

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use (HYCAMTIN) safely and effectively. See full prescribing information for (HYCAMTIN).

### HYCAMTIN® (topotecan hydrochloride) for Injection

Initial U.S. Approval: 1996

#### **WARNING: BONE MARROW SUPPRESSION**

See full prescribing information for complete boxed warning.

Do not give HYCAMTIN to patients with baseline neutrophil counts less than 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection and death, monitor peripheral blood cell counts frequently on all patients receiving HYCAMTIN. (5.1)

#### -----INDICATIONS AND USAGE-----

HYCAMTIN for Injection is a topoisomerase inhibitor indicated for:

- metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy. (1)
- small cell lung cancer sensitive disease after failure of first-line chemotherapy. (1)
- combination therapy with cisplatin for stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy. (1)

#### -----DOSAGE AND ADMINISTRATION-----

- Ovarian cancer and small cell lung cancer: 1.5mg/m<sup>2</sup> by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day one of a 21-day course. (2.1)
- Cervical cancer: 0.75mg/m<sup>2</sup> by intravenous infusion over 30 minutes on days 1, 2, and 3 followed by cisplatin 50mg/m<sup>2</sup> by intravenous infusion on day 1 repeated every 21 days. (2.2)

See Dosage Modification Guidelines for patients with neutropenia or reduced platelets. (2.1, 2.2)

See Dosage Adjustment in Renal Impairment. (2.3)

#### -----DOSAGE FORMS AND STRENGTHS-----

4-mg (free base) single-dose vial. (3)

#### -----CONTRAINDICATIONS-----

- History of severe hypersensitivity reactions (e.g., anaphylactoid reactions) to topotecan or any of its ingredients (4)
- Severe bone marrow depression (4)

#### -----WARNINGS AND PRECAUTIONS-----

- Bone marrow suppression: Administer HYCAMTIN only to patients with adequate bone marrow reserves. Monitor peripheral blood counts and adjust the dose if needed. (5.1)
- Topotecan-induced neutropenia can lead to neutropenic colitis. (5.2)
- Interstitial lung disease: HYCAMTIN has been associated with reports of interstitial lung disease. Monitor patients for symptoms and discontinue HYCAMTIN if the diagnosis is confirmed. (5.3)
- Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus. (5.4, 8.1)

#### -----ADVERSE REACTIONS-----

Ovarian and small cell lung cancer:

- The most common hematologic adverse reactions were: neutropenia (97%), leukopenia (97%), anemia (89%), and thrombocytopenia (69%). (6.1)
- The most common (>25%) non-hematologic adverse reactions (all grades) were: nausea, alopecia, vomiting, sepsis or pyrexia/infection with neutropenia, diarrhea, constipation, fatigue, and pyrexia. (6.1)

Cervical cancer (HYCAMTIN plus cisplatin):

- The most common hematologic adverse reactions (all grades) were: anemia (94%), leukopenia (91%), neutropenia (89%), and thrombocytopenia (74%). (6.1)
- The most common (>25%) non-hematologic adverse reactions (all grades) were: pain, nausea, vomiting, and infection/febrile neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact

GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### -----DRUG INTERACTIONS-----

- Do not initiate G-CSF until 24 hours after completion of treatment with HYCAMTIN. Concomitant administration can prolong duration of neutropenia. (7)
- Greater myelosuppression is likely to be seen when used in combination with other cytotoxic agents. (7)

#### -----USE IN SPECIFIC POPULATIONS-----

- Nursing Mothers: Discontinue nursing when receiving HYCAMTIN. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: Month Year

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: BONE MARROW SUPPRESSION**

3 Do not give Hycamtin to patients with baseline neutrophil counts less than  
4 1,500 cells/mm<sup>3</sup>. In order to monitor the occurrence of bone marrow suppression, primarily  
5 neutropenia, which may be severe and result in infection and death, monitor peripheral blood  
6 counts frequently on all patients receiving Hycamtin [see Warnings and Precautions (5.1)].

7 **1 INDICATIONS AND USAGE**

8 Hycamtin is indicated for the treatment of:

- 9 • metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.  
10 • small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical  
11 studies submitted to support approval, sensitive disease was defined as disease responding to  
12 chemotherapy but subsequently progressing at least 60 days (in the Phase 3 study) or at least  
13 90 days (in the Phase 2 studies) after chemotherapy [see Clinical Studies(14)].

14 Hycamtin in combination with cisplatin is indicated for the treatment of:

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

17 **2 DOSAGE AND ADMINISTRATION**

18 Prior to administration of the first course of Hycamtin, patients must have a baseline  
19 neutrophil count of >1,500 cells/mm<sup>3</sup> and a platelet count of >100,000 cells/mm<sup>3</sup>.

20 **2.1 Ovarian Cancer and Small Cell Lung Cancer**

21 Recommended Dosage:

- 22 • The recommended dose of Hycamtin is 1.5 mg/m<sup>2</sup> by intravenous infusion over  
23 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course.  
24 • In the absence of tumor progression, a minimum of 4 courses is recommended because tumor  
25 response may be delayed. The median time to response in 3 ovarian clinical trials was 9 to  
26 12 weeks, and median time to response in 4 small cell lung cancer trials was 5 to 7 weeks.

27 Dosage Modification Guidelines:

- 28 • In the event of severe neutropenia (defined as <500 cells/mm<sup>3</sup>) during any course, reduce the  
29 dose by 0.25 mg/m<sup>2</sup> (to 1.25 mg/m<sup>2</sup>) for subsequent courses.  
30 • Alternatively, in the event of severe neutropenia, administer G-CSF (granulocyte-colony  
31 stimulating factor) following the subsequent course (before resorting to dose reduction)  
32 starting from day 6 of the course (24 hours after completion of topotecan administration).  
33 • In the event the platelet count falls below 25,000 cells/mm<sup>3</sup>, reduce doses by 0.25 mg/m<sup>2</sup> (to  
34 1.25 mg/m<sup>2</sup>) for subsequent courses.

35 **2.2 Cervical Cancer**

36            **Recommended Dosage:** The recommended dose of HYCAMTIN is 0.75 mg/m<sup>2</sup> by  
37 intravenous infusion over 30 minutes daily on days 1, 2, and 3; followed by cisplatin 50 mg/m<sup>2</sup>  
38 by intravenous infusion on day 1 repeated every 21 days (a 21-day course).

