HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TOPOTECAN INJECTION safely and effectively. See full prescribing information for TOPOTECAN INJECTION.

TOPOTECAN INJECTION, for intravenous use
Initial U.S. Approval: 1996

WARNING: BONE MARROW SUPPRESSION
See full prescribing information for complete boxed warning.
Do not initiate topotecan treatment in patients with bone marrow suppression (e.g., neutrophil counts less than 1,500 cells/mm^3). Monitor peripheral blood counts frequently during treatment. Reduce or withhold topotecan dosing as recommended [*see Dosage and Administration (*2.1, 2.2*), Warnings and Precautions (*5.1*)*].

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

Topotecan Injection is a topoisomerase inhibitor indicated:

- for the treatment of small cell lung cancers in patients with chemotherapy-sensitive disease after failure of first-line chemotherapy. (1.1)
- in combination therapy with cisplatin, for the treatment of stage IVB, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery or radiation therapy. (1.2)

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

Small cell lung cancer: Topotecan Injection 1.5 mg/m^2 by intravenous infusion over 30 minutes daily on days 1 to 5 of each 21-day cycle. (2.1)

Cervical cancer: Topotecan Injection 0.75 mg/m^2 by intravenous infusion over 30 minutes daily on days 1, 2, and 3 of each 21-day cycle. (2.2)

See Dosage Modification Guidelines for patients with neutropenia, thrombocytopenia, or renal impairment. (2.1, 2.2)

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

Single-use vial containing 4 mg of topotecan free base as a 4 mg/4 mL (1 mg/mL) solution. (3)

----------CONTRAINDICATIONS----------

History of severe hypersensitivity reactions (e.g., anaphylactoid reactions) to topotecan. (4)

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

- Bone marrow suppression: Administer topotecan only to patients with adequate bone marrow reserves. Monitor peripheral blood counts and adjust the dose if needed. (5.1)
- Neutropenia colitis, in some cases fatal, can occur. (5.2)
- Interstitial lung disease: Topotecan can cause interstitial lung disease. Monitor patients for symptoms and discontinue topotecan if the diagnosis is confirmed. (5.3)
- Embryofetal Toxicity: Topotecan can cause fetal harm. Advise women of potential risk to a fetus. (5.4, 8.1)

----------ADVERSE REACTIONS----------

In patients with small cell lung cancer or other malignancies, the most common (≥ 25%) adverse reactions are neutropenia (97%), anemia (89%), thrombocytopenia (69%), nausea (64%), alopecia (49%), vomiting (45%), sepsis or pyrexia/infection with neutropenia (43%), diarrhea (32%), constipation (29%), fatigue (29%), and pyrexia (28%). (6.1)

In patients with cervical cancer, the most common adverse reactions (≥ 25%) are: anemia (94%), neutropenia (89%), thrombocytopenia (74%), pain (59%), nausea (55%), dermatologic (48%), vomiting (40%), neurologic/non-neuropathy (35%), and infection/febrile neutropenia (28%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TEVA USA, PHARMACOVIGILANCE at 1-866-832-8537 or drug.safety@tevapharm.com; or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Nursing Mothers: Discontinue nursing when receiving topotecan. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2012

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 initiate Topotecan Injection treatment in patients with bone marrow suppression (e.g., neutrophil counts less than 1,500 cells/mm^3). Monitor peripheral blood counts frequently during treatment. Reduce or withhold Topotecan Injection dosing as recommended [*see Dosage and Administration (2.1, 2.2) and Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Small Cell Lung Cancer

Topotecan Injection is indicated for the treatment of chemotherapy-sensitive small cell lung cancer (SCLC) after failure of first-line chemotherapy. Chemotherapy-sensitive SCLC is defined as responding to first-line chemotherapy but subsequently progressing at least 60 days after chemotherapy.

1.2 Cervical Cancer

Topotecan Injection, in combination with cisplatin, is indicated for the treatment of stage IVB, recurrent or persistent carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Small Cell Lung Cancer

Recommended Dosage: The recommended dose of Topotecan Injection is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily on days 1 to 5 of each 21-day cycle until disease progression.

