

1 **ETHYOL® (amifostine) for Injection**

RX only

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3 **DESCRIPTION**

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



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11 Amifostine is a white crystalline powder which is freely soluble in water. Its empirical formula is
12 $\text{C}_5\text{H}_{15}\text{N}_2\text{O}_3\text{PS}$ and it has a molecular weight of 214.22.

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

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18 **CLINICAL PHARMACOLOGY**

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

30
31 **Pharmacokinetics:** Clinical pharmacokinetic studies show that ETHYOL is rapidly cleared from

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

41

42 **Clinical Studies**

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

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TABLE 1
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

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

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58
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TABLE 2
NCI Toxicity Grades of Serum Magnesium Levels
for Each Patient's Last Cycle of Therapy

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

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

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

TABLE 3
Comparison of Principal Efficacy Findings

	ETHYOL+CP	CP
Complete pathologic tumor response rate	21.3%	15.8%
Time to progression (months)		
Median (± 95% CI)	15.8 (13.2, 25.1)	18.1 (12.5, 20.4)
Mean (± Std error)	19.8 (±1.04)	19.1 (±1.58)
Hazard ratio (95%	.98 (.64, 1.4)	

Confidence Interval)

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)	

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69

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

77

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

82

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

91

TABLE 4

**Incidence of Grade 2 or Higher Xerostomia
(RTOG criteria)**

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

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

93

94

95 At one year following radiation, whole saliva collection following radiation showed that
96 more patients given ETHYOL produced > 0.1 gm of saliva (72% vs. 49%). In
97 addition, the median saliva production at one year was higher in those patients who
98 received Ethyol (0.26 gm vs. 0.1 gm). Stimulated saliva collections did not show a
99 difference between treatment arms. These improvements in saliva production were
100 supported by the patients' subjective responses to a questionnaire regarding oral dryness.

101

102 In the randomized head and neck cancer study, locoregional control, disease-free survival
103 and overall survival were all comparable in the two treatment groups after one year of
104 follow-up (see Table 5).

105

**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%	70.4%
Hazard Ratio ^b	1.035	
95% Confidence Interval	(0.702, 1.528)	
Overall Survival Rate^a	89.4%	82.4%
Hazard ratio ^b	1.585	
95% Confidence Interval	(0.961, 2.613)	

^a 1 year rates estimated using Kaplan-Meier method

^b Hazard ratio >1.0 is in favor of the Ethyol + RT arm

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INDICATIONS AND USAGE

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

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

For the approved indications, the clinical data do not suggest that the effectiveness of cisplatin based chemotherapy regimens or radiation therapy is altered by ETHYOL. There are at present only limited data on the effects of ETHYOL on the efficacy of chemotherapy or radiotherapy in other settings. ETHYOL should not be administered to patients in other settings where chemotherapy can produce a significant survival benefit or cure, or in patients receiving definitive radiotherapy, except in the context of a clinical study (see WARNINGS).

CONTRAINDICATIONS

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

WARNINGS

1. Effectiveness of the Cytotoxic Regimen

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

139

140 2. Effectiveness of Radiotherapy

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

147

148 3. Hypotension

149 Patients who are hypotensive or in a state of dehydration should not receive ETHYOL. Patients
150 receiving ETHYOL at doses recommended for chemotherapy who are taking antihypertensive
151 therapy that cannot be stopped for 24 hours preceding ETHYOL treatment, should not receive
152 ETHYOL. Patients should be adequately hydrated prior to ETHYOL infusion and kept in a supine
153 position during the infusion. Blood pressure should be monitored every 5 minutes during the
154 infusion, and thereafter as clinically indicated. It is important that the duration of the 910 mg/m^2
155 infusion not exceed 15 minutes, as administration of ETHYOL as a longer infusion is associated with
156 a higher incidence of side effects. For infusion durations less than 5 minutes, blood pressure should
157 be monitored at least before and immediately after the infusion, and thereafter as clinically indicated.
158 If hypotension occurs, patients should be placed in the Trendelenburg position and be given an
159 infusion of normal saline using a separate i.v. line. Guidelines for interrupting and restarting
160 ETHYOL infusion if a decrease in systolic blood pressure should occur are provided in the
161 DOSAGE AND ADMINISTRATION section. Hypotension may occur during or shortly after
162 ETHYOL infusion, despite adequate hydration and positioning of the patient (see ADVERSE
163 REACTIONS and GENERAL PRECAUTIONS). Hypotension has been reported to be associated
164 with dyspnea, apnea, hypoxia, and in rare cases seizures, unconsciousness, respiratory arrest and
165 renal failure.