39            **Dosage Modification Guidelines:** Dosage adjustments for subsequent courses of  
40 HYCAMTIN in combination with cisplatin are specific for each drug. See manufacturer's  
41 prescribing information for cisplatin administration and hydration guidelines and for cisplatin  
42 dosage adjustment in the event of hematologic toxicity.

- 43 • In the event of severe febrile neutropenia (defined as <1000 cells/mm<sup>3</sup> with temperature of  
44 38.0°C or 100.4°F), reduce the dose of HYCAMTIN to 0.60 mg/m<sup>2</sup> for subsequent courses.
- 45 • Alternatively, in the event of severe febrile neutropenia, administer G-CSF following the  
46 subsequent course (before resorting to dose reduction) starting from day 4 of the course  
47 (24 hours after completion of administration of HYCAMTIN).
- 48 • If febrile neutropenia occurs despite the use of G-CSF, reduce the dose of HYCAMTIN to  
49 0.45 mg/m<sup>2</sup> for subsequent courses.
- 50 • In the event the platelet count falls below 25,000 cells/mm<sup>3</sup>, reduce doses to 0.60 mg/m<sup>2</sup> for  
51 subsequent courses.

### 52 **2.3 Dosage Adjustment in Specific Populations**

53            **Renal Impairment:** No dosage adjustment of HYCAMTIN appears to be required for  
54 patients with mild renal impairment (Cl<sub>cr</sub> 40 to 60 mL/min.). Dosage adjustment of HYCAMTIN  
55 to 0.75 mg/m<sup>2</sup> is recommended for patients with moderate renal impairment (20 to 39 mL/min.).  
56 Insufficient data are available in patients with severe renal impairment to provide a dosage  
57 recommendation for HYCAMTIN [*see Use in Specific Populations (8.6) and Clinical*  
58 *Pharmacology (12.3)*].

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

### 64 **2.4 Instructions for Handling, Preparation and Intravenous Administration**

65            **Handling:** HYCAMTIN is a cytotoxic anticancer drug. Prepare HYCAMTIN under a  
66 vertical laminar flow hood while wearing gloves and protective clothing. If HYCAMTIN  
67 solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If  
68 HYCAMTIN contacts mucous membranes, flush thoroughly with water.

69            Use procedures for proper handling and disposal of anticancer drugs. Several guidelines  
70 on this subject have been published.<sup>1-4</sup>

71            **Preparation and Administration:** Each 4-mg vial of HYCAMTIN is reconstituted with  
72 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is  
73 diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous  
74 Infusion prior to administration.

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

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

### 81    **3        DOSAGE FORMS AND STRENGTHS**

82                    4-mg (free base) single-dose vial, light yellow to greenish powder.

### 83    **4        CONTRAINDICATIONS**

84                    HYCAMTIN is contraindicated in patients who have a history of severe hypersensitivity  
85 reactions (e.g., anaphylactoid reactions) to topotecan or to any of its ingredients. HYCAMTIN  
86 should not be used in patients with severe bone marrow depression.

### 87    **5        WARNINGS AND PRECAUTIONS**

#### 88    **5.1      Bone Marrow Suppression**

89                    Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of  
90 HYCAMTIN. Neutropenia is not cumulative over time. In ovarian cancer, the overall  
91 treatment-related death rate was 1%. In the comparative study in small cell lung cancer,  
92 however, the treatment-related death rates were 5% for HYCAMTIN and 4% for CAV  
93 (cyclophosphamide-doxorubicin-vincristine).

#### 94                    Neutropenia:

- 95                    • Ovarian and small cell lung cancer experience: Grade 4 neutropenia (<500 cells/mm<sup>3</sup>) was  
96 most common during course 1 of treatment (60% of patients) and occurred in 39% of all  
97 courses, with a median duration of 7 days. The nadir neutrophil count occurred at a median  
98 of 12 days. Therapy-related sepsis or febrile neutropenia occurred in 23% of patients, and  
99 sepsis was fatal in 1%. Pancytopenia has been reported.
- 100                    • Cervical cancer experience: Grade 3 and grade 4 neutropenia affected 26% and 48% of  
101 patients, respectively.

#### 102                    Thrombocytopenia:

- 103                    • Ovarian and small cell lung cancer experience: Grade 4 thrombocytopenia (<25,000/mm<sup>3</sup>)  
104 occurred in 27% of patients and in 9% of courses, with a median duration of 5 days and  
105 platelet nadir at a median of 15 days. Platelet transfusions were given to 15% of patients in  
106 4% of courses.
- 107                    • Cervical cancer experience: Grade 3 and grade 4 thrombocytopenia affected 26% and 7% of  
108 patients, respectively.

#### 109                    Anemia:

- 110                    • Ovarian and small cell lung cancer experience: Grade 3/4 anemia (<8 g/dL) occurred in 37%  
111 of patients and in 14% of courses. Median nadir was at day 15. Transfusions were needed in  
112 52% of patients in 22% of courses.

- 113 • Cervical cancer experience: Grade 3 and grade 4 anemia affected 34% and 6% of patients,  
114 respectively.

115 **Monitoring of Bone Marrow Function:** Administer HYCAMTIN only in patients with  
116 adequate bone marrow reserves, including baseline neutrophil count of at least 1,500 cells/mm<sup>3</sup>  
117 and platelet count at least 100,000/mm<sup>3</sup>. Monitor peripheral blood counts frequently during  
118 treatment with HYCAMTIN. Do not treat patients with subsequent courses of HYCAMTIN until  
119 neutrophils recover to >1,000 cells/mm<sup>3</sup>, platelets recover to >100,000 cells/mm<sup>3</sup>, and  
120 hemoglobin levels recover to 9.0 g/dL (with transfusion if necessary). Severe myelotoxicity has  
121 been reported when HYCAMTIN is used in combination with cisplatin [*see Drug Interactions*  
122 (7)].

## 123 **5.2 Neutropenic Colitis**

124 Topotecan-induced neutropenia can lead to neutropenic colitis. Fatalities due to  
125 neutropenic colitis have been reported in clinical trials with HYCAMTIN. In patients presenting  
126 with fever, neutropenia, and a compatible pattern of abdominal pain, consider the possibility of  
127 neutropenic colitis.