Dosage Modification Guidelines: Recommended dose modifications in patients with bone marrow suppression or renal impairment are provided in the table below [*see Warnings and Precautions (5.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Table 1. Recommended Dose Modifications in Patients with Small Cell Lung Cancer

Adverse Reaction or Laboratory Values	Recommended Dose Modification
On Day 1 of first cycle --neutrophil count of ≤ 1,500 cells/mm^3 **or** --platelet count ≤ 100,000 cells/mm^3 **or** --serum creatinine > 1.5 mg/dL	Delay initiation of Topotecan Injection until hematologic or renal recovery
On Day 1 of subsequent cycles (cycle 2 and beyond) --neutrophil count of ≤ 1,000 cells/mm^3 **or** --platelet count ≤ 100,000 cells/mm^3 **or** --hemoglobin < 9.0 gm/dL **or** --serum creatinine > 1.5 mg/dL	Delay next cycle of Topotecan Injection until hematologic or renal recovery
For neutropenia < 500 cells/mm^3 in preceding cycle	Permanently reduce Topotecan Injection dose to 1.25 mg/m^2 or administer prophylactic granulocyte colony-stimulating factor during subsequent cycles.
For platelets < 25,000 cells/mm^3 in preceding cycle	Permanently reduce Topotecan Injection dose to 1.25 mg/m^2
For creatinine clearance 20-39 mL/min	Reduce the Topotecan Injection dose to 0.75 mg/m^2

2.2 Cervical Cancer

Recommended Dosage: The recommended dose of Topotecan Injection is 0.75 mg/m^2 by intravenous infusion over 30 minutes daily on days 1, 2, and 3 of each 21-day cycle. Administer cisplatin 50 mg/m^2 by intravenous infusion on day 1 of each 21-day cycles.

Dosage Modification Guidelines: Recommended dose modifications in patients with bone marrow suppression or renal impairment are provided in the table below [*see Warnings and Precautions (*5.1*), Use in Specific Populations (*8.6*) and Clinical Pharmacology (*12.3*)*]. See manufacturer's prescribing information for cisplatin administration and hydration guidelines and for cisplatin dosage adjustment in the event of hematologic toxicity.

Table 2. Recommended Dose Modifications in Patients with Cervical Cancer

Adverse Reaction or Laboratory Values	**Recommended Dose Modification**
On Day 1 of first cycle --neutrophil count of ≤ 1,500 cells/mm^3 **or** --platelet count ≤ 100,000 cells/mm^3 **or** --serum creatinine > 1.5 mg/dL	Delay initiation of Topotecan Injection until hematologic or renal recovery
On Day 1 of subsequent cycles (cycle 2 and beyond) --neutrophil count of ≤ 1,000 cells/mm^3 **or** --platelet count ≤ 100,000 cells/mm^3 **or** --hemoglobin < 9.0 gm/dL or --serum creatinine > 1.5 mg/dL	Delay next cycle of Topotecan Injection until hematologic or renal recovery
For the **first** occurrence of febrile neutropenia [< 1,000 neutrophils/mm^3 with fever ≥ 38.0°C (≥ 100.4°F) in preceding cycle	Permanently reduce the daily Topotecan Injection dose to 0.60 mg/m^2 or administer prophylactic granulocyte colony-stimulating factor (G-CSF) during subsequent cycles.
For **re-occurrence** of febrile neutropenia [< 1,000 neutrophils/mm^3 with fever ≥ 38.0°C (≥ 100.4°F) in preceding cycle despite use of G-CSF	Permanently reduce the daily Topotecan Injection dose to 0.45 mg/m^2
For platelet nadir < 25,000 cells/mm^3 in preceding cycle	Permanently reduce the daily Topotecan Injection dose to 0.60 mg/m^2
For serum creatinine > 1.5 mg/dL in subsequent cycles	Permanently discontinue cisplatin and Topotecan Injection

2.3 Instructions for Handling, and Preparation for Intravenous Administration

Use procedures for proper handling and disposal of anticancer drugs [*see References (*15*)*].

Dilute Topotecan Injection in either 0.9% Sodium Chloride USP or 5% Dextrose USP. Store diluted Topotecan Injection solutions at approximately 20°C to 25°C (68°F to 77°F) for no more than 4 hours or under refrigerated (2°C to 8°C) conditions for no more than 12 hours.

