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3 **HYCAMTIN[®]**
4 **(topotecan hydrochloride)**
5 **For Injection**
6 **FOR INTRAVENOUS USE**

7 **WARNING**

8 HYCAMTIN (topotecan hydrochloride) for Injection should be administered under the
9 supervision of a physician experienced in the use of cancer chemotherapeutic agents.
10 Appropriate management of complications is possible only when adequate diagnostic and
11 treatment facilities are readily available.

12 Therapy with HYCAMTIN should not be given to patients with baseline neutrophil counts of
13 less than 1,500 cells/mm³. In order to monitor the occurrence of bone marrow suppression,
14 primarily neutropenia, which may be severe and result in infection and death, frequent peripheral
15 blood cell counts should be performed on all patients receiving HYCAMTIN.

16 **DESCRIPTION**

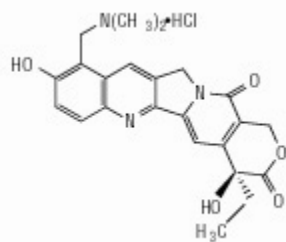
17 HYCAMTIN (topotecan hydrochloride) is a semi-synthetic derivative of camptothecin and is
18 an anti-tumor drug with topoisomerase I-inhibitory activity.

19 HYCAMTIN for Injection is supplied as a sterile lyophilized, buffered, light yellow to
20 greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride
21 equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from
22 yellow to yellow-green and is intended for administration by intravenous infusion.

23 Inactive ingredients are mannitol, 48 mg, and tartaric acid, 20 mg. Hydrochloric acid and
24 sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.5 to 3.5.

25 The chemical name for topotecan hydrochloride is (*S*)-10-[(dimethylamino)methyl]-4-ethyl-
26 4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione
27 monohydrochloride. It has the molecular formula C₂₃H₂₃N₃O₅•HCl and a molecular weight of
28 457.9.

29 Topotecan hydrochloride has the following structural formula:



30
31 It is soluble in water and melts with decomposition at 213° to 218°C.

32 **CLINICAL PHARMACOLOGY**

33 **Mechanism of Action:** Topoisomerase I relieves torsional strain in DNA by inducing
34 reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and
35 prevents religation of these single strand breaks. The cytotoxicity of topotecan is thought to be
36 due to double strand DNA damage produced during DNA synthesis, when replication enzymes
37 interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian
38 cells cannot efficiently repair these double strand breaks.

39 **Pharmacokinetics:** The pharmacokinetics of topotecan have been evaluated in cancer patients
40 following doses of 0.5 to 1.5 mg/m² administered as a 30-minute infusion. Topotecan exhibits
41 multiexponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure
42 (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about
43 35%.

44 **Metabolism and Elimination:** Topotecan undergoes a reversible pH dependent hydrolysis
45 of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤4, the
46 lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at
47 physiologic pH. In vitro studies in human liver microsomes indicate topotecan is metabolized to
48 an N-demethylated metabolite. The mean metabolite:parent AUC ratio was about 3% for total
49 topotecan and topotecan lactone following IV administration.

50 Renal clearance is an important determinant of topotecan elimination (see Special
51 Populations: Renal Impairment).

52 In a mass balance/excretion study in 4 patients with solid tumors, the overall recovery of total
53 topotecan and its N-desmethyl metabolite in urine and feces over 9 days averaged 73.4 ± 2.3% of
54 the administered IV dose. Mean values of 50.8 ± 2.9% as total topotecan and 3.1 ± 1.0% as N-
55 desmethyl topotecan were excreted in the urine following IV administration. Fecal elimination of
56 total topotecan accounted for 17.9 ± 3.6% while fecal elimination of N-desmethyl topotecan was
57 1.7 ± 0.6%. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been
58 identified in the urine. These metabolites, topotecan-O-glucuronide and N-desmethyl topotecan-
59 O-glucuronide, were less than 2% of the administered dose.

60 **Special Populations: Gender:** The overall mean topotecan plasma clearance in male patients
61 was approximately 24% higher than that in female patients, largely reflecting difference in body
62 size.

63 **Geriatrics:** Topotecan pharmacokinetics have not been specifically studied in an elderly
64 population, but population pharmacokinetic analysis in female patients did not identify age as a
65 significant factor. Decreased renal clearance, which is common in the elderly, is a more
66 important determinant of topotecan clearance (see PRECAUTIONS and DOSAGE AND
67 ADMINISTRATION).

68 **Race:** The effect of race on topotecan pharmacokinetics has not been studied.

69 **Renal Impairment:** In patients with mild renal impairment (creatinine clearance of 40 to
70 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients
71 with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to

72 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control
73 patients, with an increase in half-life. Mean half-life, estimated in 3 renally impaired patients,
74 was about 5.0 hours. Dosage adjustment is recommended for these patients (see DOSAGE AND
75 ADMINISTRATION).

76 **Hepatic Impairment:** Plasma clearance in patients with hepatic impairment (serum
77 bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients
78 without hepatic impairment. Topotecan half-life increased slightly, from 2.0 hours to 2.5 hours,
79 but these hepatically impaired patients tolerated the usual recommended topotecan dosage
80 regimen (see DOSAGE AND ADMINISTRATION).

81 **Drug Interactions:** Pharmacokinetic studies of the interaction of topotecan with concomitantly
82 administered medications have not been formally investigated. In vitro inhibition studies using
83 marker substrates known to be metabolized by human P450 CYP1A2, CYP2A6, CYP2C8/9,
84 CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or dihydropyrimidine dehydrogenase indicate
85 that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by
86 topotecan has not been evaluated in vivo.

87 Administration of cisplatin (60 or 75 mg/m² on Day 1) before topotecan (0.75 mg/m²/day on
88 Days 1-5 in 9 patients with ovarian cancer had no significant effect on the C_{max} and AUC of
89 total topotecan.

90 Topotecan had no effect on the pharmacokinetics of free platinum in 15 patients with ovarian
91 cancer who were administered cisplatin 50 mg/m² (n = 9) or 75 mg/m² (n = 6) on day 2 after
92 paclitaxel 110 mg/m² on day 1 before topotecan 0.3 mg/m² IV daily on days 2-6. Topotecan had
93 no effect on dose-normalized (60 mg/m²) C_{max} values of free platinum in 13 patients with ovarian
94 cancer who were administered 60 mg/m² (n = 10) or 75 mg/m² (n = 3) cisplatin on day 1 before
95 topotecan 0.75 mg/m² IV daily on days 1-5.

