)	80/150 (53%)	233/4314 (5%)
Hypotension				
Grade 3 ^a	10/122 (8%)		4/150 (3%)	
All Grades	75/122 (61%)	159/592 (27%)	22/150 (15%)	46/4314 (1%)

266 ^aAccording to protocol-defined criteria. WR-1: requiring interruption of infusion; WR-
 267 38: drop of >20mm Hg.

268 In the randomized study of patients with head and neck cancer, 17% (26/150)
 269 discontinued ETHYOL due to adverse events. All but one of these patients continued to
 270 receive radiation treatment until completion.

271 Hypotension that requires interruption of the ETHYOL infusion should be treated with
 272 fluid infusion and postural management of the patient (supine or Trendelenburg position).
 273 If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic,
 274 the infusion may be restarted, so that the full dose of ETHYOL can be administered.

275 Short term, reversible loss of consciousness has been reported rarely

276

277 Nausea and/or vomiting occur frequently after ETHYOL infusion and may be severe. In
278 the ovarian cancer randomized study, the incidence of severe nausea/vomiting on day 1
279 of cyclophosphamide-cisplatin chemotherapy was 10% in patients who did not receive
280 ETHYOL, and 19% in patients who did receive ETHYOL. In the randomized study of
281 patients with head and neck cancer, the incidence of severe nausea/vomiting was 8% in
282 patients who received ETHYOL and 1% in patients who did not receive ETHYOL.

283

284 Decrease in serum calcium concentrations is a known pharmacological effect of
285 ETHYOL. At the recommended doses, clinically significant hypocalcemia has occurred
286 rarely (<1%) (see WARNINGS).

287

288 Other effects, which have been described during, or following ETHYOL infusion are
289 flushing/feeling of warmth, chills/feeling of coldness, fever, dizziness, somnolence,
290 hiccups and sneezing. These effects have not generally precluded the completion of
291 therapy.

292

293 Clinical Trials and Pharmacovigilance Reports

294 Allergic reactions characterized by one or more of the following manifestations have
295 been observed during or after ETHYOL administration: hypotension, fever, chills/rigors,
296 dyspnea, hypoxia, chest tightness, cutaneous eruptions, urticaria and laryngeal edema.
297 Serious, sometimes fatal skin reactions including erythema multiforme, and in rare cases,
298 exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have
299 occurred. The reported incidence of serious skin reactions associated with ETHYOL is
300 higher in patients receiving Ethyol as a radioprotectant than in patients receiving Ethyol
301 as a chemoprotectant. Rare anaphylactoid reactions and cardiac arrest have also been
302 reported.

303 Hypotension, usually brief systolic and diastolic, has been associated with one or more of
304 the following adverse events: apnea, dyspnea, hypoxia, tachycardia, bradycardia,
305 extrasystoles, chest pain, myocardial ischemia and convulsion. Rare cases of renal
306 failure, myocardial infarction, respiratory and cardiac arrest have been observed during or
307 after hypotension. (See WARNINGS and PRECAUTIONS)

308 Rare cases of arrhythmias such as atrial fibrillation/flutter and supraventricular
309 tachycardia have been reported. These are sometimes associated with hypotension or
310 allergic reactions.

311 Transient hypertension and exacerbations of preexisting hypertension have been observed
312 rarely after ETHYOL administration.

313 Seizures and syncope have been reported rarely. (See WARNINGS and PRECAUTIONS)

314

315 **OVERDOSAGE**

316 In clinical trials, the maximum single dose of ETHYOL was 1300 mg/m². No
317 information is available on single doses higher than this in adults. In the setting of a

318 clinical trial, pediatric patients have received single ETHYOL doses of up to 2700
 319 mg/m². At the higher doses, anxiety and reversible urinary retention occurred.
 320 Administration of ETHYOL at 2 and 4 hours after the initial dose has not led to increased
 321 nausea and vomiting or hypotension. The most likely symptom of overdose is
 322 hypotension, which should be managed by infusion of normal saline and other supportive
 323 measures, as clinically indicated.