## 128 **5.3 Interstitial Lung Disease**

129 HYCAMTIN has been associated with reports of interstitial lung disease (ILD), some of  
130 which have been fatal [*see Adverse Reactions (6.2)*]. Underlying risk factors include history of  
131 ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation, and use of pneumotoxic  
132 drugs and/or colony stimulating factors. Monitor patients for pulmonary symptoms indicative of  
133 interstitial lung disease (e.g., cough, fever, dyspnea, and/or hypoxia), and discontinue  
134 HYCAMTIN if a new diagnosis of ILD is confirmed.

## 135 **5.4 Pregnancy**

136 Pregnancy Category D

137 HYCAMTIN can cause fetal harm when administered to a pregnant woman.

138 Topotecan caused embryoletality, fetotoxicity, and teratogenicity in rats and rabbits  
139 when administered during organogenesis. There are no adequate and well controlled studies of  
140 HYCAMTIN in pregnant women. If this drug is used during pregnancy, or if a patient becomes  
141 pregnant while receiving HYCAMTIN, the patient should be apprised of the potential hazard to  
142 the fetus. [*see Use in Specific Populations, Pregnancy (8.1)*].

## 143 **5.5 Inadvertent Extravasation**

144 Inadvertent extravasation with HYCAMTIN has been observed, most reactions have been  
145 mild but severe cases have been reported.

# 146 **6 ADVERSE REACTIONS**

## 147 **6.1 Clinical Trials Experience**

148 Because clinical trials are conducted under widely varying conditions, adverse reaction  
149 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
150 trials of another drug and may not reflect the rates observed in practice.

151 **Ovarian Cancer and Small Cell Lung Cancer:** Data in the following section are based

152 on the combined experience of 453 patients with metastatic ovarian carcinoma, and 426 patients  
153 with small cell lung cancer treated with Hycamtin. Table 1 lists the principal hematologic  
154 adverse reactions and Table 2 lists non-hematologic adverse reactions occurring in at least 15%  
155 of patients.

156 **Table 1. Hematologic Adverse Reactions Experienced in ≥15% Ovarian Cancer and Small**  
157 **Cell Lung Cancer Patients Receiving HYCAMTIN**

Hematologic Adverse Reaction	Patients (n = 879) % Incidence
Neutropenia <1,500 cells/mm <sup>3</sup> <500 cells/mm <sup>3</sup>	97 78
Leukopenia <3,000 cells/mm <sup>3</sup> <1,000 cells/mm <sup>3</sup>	97 32
Thrombocytopenia <75,000/mm <sup>3</sup> <25,000/mm <sup>3</sup>	69 27
Anemia <10 g/dL <8 g/dL	89 37

158  
159 **Table 2. Non-hematologic Adverse Reactions Experienced by ≥15% of Ovarian Cancer and**  
160 **Small Cell Lung Cancer Patients Receiving HYCAMTIN**

Non-hematologic Adverse Reaction	Percentage of Patients with Adverse Reaction (879 Patients)		
	All Grades	Grade 3	Grade 4
<b>Infections and infestations</b> Sepsis or pyrexia/infection with neutropenia <sup>a</sup>	43	NR	23
<b>Metabolism and nutrition disorders</b> Anorexia	19	2	<1
<b>Nervous system disorders</b> Headache	18	1	<1
<b>Respiratory, thoracic, and mediastinal disorders</b> Dyspnea Coughing	22 15	5 1	3 0
<b>Gastrointestinal disorders</b> Nausea Vomiting Diarrhea Constipation Abdominal pain Stomatitis	64 45 32 29 22 18	7 4 3 2 2 1	1 1 1 1 2 <1

<b>Skin and subcutaneous tissue disorders</b>			
Alopecia	49	NA	NA
Rash <sup>b</sup>	16	1	0
<b>General disorders and administrative site conditions</b>			
Fatigue	29	5	0
Pyrexia	28	1	<1
Pain <sup>c</sup>	23	2	1
Asthenia	25	4	2

161 NA = Not applicable

162 NR = Not reported separately

163 <sup>a</sup> Does not include Grade 1 sepsis or pyrexia.

164 <sup>b</sup> Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and  
165 maculopapular rash.

166 <sup>c</sup> Pain includes body pain, back pain, and skeletal pain.

167

168 **Nervous System Disorders:** Paresthesia occurred in 7% of patients but was generally  
169 grade 1.

170 **Hepatobiliary Disorders:** Grade 1 transient elevations in hepatic enzymes occurred in  
171 8% of patients. Greater elevations, grade 3/4, occurred in 4%. Grade 3/4 elevated bilirubin  
172 occurred in <2% of patients.

173 Table 3 shows the grade 3/4 hematologic and major non-hematologic adverse reactions in  
174 the topotecan/paclitaxel comparator trial in ovarian cancer.

175

176 **Table 3. Adverse Reactions Experienced by ≥5% of Ovarian Cancer Patients Randomized**  
177 **to Receive Hycamtin or Paclitaxel**

Adverse Reaction	HYCAMTIN (n = 112)	Paclitaxel (n = 114)
<b>Hematologic Grade 3/4</b>	<b>%</b>	<b>%</b>
Grade 4 neutropenia (<500 cells/mm <sup>3</sup> )	80	21
Grade 3/4 anemia (Hgb <8 g/dL)	41	6
Grade 4 thrombocytopenia (<25,000 plts/mm <sup>3</sup> )	27	3
Pyrexia/Grade 4 neutropenia	23	4
<b>Non-hematologic Grade 3/4</b>	<b>%</b>	<b>%</b>
<b>Infections and infestations</b>		
Documented sepsis <sup>a</sup>	5	2
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Dyspnea	6	5
<b>Gastrointestinal disorders</b>		
Abdominal pain	5	4
Constipation	5	0
Diarrhea	6	1
Intestinal obstruction	5	4
Nausea	10	2
Vomiting	10	3
<b>General disorders and administrative site conditions</b>		
Fatigue	7	6
Asthenia	5	3
Pain <sup>b</sup>	5	7

178 <sup>a</sup> Death related to sepsis occurred in 2% of patients receiving Hycamtin, and 0% of patients  
179 receiving paclitaxel.

180 <sup>b</sup> Pain includes body pain, skeletal pain, and back pain.

181

182 Table 4 shows the grade 3/4 hematologic and major non-hematologic adverse reactions in  
183 the topotecan/CAV comparator trial in small cell lung cancer.