96 No pharmacokinetic data are available following topotecan (0.75 mg/m²/day for 3 consecutive
97 days) and cisplatin (50 mg/m²/day on day 1) in patients with cervical cancer.

98 **Pharmacodynamics:** The dose-limiting toxicity of topotecan is leukopenia. White blood cell
99 count decreases with increasing topotecan dose or topotecan AUC. When topotecan is
100 administered at a dose of 1.5 mg/m²/day for 5 days, an 80% to 90% decrease in white blood cell
101 count at nadir is typically observed after the first cycle of therapy.

102 **CLINICAL STUDIES**

103 **Ovarian Cancer:** HYCAMTIN was studied in 2 clinical trials of 223 patients given topotecan
104 with metastatic ovarian carcinoma. All patients had disease that had recurred on, or was
105 unresponsive to, a platinum-containing regimen. Patients in these 2 studies received an initial
106 dose of 1.5 mg/m² given by intravenous infusion over 30 minutes for 5 consecutive days, starting
107 on day 1 of a 21-day course.

108 One study was a randomized trial of 112 patients treated with HYCAMTIN (1.5 mg/m²/day ×
109 5 days starting on day 1 of a 21-day course) and 114 patients treated with paclitaxel (175 mg/m²
110 over 3 hours on day 1 of a 21-day course). All patients had recurrent ovarian cancer after a

111 platinum-containing regimen or had not responded to at least 1 prior platinum-containing
 112 regimen. Patients who did not respond to the study therapy, or who progressed, could be given
 113 the alternative treatment.

114 Response rates, response duration, and time to progression are shown in Table 1.

115

116 **Table 1. Efficacy of HYCAMTIN Versus Paclitaxel in Ovarian Cancer**

Parameter	HYCAMTIN (n = 112)	Paclitaxel (n = 114)
Complete response rate	5%	3%
Partial response rate	16%	11%
Overall response rate	21%	14%
95% Confidence interval (p-value)	13 to 28%	8 to 20%
		(0.20)
Response duration* (weeks)	n = 23	n = 16
Median	25.9	21.6
95% Confidence interval	22.1 to 32.9	16.0 to 34.0
hazard-ratio (HYCAMTIN:paclitaxel) (p-value)		0.78 (0.48)
Time to progression (weeks)		
Median	18.9	14.7
95% Confidence interval	12.1 to 23.6	11.9 to 18.3
hazard-ratio (HYCAMTIN:paclitaxel) (p-value)		0.76 (0.07)
Survival (weeks)		
Median	63.0	53.0
95% Confidence interval	46.6 to 71.9	42.3 to 68.7
hazard-ratio (HYCAMTIN:paclitaxel) (p-value)		0.97 (0.87)

117 * The calculation for duration of response was based on the interval between first response and
 118 time to progression.

119

120 The median time to response was 7.6 weeks (range 3.1 to 21.7) with HYCAMTIN compared
 121 to 6.0 weeks (range 2.4 to 18.1) with paclitaxel. Consequently, the efficacy of HYCAMTIN may
 122 not be achieved if patients are withdrawn from treatment prematurely.

123 In the crossover phase, 8 of 61 (13%) patients who received HYCAMTIN after paclitaxel had
 124 a partial response and 5 of 49 (10%) patients who received paclitaxel after HYCAMTIN had a
 125 response (2 complete responses).

126 HYCAMTIN was active in ovarian cancer patients who had developed resistance to
127 platinum-containing therapy, defined as tumor progression while on, or tumor relapse within
128 6 months after completion of, a platinum-containing regimen. One complete and 6 partial
129 responses were seen in 60 patients, for a response rate of 12%. In the same study, there were no
130 complete responders and 4 partial responders on the paclitaxel arm, for a response rate of 7%.

131 HYCAMTIN was also studied in an open-label, non-comparative trial in 111 patients with
132 recurrent ovarian cancer after treatment with a platinum-containing regimen, or who had not
133 responded to 1 prior platinum-containing regimen. The response rate was 14% (95% CI = 7% to
134 20%). The median duration of response was 22 weeks (range 4.6 to 41.9 weeks). The time to
135 progression was 11.3 weeks (range 0.7 to 72.1 weeks). The median survival was 67.9 weeks
136 (range 1.4 to 112.9 weeks).

137 **Small Cell Lung Cancer:** HYCAMTIN was studied in 426 patients with recurrent or
138 progressive small cell lung cancer in 1 randomized, comparative study and in 3 single-arm
139 studies.

140 **Randomized Comparative Study:** In a randomized, comparative, Phase 3 trial,
141 107 patients were treated with HYCAMTIN (1.5 mg/m²/day × 5 days starting on day 1 of a
142 21-day course) and 104 patients were treated with CAV (1,000 mg/m² cyclophosphamide,
143 45 mg/m² doxorubicin, 2 mg vincristine administered sequentially on day 1 of a 21-day course).
144 All patients were considered sensitive to first-line chemotherapy (responders who then
145 subsequently progressed ≥60 days after completion of first-line therapy). A total of 77% of
146 patients treated with HYCAMTIN and 79% of patients treated with CAV received
147 platinum/etoposide with or without other agents as first-line chemotherapy.

148 Response rates, response duration, time to progression, and survival are shown in Table 2.

149

150 **Table 2. Efficacy of HYCAMTIN Versus CAV (cyclophosphamide-doxorubicin-vincristine)**
 151 **in Small Cell Lung Cancer Patients Sensitive to First-Line Chemotherapy**

Parameter	HYCAMTIN (n = 107)	CAV (n = 104)
Complete response rate	0%	1%
Partial response rate	24%	17%
Overall response rate	24%	18%
Difference in overall response rates	6%	
95% Confidence interval of the difference	(-6 to 18%)	
Response duration* (weeks)	n = 26	n = 19
Median	14.4	15.3
95% Confidence interval	13.1 to 18.0	13.1 to 23.1
hazard-ratio (HYCAMTIN:CAV) (95% CI) (p-value)	1.42 (0.73 to 2.76) (0.30)	
Time to progression (weeks)		
Median	13.3	12.3
95% Confidence interval	11.4 to 16.4	11.0 to 14.1
hazard-ratio (HYCAMTIN:CAV) (95% CI) (p-value)	0.92 (0.69 to 1.22) (0.55)	
Survival (weeks)		
Median	25.0	24.7
95% Confidence interval	20.6 to 29.6	21.7 to 30.3
hazard-ratio (HYCAMTIN:CAV) (95% CI) (p-value)	1.04 (0.78 to 1.39) (0.80)	

152 * The calculation for duration of response was based on the interval between first response and
 153 time to progression.
 154

155 The time to response was similar in both arms: HYCAMTIN median of 6 weeks (range 2.4 to
 156 15.7) versus CAV median 6 weeks (range 5.1 to 18.1).

