FRESENIUS KABI

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Topotecan Hydrochloride
for Injection

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

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

WARNING: BONE MARROW SUPPRESSION
See full prescribing information for complete boxed warning.
Topotecan hydrochloride can cause severe myelosuppression. Administer only to patients with baseline neutrophil counts greater than or equal to 1,500 cells/mm³ and platelet count greater than or equal to 100,000/mm³. Monitor blood cell counts. (5.1)

RECENT MAJOR CHANGES

Contraindications, Bone Marrow Depression, removed (4) 06/2015

INDICATIONS AND USAGE

Topotecan hydrochloride for injection is a topoisomerase inhibitor indicated for:
- metastatic carcinoma of the ovary after disease progression on or after initial or subsequent chemotherapy. (1.1)
- small cell lung cancer platinum-sensitive disease in patients who progressed after first-line chemotherapy. (1.2)
- combination therapy with cisplatin for Stage IV-B, recurrent, or persistent carcinoma of the cervix which is not amenable to curative treatment. (1.3)

DOSAGE AND ADMINISTRATION

- Ovarian cancer and small cell lung cancer: 1.5 mg/m² by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on Day 1 of a 21-day course. (2.1, 2.2)
- Cervical cancer: 0.75 mg/m² by intravenous infusion over 30 minutes on Days 1, 2, and 3 repeated every 21 days in combination with cisplatin 50 mg/m² on Day 1. (2.3)
- Renal impairment: Dose reduce topotecan hydrochloride for injection in patients with moderate renal impairment (20 to 39 mL/min). (2.4)

DOSAGE FORMS AND STRENGTHS

4 mg (free base) lyophilized powder in a single dose vial. (3)

CONTRAINDICATIONS

History of severe hypersensitivity reactions to topotecan. (4)

WARNINGS AND PRECAUTIONS

- Bone marrow suppression: Administer topotecan hydrochloride only to patients with adequate bone marrow reserves. Monitor peripheral blood counts and adjust the dose as needed. (2.4, 5.1)
- Neutropenic enterocolitis: Fatal typhlitis can occur. (5.2)
- Interstitial lung disease (ILD): Fatal cases have occurred. Permanently discontinue for confirmed ILD. (5.3)
- Embryofetal toxicity: Can cause fetal harm. Advise women of potential risk to the fetus. (5.4, 8.1, 8.3)
- Extravasation and tissue injury: Severe cases have been reported. If extravasation occurs, immediately stop administration and institute recommended management procedures. (5.5)

ADVERSE REACTIONS

Ovarian cancer:
- The most common hematologic adverse reactions were: neutropenia (Grade 4: 80%), anemia (Grade 3/4: 41%), thrombocytopenia (Grade 4: 27%), and febrile neutropenia (23%). (6.1)
- The most common (> 5%) non-hematologic adverse reactions (all grades) were: nausea, vomiting, fatigue, diarrhea, and dyspnea. (6.1)

Small cell lung cancer:
- The most common hematologic adverse reactions were: neutropenia (Grade 4: 70%), anemia (Grade 3/4: 42%), thrombocytopenia (Grade 4: 29%), and febrile neutropenia (28%).
- The most common (> 5%) non-hematologic adverse reactions (all grades) were: asthenia, dyspnea, nausea, pneumonia, abdominal pain, and fatigue.

Cervical cancer (topotecan hydrochloride plus cisplatin):
- The most common hematologic adverse reactions were: neutropenia (Grade 3/4: 74%), anemia (Grade 3/4: 40%), and thrombocytopenia (Grade 3/4: 33%). (6.1)
- The most common (> 25% and greater than or equal to 2% more than cisplatin alone) non-hematologic adverse reactions (all grades) were: pain, vomiting, and infection/febrile neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 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 hydrochloride. Concomitant administration can prolong duration of neutropenia. (7)

USE IN SPECIFIC POPULATIONS

Lactation: Discontinue breastfeeding. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2016

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FULL PRESCRIBING INFORMATION

WARNING: BONE MARROW SUPPRESSION

Topotecan hydrochloride can cause severe myelosuppression. Administer only to patients with baseline neutrophil counts of greater than or equal to 1,500 cells/mm³ and platelet counts greater than or equal to 100,000 cells/mm³. Monitor blood cell counts *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer
Topotecan hydrochloride for injection, as a single agent, is indicated for the treatment of patients with metastatic carcinoma of the ovary after disease progression on or after initial or subsequent chemotherapy.

