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^3. 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)

RECENT MAJOR CHANGES

Dosage and Administration (2) 02/2014

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: 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day one of a 21-day course. (2.1)
- Cervical cancer: 0.75 mg/m^2 by intravenous infusion over 30 minutes on days 1, 2, and 3 followed by cisplatin 50 mg/m^2 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.

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: 02/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BONE MARROW SUPPRESSION

Do not give HYCAMTIN® to patients with baseline neutrophil counts less than 1,500 cells/mm^3. 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 counts frequently on all patients receiving HYCAMTIN *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

HYCAMTIN is indicated for the treatment of:

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

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

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

2 DOSAGE AND ADMINISTRATION

Verify dose using body surface area prior to dispensing. Recommended dosage should generally not exceed 4 mg intravenously *[see Overdosage (10)]*.

Prior to administration of the first course of HYCAMTIN, patients must have a baseline neutrophil count of >1,500 cells/mm^3 and a platelet count of >100,000 cells/mm^3.

2.1 Ovarian Cancer and Small Cell Lung Cancer

Recommended Dosage:

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

Dosage Modification Guidelines:

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

2.2 Cervical Cancer

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

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

- In the event of severe febrile neutropenia (defined as <1,000 cells/mm^3 with temperature of 38.0°C or 100.4°F), reduce the dose of HYCAMTIN to 0.60 mg/m^2 for subsequent courses.
- Alternatively, in the event of severe febrile neutropenia, administer G-CSF following the subsequent course (before resorting to dose reduction) starting from day 4 of the course (24 hours after completion of administration of HYCAMTIN).
- If febrile neutropenia occurs despite the use of G-CSF, reduce the dose of HYCAMTIN to 0.45 mg/m^2 for subsequent courses.
- In the event the platelet count falls below 25,000 cells/mm^3, reduce doses to 0.60 mg/m^2 for subsequent courses.

2.3 Dosage Adjustment in Specific Populations

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

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

2.4 Instructions for Handling, Preparation, and Intravenous Administration

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

Use procedures for proper handling and disposal of anticancer drugs. Several guidelines on this subject have been published.[1-4]

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

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

Neutropenia:

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

Thrombocytopenia:

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

Anemia:

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

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

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

5.2 Neutropenic Colitis

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

5.3 Interstitial Lung Disease

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

5.4 Pregnancy

Pregnancy Category D.

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

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

5.5 Inadvertent Extravasation

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

Table 2. Non-hematologic Adverse Reactions Experienced by ≥15% of Ovarian Cancer and 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
Infections and infestations			
Sepsis or pyrexia/infection with neutropenia [a]	43	NR	23
Metabolism and nutrition disorders			
Anorexia	19	2	<1
Nervous system disorders			
Headache	18	1	<1
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	22	5	3
Coughing	15	1	0
Gastrointestinal disorders			
Nausea	64	7	1
Vomiting	45	4	1
Diarrhea	32	3	1
Constipation	29	2	1
Abdominal pain	22	2	2
Stomatitis	18	1	<1
Skin and subcutaneous tissue disorders			
Alopecia	49	NA	NA
Rash[b]	16	1	0
General disorders and administrative site conditions			
Fatigue	29	5	0
Pyrexia	28	1	<1
Pain[c]	23	2	1
Asthenia	25	4	2

NA = Not applicable.

NR = Not reported separately.

[a] Does not include Grade 1 sepsis or pyrexia.

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

[c] Pain includes body pain, back pain, and skeletal pain.

Nervous System Disorders: Paresthesia occurred in 7% of patients but was generally Grade 1.

Hepatobiliary Disorders: Grade 1 transient elevations in hepatic enzymes occurred in

8% of patients. Greater elevations, Grade 3/4, occurred in 4%. Grade 3/4 elevated bilirubin occurred in <2% of patients.

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

Table 3. Adverse Reactions Experienced by ≥5% of Ovarian Cancer Patients Randomized to Receive HYCAMTIN or Paclitaxel

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

[a] Death related to sepsis occurred in 2% of patients receiving HYCAMTIN and 0% of patients receiving paclitaxel.

[b] Pain includes body pain, skeletal pain, and back pain.

Table 4 shows the Grade 3/4 hematologic and major non-hematologic adverse reactions in the topotecan/CAV (cyclophosphamide-doxorubicin-vincristine) comparator trial in small cell lung cancer.

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

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

[a] Death related to sepsis occurred in 3% of patients receiving HYCAMTIN, and 1% of patients receiving CAV.

[b] Pain includes body pain, skeletal pain, and back pain.

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

Table 5. Hematologic Adverse Reactions in Patients with Cervical Cancer Treated with HYCAMTIN Plus Cisplatin or Cisplatin Monotherapy[a]

Hematologic Adverse Reaction	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%)

[a] Includes patients who were eligible and treated.