157 Changes on a disease-related symptom scale in patients who received HYCAMTIN or who
 158 received CAV are presented in Table 3. It should be noted that not all patients had all symptoms,
 159 nor did all patients respond to all questions. Each symptom was rated on a 4-category scale with
 160 an improvement defined as a change in 1 category from baseline sustained over 2 courses.

161 Limitations in interpretation of the rating scale and responses preclude formal statistical analysis.
 162

163 **Table 3. Percentage of Patients With Symptom Improvement* : HYCAMTIN Versus CAV**
 164 **in Patients With Small Cell Lung Cancer**

Symptom	HYCAMTIN (n = 107)		CAV (n = 104)	
	n [†]	(%)	n [†]	(%)
Shortness of breath	68	(28)	61	(7)
Interference with daily activity	67	(27)	63	(11)
Fatigue	70	(23)	65	(9)
Hoarseness	40	(33)	38	(13)
Cough	69	(25)	61	(15)
Insomnia	57	(33)	53	(19)
Anorexia	56	(32)	57	(16)
Chest pain	44	(25)	41	(17)
Hemoptysis	15	(27)	12	(33)

* Defined as improvement sustained over at least 2 courses compared to baseline.

† Number of patients with baseline and at least 1 post-baseline assessment.

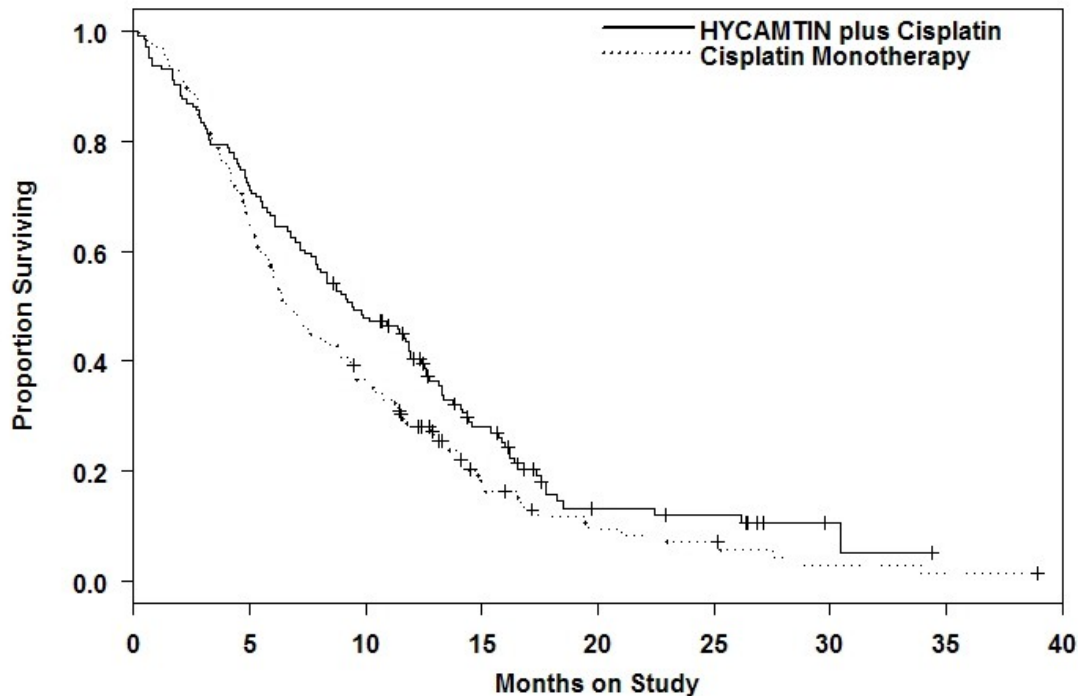
165
 166
 167
 168 **Single-Arm Studies:** HYCAMTIN was also studied in 3 open-label, non-comparative trials
 169 in a total of 319 patients with recurrent or progressive small cell lung cancer after treatment with
 170 first-line chemotherapy. In all 3 studies, patients were stratified as either sensitive (responders
 171 who then subsequently progressed ≥ 90 days after completion of first-line therapy) or refractory
 172 (no response to first-line chemotherapy or who responded to first-line therapy and then
 173 progressed within 90 days of completing first-line therapy). Response rates ranged from 11% to
 174 31% for sensitive patients and 2% to 7% for refractory patients. Median time to progression and
 175 median survival were similar in all 3 studies and the comparative study.

176 **Cervical Cancer:** In a comparative trial, 147 eligible women were randomized to HYCAMTIN
 177 (0.75 mg/m²/day IV over 30 minutes \times 3 consecutive days starting on day 1 of a 21-day course)
 178 plus cisplatin (50 mg/m² on day 1) and 146 eligible women were randomized to cisplatin
 179 (50 mg/m² IV on day 1 of a 21-day course). All patients had histologically confirmed Stage IV-
 180 B, recurrent, or persistent carcinoma of the cervix considered not amenable to curative treatment
 181 with surgery and/or radiation. Fifty six percent (56%) of patients treated with HYCAMTIN plus
 182 cisplatin and 56% of patients treated with cisplatin had received prior cisplatin with or without
 183 other agents as first-line chemotherapy.

184 Median survival of eligible patients in the HYCAMTIN plus cisplatin treatment arm was 9.4
 185 months (95% CI: 7.9 to 11.9) compared to 6.5 months (95% CI: 5.8 to 8.8) among patients
 186 randomized to cisplatin alone with a log rank p-value of 0.033 (significance level was 0.044 after
 187 adjusting for the interim analysis). The unadjusted hazard ratio for overall survival was 0.76
 188 (95% CI: 0.59 to 0.98).

