

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200582Orig1s000

LABELING

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

Must be diluted before intravenous infusion

Initial U.S. Approval: 1996

WARNING: BONE MARROW SUPPRESSION

See full prescribing information for complete boxed warning.

Do not give topotecan injection to patients with baseline neutrophil counts of less than 1,500 cells/mm³. 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 topotecan injection. (5.1)

INDICATIONS AND USAGE

Topotecan Injection is a topoisomerase inhibitor indicated for the treatment of small cell lung cancer sensitive disease after failure of first-line chemotherapy. (1)

DOSAGE AND ADMINISTRATION

- 1.5 mg/m² 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. (2.1)
- See Dosage Modification Guidelines for patients with severe neutropenia or reduced platelets. (2.1)
- See Dosage Adjustment in Renal Impairment. (2.2)

DOSAGE FORMS AND STRENGTHS

4 mg/4 mL (1 mg/mL) injection single use vial (3)

Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base.

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 topotecan injection 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: Topotecan has been associated with reports of interstitial lung disease. Monitor patients for symptoms and discontinue Topotecan Injection 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

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)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 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 topotecan injection. Concomitant administration can prolong duration of neutropenia. (7)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2011

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FULL PRESCRIBING INFORMATION

WARNING: BONE MARROW SUPPRESSION

Do not give Topotecan Injection to patients with baseline neutrophil counts of less than 1,500 cells/mm³. 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 Topotecan Injection [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

Topotecan Injection is indicated for the treatment of 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)].

2 DOSAGE AND ADMINISTRATION

Prior to administration of the first course of Topotecan Injection, patients must have a baseline neutrophil count of $>1,500$ cells/mm³ and a platelet count of $>100,000$ cells/mm³.

2.1 Small Cell Lung Cancer

Recommended Dosage

- The recommended dose of Topotecan Injection is 1.5 mg/m² 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 4 small cell lung cancer trials was 5 to 7 weeks.

Dosage Modification Guidelines

- In the event of severe neutropenia (defined as <500 cells/mm³) during any course, reduce the dose by 0.25 mg/m² (to 1.25 mg/m²) 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/mm³, reduce doses by 0.25 mg/m² (to 1.25 mg/m²) for subsequent courses.

2.2 Dosage Adjustment in Special Populations

Renal Impairment

No dosage adjustment of Topotecan Injection appears to be required for patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min.). Dosage adjustment of Topotecan Injection to 0.75 mg/m² 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 Topotecan Injection [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

2.3 Instructions for Handling, Preparation and Intravenous Administration

Handling

Topotecan Injection is a cytotoxic anticancer drug. Prepare topotecan hydrochloride injection under a vertical laminar flow hood while wearing gloves and protective clothing. If Topotecan Injection solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Topotecan Injection 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

The appropriate volume of Topotecan Injection is diluted in a minimum of 50 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP prior to administration. Infuse over 30 minutes. Topotecan Injection diluted for infusion is stable between 20°C and 25°C (68°F and 77°F) in ambient lighting conditions for 24 hours.

Each vial of Topotecan Injection is intended for single use only. Any unused drug remaining after injection must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Topotecan Injection is supplied as a single use vial, containing 4 mg/4 mL of a 1 mg/mL solution. Each mL contains topotecan hydrochloride equivalent to 1 mg of topotecan free base for intravenous infusion only following dilution.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan. Neutropenia is not cumulative over time. In the comparative study in small cell lung cancer, the treatment-related death rates were 5% for topotecan injection and 4% for CAV (cyclophosphamide-doxorubicin-vincristine).

Neutropenia

From a combined experience of patients receiving topotecan which included patients treated for small cell lung cancer: Grade 4 neutropenia (<500 cells/mm³) 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.

Thrombocytopenia

From a combined experience of patients receiving topotecan which included patients treated for small cell lung cancer: Grade 4 thrombocytopenia ($<25,000$ /mm³) 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.

Anemia

From a combined experience of patients receiving topotecan which included patients treated for small cell lung cancer: 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.

Monitoring of Bone Marrow Function

Administer Topotecan Injection only in patients with adequate bone marrow reserves, including baseline neutrophil count of at least 1,500 cells/mm³ and platelet count at least 100,000/mm³. Monitor peripheral blood counts frequently during treatment with Topotecan Injection. Do not treat patients with

subsequent courses of Topotecan Injection until neutrophils recover to $>1,000$ cells/mm³, platelets recover to $>100,000$ cells/mm³, and hemoglobin levels recover to 9.0 g/dL (with transfusion if necessary).

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 neutropenia colitis.

5.3 Interstitial Lung Disease

Topotecan has been associated with reports of interstitial lung disease (ILD), some 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 Topotecan Injection if a new diagnosis of ILD is confirmed.

5.4 Pregnancy

Pregnancy Category D

Topotecan Injection can cause fetal harm when administered to a pregnant woman.

Topotecan caused embryoletality, 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 Injection, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations, Pregnancy (8.1)*].

5.5 Inadvertent Extravasation

Inadvertent extravasation with topotecan has been observed. Most reactions have been mild but severe cases have been reported.