3 DOSAGE FORMS AND STRENGTHS

Topotecan Injection is supplied as single-use vial containing 4 mg/4 mL as a 1 mg/mL solution. Each 1 mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base.

4 CONTRAINDICATIONS

Topotecan Injection is contraindicated in patients who have a history of severe hypersensitivity reactions (e.g., anaphylactoid reactions) to topotecan.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

Severe and life-threatening bone marrow suppression, resulting in neutropenia, thrombocytopenia, and anemia is the dose-limiting toxicity of topotecan, observed in approximately 50%-75% of patients across clinical trials. Pancytopenia has been reported. In clinical trials, neutropenia resulting in death due to infection or sepsis ranged from 1-4% across clinical studies.

Neutropenia: Small cell lung cancer and other malignancies 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%. Cervical cancer experience: Grade 3 and grade 4 neutropenia affected 26% and 48% of patients, respectively.

Thrombocytopenia: Small cell lung cancer and other malignancies 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: Small cell lung cancer and other malignancies 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.

Do not initiate topotecan treatment in patients with a neutrophil count of less than 1,500 cells/mm^3 or a platelet count less than 100,000/mm^3. Monitor peripheral blood counts frequently during treatment with topotecan. Delay subsequent cycles of topotecan 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 [*see Dosage and Administration (*2.1, 2.2*)*].

5.2 Neutropenic Colitis

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

5.3 Interstitial Lung Disease

Topotecan treatment can result in interstitial lung disease (ILD), some cases of ILD have been fatal based on post-marketing reports of serious adverse reactions. Underlying risk factors for development of ILD with topotecan 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 topotecan if a new diagnosis of ILD is confirmed.

5.4 Embryofetal Toxicity

Topotecan 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 topotecan in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving topotecan, the patient should be apprised of the potential hazard to the fetus [*see Use in Specific Populations (*8.1*)*].

5.5 Extravasation

Inadvertent extravasation of topotecan can result in severe injury to local tissues based on post-marketing reports of serious adverse reactions.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Bone Marrow Suppression [*see Boxed Warnings and Warnings and Precautions (*5.1*)*]
- Neutropenic Colitis [*see Warnings and Precautions (*5.2*)*]
- Interstitial Lung Disease [*see Warnings and Precautions (*5.3*)*]
- Extravasation [*see Warnings and Precautions (*5.5*)*]

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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect the combined experience of 426 patients with small cell lung cancer and 453 patients with other malignancies who received topotecan. **Table 3** lists hematologic adverse reactions and **Table 4** lists non-hematologic adverse reactions occurring in at least 15% of patients.

Table 3. Hematologic Adverse Reactions in ≥ 15% Small Cell Lung Cancer and Other Malignancies Patients Receiving Topotecan

Hematologic Adverse Reaction	Percentage of Patients with Adverse Reaction (n = 879)
Neutropenia	
< 1,500 neutrophils/ mm^3	97%
< 500 neutrophils/ mm^3	78%
Thrombocytopenia	
< 75,000 platelets/ mm^3	69%
< 25,000 platelets/ mm^3	27%
Anemia	
hemoglobin < 10 g/dL	89%
hemoglobin < 8 g/dL	37%

Table 4. Non-Hematologic Adverse Reactions by ≥ 15% of Small Cell Lung Cancer and Other Malignancies Patients Receiving Topotecan

Non-hematologic Adverse Reaction	Percentage of Patients with Adverse Reaction (n = 879)	
	All Grades	Grade 3-4
Infections and infestations		
Sepsis or pyrexia/infection with neutropenia	43%[a]	23%
Metabolism and nutrition disorders		
Anorexia	19%	3%
Nervous system disorders		
Headache	18%	2%
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	22%	8%
Coughing	15%	1%
Gastrointestinal disorders		
Nausea	64%	8%
Vomiting	45%	5%
Diarrhea	32%	4%
Constipation	29%	3%
Abdominal pain	22%	4%
Stomatitis	18%	3%
Skin and subcutaneous tissue disorders		
Alopecia	49%	NA
Rash[b]	16%	1%
General disorders and administrative site conditions		
Fatigue	29%	5%
Pyrexia	28%	2%
Pain[c]	23%	3%
Asthenia	25%	6%

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.