189

190 **Figure 1. Overall Survival Curves Comparing HYCAMTIN plus Cisplatin versus Cisplatin**
 191 **Monotherapy in Cervical Cancer Patients**



	Number at Risk								
HYCAMTIN plus Cisplatin	147	104	69	32	10	8	2	0	0
Cisplatin Monotherapy	146	93	52	17	8	6	2	1	0

192
193

194 **INDICATIONS AND USAGE**

195 HYCAMTIN is indicated for the treatment of:

- 196 • metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.
 197 • small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical
 198 studies submitted to support approval, sensitive disease was defined as disease responding to
 199 chemotherapy but subsequently progressing at least 60 days (in the Phase 3 study) or at least
 200 90 days (in the Phase 2 studies) after chemotherapy (see CLINICAL STUDIES).

201 HYCAMTIN in combination with cisplatin is indicated for the treatment of:

- 202 • stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative
 203 treatment with surgery and/or radiation therapy.

204 **CONTRAINDICATIONS**

205 HYCAMTIN is contraindicated in patients who have a history of hypersensitivity reactions to
 206 topotecan or to any of its ingredients. HYCAMTIN should not be used in patients who are

207 pregnant or breast-feeding, or those with severe bone marrow depression.

208 **WARNINGS**

209 **Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of**
210 **HYCAMTIN.** Neutropenia is not cumulative over time. The following data on
211 myelosuppression is based on:

- 212 • the combined experience of 879 patients with metastatic ovarian cancer or small cell lung
213 cancer treated with HYCAMTIN monotherapy at a dose of 1.5 mg/m²/day x 5 days.
- 214 • the experience of 140 patients with cervical cancer randomized to receive HYCAMTIN
215 0.75 mg/m²/day on days 1, 2, and 3 plus cisplatin 50 mg/m² on day 1.

216 **Neutropenia:**

- 217 • Ovarian and small cell lung cancer experience: Grade 4 neutropenia (<500 cells/mm³)
218 was most common during course 1 of treatment (60% of patients) and occurred in 39% of
219 all courses, with a median duration of 7 days. The nadir neutrophil count occurred at a
220 median of 12 days. Therapy-related sepsis or febrile neutropenia occurred in 23% of
221 patients, and sepsis was fatal in 1%.
- 222 • Cervical cancer experience: Grade 3 and grade 4 neutropenia affected 26% and 48% of
223 patients, respectively.

224 **Thrombocytopenia:**

- 225 • Ovarian and small cell lung cancer experience: Grade 4 thrombocytopenia
226 (<25,000/mm³) occurred in 27% of patients and in 9% of courses, with a median duration
227 of 5 days and platelet nadir at a median of 15 days. Platelet transfusions were given to
228 15% of patients in 4% of courses.
- 229 • Cervical cancer experience: Grade 3 and grade 4 thrombocytopenia affected 26% and 7%
230 of patients, respectively.

231 **Anemia:**

- 232 • Ovarian and small cell lung cancer experience: Grade 3/4 anemia (<8 g/dL) occurred in
233 37% of patients and in 14% of courses. Median nadir was at day 15. Transfusions were
234 needed in 52% of patients in 22% of courses.
- 235 • Cervical cancer experience: Grade 3 and grade 4 anemia affected 34% and 6% of
236 patients, respectively.

237 In ovarian cancer, the overall treatment-related death rate was 1%. In the comparative study in
238 small cell lung cancer, however, the treatment-related death rates were 5% for HYCAMTIN and
239 4% for CAV.

240 **Monitoring of Bone Marrow Function:** HYCAMTIN should be administered only in
241 patients with adequate bone marrow reserves, including baseline neutrophil count of at least
242 1,500 cells/mm³ and platelet count at least 100,000/mm³. Frequent monitoring of peripheral
243 blood cell counts should be instituted during treatment with HYCAMTIN. Patients should not be
244 treated with subsequent courses of HYCAMTIN until neutrophils recover to >1,000 cells/mm³,
245 platelets recover to >100,000 cells/mm³, and hemoglobin levels recover to 9.0 g/dL (with

246 transfusion if necessary). Severe myelotoxicity has been reported when HYCAMTIN is used in
247 combination with cisplatin (see Drug Interactions).

248 **Pregnancy:** HYCAMTIN may cause fetal harm when administered to a pregnant woman. The
249 effects of topotecan on pregnant women have not been studied. If topotecan is used during a
250 patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be
251 warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming
252 pregnant. In rabbits, a dose of 0.10 mg/kg/day (about equal to the clinical dose on a mg/m² basis)
253 given on days 6 through 20 of gestation caused maternal toxicity, embryoletality, and reduced
254 fetal body weight. In the rat, a dose of 0.23 mg/kg/day (about equal to the clinical dose on a
255 mg/m² basis) given for 14 days before mating through gestation day 6 caused fetal resorption,
256 microphthalmia, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/day (about
257 half the clinical dose on a mg/m² basis) given to rats on days 6 through 17 of gestation caused an
258 increase in post-implantation mortality. This dose also caused an increase in total fetal
259 malformations. The most frequent malformations were of the eye (microphthalmia,
260 anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain
261 (dilated lateral and third ventricles), skull, and vertebrae.

262 **PRECAUTIONS**

263 **General:** Inadvertent extravasation with HYCAMTIN has been associated only with mild local
264 reactions such as erythema and bruising.

265 **Information for Patients:** As with other chemotherapeutic agents, HYCAMTIN may cause
266 asthenia or fatigue; if these symptoms occur, caution should be observed when driving or
267 operating machinery.

268 **Hematology:** Monitoring of bone marrow function is essential (see WARNINGS and
269 DOSAGE AND ADMINISTRATION).

270 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity testing of
271 topotecan has not been performed. Topotecan, however, is known to be genotoxic to mammalian
272 cells and is a probable carcinogen. Topotecan was mutagenic to L5178Y mouse lymphoma cells
273 and clastogenic to cultured human lymphocytes with and without metabolic activation. It was
274 also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

275 **Drug Interactions:** Concomitant administration of G-CSF can prolong the duration of
276 neutropenia, so if G-CSF is to be used, it should not be initiated until day 6 of the course of
277 therapy, 24 hours after completion of treatment with HYCAMTIN.