184 **Table 4. Adverse Reactions Experienced by ≥5% of Small Cell Lung Cancer Patients**  
185 **Randomized to Receive HYCAMTIN or CAV**

Adverse Reaction	HYCAMTIN (n = 107)	CAV (n = 104)
<b>Hematologic Grade 3/4</b>	<b>%</b>	<b>%</b>
Grade 4 neutropenia ( $<500$ cells/mm <sup>3</sup> )	70	72
Grade 3/4 anemia (Hgb $<8$ g/dL)	42	20
Grade 4 thrombocytopenia ( $<25,000$ plts/mm <sup>3</sup> )	29	5
Pyrexia/Grade 4 neutropenia	28	26
<b>Non-hematologic Grade 3/4</b>	<b>%</b>	<b>%</b>
<b>Infections and infestations</b>		
Documented sepsis <sup>a</sup>	5	5
<b>Respiratory, thoracic, and mediastinal disorders</b>		
Dyspnea	9	14
Pneumonia	8	6
<b>Gastrointestinal disorders</b>		
Abdominal pain	6	4
Nausea	8	6
<b>General disorders and administrative site conditions</b>		
Fatigue	6	10
Asthenia	9	7
Pain <sup>b</sup>	5	7

186 <sup>a</sup> Death related to sepsis occurred in 3% of patients receiving HYCAMTIN, and 1% of patients  
187 receiving CAV.

188 <sup>b</sup> Pain includes body pain, skeletal pain, and back pain.

189

190 Cervical Cancer: In the comparative trial with HYCAMTIN plus cisplatin versus  
191 cisplatin in patients with cervical cancer, the most common dose-limiting adverse reaction was  
192 myelosuppression. Table 5 shows the hematologic adverse reactions and Table 6 shows the  
193 non-hematologic adverse reactions in patients with cervical cancer.

194

195 **Table 5. Hematologic Adverse Reactions in Patients with Cervical Cancer Treated with**  
196 **HYCAMTIN Plus Cisplatin or Cisplatin Monotherapy<sup>a</sup>**

Hematologic Adverse Reaction	HYCAMTIN Plus Cisplatin (n = 140)	Cisplatin (n = 144)
<b>Anemia</b>		
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%)
<b>Leukopenia</b>		
All grades (<3,800 cells/mm <sup>3</sup> )	128 (91%)	43 (30%)
Grade 3 (<2,000-1,000 cells/mm <sup>3</sup> )	58 (41%)	1 (1%)
Grade 4 (<1,000 cells/mm <sup>3</sup> )	35 (25%)	0 (0%)
<b>Neutropenia</b>		
All grades (<2,000 cells/mm <sup>3</sup> )	125 (89%)	28 (19%)
Grade 3 (<1,000-500 cells/mm <sup>3</sup> )	36 (26%)	1 (1%)
Grade 4 (<500 cells/mm <sup>3</sup> )	67 (48%)	1 (1%)
<b>Thrombocytopenia</b>		
All grades (<130,000 cells/mm <sup>3</sup> )	104 (74%)	21 (15%)
Grade 3 (<50,000-10,000 cells/mm <sup>3</sup> )	36 (26%)	5 (3%)
Grade 4 (<10,000 cells/mm <sup>3</sup> )	10 (7%)	0 (0%)

197 <sup>a</sup> Includes patients who were eligible and treated.

198

199 **Table 6. Non-hematologic Adverse Reactions Experienced by ≥5% of Patients with**  
200 **Cervical Cancer Treated with Hycamtin Plus Cisplatin or Cisplatin Monotherapy<sup>a</sup>**

Adverse Reactions	HYCAMTIN Plus Cisplatin (n = 140)			Cisplatin (n = 144)		
	All Grades <sup>b</sup>	Grade 3	Grade 4	All Grades <sup>b</sup>	Grade 3	Grade 4
<b>General disorders and administrative site conditions</b>						
Constitutional <sup>c</sup>	96 (69%)	11 (8%)	0	89 (62%)	17 (12%)	0
Pain <sup>d</sup>	82 (59%)	28 (20%)	3 (2%)	72 (50%)	18 (13%)	5 (3%)
<b>Gastrointestinal disorders</b>						
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%)
<b>Dermatology</b>	67 (48%)	1 (<1%)	0	29 (20%)	0	0
<b>Metabolic-Laboratory</b>	55 (39%)	13 (9%)	7 (5%)	44 (31%)	14 (10%)	1 (<1%)
<b>Genitourinary</b>	51 (36%)	9 (6%)	9 (6%)	49 (34%)	7 (5%)	7 (5%)
<b>Nervous system disorders</b>						
Neuropathy	4 (3%)	1 (<1%)	0	3 (2%)	1 (<1%)	0
Other	49 (35%)	3 (2%)	1 (<1%)	43 (30%)	7 (5%)	2 (1%)
<b>Infection-febrile neutropenia</b>	39 (28%)	21 (15%)	5 (4%)	26 (18%)	11 (8%)	0
<b>Cardiovascular</b>	35 (25%)	7 (5%)	6 (4%)	22 (15%)	8 (6%)	3 (2%)
<b>Hepatic</b>	34 (24%)	5 (4%)	2 (1%)	23 (16%)	2 (1%)	0
<b>Pulmonary</b>	24 (17%)	4 (3%)	0	23 (16%)	5 (3%)	3 (2%)
<b>Vascular disorders</b>						
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
<b>Musculoskeletal</b>	19 (14%)	3 (2%)	0	7 (5%)	1 (<1%)	1 (<1%)
<b>Allergy-Immunology</b>	8 (6%)	2 (1%)	1 (<1%)	4 (3%)	0	1 (<1%)
<b>Endocrine</b>	8 (6%)	0	0	4 (3%)	2 (1%)	0
<b>Sexual reproduction function</b>	7 (5%)	0	0	10 (7%)	1 (<1%)	0
<b>Ocular-visual</b>	7 (5%)	0	0	7 (5%)	1 (<1%)	0

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

202 <sup>a</sup> Includes patients who were eligible and treated.

203 <sup>b</sup> Grades 1 through 4 only. There were 3 patients who experienced grade 5 deaths with investigator-  
204 designated attribution. One was a grade 5 hemorrhage in which the drug-related thrombocytopenia  
205 aggravated the event. A second patient experienced bowel obstruction, cardiac arrest, pleural effusion  
206 and respiratory failure which were not treatment related but probably aggravated by treatment. A third  
207 patient experienced a pulmonary embolism and adult respiratory distress syndrome, the latter was  
208 indirectly treatment-related.