NA = Not applicable

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. Grade 3 or 4 elevation in hepatic enzymes occurred in 4%. Grade 3 or 4 hyperbilirubinemia occurred in < 2% of patients.

Table 5 shows the per-patient incidence of Grades 3 and 4 hematologic and non-hematologic adverse reactions in a randomized trial comparing topotecan to CAV combination chemotherapy in patients with small cell lung cancer.

Table 5. Selected Common (≥ 5%) Grade 3-4 Adverse Reactions in Patients with Small Cell Lung Cancer Randomized to Receive Topotecan or Cyclophosphamide, Doxorubicin, Vincristine (CAV) Chemotherapy

Adverse Reaction	Percentage of Patients with Adverse Reaction Topotecan (n = 107)	Percentage of Patients with Adverse Reaction CAV (n = 104)
Hematologic		
Grade 4 neutropenia (< 500 neutrophils/mm^3)	70%	72%
Grade 3 or 4 anemia (hemoglobin < 8 g/dL)	42%	20%
Grade 4 thrombocytopenia (< 25,000 platelets/mm^3)	29%	5%
Pyrexia with Grade 4 neutropenia	28%	26%
Non-hematologic		
Infections and infestations		
Documented sepsis[a]	5%	5%
Respiratory, thoracic, and mediastinal disorders		
Pneumonia	8%	6%
Gastrointestinal disorders		
Abdominal pain	6%	4%
Nausea	8%	6%
General disorders and administrative site conditions		
Asthenia	9%	7%

a) Include septic deaths in 3% of patients receiving topotecan and 1% of patients receiving CAV.

Cervical Cancer: In the comparative trial with topotecan plus cisplatin versus cisplatin in patients with cervical cancer, the most common dose-limiting adverse reaction was myelosuppression. **Table 6** shows the hematologic adverse reactions and **Table 7** shows the non-hematologic adverse reactions in patients with cervical cancer.

Table 6. Hematologic Adverse Reactions in Patients With Cervical Cancer

Hematologic Adverse Reaction	Percentage of Patients with Adverse Reaction Topotecan Plus Cisplatin (n = 140)	Percentage of Patients with Adverse Reaction Cisplatin (n = 144)
Anemia		
All grades (hemoglobin < 12 g/dL)	94%	90%
Grade 3 (hemoglobin < 8 to 6.5 g/dL)	34%	19%
Grade 4 (hemoglobin < 6.5 g/dL)	6%	3%
Neutropenia		
All grades (< 2,000 neutrophils/ mm^3)	89%	19%
Grade 3 (< 1,000 to 500 neutrophils/ mm^3)	26%	1%
Grade 4 (< 500 neutrophils/ mm^3)	48%	1%
Thrombocytopenia		
All grades (< 130,000 platelets/ mm^3)	74%	15%
Grade 3 (< 50,000 to 10,000 platelets/ mm^3)	26%	3%
Grade 4 (< 10,000 platelets/ mm^3)	7%	0

Table 7. Selected Common (≥ 5%) Non-Hematologic Adverse Reactions in Patients With Cervical Cancer

Adverse Reactions	Percentage of Patients with Adverse Reaction Topotecan Plus Cisplatin (n = 140)		Percentage of Patients with Adverse Reaction Cisplatin (n = 144)	
	Grades 1-4[a,b]	Grades 3-4[a]	Grades 1-4[a,b]	Grades 3-4[a]
General disorders and administrative site conditions				
Constitutional[c]	69%	8%	62%	12%
Pain[d]	59%	23%	50%	16%
Gastrointestinal disorders				
Vomiting	40%	15%	37%	9%
Nausea	55%	14%	55%	9%
Stomatitis-pharyngitis	6%	< 1%	0	0
Other	63%	14%	56%	10%
Dermatology	48%	< 1%	20%	0
Metabolic-Laboratory	39%	14%	31%	11%
Genitourinary	36%	12%	34%	10%
Nervous system disorders				
Neuropathy	3%	< 1%	2%	< 1%
Neurologic, non-neuropathy	35%	3%	30%	6%
Infection-febrile neutropenia	28%	19%	18%	8%
Cardiovascular	25%	9%	15%	8%
Hepatic	24%	5%	16%	1%
Pulmonary	17%	3%	16%	5%
Vascular disorders				
Hemorrhage	15%	6%	14%	3%
Musculoskeletal	14%	2%	5%	1%
Allergy-Immunology	6%	2%	3%	< 1%
Endocrine	6%	0	3%	1%