Table 6. Non-hematologic Adverse Reactions Experienced by ≥5% of Patients with Cervical Cancer Treated with HYCAMTIN Plus Cisplatin or Cisplatin Monotherapy[a]

	HYCAMTIN Plus Cisplatin (n = 140)			Cisplatin (n = 144)		
Adverse Reaction	**All Grades[b]**	**Grade 3**	**Grade 4**	**All Grades[b]**	**Grade 3**	**Grade 4**
General disorders and administrative site conditions						
Constitutional[c]	96 (69%)	11 (8%)	0	89 (62%)	17 (12%)	0
Pain[d]	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

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

[a] Includes patients who were eligible and treated.

[b] Grades 1 through 4 only. There were 3 patients who experienced Grade 5 deaths with investigator-designated attribution. One was a Grade 5 hemorrhage in which the drug-related thrombocytopenia aggravated the event. A second patient experienced bowel obstruction, cardiac arrest, pleural effusion and respiratory failure which were not treatment related but probably aggravated by treatment. A third

patient experienced a pulmonary embolism and adult respiratory distress syndrome; the latter was indirectly treatment-related.

[c] Constitutional includes fatigue (lethargy, malaise, asthenia), fever (in the absence of neutropenia), rigors, chills, sweating, and weight gain or loss.

[d] Pain includes abdominal pain or cramping, arthralgia, bone pain, chest pain (non-cardiac and non-pleuritic), dysmenorrhea, dyspareunia, earache, headache, hepatic pain, myalgia, neuropathic pain, pain due to radiation, pelvic pain, pleuritic pain, rectal or perirectal pain, and tumor pain.

6.2 Postmarketing Experience

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

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

Immune System Disorders: Allergic manifestations, anaphylactoid reactions.

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

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

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

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

7 DRUG INTERACTIONS

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

Platinum and Other Cytotoxic Agents: Myelosuppression was more severe when HYCAMTIN, at a dose of 1.25 mg/m^2/day for 5 days, was given in combination with cisplatin at a dose of 50 mg/m^2 in Phase 1 trials. In one trial, 1 of 3 patients had severe neutropenia for 12 days and a second patient died with neutropenic sepsis.

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

For information on the pharmacokinetics, efficacy, safety, and dosing of HYCAMTIN at a dose of 0.75 mg/m^2/day on days 1, 2, and 3 in combination with cisplatin 50 mg/m^2 on day 1 for cervical cancer, *see Dosage and Administration (2), Adverse Reactions (6), Clinical Pharmacology (12.3), and Clinical Studies (14).*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 879 patients with metastatic ovarian cancer or small cell lung cancer in clinical trials of HYCAMTIN, 32% (n = 281) were 65 years of age and older, while 3.8% (n = 33) were 75 years of age and older. Of the 140 patients with Stage IV-B, relapsed, or refractory cervical cancer in clinical trials of HYCAMTIN who received HYCAMTIN plus cisplatin in the randomized clinical trial, 6% (n = 9) were 65 years of age and older, while 3% (n = 4) were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients, and other reported clinical experience has not

identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

There were no apparent differences in the pharmacokinetics of topotecan in elderly patients, once the age-related decrease in renal function was considered *[see Clinical Pharmacology (12.3)]*.

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

8.6 Renal Impairment

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

10 OVERDOSAGE

Overdoses (up to 10-fold of the prescribed dose) occurred in patients treated with intravenous topotecan. The primary complication of overdosage is bone marrow suppression. The observed signs and symptoms of overdose are consistent with the known adverse reactions associated with HYCAMTIN for intravenous use *[see Adverse Reactions (6.1, 6.2)]*. In addition, elevated hepatic enzymes and mucositis have been reported following overdose. One patient received a single dose of 40 mg/m^2 of intravenous topotecan and developed gastrointestinal toxicity, skin toxicity, and myelosuppresion leading to septic shock. Another patient received a single dose of 35 mg/m^2 and experienced severe, reversible neutropenia.

There is no known antidote for overdosage with HYCAMTIN. If an overdose is suspected, monitor the patient for bone marrow suppression and institute supportive-care measures (such as prophylactic G-CSF and antibiotic therapy) as appropriate.

11 DESCRIPTION

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

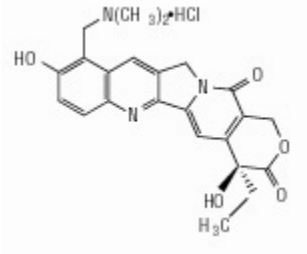
HYCAMTIN for Injection is supplied as a sterile, lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is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

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

The chemical name for topotecan hydrochloride is (*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione

monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5$•HCl and a molecular weight of 457.9.

Topotecan hydrochloride has the following structural formula:



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

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

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

In a mass balance/excretion trial in 4 patients with solid tumors, the overall recovery of total topotecan and its N-desmethyl metabolite in urine and feces over 9 days averaged 73.4% ± 2.3% of the administered IV dose. Mean values of 50.8% ± 2.9% as total topotecan and

3.1% ± 1.0% as N-desmethyl topotecan were excreted in the urine following IV administration. Fecal elimination of total topotecan accounted for 17.9% ± 3.6% while fecal elimination of N-desmethyl topotecan was 1.7% ± 0.6%. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine. These metabolites, topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide, were less than 2% of the administered dose.