- 209 <sup>c</sup> Constitutional includes fatigue (lethargy, malaise, asthenia), fever (in the absence of neutropenia),  
210 rigors, chills, sweating, and weight gain or loss.  
211 <sup>d</sup> Pain includes abdominal pain or cramping, arthralgia, bone pain, chest pain (non-cardiac and non-  
212 pleuritic), dysmenorrhea, dyspareunia, earache, headache, hepatic pain, myalgia, neuropathic pain,  
213 pain due to radiation, pelvic pain, pleuritic pain, rectal or perirectal pain, and tumor pain.  
214

## 215 **6.2 Postmarketing Experience**

216 In addition to adverse reactions reported from clinical trials or listed in other sections of  
217 the prescribing information, the following reactions have been identified during post-marketing  
218 use of HYCAMTIN. Because they are reported voluntarily from a population of unknown size,  
219 estimates of frequency cannot be made. These reactions have been chosen for inclusion due to a  
220 combination of their seriousness, frequency of reporting, or potential causal connection to  
221 HYCAMTIN.

222 Blood and Lymphatic System Disorders: Severe bleeding (in association with  
223 thrombocytopenia) [see Warnings and Precautions (5.1)].

224 Immune System Disorders: Allergic manifestations; Anaphylactoid reactions.

225 Gastrointestinal Disorders: Abdominal pain potentially associated with neutropenic  
226 colitis [see Warnings and Precautions (5.2)].

227 Pulmonary Disorders: Interstitial lung disease [see Warnings and Precautions (5.3)].

228 Skin and Subcutaneous Tissue Disorders: Angioedema, severe dermatitis, severe  
229 pruritus.

230 General Disorders and Administration Site Conditions: Inadvertent extravasation  
231 [see Warnings and Precautions (5.5)].

## 232 **7 DRUG INTERACTIONS**

233 *G-CSF:* Concomitant administration of G-CSF can prolong the duration of neutropenia,  
234 so if G-CSF is to be used, do not initiate it until day 6 of the course of therapy, 24 hours after  
235 completion of treatment with HYCAMTIN.

236 *Platinum and Other Cytotoxic Agents:* Myelosuppression was more severe when  
237 HYCAMTIN, at a dose of 1.25 mg/m<sup>2</sup>/day for 5 days, was given in combination with cisplatin at  
238 a dose of 50 mg/m<sup>2</sup> in Phase 1 studies. In one study, 1 of 3 patients had severe neutropenia for  
239 12 days and a second patient died with neutropenic sepsis.

240 Greater myelosuppression is also likely to be seen when HYCAMTIN is used in  
241 combination with other cytotoxic agents, thereby necessitating a dose reduction. However, when  
242 combining HYCAMTIN with platinum agents (e.g., cisplatin or carboplatin), a distinct  
243 sequence-dependent interaction on myelosuppression has been reported. Coadministration of a  
244 platinum agent on day 1 of dosing with HYCAMTIN required lower doses of each agent  
245 compared to co-administration on day 5 of the dosing schedule for HYCAMTIN.

246 For information on the pharmacokinetics, efficacy, safety, and dosing of HYCAMTIN at  
247 a dose of 0.75 mg/m<sup>2</sup>/day on days 1, 2, and 3 in combination with cisplatin 50 mg/m<sup>2</sup> on day 1  
248 for cervical cancer, see Dosage and Administration (2), Adverse Reactions (6), Clinical

249 Pharmacology (12.3), and Clinical Studies (14).

## 250 **8 USE IN SPECIFIC POPULATIONS**

### 251 **8.1 Pregnancy**

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

253 HYCAMTIN can cause fetal harm when administered to a pregnant woman. In rabbits, a  
254 dose of 0.10 mg/kg/day (about equal to the clinical dose on a mg/m<sup>2</sup> basis) given on days 6  
255 through 20 of gestation caused maternal toxicity, embryoletality, and reduced fetal body  
256 weight. In the rat, a dose of 0.23 mg/kg/day (about equal to the clinical dose on a mg/m<sup>2</sup> basis)  
257 given for 14 days before mating through gestation day 6 caused fetal resorption, microphthalmia,  
258 pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/day (about half the clinical  
259 dose on a mg/m<sup>2</sup> basis) given to rats on days 6 through 17 of gestation caused an increase in  
260 post-implantation mortality. This dose also caused an increase in total fetal malformations. The  
261 most frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation  
262 of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles),  
263 skull, and vertebrae.

264 There are no adequate and well controlled studies of HYCAMTIN in pregnant women. If  
265 this drug is used during pregnancy, or if a patient becomes pregnant while receiving  
266 HYCAMTIN, the patient should be apprised of the potential hazard to the fetus. [*see Warnings*  
267 *and Precautions (5.4)*]

### 268 **8.3 Nursing Mothers**

269 Rats excrete high concentrations of topotecan into milk. Lactating female rats given  
270 4.72 mg/m<sup>2</sup> IV (about twice the clinical dose on a mg/m<sup>2</sup> basis) excreted topotecan into milk at  
271 concentrations up to 48-fold higher than those in plasma. It is not known whether the drug is  
272 excreted in human milk. Because many drugs are excreted in human milk and because of the  
273 potential for serious adverse reactions in nursing infants from HYCAMTIN, discontinue  
274 breastfeeding when women are receiving HYCAMTIN.

### 275 **8.4 Pediatric Use**

276 Safety and effectiveness in pediatric patients have not been established.

### 277 **8.5 Geriatric Use**

278 Of the 879 patients with metastatic ovarian cancer or small cell lung cancer in clinical  
279 studies of HYCAMTIN, 32% (n = 281) were 65 years of age and older, while 3.8% (n = 33)  
280 were 75 years of age and older. Of the 140 patients with stage IV-B, relapsed, or refractory  
281 cervical cancer in clinical studies of HYCAMTIN who received HYCAMTIN plus cisplatin in  
282 the randomized clinical trial, 6% (n = 9) were 65 years of age and older, while 3% (n = 4) were  
283 75 years of age and older. No overall differences in effectiveness or safety were observed  
284 between these patients and younger adult patients, and other reported clinical experience has not  
285 identified differences in responses between the elderly and younger adult patients, but greater  
286 sensitivity of some older individuals cannot be ruled out.

287 There were no apparent differences in the pharmacokinetics of topotecan in elderly

288 patients, once the age-related decrease in renal function was considered [see *Clinical*  
289 *Pharmacology (12.3)*].