278 Myelosuppression was more severe when HYCAMTIN, at a dose of 1.25 mg/m²/day ×
279 5 days, was given in combination with cisplatin at a dose of 50 mg/m² in Phase 1 studies. In one
280 study, 1 of 3 patients had severe neutropenia for 12 days and a second patient died with
281 neutropenic sepsis.

282 Greater myelosuppression is also likely to be seen when HYCAMTIN is used in combination
283 with other cytotoxic agents, thereby necessitating a dose reduction. However, when combining
284 HYCAMTIN with platinum agents (e.g., cisplatin or carboplatin), a distinct sequence-dependent

285 interaction on myelosuppression has been reported. Coadministration of a platinum agent on
286 day 1 of HYCAMTIN dosing required lower doses of each agent compared to coadministration
287 on day 5 of the HYCAMTIN dosing schedule.

288 For information on the pharmacokinetics, efficacy, safety, and dosing of HYCAMTIN at a
289 dose of 0.75 mg/m²/day days 1, 2, and 3 in combination with cisplatin 50 mg/m² on day 1 for
290 cervical cancer, see CLINICAL PHARMACOLOGY, CLINICAL STUDIES, ADVERSE
291 REACTIONS, and DOSAGE AND ADMINISTRATION.

292 **Pregnancy:** Pregnancy Category D. (See WARNINGS.)

293 **Nursing Mothers:** It is not known whether the drug is excreted in human milk. Breast-feeding
294 should be discontinued when women are receiving HYCAMTIN (see
295 CONTRAINDICATIONS).

296 **Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

297 **Geriatric Use:** Of the 879 patients with metastatic ovarian cancer or small cell lung cancer in
298 clinical studies of HYCAMTIN, 32% (n = 281) were 65 years of age and older, while 3.8%
299 (n = 33) were 75 years of age and older. Of the 140 patients with stage IVB, relapsed, or
300 refractory cervical cancer in clinical studies of HYCAMTIN who received HYCAMTIN plus
301 cisplatin in the randomized clinical trial, 6% (n = 9) were 65 years of age and older, while 3%
302 (n = 4) were 75 years of age and older. No overall differences in effectiveness or safety were
303 observed between these patients and younger adult patients, and other reported clinical
304 experience has not identified differences in responses between the elderly and younger adult
305 patients, but greater sensitivity of some older individuals cannot be ruled out.

306 There were no apparent differences in the pharmacokinetics of topotecan in elderly patients,
307 once the age-related decrease in renal function was considered (see CLINICAL
308 PHARMACOLOGY).

309 This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions
310 to this drug may be greater in patients with impaired renal function. Because elderly patients are
311 more likely to have decreased renal function, care should be taken in dose selection, and it may
312 be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

313 **ADVERSE REACTIONS**

314 **Ovarian Cancer and Small Cell Lung Cancer:** Data in the following section are based on
315 the combined experience of 453 patients with metastatic ovarian carcinoma, and 426 patients
316 with small cell lung cancer treated with HYCAMTIN. Table 5 lists the principal hematologic
317 toxicities, and Table 6 lists non-hematologic toxicities occurring in at least 15% of patients.

318

319

Table 5. Summary of Hematologic Adverse Events in Patients Receiving HYCAMTIN

Hematologic Adverse Event	Patients n = 879 % Incidence	Courses n = 4124 % Incidence
Neutropenia <1,500 cells/mm ³ <500 cells/mm ³	97 78	81 39
Leukopenia <3,000 cells/mm ³ <1,000 cells/mm ³	97 32	80 11
Thrombocytopenia <75,000/mm ³ <25,000/mm ³	69 27	42 9
Anemia <10 g/dL <8 g/dL	89 37	71 14
Platelet transfusions	15	4
RBC transfusions	52	22

320

321 **Table 6. Summary of Non-hematologic Adverse Events in Patients Receiving HYCAMTIN**

Non-hematologic Adverse Event	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	n = 879 Patients	n = 4124 Courses	n = 879 Patients	n = 4124 Courses	n = 879 Patients	n = 4124 Courses
Infections and infestations						
Sepsis or pyrexia/infection with neutropenia*	43	15	NR	NR	23	7
Metabolism and nutrition disorders						
Anorexia	19	9	2	1	<1	<1
Nervous system disorders						
Headache	18	7	1	<1	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	22	11	5	2	3	1
Coughing	15	7	1	<1	0	0
Gastrointestinal disorders						
Nausea	64	42	7	2	1	<1
Vomiting	45	22	4	1	1	<1
Diarrhea	32	14	3	1	1	<1
Constipation	29	15	2	1	1	<1
Abdominal pain	22	10	2	1	2	<1
Stomatitis	18	8	1	<1	<1	<1
Skin and subcutaneous tissue disorders						
Alopecia	49	54	NA	NA	NA	NA
Rash†	16	6	1	<1	0	0
General disorders and administrative site conditions						
Fatigue	29	22	5	2	0	0
Pyrexia	28	11	1	<1	<1	<1
Pain‡	23	11	2	1	1	<1
Asthenia	25	13	4	1	2	<1

322 NA = Not applicable

323 NR = Not reported separately

324 * Does not include Grade 1 sepsis or pyrexia.

325 † Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.

326 ‡ Pain includes body pain, back pain, and skeletal pain.

327

328 Premedications were not routinely used in these clinical studies.

329 **Hematologic:** (See WARNINGS.)

330 **Nervous System Disorders:** Headache (18% of patients) was the most frequently reported
331 neurologic toxicity. Paresthesia occurred in 7% of patients but was generally grade 1.

332 **Respiratory, Thoracic, and Mediastinal Disorders:** The incidence of grade 3/4 dyspnea
333 was 4% in ovarian cancer patients and 12% in small cell lung cancer patients.

334 **Gastrointestinal Disorders:** The incidence of nausea was 64% (8% grade 3/4), and vomiting
335 occurred in 45% (6% grade 3/4) of patients (see Table 5). The prophylactic use of antiemetics
336 was not routine in patients treated with HYCAMTIN. Thirty-two percent of patients had diarrhea
337 (4% grade 3/4), 29% constipation (2% grade 3/4), and 22% had abdominal pain (4% grade 3/4).