a) NCI CTCAE version 2.0

b) Excludes 3 patients with fatal events due to thrombocytopenia/hemorrhage (n = 1), bowel obstruction, cardiac arrest, pleural effusion and respiratory failure (n = 1), and pulmonary embolism/ adult respiratory distress syndrome (n = 1).

c) "Constitutional" is a composite term that includes fatigue (lethargy, malaise, asthenia), fever (in the absence of neutropenia), rigors, chills, sweating, and weight gain or loss.

d) "Pain" is a composite term that 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

The following reactions have been identified during postmarketing use of topotecan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to topotecan.

Blood and Lymphatic System Disorders: Hemorrhage [*see Warnings and Precautions (*5.1*)*].

Immune System Disorders: Anaphylactoid reactions.

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

7 DRUG INTERACTIONS

There have been no formal studies of drug interactions with topotecan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Topotecan 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 topotecan in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving topotecan, the patient should be apprised of the potential hazard to a fetus.

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 this 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 topotecan, discontinue breastfeeding when women are receiving topotecan.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 879 patients in clinical studies of topotecan, 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 IVB, relapsed, or refractory cervical cancer in clinical studies of topotecan who received topotecan 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.

8.6 Renal Impairment

No dosage adjustment of topotecan is recommended for patients with creatinine clearance (CLcr) of 40 to 60 mL/min. Reduce topotecan dose in patients with CLcr of 20 to 39 mL/min. Insufficient data are available to provide a dosage recommendation in patients with CLcr < 20 mL/min [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

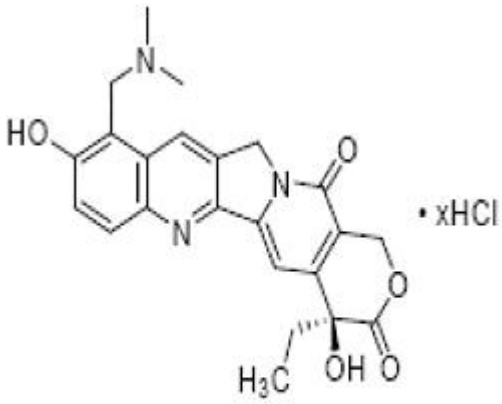
One patient on a single-dose regimen of 17.5 mg/m^2 given on day 1 of a 21 day cycle received a single dose of 35 mg/m^2. This patient experienced severe neutropenia (nadir of 320/mm^3) 14 days later but recovered without incident.

11 DESCRIPTION

Topotecan is a topoisomerase I-inhibitor that is a semi-synthetic derivative of camptothecin.

The chemical name for topotecan free base 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. It has the molecular formula $C_{23}H_{23}N_3O_5$ and a molecular weight of 421.45. The hydrochloride salt of topotecan is freely soluble in water and melts with decomposition at 213°C to 218°C.

As formulated in Topotecan Injection, topotecan hydrochloride has the following structural formula:



Note: x = 1.25

Topotecan Injection is supplied as a sterile, non-pyrogenic, clear, light yellow to greenish solution in single-use vials at a topotecan free base concentration of 4 mg/4 mL (1 mg/mL).

Each mL contains topotecan hydrochloride (equivalent to 1 mg of topotecan free base), 12 mg of mannitol, USP, and 5 mg of tartaric acid, NF. It may also contain hydrochloric acid and sodium hydroxide to adjust the pH. The solution pH ranges from 2.0 to 2.5.

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 multi-exponential 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 study 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: The effect of age on topotecan pharmacokinetics has not been studied.