290 This drug is known to be substantially excreted by the kidney, and the risk of toxic  
291 reactions to this drug may be greater in patients with impaired renal function. Because elderly  
292 patients are more likely to have decreased renal function, care should be taken in dose selection,  
293 and it may be useful to monitor renal function [see *Dosage and Administration (2.3)*].

#### 294 **8.6 Renal Impairment**

295 No dosage adjustment of HYCAMTIN appears to be required for patients with mild renal  
296 impairment ( $Cl_{cr}$  40 to 60 mL/min.). Dosage reduction is recommended for patients with  
297 moderate renal impairment ( $Cl_{cr}$  20 to 39 mL/min.). Insufficient data are available in patients  
298 with severe renal impairment to provide a dosage recommendation for HYCAMTIN. [see  
299 *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

### 300 **10 OVERDOSAGE**

301 There is no known antidote for overdose with HYCAMTIN. The primary anticipated  
302 complication of overdose would consist of bone marrow suppression.

303 One patient on a single-dose regimen of 17.5 mg/m<sup>2</sup> given on day 1 of a 21-day cycle had  
304 received a single dose of 35 mg/m<sup>2</sup>. This patient experienced severe neutropenia (nadir of  
305 320/mm<sup>3</sup>) 14 days later but recovered without incident.

306 Observe patients closely for bone marrow suppression, and consider supportive measures  
307 (such as the prophylactic use of G-CSF and/or antibiotic therapy).

### 308 **11 DESCRIPTION**

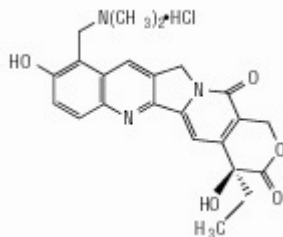
309 HYCAMTIN (topotecan hydrochloride) is a semi-synthetic derivative of camptothecin  
310 and is an anti-tumor drug with topoisomerase I-inhibitory activity.

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

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

317 The chemical name for topotecan hydrochloride is (S)-10-[(dimethylamino)methyl]-4-  
318 ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7] indolizino [1,2-b]quinoline-3,14-(4H,12H)-dione  
319 monohydrochloride. It has the molecular formula C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>•HCl and a molecular weight of  
320 457.9.

321 Topotecan hydrochloride has the following structural formula:



322  
323

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

## 324 **12 CLINICAL PHARMACOLOGY**

### 325 **12.1 Mechanism of Action**

326 Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand  
327 breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these  
328 single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA  
329 damage produced during DNA synthesis, when replication enzymes interact with the ternary  
330 complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently  
331 repair these double strand breaks.

### 332 **12.2 Pharmacodynamics**

333 The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases  
334 with increasing topotecan dose or topotecan AUC. When topotecan is administered at a dose of  
335 1.5 mg/m<sup>2</sup>/day for 5 days, an 80% to 90% decrease in white blood cell count at nadir is typically  
336 observed after the first cycle of therapy.

### 337 **12.3 Pharmacokinetics**

338 The pharmacokinetics of topotecan have been evaluated in cancer patients following  
339 doses of 0.5 to 1.5 mg/m<sup>2</sup> administered as a 30-minute infusion. Topotecan exhibits  
340 multiexponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure  
341 (AUC) is approximately dose-proportional.

342 **Distribution:** Binding of topotecan to plasma proteins is about 35%.

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

349 **Excretion:** Renal clearance is an important determinant of topotecan elimination.

350 In a mass balance/excretion study in 4 patients with solid tumors, the overall recovery of  
351 total topotecan and its N-desmethyl metabolite in urine and feces over 9 days averaged  
352 73.4 ± 2.3% of the administered IV dose. Mean values of 50.8 ± 2.9% as total topotecan and  
353 3.1 ± 1.0% as N-desmethyl topotecan were excreted in the urine following IV administration.  
354 Fecal elimination of total topotecan accounted for 17.9 ± 3.6% while fecal elimination of N-  
355 desmethyl topotecan was 1.7 ± 0.6%. An O-glucuronidation metabolite of topotecan and N-

356 desmethyl topotecan has been identified in the urine. These metabolites, topotecan-O-  
357 glucuronide and N-desmethyl topotecan-O-glucuronide, were less than 2% of the administered  
358 dose.

359 Effect of Gender: The overall mean topotecan plasma clearance in male patients was  
360 approximately 24% higher than that in female patients, largely reflecting difference in body size.

361 Effect of Age: Topotecan pharmacokinetics have not been specifically studied in an  
362 elderly population, but population pharmacokinetic analysis in female patients did not identify  
363 age as a significant factor. Decreased renal clearance, which is common in the elderly, is a more  
364 important determinant of topotecan clearance [*see Dosage and Administration (2.3) and Use in*  
365 *Specific Populations (8.5)*].

366 Effect of Race: The effect of race on topotecan pharmacokinetics has not been studied.

367 Effect of Renal Impairment: In patients with mild renal impairment (creatinine  
368 clearance of 40 to 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the  
369 value in patients with normal renal function. In patients with moderate renal impairment ( $Cl_{cr}$  of  
370 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control  
371 patients, with an increase in half-life. Mean half-life, estimated in 3 renally impaired patients,  
372 was about 5.0 hours. Dosage adjustment is recommended for these patients [*see Dosage and*  
373 *Administration (2.3)*].

374 Effect of Hepatic Impairment: Plasma clearance in patients with hepatic impairment  
375 (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in  
376 patients without hepatic impairment. Topotecan half-life increased slightly, from 2.0 hours to  
377 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan  
378 dosage regimen.

379 Drug Interactions: Pharmacokinetic studies of the interaction of topotecan with  
380 concomitantly administered medications have not been formally investigated.

381 In vitro inhibition studies using marker substrates known to be metabolized by human  
382 P450 CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or  
383 dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered  
384 by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

385 Cisplatin: Administration of cisplatin (60 or 75 mg/m<sup>2</sup> on day 1) before topotecan  
386 (0.75 mg/m<sup>2</sup>/day on days 1 to 5) in 9 patients with ovarian cancer had no significant effect on the  
387 C<sub>max</sub> and AUC of total topotecan.