6 ADVERSE REACTIONS

6.1 Clinical Studies 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 clinical trials of another drug and may not reflect the rates observed in practice.

Small Cell Lung Cancer

Data in the following section are based on the combined experience of 879 patients treated with topotecan, of which 426 patients had small cell lung cancer. 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% of 879 Patients, Including 426 Patients With Small Cell Lung Cancer,
Receiving Topotecan

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 in ≥15% of 879 Patients, Including 426 Patients With Small Cell Lung Cancer,
Receiving Topotecan

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 Coughing	22 15	5 1	3 0
Gastrointestinal disorders 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
Skin and subcutaneous tissue disorders Alopecia Rash ^b	49 16	NA 1	NA 0
General disorders and administrative site conditions Fatigue Pyrexia Pain ^c Asthenia	29 28 23 25	5 1 2 4	0 <1 1 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/CAV comparator trial in small cell lung cancer.

Table 3.
Adverse Reactions Experienced in ≥15% of Small Cell Lung Cancer Patients
Randomized to Receive Topotecan or CAV

Adverse Reaction	Topotecan 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 topotecan, and in 1% of patients receiving CAV.

^b Pain includes body pain, skeletal pain, and back 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 post-marketing use of topotecan. 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 casual connection to topotecan.

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 Topotecan Injection.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

Topotecan Injection 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/m² basis) given on days 6 through 20 of gestation caused maternal toxicity, embryoletality, 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/m² 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/m² 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 Injection, the patient should be apprised of the potential hazard to a fetus. [see *Warnings and Precautions* (5.4)]

8.3 Nursing Mothers

Rats excrete high concentrations of topotecan into milk. Lactating female rats given 4.7 mg/m² IV (about thrice the clinical dose on a mg/m² 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 Topotecan Injection, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 879 patients in a combined experience of topotecan which included patients with small cell lung cancer, 32% (n = 281) were 65 years of age and older, while 3.8% (n = 33) 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* (2.2)].

8.6 Renal Impairment

No dosage adjustment of Topotecan Injection appears to be required for patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min.). Dosage reduction is recommended for patients with moderate renal impairment (Cl_{cr} 20 to 39 mL/min.). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation for Topotecan Injection [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

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

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

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

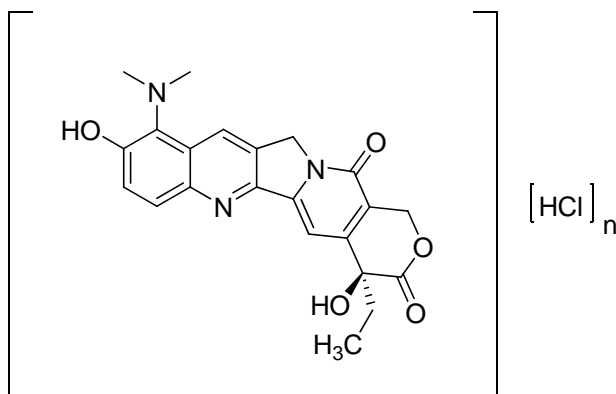
11 DESCRIPTION

Topotecan is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity.

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 C₂₃H₂₃N₃O₅ and a molecular weight of 421.45.

Topotecan has three pK_a values: pK_{a1} = 10.50 corresponding to the benzyldimethylamino group, pK_{a2} = 6.99 corresponding to the phenol group and pK_{a3} = 0.60 corresponding to the quinoline group.

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



where n is >1, corresponding to HCl added to adjust the pH to approximately 2.6 to 3.2.

Topotecan Injection is supplied as a sterile, non-pyrogenic, clear, yellow to yellow-green solution at a topotecan free base concentration of 4 mg/4 mL (1 mg/mL) available in single use vials. Each mL of Topotecan Injection contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base, 5 mg tartaric acid, NF and water for injection, USP. Hydrochloric acid and/or sodium hydroxide may be used for pH adjustment. The hydrochloride salt of topotecan is soluble in water and melts with decomposition at 213°C to 218°C.

The solution must be diluted before administration by intravenous infusion.

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/m²/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/m² 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 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 $73.4 \pm 2.3\%$ of the administered IV dose. Mean values of $50.8 \pm 2.9\%$ as total topotecan and $3.1 \pm 1.0\%$ as N-desmethyl topotecan were excreted in the urine following IV administration. Fecal elimination of total topotecan accounted for $17.9 \pm 3.6\%$ while fecal elimination of N-desmethyl topotecan was $1.7 \pm 0.6\%$. 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* (2.2) 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 (Cl_{cr} 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 renally impaired patients, was about 5.0 hours. Dosage adjustment is recommended for these patients [see *Dosage and Administration* (2.2)].

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 hepatically impaired patients tolerated the usual recommended topotecan dosage regimen.