338 Grade 3/4 abdominal pain was 6% in ovarian cancer patients and 2% in small cell lung cancer
339 patients.

340 **Skin and Subcutaneous Tissue Disorders:** Total alopecia (grade 2) occurred in 31% of
341 patients.

342 **Hepatobiliary Disorders:** Grade 1 transient elevations in hepatic enzymes occurred in 8% of
343 patients. Greater elevations, grade 3/4, occurred in 4%. Grade 3/4 elevated bilirubin occurred in
344 <2% of patients.

345 Table 7 shows the grade 3/4 hematologic and major non-hematologic adverse events in the
346 topotecan/paclitaxel comparator trial in ovarian cancer.

347

348 **Table 7. Comparative Toxicity Profiles for Ovarian Cancer Patients Randomized to**
 349 **Receive HYCAMTIN or Paclitaxel**

Adverse Event	HYCAMTIN		Paclitaxel	
	Patients n = 112	Courses n = 597	Patients n = 114	Courses n = 589
Hematologic Grade 3/4	%	%	%	%
Grade 4 neutropenia (<500 cells/mm ³)	80	36	21	9
Grade 3/4 anemia (Hgb <8 g/dL)	41	16	6	2
Grade 4 thrombocytopenia ($<25,000$ plts/mm ³)	27	10	3	<1
Pyrexia/Grade 4 neutropenia	23	6	4	1
Non-hematologic Grade 3/4	%	%	%	%
Infections and infestations				
Documented sepsis	5	1	2	<1
Death related to sepsis	2	NA	0	NA
Metabolism and nutrition disorders				
Anorexia	4	1	0	0
Nervous system disorders				
Headache	1	<1	2	1
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	6	2	5	1
Gastrointestinal disorders				
Abdominal pain	5	1	4	1
Constipation	5	1	0	0
Diarrhea	6	2	1	<1
Intestinal obstruction	5	1	4	1
Nausea	10	3	2	<1
Stomatitis	1	<1	1	<1
Vomiting	10	2	3	<1
Hepatobiliary Disorders				
Hepatic enzymes increased*	1	<1	1	<1
Skin and subcutaneous tissue disorders				
Rash [†]	0	0	1	<1
Musculoskeletal, connective tissue, and bone disorders				
Arthralgia	1	<1	3	<1
General disorders and administrative site conditions				
Fatigue	7	2	6	2
Malaise	2	<1	2	<1

Asthenia	5	2	3	1
Chest pain	2	<1	1	<1
Myalgia	0	0	3	2
Pain [‡]	5	1	7	2

350 * Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT, and increased hepatic
351 enzymes.

352 † Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.

353 ‡ Pain includes body pain, skeletal pain, and back pain.

354

355 Premedications were not routinely used in patients randomized to HYCAMTIN, whereas
356 patients receiving paclitaxel received routine pretreatment with corticosteroids,
357 diphenhydramine, and histamine receptor type 2 blockers.

358 Table 8 shows the grade 3/4 hematologic and major non-hematologic adverse events in the
359 topotecan/CAV comparator trial in small cell lung cancer.

360

361 **Table 8. Comparative Toxicity Profiles for Small Cell Lung Cancer Patients Randomized**
362 **to Receive HYCAMTIN or CAV**

Adverse Event	HYCAMTIN		CAV	
	Patients n = 107	Courses n = 446	Patients n = 104	Courses n = 359
Hematologic Grade 3/4	%	%	%	%
Grade 4 neutropenia (<500 cells/mm ³)	70	38	72	51
Grade 3/4 anemia (Hgb <8 g/dL)	42	18	20	7
Grade 4 thrombocytopenia ($<25,000$ plts/mm ³)	29	10	5	1
Pyrexia/Grade 4 neutropenia	28	9	26	13
Non-hematologic Grade 3/4	%	%	%	%
Infections and infestations				
Documented sepsis	5	1	5	1
Death related to sepsis	3	NA	1	NA
Metabolism and nutrition disorders				
Anorexia	3	1	4	2
Nervous system disorders				
Headache	0	0	2	<1
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	9	5	14	7
Coughing	2	1	0	0
Pneumonia	8	2	6	2
Gastrointestinal disorders				
Abdominal pain	6	1	4	2

Constipation	1	<1	0	0
Diarrhea	1	<1	0	0
Nausea	8	2	6	2
Stomatitis	2	<1	1	<1
Vomiting	3	<1	3	1
Hepatobiliary Disorders				
Increased hepatic enzymes*	1	<1	0	0
Skin and subcutaneous tissue disorders				
Rash [†]	1	<1	1	<1
General disorders and administrative site conditions				
Fatigue	6	4	10	3
Asthenia	9	4	7	2
Pain [‡]	5	2	7	4

363 * Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT, and increased hepatic
364 enzymes.

365 [†] Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.

366 [‡] Pain includes body pain, skeletal pain, and back pain.

367

368 Premedications were not routinely used in patients randomized to HYCAMTIN, whereas
369 patients receiving CAV received routine pretreatment with corticosteroids, diphenhydramine,
370 and histamine receptor type 2 blockers.

371 **Cervical Cancer:** In the HYCAMTIN plus cisplatin versus cisplatin comparative trial in
372 cervical cancer patients, the most common dose-limiting toxicity was myelosuppression. Table 9
373 shows the hematologic adverse events and Table 10 shows the non-hematologic adverse events
374 in cervical cancer patients.