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

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

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

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

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

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

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

Cisplatin: Administration of cisplatin (60 or 75 mg/m^2 on day 1) before topotecan (0.75 mg/m^2/day on days 1 to 5) in 9 patients with ovarian cancer had no significant effect on the C_{max} and AUC of total topotecan.

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

cisplatin on day 1 before topotecan 0.75 mg/m^2 IV daily on days 1 to 5.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

14.1 Ovarian Cancer

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

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

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

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%
(*P*-value)	(0.20)	
Response duration[a] (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	
(*P*-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	
(*P*-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	
(*P*-value)	(0.87)	

[a] The calculation for duration of response was based on the interval between first response and time to progression.

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

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

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

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

14.2 Small Cell Lung Cancer

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

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

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

Table 8. Efficacy of HYCAMTIN Versus CAV (cyclophosphamide-doxorubicin-vincristine) 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[a] (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)	1.42 (0.73 to 2.76)	
(*P*-value)	(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)	0.92 (0.69 to 1.22)	
(*P*-value)	(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)	1.04 (0.78 to 1.39)	
(*P*-value)	(0.80)	

[a] The calculation for duration of response was based on the interval between first response and time to progression.

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

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

Table 9. Percentage of Patients With Symptom Improvement[a]: HYCAMTIN Versus CAV in Patients With Small Cell Lung Cancer

Symptom	HYCAMTIN (n = 107)		CAV (n = 104)	
	n[b]	(%)	n[b]	(%)
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)

[a] Defined as improvement sustained over at least 2 courses compared with baseline.

[b] Number of patients with baseline and at least 1 post-baseline assessment.

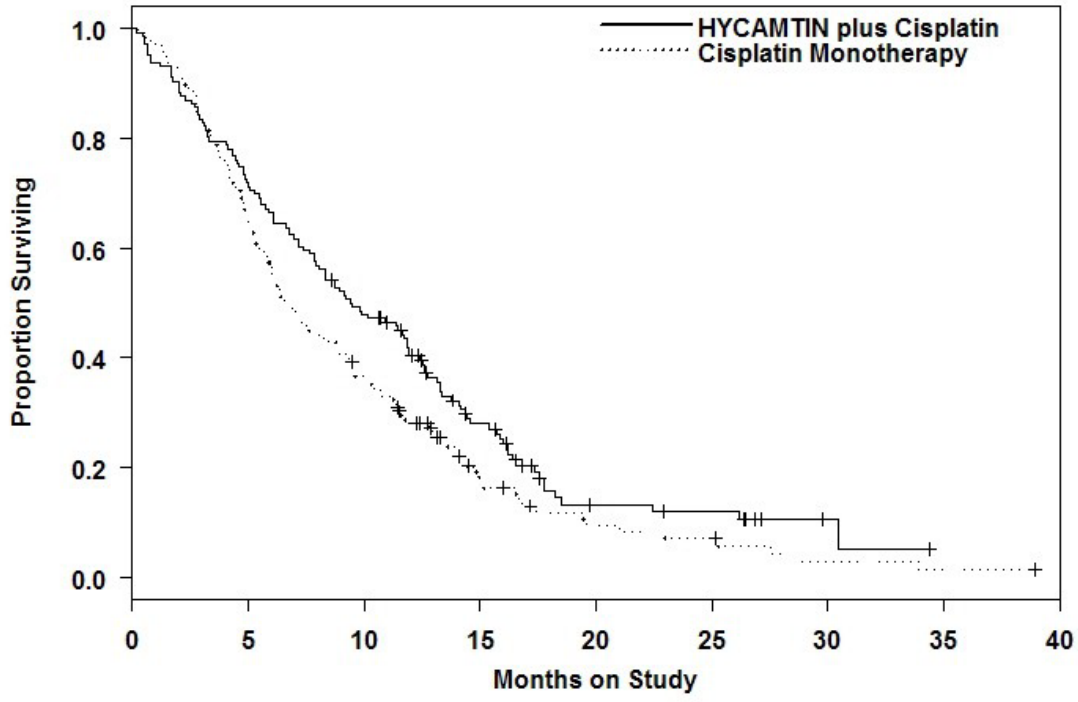
Single-Arm Trials: HYCAMTIN was also studied in 3 open-label, non-comparative trials in a total of 319 patients with recurrent or progressive small cell lung cancer after treatment with first-line chemotherapy. In all 3 trials, patients were stratified as either sensitive (responders who then subsequently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

14.3 Cervical Cancer

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

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

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



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3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling Hazardous Drugs. *Am J Health-Syst Pharm*. 2006;63:1172-1193.
4. Polovich M, White JM, Kelleher LO (eds.) 2005. Chemotherapy and Biotherapy Guidelines and Recommendations for Practice. (2nd ed) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC 0007-4201-01 (package of 1)

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

17 PATIENT COUNSELING INFORMATION

17.1 Bone Marrow Suppression

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

17.2 Pregnancy and Breastfeeding

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

17.3 Asthenia and Fatigue

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

HYCAMTIN is a registered trademark of the GlaxoSmithKline group of companies.

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