324 **DOSAGE AND ADMINISTRATION**

325 **For Reduction of Cumulative Renal Toxicity with Chemotherapy:** The recommended
 326 starting dose of ETHYOL is 910 mg/m² administered once daily as a 15-minute i.v.
 327 infusion, starting 30 minutes prior to chemotherapy.
 328 The 15-minute infusion is better tolerated than more extended infusions. Further
 329 reductions in infusion times for chemotherapy regimens have not been systematically
 330 investigated.
 331 Patients should be adequately hydrated prior to ETHYOL infusion and kept in a supine
 332 position during the infusion. Blood pressure should be monitored every 5 minutes during
 333 the infusion, and thereafter as clinically indicated.
 334 The infusion of ETHYOL should be interrupted if the systolic blood pressure decreases
 335 significantly from the baseline value as listed in the guideline below:

336 **Guideline for Interrupting ETHYOL Infusion Due to Decrease**
 337 **in Systolic Blood Pressure**

	Baseline Systolic Blood Pressure (mm Hg)				
	<100	100-119	120-139	140-179	180
Decrease in systolic blood pressure during infusion of ETHYOL (mm Hg)	20	25	30	40	50

338 If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic,
 339 the infusion may be restarted so that the full dose of ETHYOL may be administered. If
 340 the full dose of ETHYOL cannot be administered, the dose of ETHYOL for subsequent
 341 chemotherapy cycles should be 740 mg/m².
 342 It is recommended that antiemetic medication, including dexamethasone 20 mg i.v. and a
 343 serotonin 5HT₃ receptor antagonist, be administered prior to and in conjunction with
 344 ETHYOL. Additional antiemetics may be required based on the chemotherapy drugs
 345 administered.

346
 347 **For Reduction of Moderate to Severe Xerostomia from Radiation of the Head and**
 348 **Neck:** The recommended dose of ETHYOL is 200 mg/m² administered once daily as a 3-
 349 minute i.v. infusion, starting 15-30 minutes prior to standard fraction radiation therapy
 350 (1.8-2.0 Gy).
 351 Patients should be adequately hydrated prior to ETHYOL infusion. Blood pressure
 352 should be monitored at least before and immediately after the infusion, and thereafter as
 353 clinically indicated.

354 It is recommended that antiemetic medication be administered prior to and in conjunction
355 with ETHYOL. Oral 5HT₃ receptor antagonists, alone or in combination with other
356 antiemetics, have been used effectively in the radiotherapy setting.

357 **Reconstitution**

358 ETHYOL (amifostine) for Injection is supplied as a sterile lyophilized powder requiring
359 reconstitution for intravenous infusion. Each single-use vial contains 500 mg of
360 amifostine on the anhydrous basis.

361 Prior to intravenous injection, ETHYOL is reconstituted with 9.7 mL of sterile 0.9%
362 Sodium Chloride Injection, USP. The reconstituted solution (500 mg amifostine/10 mL)
363 is chemically stable for up to 5 hours at room temperature (approximately 25°C) or up to
364 24 hours under refrigeration (2°C to 8°C).

365 ETHYOL prepared in polyvinylchloride (PVC) bags at concentrations ranging from 5
366 mg/mL to 40 mg/mL is chemically stable for up to 5 hours when stored at room
367 temperature (approximately 25°C) or up to 24 hours when stored under refrigeration (2°C
368 to 8°C).

369 CAUTION: Parenteral products should be inspected visually for particulate matter and
370 discoloration prior to administration whenever solution and container permit. Do not use
371 if cloudiness or precipitate is observed.

372 **Incompatibilities**

373 The compatibility of ETHYOL with solutions other than 0.9% Sodium Chloride for
374 Injection, or Sodium Chloride solutions with other additives, has not been examined. The
375 use of other solutions is not recommended.

376 **HOW SUPPLIED**

377 ETHYOL (amifostine) for Injection is supplied as a sterile lyophilized powder in 10 mL
378 single-use vials (NDC 58178-017-01). Each single-use vial contains 500 mg of
379 amifostine on the anhydrous basis. The vials are available packaged as follows:

380 3 pack - 3 vials per carton (NDC 58178-017-03)

381 Store the lyophilized dosage form at Controlled Room Temperature 20°-25°C (68°-77°F)
382 [See USP].

383 U.S. Patents 5,424,471; 5,591,731; 5,994,409

384 Manufactured by:
385 MedImmune Pharma B.V.
386 6545 CG Nijmegen
387 The Netherlands

388 Or:
389 Ben Venue, Inc.
390 Bedford, Ohio 44146

391 Marketed by:
392 MedImmune Oncology, Inc.
393 a subsidiary of MedImmune, Inc.,
394 Gaithersburg, MD 20878

395

396

397 For product information, please call 1 877 633 4411

398 © 2003 MedImmune Oncology, Inc.
399 Revision Date 3/2003