1.2 Small Cell Lung Cancer
Topotecan hydrochloride for injection, as a single agent, is indicated for the treatment of patients with small cell lung cancer with platinum-sensitive disease who progressed at least 60 days after initiation of first-line chemotherapy.

1.3 Cervical Cancer
Topotecan hydrochloride for injection in combination with cisplatin is indicated for the treatment of patients with Stage IV-B, recurrent, or persistent carcinoma of the cervix not amenable to curative treatment.

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)]*.

2.1 Ovarian Cancer
Recommended Dose and Schedule
The recommended dose of topotecan hydrochloride 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.

2.2 Small Cell Lung Cancer
Recommended Dose and Schedule
The recommended dose of topotecan hydrochloride 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.

2.3 Cervical Cancer
Recommended Dose and Schedule
The recommended dose of topotecan hydrochloride is 0.75 mg/m² by intravenous infusion over 30 minutes daily on Days 1, 2, and 3 in combination with cisplatin 50 mg/m² on Day 1, repeated every 21 days.

2.4 Dose Modifications
Hematologic Toxicities
For single-agent use, dose reduce topotecan hydrochloride to 1.25 mg/m² for:
- neutrophil counts of less than 500 cells/mm³, or administer granulocyte-colony stimulating factor (G-CSF) starting no sooner than 24 hours following the last dose of topotecan hydrochloride.
- platelet counts less than 25,000 cells/mm³ during previous cycle.

For combination use with cisplatin, dose reduce topotecan hydrochloride to 0.60 mg/m² (and further to 0.45 mg/m² if necessary) for:
- febrile neutropenia (defined as neutrophil counts less than 1,000 cells/mm³ with temperature of greater than or equal to 38.0°C (100.4°F), or administer G-CSF starting no sooner than 24 hours following the last dose of topotecan hydrochloride.
- platelet counts less than 25,000 cells/mm³ during previous cycle.

Renal Impairment
For single-agent use, dose reduce topotecan hydrochloride to 0.75 mg/m² in patients with moderate renal impairment (creatinine clearance [ClCr] = 20 to 39 mL/min). Insufficient data are available in patients with severe renal impairment (ClCr less than 20 mL/min) to provide a dosage recommendation for topotecan hydrochloride *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.5 Preparation and Intravenous Administration
Topotecan hydrochloride is a cytotoxic drug. Follow applicable special handling and disposable procedures.[1]

Preparation and Administration
Reconstitute each 4 mg vial of topotecan hydrochloride with 4 mL Sterile Water for Injection, USP. Dilute the appropriate volume of the reconstituted solution in either 0.9% Sodium Chloride Intravenous Infusion, USP or 5% Dextrose in Water Injection, USP prior to administration.

Stability
Unopened vials of topotecan hydrochloride 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 carton. Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of topotecan hydrochloride 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
For injection: 4 mg (topotecan free base) lyophilized powder in a single dose vial for reconstitution; light yellow to greenish powder.

4 CONTRAINDICATIONS
Topotecan hydrochloride is contraindicated in patients who have a history of severe hypersensitivity reactions to topotecan.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression
Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan hydrochloride. Neutropenia is not cumulative over time. Severe myelotoxicity has been reported when topotecan hydrochloride is used in combination with cisplatin *[see Drug Interactions (7)]*.
- The following data on myelosuppression are based on an integrated safety database from 8 trials (N = 879) using topotecan hydrochloride injection at 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 patients with ovarian cancer and small cell lung cancer and from one trial in patients with cervical cancer (N = 147) using topotecan hydrochloride 0.75 mg/m² by intravenous infusion over 30 minutes daily on Days 1, 2, and 3 repeated every 21 days in combination with cisplatin 50 mg/m² on Day 1.