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

Effect of Renal Impairment: As compared to the patients with creatinine clearance (CLcr) of > 60 mL/min, topotecan plasma clearance was decreased by 33% in patients with CLcr of 40 to 60 mL/min, and by 66% in patients with CLcr of 20 to 39 mL/min. Dosage adjustment is recommended for patients with CLcr of 20 to 39 mL/min [*see Dosage and Administration (2.3) and Use in Specific Populations (8.5)*].

Topotecan 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 topotecan after cisplatin discontinuation in patients with cervical cancer.

Effect of Hepatic Impairment: Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased by 33% as compared to that in patients without hepatic impairment.

Drug Interactions: No formal drug interactions studies have been conducted. *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*.

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 Small Cell Lung Cancer

The safety and efficacy of topotecan were evaluated in 426 patients receiving second-line chemotherapy for recurrent or progressive small cell lung cancer in a single, randomized, open-label, active-controlled trial and in 3 single-arm trials.

Randomized, Active-Comparator Study: The major efficacy trial was a randomized (1:1), open-label, active-controlled trial, that enrolled 211 patients with recurrent or progressive small cell lung cancer; of these, 107 patients were randomized to single-agent topotecan and 104 patients were randomized to cyclophosphamide, doxorubicin, and vincristine (CAV) combination chemotherapy. Topotecan was administered at a dose of 1.5 mg/m^2 daily intravenously on days 1-5 of a 21-day cycle and CAV chemotherapy was administered at 1,000 mg/m^2 cyclophosphamide intavenously, 45 mg/m^2 doxorubicin intravenously, and 2 mg vincristine intravenously on day 1 of a 21-day cycle. 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 in the topotecan arm and 79% of patients in the CAV arm have received platinum and etoposide with or without other agents as first-line chemotherapy.

The major efficacy outcomes are shown in **Table 8**.

Table 8. Efficacy of Topotecan Versus Cyclophosphamide, Doxorubicin, Vincristine (CAV) Chemotherapy in Patients with Chemotherapy-Sensitive Small Cell Lung Cancer

Efficacy Result	**Topotecan (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%)	
Number of responding patients	26	19
Median response duration (weeks)	14.4	15.3
95% Confidence interval	13.1 to 18.0	13.1 to 23.1
Median Time to progression (weeks)	13.3	12.3
95% Confidence interval	11.4 to 16.4	11.0 to 14.1
Hazard ratio (topotecan:CAV)	0.92	
95% Confidence interval	0.69 to 1.22	
p-value	0.55	
Median Survival (weeks)	25.0	24.7
95% Confidence interval	20.6 to 29.6	21.7 to 30.3
Hazard ratio (topotecan:CAV)	1.04	
95% Confidence interval	0.78 to 1.39	
p-value	0.80	

Single-Arm Studies: The clinical activity of topotecan was also studied in three open-label, single-arm trials enrolling a total of 319 patients with recurrent or progressive small cell lung cancer after treatment with first-line chemotherapy. Outcomes were separately evaluated in subgroups defined as chemo-sensitive (patients with objective responses to first-line chemotherapy who progressed ≥ 90 days after completion of first-line therapy) or chemo-refractory (patients with no objective response to first-line chemotherapy or with an objective response to first-line therapy that progressed within 90 days of completing first-line therapy). Response rates ranged from 11% to 31% for chemo-sensitive patients and 2% to 7% for chemotherapy refractory patients.

14.2 Cervical Cancer

The safety and efficacy of topotecan was evaluated in a randomized (1:1), open-label, active-controlled trial of 293 women with histologically-confirmed Stage IVB, recurrent, or persistent carcinoma of the cervix considered not amenable to curative treatment with surgery or radiation. All patients received cisplatin at a dose of 50 mg/m^2 by intravenous infusion on day 1 of each 21-day cycle either alone (n = 146) or in combination with topotecan (n = 147). In the combination arm, topotecan was administered at a dose of 0.75 mg/m^2/day intravenously over 30 minutes on days 1, 2 and 3 of each 21-day cycle. Fifty-six percent (56%) of patients treated with topotecan plus cisplatin and 56% of patients treated with cisplatin had received prior cisplatin with or without other agents as first-line chemotherapy.