388 Topotecan had no effect on the pharmacokinetics of free platinum in 15 patients with  
389 ovarian cancer who were administered cisplatin 50 mg/m<sup>2</sup> (n = 9) or 75 mg/m<sup>2</sup> (n = 6) on day 2  
390 after paclitaxel 110 mg/m<sup>2</sup> on day 1 before topotecan 0.3 mg/m<sup>2</sup> IV daily on days 2-6. Topotecan  
391 had no effect on dose-normalized (60 mg/m<sup>2</sup>) C<sub>max</sub> values of free platinum in 13 patients with  
392 ovarian cancer who were administered 60 mg/m<sup>2</sup> (n = 10) or 75 mg/m<sup>2</sup> (n = 3) cisplatin on day 1  
393 before topotecan 0.75 mg/m<sup>2</sup> IV daily on days 1 to 5.

394 No pharmacokinetic data are available following topotecan (0.75 mg/m<sup>2</sup>/day for  
395 3 consecutive days) and cisplatin (50 mg/m<sup>2</sup>/day on day 1) in patients with cervical cancer.

396 Myelosuppression was more severe when HYCAMTIN was given in combination with  
397 cisplatin. [see *Drug Interactions (7)*].

### 398 **13 NONCLINICAL TOXICOLOGY**

#### 399 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

400 Carcinogenicity testing of topotecan has not been performed. Topotecan is known to be  
401 genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to  
402 L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and  
403 without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not  
404 cause mutations in bacterial cells.

405 Topotecan given to female rats prior to mating at a dose of 1.4 mg/m<sup>2</sup> IV (about equal to  
406 the clinical dose on a mg/m<sup>2</sup> basis) caused superovulation possibly related to inhibition of  
407 follicular atresia. This dose given to pregnant female rats also caused increased pre-implantation  
408 loss. Studies in dogs given 0.4 mg/m<sup>2</sup> IV (about 1/4th the clinical dose on a mg/m<sup>2</sup> basis) of  
409 topotecan daily for a month suggest that treatment may cause an increase in the incidence of  
410 multinucleated spermatogonial giant cells in the testes. Topotecan may impair fertility in women  
411 and men.

### 412 **14 CLINICAL STUDIES**

#### 413 **14.1 Ovarian Cancer**

414 HYCAMTIN was studied in 2 clinical trials of 223 patients given topotecan with  
415 metastatic ovarian carcinoma. All patients had disease that had recurred on, or was unresponsive  
416 to, a platinum-containing regimen. Patients in these 2 studies received an initial dose of  
417 1.5 mg/m<sup>2</sup> given by intravenous infusion over 30 minutes for 5 consecutive days, starting on day  
418 1 of a 21-day course.

419 One study was a randomized trial of 112 patients treated with HYCAMTIN  
420 (1.5 mg/m<sup>2</sup>/day × 5 days starting on day 1 of a 21-day course) and 114 patients treated with  
421 paclitaxel (175 mg/m<sup>2</sup> over 3 hours on day 1 of a 21-day course). All patients had recurrent  
422 ovarian cancer after a platinum-containing regimen or had not responded to at least 1 prior  
423 platinum-containing regimen. Patients who did not respond to the study therapy, or who  
424 progressed, could be given the alternative treatment.

425 Response rates, response duration, and time to progression are shown in Table 7.

426

427 **Table 7. 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	13 to 28%	8 to 20%
( <i>P</i> -value)	(0.20)	
Response duration <sup>a</sup> (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)	0.78	
( <i>P</i> -value)	(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)	0.76	
( <i>P</i> -value)	(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)	0.97	
( <i>P</i> -value)	(0.87)	

428 <sup>a</sup> The calculation for duration of response was based on the interval between first response and  
429 time to progression.

430

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

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

437 HYCAMTIN was active in ovarian cancer patients who had developed resistance to  
438 platinum-containing therapy, defined as tumor progression while on, or tumor relapse within  
439 6 months after completion of, a platinum-containing regimen. One complete and 6 partial  
440 responses were seen in 60 patients, for a response rate of 12%. In the same study, there were no  
441 complete responders and 4 partial responders on the paclitaxel arm, for a response rate of 7%.

442 HYCAMTIN was also studied in an open-label, non-comparative trial in 111 patients  
443 with recurrent ovarian cancer after treatment with a platinum-containing regimen, or who had not  
444 responded to 1 prior platinum-containing regimen. The response rate was 14% (95% CI = 7% to  
445 20%). The median duration of response was 22 weeks (range 4.6 to 41.9 weeks). The time to  
446 progression was 11.3 weeks (range 0.7 to 72.1 weeks). The median survival was 67.9 weeks  
447 (range 1.4 to 112.9 weeks).

#### 448 **14.2 Small Cell Lung Cancer**

449 HYCAMTIN was studied in 426 patients with recurrent or progressive small cell lung  
450 cancer in 1 randomized, comparative study and in 3 single-arm studies.

451 Randomized Comparative Study: In a randomized, comparative, Phase 3 trial,  
452 107 patients were treated with HYCAMTIN (1.5 mg/m<sup>2</sup>/day × 5 days starting on day 1 of a  
453 21-day course) and 104 patients were treated with CAV (1,000 mg/m<sup>2</sup> cyclophosphamide,  
454 45 mg/m<sup>2</sup> doxorubicin, 2 mg vincristine administered sequentially on day 1 of a 21-day course).  
455 All patients were considered sensitive to first-line chemotherapy (responders who then  
456 subsequently progressed ≥60 days after completion of first-line therapy). A total of 77% of  
457 patients treated with HYCAMTIN and 79% of patients treated with CAV received  
458 platinum/etoposide with or without other agents as first-line chemotherapy.

459 Response rates, response duration, time to progression, and survival are shown in Table  
460 8.

461

462 **Table 8. Efficacy of HYCAMTIN Versus CAV (cyclophosphamide-doxorubicin-vincristine)**  
463 **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 <sup>a</sup> (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)	

464 <sup>a</sup> The calculation for duration of response was based on the interval between first response and  
465 time to progression.  
466

467 The time to response was similar in both arms: HYCAMTIN median of 6 weeks (range  
468 2.4 to 15.7) versus CAV median 6 weeks (range 5.1 to 18.1).

469 Changes on a disease-related symptom scale in patients who received HYCAMTIN or  
470 who received CAV are presented in Table 9. It should be noted that not all patients had all  
471 symptoms, nor did all patients respond to all questions. Each symptom was rated on a 4-category  
472 scale with an improvement defined as a change in 1 category from baseline sustained over 2  
473 courses. Limitations in interpretation of the rating scale and responses preclude formal statistical  
474 analysis.  
475

476 **Table 9. Percentage of Patients With Symptom Improvement<sup>a</sup>: HYCAMTIN Versus CAV**  
477 **in Patients With Small Cell Lung Cancer**

Symptom	HYCAMTIN (n = 107)		CAV (n = 104)	
	n <sup>b</sup>	(%)	n <sup>b</sup>	(%)
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)

478 <sup>a</sup> Defined as improvement sustained over at least 2 courses compared to baseline.