166

167 4. Nausea and Vomiting.

168 Antiemetic medication should be administered prior to and in conjunction with ETHYOL (see
169 DOSAGE AND ADMINISTRATION). When ETHYOL is administered with highly emetogenic

170 chemotherapy, the fluid balance of the patient should be carefully monitored.

171

172 5. Hypocalcemia

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

176

177 **PRECAUTIONS**

178

179 **General**

180

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

183

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

189

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

193

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

197

198 **Drug Interactions**

199

200 Special consideration should be given to the administration of ETHYOL in patients receiving

201 antihypertensive medications or other drugs that could cause or potentiate hypotension.

202

203 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

204

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

210

211 **Pregnancy**

212

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

217

218 **Nursing Mothers**

219

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

224

225 **Pediatric Use**

226

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

228

229 **ADVERSE REACTIONS**

230

231 In the randomized study of patients with ovarian cancer given Ethyol at a dose of 910 mg/m² prior to

232 chemotherapy, transient hypotension was observed in 62% of patients treated. The mean time of
233 onset was 14 minutes into the 15-minute period of ETHYOL infusion, and the mean duration was 6
234 minutes. In some cases, the infusion had to be prematurely terminated due to a more pronounced
235 drop in systolic blood pressure. In general, the blood pressure returned to normal within 5-15
236 minutes. Fewer than 3% of patients discontinued ETHYOL due to blood pressure reductions. In
237 the randomized study of patients with head and neck cancer given Ethyol at a dose of 200 mg/m²
238 prior to radiotherapy, hypotension was observed in 15% of patients treated.

239

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

244

245 Short term, reversible loss of consciousness has been reported rarely. Blood pressure reductions
246 during Ethyol administration have not been reported to cause long term CNS, cardiovascular or
247 renal sequelae, but clinical studies performed to date have not evaluated the safety of Ethyol in
248 elderly patients or in patients with preexisting cardiovascular or cerebrovascular conditions.

249

250 Nausea and/or vomiting occur frequently after ETHYOL infusion and may be severe. In the ovarian
251 cancer randomized study, the incidence of severe nausea/vomiting on day 1 of cyclophosphamide-
252 cisplatin chemotherapy was 10% in patients who did not receive ETHYOL, and 19% in patients who
253 did receive ETHYOL. In the randomized study of patients with head and neck cancer, the incidence
254 of severe nausea/vomiting was 8% in patients who received ETHYOL and 1% in patients who did
255 not receive ETHYOL.

256

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

260

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

263 WARNINGS).

264

265 Allergic reactions have been reported with the use of ETHYOL. The majority of cases presented
266 with the following symptoms: hypotension, fever, chills/rigors, dyspnea, skin rashes and urticaria.

267 Other skin reactions including erythema multiforme, and in rare cases Stevens-Johnson Syndrome
268 and toxic epidermal necrolysis, have been reported. There have been rare reports of anaphylactoid
269 reactions including hypoxia, laryngeal edema, chest tightness, and possible cardiac arrest.

270

271 There have been rare reports of seizures in patients receiving ETHYOL.

272

273 Table 6 contains a summary of the more common adverse events from the two approved doses of
274 ETHYOL:

275

TABLE 6
Incidence of Common Adverse Events in Patients Receiving ETHYOL

	Phase III Ovarian Cancer Trial (WR-1) 910 mg/m ²		Phase III Head and Neck Cancer Trial (WR-38) 200 mg/m ²	
	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%)

276 ^a According to protocol-defined criteria. WR-1: requiring interruption of infusion; WR-38: drop of
277 >20mm Hg.