Neutropenia
- Monotherapy: Grade 4 neutropenia (less than 500 cells/mm³) occurred in 78% of patients, with a median duration of 7 days and was most common during Course 1 of treatment (68% of patients). Grade 4 neutropenia associated with infection occurred in 13% of patients and febrile neutropenia occurred in 5% of patients. Sepsis occurred in 4% of patients and was fatal in 1% of patients. Pancytopenia has been reported.
- Combination with cisplatin: Grade 4 neutropenia occurred in 48% of patients.

Thrombocytopenia
- Monotherapy: Grade 4 thrombocytopenia (less than 25,000/mm³) occurred in 27% of patients, with a median duration of 5 days.
- Combination with cisplatin: Grade 4 thrombocytopenia occurred in 7% of patients.

Anemia
- Monotherapy: Grade 3 or 4 anemia (less than 8 g/dL) occurred in 37% of patients.
- Combination with cisplatin: Grade 3 or Grade 4 anemia occurred in 40% of patients.

Administer topotecan hydrochloride only to patients with a baseline neutrophil count of greater than or equal to 1,500 cells/mm³ and a platelet count greater than or equal to 100,000/mm³. Monitor peripheral blood counts frequently during treatment with topotecan hydrochloride. Refer to Section 2.4 for dose modification guidelines for hematological toxicities in subsequent courses. Do not treat patients with subsequent courses of topotecan hydrochloride until neutrophils recover to greater than 1,000 cells/mm³, platelets recover to greater than 100,000 cells/mm³, and hemoglobin levels recover to 9.0 g/dL (with transfusion if necessary).

5.2 Neutropenic Enterocolitis
Topotecan can cause fatal typhlitis (neutropenic enterocolitis). Consider the possibility of typhlitis in patients presenting with fever, neutropenia, and abdominal pain.

5.3 Interstitial Lung Disease
Interstitial lung disease (ILD), including fatalities, has occurred with topotecan hydrochloride. Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic radiation, and use of pneumotoxic drugs and/or colony stimulating factors. Monitor patients for pulmonary symptoms indicative of ILD (e.g., cough, fever, dyspnea, and/or hypoxia), and discontinue topotecan hydrochloride if a new diagnosis of ILD is confirmed.

5.4 Embryofetal Toxicity
Based on animal data, topotecan hydrochloride can cause fetal harm when administered to a pregnant woman. Topotecan caused embryolethality, fetotoxicity, and teratogenicity in rats and rabbits when administered during organogenesis. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose of topotecan hydrochloride. Advise women of the potential risk to a fetus *[see Use in Specific Populations (8.1, 8.3)]*.

5.5 Extravasation and Tissue Injury
Extravasation with topotecan hydrochloride has been observed; severe cases have been reported. If signs or symptoms of extravasation occur, immediately stop administration of topotecan hydrochloride and institute recommended management procedures *[see Adverse Reactions (6)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described below and elsewhere in the labeling:
- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*
- Neutropenic Enterocolitis *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*
- Extravasation and Tissue Injury *[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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Ovarian Cancer
Table 1 shows the Grade 3/4 hematologic and major non-hematologic adverse reactions in the topotecan/paclitaxel comparator trial in ovarian cancer.

Table 1. Adverse Reactions Experienced by ≥ 5% of Ovarian Cancer Patients Randomized to Receive Topotecan Hydrochloride or Paclitaxel

Adverse Reaction	Topotecan Hydrochloride (n = 112)	Paclitaxel (n = 114)
Hematologic Grade 3/4	%	%
Grade 4 neutropenia (< 500 cells/mm³)	80	21
Grade 3/4 anemia (Hgb < 8 g/dL)	41	6
Grade 4 thrombocytopenia (< 25,000 plts/mm³)	27	3
Febrile neutropenia	23	4
Non-hematologic Grade 3/4	%	%
Infections and infestations		
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 topotecan hydrochloride and 0% of patients receiving paclitaxel.
[b] Pain includes body pain, skeletal pain, and back pain.