Drug Interactions:

Pharmacokinetic studies 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*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity testing of topotecan has not been performed. Topotecan, however, 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/m² IV (about equal to the clinical dose on a mg/m² 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/m² IV (about 1/4 the clinical dose on a mg/m² 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

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

Randomized Comparative Study: In a randomized, comparative, Phase 3 trial, 107 patients were treated with topotecan (1.5 mg/m²/day × 5 days starting on day 1 of a 21-day course) and 104 patients were treated with CAV (1,000 mg/m² cyclophosphamide, 45 mg/m² 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 topotecan 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 4.

Table 4.
Efficacy of Topotecan Versus CAV (cyclophosphamide-doxorubicin-vincristine)
in Small Cell Lung Cancer Patients Sensitive to First-Line Chemotherapy

Parameter	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%)	
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 (topotecan: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 (topotecan: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 (topotecan:CAV) (95% CI) (p-value)	1.04 (0.78 to 1.39) (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: topotecan 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 topotecan or who received CAV are presented in Table 5. 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 5.
Percentage of Patients With Symptom Improvement^a: Topotecan Versus
CAV in Patients With Small Cell Lung Cancer

Symptom	Topotecan (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 to baseline.

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

Single-Arm Studies: Topotecan 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 studies, 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 studies and the comparative study.

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

How Supplied

Topotecan Injection is supplied in 4 mg/4 mL (1 mg/mL) single use vials, in packages of 1 vial per carton.

NDC 0409-0302-01
(package of 1)

Storage

Unopened vials of Topotecan Injection are stable until the date indicated on the package when stored at 2°C to 8°C (36°F to 46°F) and protected from light in the original package.

Topotecan Injection diluted for infusion is stable between 20°C and 25°C (68°F and 77°F) in ambient lighting conditions for 24 hours.

17 PATIENT COUNSELING INFORMATION

17.1 Bone Marrow Suppression

Inform patients that topotecan 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 Topotecan Injection 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 topotecan.

17.3 Asthenia and Fatigue

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

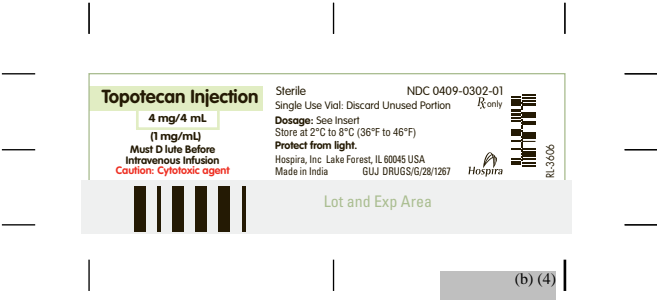
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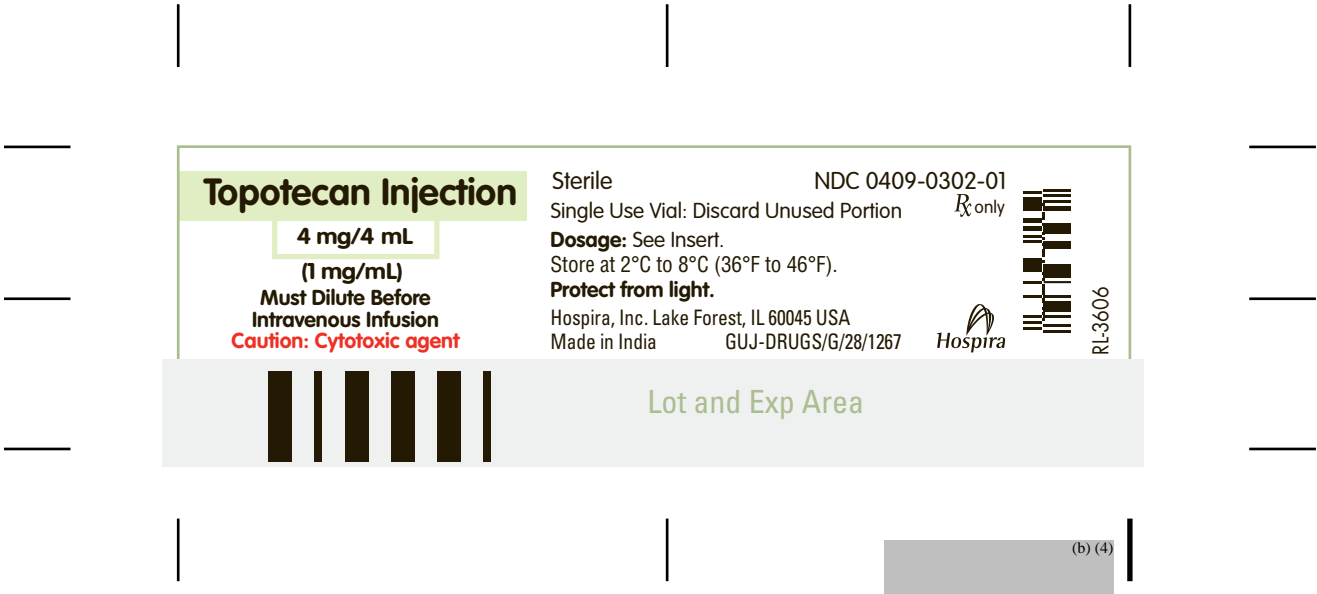
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02/02/2011