Patients randomized to receive topotecan in combination with cisplatin had a statistically significantly longer overall survival [HR 0.76, (95% CI: 0.59 to 0.98), p = 0.044, unadjusted log-rank test}. The median survival in patients receiving topotecan plus cisplatin was 9.4 months (95% CI: 7.9 to 11.9) compared to 6.5 months (95% CI: 5.8 to 8.8) among patients randomized to cisplatin alone.

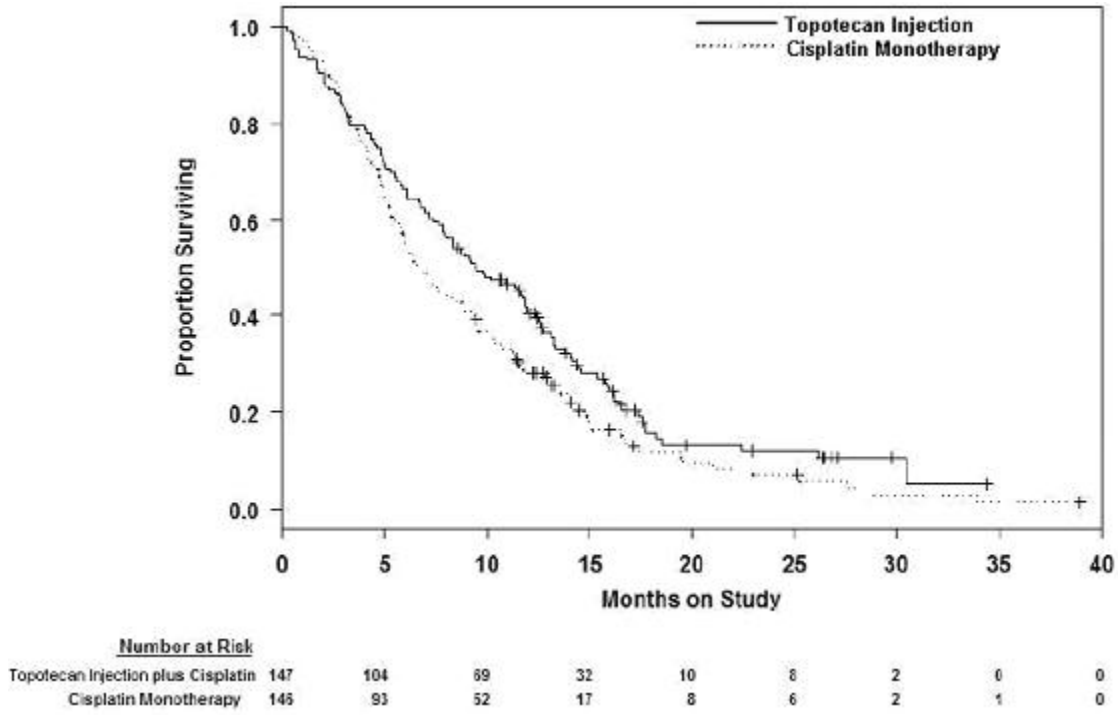


Figure 1. Overall Survival Curves Comparing Topotecan Plus Cisplatin Versus Cisplatin Monotherapy in Cervical Cancer Patients

15 REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
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

Topotecan Injection is supplied as single-use vials. Each vial contains 4 mL of the sterile solution. Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base.

NDC 0703-4714-01 (Package of 1 Single-Use Vial NDC 0703-4714-71)

NDC 0703-4714-02 (Package of 5 Single-Use Vials NDC 0703-4714-71)

Storage

Store the vials protected from light in the original cartons, refrigerated between 2°C and 8°C (36°F and 46°F).

17 PATIENT COUNSELING INFORMATION

- Inform patients that topotecan causes myelosuppression in most patients. Advise patients who develop fever, other signs of infection or bleeding to contact their healthcare provider immediately. Inform patients of the need to perform frequent blood tests to monitor for myelosuppression.
- Advise patients to use effective contraceptive measures to prevent pregnancy. Inform nursing mothers to discontinue nursing during treatment with topotecan.
- Inform patients that topotecan may cause asthenia or fatigue. If these symptoms occur, caution should be observed when driving or operating machinery.

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