Small Cell Lung Cancer
Table 2 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 2. Adverse Reactions Experienced by ≥ 5% of Small Cell Lung Cancer Patients Randomized to Receive Topotecan Hydrochloride or CAV

Adverse Reaction	Topotecan Hydrochloride (n = 107)	CAV (n = 104)
Hematologic Grade 3/4	%	%
Grade 4 neutropenia (< 500 cells/mm³)	70	72
Grade 3/4 anemia (Hgb < 8 g/dL)	42	20
Grade 4 thrombocytopenia (< 25,000 plts/mm³)	29	5
Febrile neutropenia	28	26
Non-hematologic Grade 3/4	%	%
Infections and infestations		
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 hydrochloride and 1% of patients receiving CAV.
[b] Pain includes body pain, skeletal pain, and back pain.

Hepatobiliary Disorders in Ovarian and Small Cell Lung Cancer Patients Receiving topotecan hydrochloride:
Based on the combined experience of 453 patients with metastatic ovarian carcinoma, and 426 patients with small cell lung cancer treated with topotecan hydrochloride, Grade 1 transient elevations in hepatic enzymes occurred in 8% of patients. Grade 3/4 elevations occurred in 4%. Grade 3/4 elevated bilirubin occurred in less than 2% of patients.

Cervical Cancer
In the comparative trial with topotecan hydrochloride plus cisplatin versus cisplatin in patients with cervical cancer, the most common dose-limiting adverse reaction was myelosuppression. Table 3 shows the hematologic and non-hematologic adverse reactions in patients with cervical cancer.

Table 3. Adverse Reactions Experienced by ≥ 5% of Patients with Cervical Cancer Randomized to Receive Topotecan Hydrochloride plus Cisplatin or Cisplatin Monotherapy (Between-Arm Difference ≥ 2%)[a]

Adverse Reaction	Topotecan Hydrochloride plus Cisplatin (n = 140) %	Cisplatin (n = 144) %
Hematologic		
Neutropenia		
Grade 3 (< 1,000 to 500 cells/mm³)	26	1
Grade 4 (< 500 cells/mm³)	48	1
Anemia		
Grade 3 (Hgb < 8 to 6.5 g/dL)	34	19
Grade 4 (Hgb < 6.5 g/dL)	6	3
Thrombocytopenia		
Grade 3 (< 50,000 to 10,000 cells/mm³)	26	3
Grade 4 (< 10,000 cells/mm³)	7	0
Non-hematologic[b,c]		
General disorders and administrative site conditions		
Constitutional[d]	69	62
Pain[e]	59	50
Gastrointestinal disorders		
Vomiting	40	37
Stomatitis-pharyngitis	6	0
Other	63	56
Dermatology[f]	48	20
Infection-febrile neutropenia[f]	28	18
Cardiovascular[f]	25	15

[a] Includes patients who were eligible and treated.
[b] Data were collected using NCI Common Toxicity Criteria, v. 2.0.
[c] Grades 1 through 4 only. There were 3 patients who experienced deaths with investigator-designated attribution. The first patient experienced 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.
[d] Constitutional includes fatigue (lethargy, malaise, asthenia), fever (in the absence of neutropenia), rigors, chills, sweating, and weight gain or loss.
[e] 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.
[f] High-level terms were included if the between-arm difference was ≥ 10%.

6.2 Postmarketing Experience
The following reactions have been identified during postmarketing use of topotecan hydrochloride. 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 topotecan hydrochloride.

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 enterocolitis *[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
Extravasation *[see Warnings and Precautions (5.5)]*.