479 <sup>b</sup> Number of patients with baseline and at least 1 post-baseline assessment.

480

481 **Single-Arm Studies:** HYCAMTIN was also studied in 3 open-label, non-comparative  
482 trials in a total of 319 patients with recurrent or progressive small cell lung cancer after treatment  
483 with first-line chemotherapy. In all 3 studies, patients were stratified as either sensitive  
484 (responders who then subsequently progressed  $\geq 90$  days after completion of first-line therapy) or  
485 refractory (no response to first-line chemotherapy or who responded to first-line therapy and then  
486 progressed within 90 days of completing first-line therapy). Response rates ranged from 11% to  
487 31% for sensitive patients and 2% to 7% for refractory patients. Median time to progression and  
488 median survival were similar in all 3 studies and the comparative study.

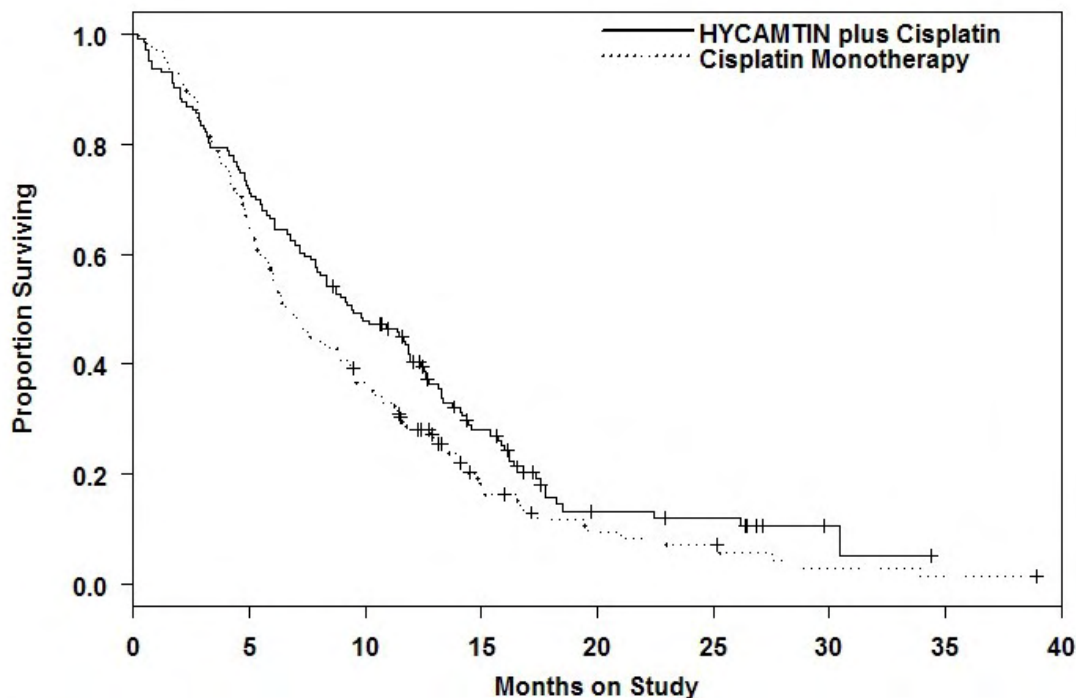
489 **14.3 Cervical Cancer**

490 In a comparative trial, 147 eligible women were randomized to HYCAMTIN  
491 (0.75 mg/m<sup>2</sup>/day IV over 30 minutes  $\times$  3 consecutive days starting on day 1 of a 21-day course)  
492 plus cisplatin (50 mg/m<sup>2</sup> on day 1) and 146 eligible women were randomized to cisplatin  
493 (50 mg/m<sup>2</sup> IV on day 1 of a 21-day course). All patients had histologically confirmed Stage IV-  
494 B, recurrent, or persistent carcinoma of the cervix considered not amenable to curative treatment  
495 with surgery and/or radiation. Fifty-six percent (56%) of patients treated with HYCAMTIN plus  
496 cisplatin and 56% of patients treated with cisplatin had received prior cisplatin with or without  
497 other agents as first-line chemotherapy.

498 Median survival of eligible patients receiving HYCAMTIN plus cisplatin was 9.4 months  
499 (95% CI: 7.9 to 11.9) compared to 6.5 months (95% CI: 5.8 to 8.8) among patients randomized  
500 to cisplatin alone with a log rank *P*-value of 0.033 (significance level was 0.044 after adjusting  
501 for the interim analysis). The unadjusted hazard ratio for overall survival was 0.76 (95% CI: 0.59  
502 to 0.98).

503

504 **Figure 1. Overall Survival Curves Comparing HYCAMTIN plus Cisplatin versus Cisplatin**  
 505 **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

506

507 **15 REFERENCES**

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517 **16 HOW SUPPLIED/STORAGE AND HANDLING**

518 HYCAMTIN for Injection is supplied in 4-mg (free base) single-dose vials.  
 519 NDC 0007-4201-01 (package of 1)  
 520 NDC 0007-4201-05 (package of 5)

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

523   **17    PATIENT COUNSELING INFORMATION**

524   **17.1   Bone Marrow Suppression**

525           Inform patients that HYCAMTIN decreases blood cell counts such as white blood cells,  
526 platelets, and red blood cells. Patients who develop fever, other signs of infection (e.g., chills,  
527 cough, or burning pain on urination), or bleeding while on therapy should notify their physician  
528 promptly. Inform patients that frequent blood tests will be performed while taking HYCAMTIN  
529 to monitor for the occurrence of bone marrow suppression.

530   **17.2   Pregnancy and Breastfeeding**

531           Advise patients to use effective contraceptive measures to prevent pregnancy and to  
532 avoid breastfeeding during treatment with HYCAMTIN.

533   **17.3   Asthenia and Fatigue**

534           Inform patients that HYCAMTIN may cause asthenia or fatigue. If these symptoms  
535 occur, caution should be observed when driving or operating machinery.

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537   HYCAMTIN is a registered trademark of GlaxoSmithKline.

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541   GlaxoSmithKline

542   Research Triangle Park, NC 27709

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