375

376 **Table 9. Hematologic Adverse Events in Cervical Cancer Patients Treated with**
 377 **HYCAMTIN Plus Cisplatin or Cisplatin Monotherapy***

Hematologic Adverse Event	HYCAMTIN Plus Cisplatin (n = 140)	Cisplatin (n = 144)
Anemia		
All grades (Hgb <12 g/dL)	131 (94%)	130 (90%)
Grade 3 (Hgb <8-6.5 g/dL)	47 (34%)	28 (19%)
Grade 4 (Hgb <6.5 g/dL)	9 (6%)	5 (3%)
Leukopenia		
All grades (<3,800 cells/mm ³)	128 (91%)	43 (30%)
Grade 3 (<2,000-1,000 cells/mm ³)	58 (41%)	1 (1%)
Grade 4 (<1,000 cells/mm ³)	35 (25%)	0 (0%)
Neutropenia		
All-grades (<2,000 cells/mm ³)	125 (89%)	28 (19%)
Grade 3 (<1,000-500 cells/mm ³)	36 (26%)	1 (1%)
Grade 4 (<500 cells/mm ³)	67 (48%)	1 (1%)
Thrombocytopenia		
All grades (<130,000 cells/mm ³)	104 (74%)	21 (15%)
Grade 3 (<50,000-10,000 cells/mm ³)	36 (26%)	5 (3%)
Grade 4 (<10,000 cells/mm ³)	10 (7%)	0 (0%)

378 * Includes patients who were eligible and treated.
 379

380 **Table 10. Non-hematologic Adverse Events Experienced by $\geq 5\%$ of Cervical Cancer**
 381 **Patients Treated with Hycamtin Plus Cisplatin or Cisplatin Monotherapy***

Adverse Event	HYCAMTIN Plus Cisplatin n = 140			Cisplatin n = 144		
	All Grades [†]	Grade 3	Grade 4	All Grades [†]	Grade 3	Grade 4
General disorders and administrative site conditions						
Constitutional [‡]	96 (69%)	11 (8%)	0	89 (62%)	17 (12%)	0
Pain [§]	82 (59%)	28 (20%)	3 (2%)	72 (50%)	18 (13%)	5 (3%)
Gastrointestinal disorders						
Vomiting	56 (40%)	20 (14%)	2 (1%)	53 (37%)	13 (9%)	0
Nausea	77 (55%)	18 (13%)	2 (1%)	79 (55%)	13 (9%)	0
Stomatitis-pharyngitis	8 (6%)	1 (<1%)	0	0	0	0
Other	88 (63%)	16 (11%)	4 (3%)	80 (56%)	12 (8%)	3 (2%)
Dermatology	67 (48%)	1 (<1%)	0	29 (20%)	0	0
Metabolic-Laboratory	55 (39%)	13 (9%)	7 (5%)	44 (31%)	14 (10%)	1 (<1%)
Genitourinary	51 (36%)	9 (6%)	9 (6%)	49 (34%)	7 (5%)	7 (5%)
Nervous system disorders						
Neuropathy	4 (3%)	1 (<1%)	0	3 (2%)	1 (<1%)	0
Other	49 (35%)	3 (2%)	1 (<1%)	43 (30%)	7 (5%)	2 (1%)
Infection-febrile neutropenia	39 (28%)	21 (15%)	5 (4%)	26 (18%)	11 (8%)	0
Cardiovascular	35 (25%)	7 (5%)	6 (4%)	22 (15%)	8 (6%)	3 (2%)
Hepatic	34 (24%)	5 (4%)	2 (1%)	23 (16%)	2 (1%)	0
Pulmonary	24 (17%)	4 (3%)	0	23 (16%)	5 (3%)	3 (2%)
Vascular disorders						
Hemorrhage	21 (15%)	8 (6%)	1 (<1%)	20 (14%)	3 (2%)	1 (<1%)
Coagulation	8 (6%)	4 (3%)	3 (2%)	10 (7%)	7 (5%)	0
Musculoskeletal	19 (14%)	3 (2%)	0	7 (5%)	1 (<1%)	1 (<1%)
Allergy-Immunology	8 (6%)	2 (1%)	1 (<1%)	4 (3%)	0	1 (<1%)
Endocrine	8 (6%)	0	0	4 (3%)	2 (1%)	0
Sexual reproduction function	7 (5%)	0	0	10 (7%)	1 (<1%)	0
Ocular-visual	7 (5%)	0	0	7 (5%)	1 (<1%)	0

382 Data were collected using NCI Common Toxicity Criteria, v. 2.0.

383 * Includes patients who were eligible and treated.

384 † Grades 1 through 4 only. There were 3 patients who experienced grade 5 deaths with investigator-designated
 385 attribution. One was a grade 5 hemorrhage in which the drug-related thrombocytopenia aggravated the event. A
 386 second patient experienced bowel obstruction, cardiac arrest, pleural effusion and respiratory failure which were
 387 not treatment related but probably aggravated by treatment. A third patient experienced a pulmonary embolism
 388 and adult respiratory distress syndrome, the latter was indirectly treatment-related.

389 ‡ Constitutional includes fatigue (lethargy, malaise, asthenia), fever (in the absence of neutropenia), rigors, chills
390 sweating, and weight gain or loss.
391 § Pain includes abdominal pain or cramping, arthralgia, bone pain, chest pain (non-cardiac and non-pleuritic),
392 dysmenorrhea, dyspareunia, earache, headache, hepatic pain, myalgia, neuropathic pain, pain due to radiation,
393 pelvic pain, pleuritic pain, rectal or perirectal pain, and tumor pain.

394

395 **Postmarketing Reports of Adverse Events:** Reports of adverse events in patients taking
396 HYCAMTIN received after market introduction, which are not listed above, include the
397 following:

398 **Blood and Lymphatic System Disorders:** *Rare:* Severe bleeding (in association with
399 thrombocytopenia).

400 **Immune System Disorders:** *Infrequent:* Allergic manifestations; *rare:* Anaphylactoid
401 reactions.

402 **Skin and Subcutaneous Tissue Disorders:** *Rare:* Angioedema, severe dermatitis,
403 severe pruritus.

404 OVERDOSAGE

405 There is no known antidote for overdosage with HYCAMTIN. The primary anticipated
406 complication of overdosage would consist of bone marrow suppression.

407 One patient on a single-dose regimen of 17.5 mg/m² given on day 1 of a 21-day cycle had
408 received a single dose of 35 mg/m². This patient experienced severe neutropenia (nadir of
409 320/mm³) 14 days later but recovered without incident.

410 The LD₁₀ in mice receiving single intravenous infusions of HYCAMTIN was 75 mg/m² (CI
411 95%: 47 to 97).

412 DOSAGE AND ADMINISTRATION

413 **Ovarian Cancer and Small Cell Lung Cancer:** Prior to administration of the first course of
414 HYCAMTIN, patients must have a baseline neutrophil count of >1,500 cells/mm³ and a platelet
415 count of >100,000 cells/mm³. The recommended dose of HYCAMTIN is 1.5 mg/m² by
416 intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day
417 course.