278

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

282

283 **OVERDOSAGE**

284

285 In clinical trials, the maximum single dose of ETHYOL was 1300 mg/m². No information is

286 available on single doses higher than this in adults. In the setting of a clinical trial, pediatric patients
287 have received single ETHYOL doses of up to 2700 mg/m². At the higher doses, anxiety and
288 reversible urinary retention occurred.

289
290 Administration of ETHYOL at 2 and 4 hours after the initial dose has not led to increased nausea
291 and vomiting or hypotension. The most likely symptom of overdose is hypotension, which should
292 be managed by infusion of normal saline and other supportive measures, as clinically indicated.

293

294 **DOSAGE AND ADMINISTRATION**

295

296 **For Reduction of Cumulative Renal Toxicity with Chemotherapy:** The recommended starting
297 dose of ETHYOL is 910 mg/m² administered once daily as a 15-minute i.v. infusion, starting 30
298 minutes prior to chemotherapy.

299

300 The 15-minute infusion is better tolerated than more extended infusions. Further reductions in
301 infusion times for chemotherapy regimens have not been systematically investigated.

302

303 Patients should be adequately hydrated prior to ETHYOL infusion and kept in a supine position
304 during the infusion. Blood pressure should be monitored every 5 minutes during the infusion, and
305 thereafter as clinically indicated.

306

307 The infusion of ETHYOL should be interrupted if the systolic blood pressure decreases significantly
308 from the baseline value as listed in the guideline below:

309

Guideline for Interrupting ETHYOL Infusion Due to Decrease 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

310

311

312 If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the

313 infusion may be restarted so that the full dose of ETHYOL may be administered. If the full dose of
314 ETHYOL cannot be administered, the dose of ETHYOL for subsequent chemotherapy cycles
315 should be 740 mg/m².

316

317 It is recommended that antiemetic medication, including dexamethasone 20 mg i.v. and a serotonin
318 5HT₃ receptor antagonist, be administered prior to and in conjunction with ETHYOL. Additional
319 antiemetics may be required based on the chemotherapy drugs administered.

320

321 **For Reduction of Moderate to Severe Xerostomia from Radiation of the Head and Neck:** The
322 recommended dose of ETHYOL is 200 mg/m² administered once daily as a 3-minute i.v. infusion,
323 starting 15-30 minutes prior to standard fraction radiation therapy (1.8-2.0 Gy).

324

325 Patients should be adequately hydrated prior to ETHYOL infusion. Blood pressure should be
326 monitored at least before and immediately after the infusion, and thereafter as clinically indicated.

327

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

331

332 **Reconstitution**

333

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

337

338 Prior to intravenous injection, ETHYOL is reconstituted with 9.7 mL of sterile 0.9% Sodium
339 Chloride Injection, USP. The reconstituted solution (500 mg amifostine/10 mL) is chemically stable
340 for up to 5 hours at room temperature (approximately 25°C) or up to 24 hours under refrigeration
341 (2°C to 8°C).

342

343 ETHYOL prepared in polyvinylchloride (PVC) bags at concentrations ranging from 5 mg/mL to 40

344 mg/mL is chemically stable for up to 5 hours when stored at room temperature (approximately
345 25°C) or up to 24 hours when stored under refrigeration (2°C to 8°C).

346

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

350

351 **Incompatibilities**

352

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

356

357 **HOW SUPPLIED**

358

359 ETHYOL (amifostine) for Injection is supplied as a sterile lyophilized powder in 10 mL single-use
360 vials (NDC 17314-7253-1). Each single-use vial contains 500 mg of amifostine on the anhydrous
361 basis. The vials are available packaged as follows:

362

363 3 pack - 3 vials per carton (NDC 17314-7253-3)

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

367

368 U.S. Patents 5,424,471; 5,591,731

369

370 Manufactured by:

371 USB Pharma B.V.

372 6545 CG Nijmegen

373 The Netherlands

374

375 Or:

376 Ben Venue, Inc.

377 Bedford, Ohio 44146

378

379 Marketed by:

380 ALZA Pharmaceuticals

381 A division of ALZA Corporation

382 Palo Alto,

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385 And:

386 U.S. Bioscience, Inc.

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