418 In the absence of tumor progression, a minimum of 4 courses is recommended because tumor
419 response may be delayed. The median time to response in 3 ovarian clinical trials was 9 to
420 12 weeks, and median time to response in 4 small cell lung cancer trials was 5 to 7 weeks.

421 In the event of severe neutropenia during any course, the dose should be reduced by
422 0.25 mg/m² (to 1.25 mg/m²) for subsequent courses. Doses should be similarly reduced if the
423 platelet count falls below 25,000 cells/mm³. Alternatively, in the event of severe neutropenia,
424 G-CSF may be administered following the subsequent course (before resorting to dose reduction)
425 starting from day 6 of the course (24 hours after completion of topotecan administration).

426 **Cervical Cancer:** Prior to administration of the first course of HYCAMTIN, patients must
427 have a baseline absolute neutrophil count of >1,500 cells/mm³ and a platelet count of >100,000
428 cells/mm³. The recommended dose of HYCAMTIN is 0.75 mg/m² by intravenous infusion over

429 30 minutes daily on days 1, 2, and 3; followed by cisplatin 50 mg/m² by intravenous infusion on
430 day 1 repeated every 21 days (a 21-day course).

431 Dosage adjustments for subsequent courses of HYCAMTIN in combination with cisplatin are
432 specific for each drug.

433 • In the event of severe febrile neutropenia (defined as <1,000 cells/mm³ with temperature of
434 38.0°C or 100.4°F), the dose of HYCAMTIN should be reduced by 20% to 0.60 mg/m² for
435 subsequent courses. Doses of HYCAMTIN should be similarly reduced (by 20% to
436 0.60 mg/m²) if the platelet count falls below 10,000 cells/mm³. Alternatively, in the event of
437 severe febrile neutropenia, G-CSF may be administered following the subsequent course
438 (before resorting to dose reduction) starting from day 4 of the course (24 hours after
439 completion of administration of HYCAMTIN). If febrile neutropenia occurs despite the use
440 of G-CSF, the dose of HYCAMTIN should be reduced by another 20% to 0.45 mg/m² for
441 subsequent courses.

442 • See manufacturer's prescribing information for cisplatin administration and hydration
443 guidelines and for cisplatin dosage adjustment in the event of hematologic toxicity.

444 **Adjustment of Dose in Special Populations: *Hepatic Impairment:*** No dosage
445 adjustment appears to be required for treating patients with impaired hepatic function (plasma
446 bilirubin >1.5 to <10 mg/dL).

447 ***Renal Functional Impairment:*** No dosage adjustment of HYCAMTIN appears to be
448 required for treating patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min.). Dosage
449 adjustment of HYCAMTIN to 0.75 mg/m² is recommended for patients with moderate renal
450 impairment (20 to 39 mL/min.). Insufficient data are available in patients with severe renal
451 impairment to provide a dosage recommendation for HYCAMTIN.

452 HYCAMTIN in combination with cisplatin for the treatment of cervical cancer should only be
453 initiated in patients with serum creatinine ≤1.5 mg/dL. In the clinical trial, cisplatin was
454 discontinued for a serum creatinine >1.5 mg/dL. Insufficient data are available regarding
455 continuing monotherapy with HYCAMTIN after cisplatin discontinuation in patients with
456 cervical cancer.

457 ***Elderly Patients:*** No dosage adjustment appears to be needed in the elderly other than
458 adjustments related to renal function (see CLINICAL PHARMACOLOGY and
459 PRECAUTIONS).

460 **PREPARATION FOR ADMINISTRATION**

461 **Precautions:** HYCAMTIN is a cytotoxic anticancer drug. As with other potentially toxic
462 compounds, HYCAMTIN should be prepared under a vertical laminar flow hood while wearing
463 gloves and protective clothing. If HYCAMTIN solution contacts the skin, wash the skin
464 immediately and thoroughly with soap and water. If HYCAMTIN contacts mucous membranes,
465 flush thoroughly with water.

466 **Preparation for Intravenous Administration:** Each HYCAMTIN 4-mg vial is
467 reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the

468 reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5%
469 Dextrose Intravenous Infusion prior to administration.
470 Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted
471 product should be used immediately.

472 **STABILITY**

473 Unopened vials of HYCAMTIN are stable until the date indicated on the package when stored
474 between 20° and 25°C (68° and 77°F) [see USP] and protected from light in the original
475 package. Because the vials contain no preservative, contents should be used immediately after
476 reconstitution.

477 Reconstituted vials of HYCAMTIN diluted for infusion are stable at approximately 20° to
478 25°C (68° to 77°F) and ambient lighting conditions for 24 hours.

479 **HOW SUPPLIED**

480 HYCAMTIN for Injection is supplied in 4-mg (free base) single-dose vials.

481 NDC 0007-4201-01 (package of 1)

482 NDC 0007-4201-05 (package of 5)

483 **Storage:** Store the vials protected from light in the original cartons at controlled room
484 temperature between 20° and 25°C (68° and 77°F) [see USP].

485 **Handling and Disposal:** Procedures for proper handling and disposal of anticancer drugs
486 should be used. Several guidelines on this subject have been published.¹⁻⁸ There is no general
487 agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

488 **REFERENCES**

- 489 1. Brown KA, Esper P, Kelleher LO, Brace O'Neill JE, Polovich M, White JM, eds. In:
490 *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*. Pittsburgh,
491 PA: Oncology Nursing Society:2001:55-73.
- 492 2. National Institutes of Health Web site. Recommendations for the safe handling of cytotoxic
493 drugs. NIH Publication 92-2621. Available at
494 <http://www.nih.gov/od/ors/ds/pubs/cyto/index.htm>. Accessed August 21, 2002.
- 495 3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics.
496 *JAMA* 1985;253(11):1590-1591.
- 497 4. National Study Commission on Cytotoxic Exposure — Recommendations for handling
498 cytotoxic agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study
499 Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health
500 Sciences, 179 Longwood Avenue, Boston, MA 02115.
- 501 5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling
502 of antineoplastic agents. *Med J Austr* 1983;1:426-428.
- 503 6. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: A report from the
504 Mount Sinai Medical Center. *CA-A Cancer J for Clin* 1983;33:258-263.

- 505 7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling
506 Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990;47:1033-1049.
507 8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines),
508 *Am J Health-Syst Pharm* 1996;53:1669-1685.
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