7 DRUG INTERACTIONS

7.1 G-CSF
Concomitant administration with G-CSF can prolong the duration of neutropenia. If G-CSF is used, it should be started no sooner than 24 hours following the last dose of topotecan hydrochloride.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Based on animal data, topotecan hydrochloride can cause fetal harm when administered to a pregnant woman. Topotecan caused embryolethality, fetotoxicity, and teratogenicity in rats and rabbits when administered during organogenesis at doses similar to the clinical dose *[see Data]*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated populations are unknown; however, the background risk in the US general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data
Animal Data: 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. Administration of an intravenous 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.

8.2 Lactation
Risk Summary
It is not known whether this drug is present in human milk; however, topotecan is excreted in rat milk at high concentrations *[see Data]*. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants with topotecan hydrochloride, advise nursing mothers to discontinue breastfeeding during treatment with topotecan hydrochloride.

Data
Animal Data: Following intravenous administration of topotecan to lactating rats at a dose of 4.72 mg/m^2 (about twice the clinical dose on a mg/m^2 basis), topotecan was excreted into milk at concentrations up to 48-fold higher than those in plasma.

8.3 Females and Males of Reproductive Potential
Contraception
Females: Advise female patients of reproductive potential to use effective contraception during treatment with topotecan hydrochloride and for one month after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking topotecan hydrochloride *[see Use in Specific Populations (8.1)]*.

Males: Topotecan hydrochloride may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for three months after treatment with topotecan hydrochloride *[see Nonclinical Toxicology (13.1)]*.

Infertility
Females: Topotecan hydrochloride may have both acute and long-term effects on fertility *[see Nonclinical Toxicology (13.1)]*.

Males: Effects on spermatogenesis have been observed in animals administered topotecan hydrochloride. Advise males of the potential risk for impaired fertility and to seek counseling on fertility and family planning options prior to starting treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Of the 679 patients with metastatic ovarian cancer or small cell lung cancer in clinical trials of topotecan hydrochloride, 32% (n = 281) were aged 65 years and older, while 3.8% (n = 33) were aged 75 years and older. Of the 140 patients with Stage IV-B, relapsed, or refractory cervical cancer in clinical trials of topotecan hydrochloride who received topotecan hydrochloride plus cisplatin in the randomized clinical trial, 6% (n = 9) were aged 65 years and older, while 3% (n = 4) were aged 75 years 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
The systemic exposure to both topotecan lactone and total topotecan increased in patients with moderate renal impairment (Clcr = 20 to 39 mL/min) compared with patients with normal renal function (Clcr greater than 60 mL/min). Reduce the dose of topotecan hydrochloride in patients with moderate renal impairment (Clcr = 20 to 39 mL/min). No dosage adjustment of topotecan hydrochloride is recommended for patients with mild renal impairment (Clcr = 40 to 60 mL/min) *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

Insufficient data are available in patients with severe renal impairment (Clcr less than 20 mL/min) to provide a dosage recommendation for topotecan hydrochloride.

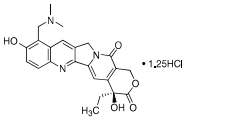
10 OVERDOSAGE
Overdoses (up to 10-fold of the prescribed dose) occurred in patients treated with intravenous topotecan. The primary complication of overdosage is bone marrow suppression. The observed signs and symptoms of overdose are consistent with the known adverse reactions associated with topotecan hydrochloride 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 myelosuppression 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 topotecan hydrochloride. If an overdose is suspected, monitor the patient closely for bone marrow suppression and institute supportive-care measures (such as the prophylactic use of G-CSF and antibiotic therapy) as appropriate.

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

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

Topotecan hydrochloride has the following structural formula:



$C_{23}H_{23}N_3O_5 \cdot 1.25HCl$ M.W. 467.02

Topotecan hydrochloride 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.

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 re-ligation 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.

12.3 Pharmacokinetics
Following administration of topotecan hydrochloride for injection at doses of 0.5 to 1.5 mg/m^2 administered as a 30-minute infusion to cancer patients, topotecan exhibited 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 approximately 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 the primary route 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% ± 2.8% 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.

Specific Populations
Gender: Plasma clearance of topotecan lactone in male patients was approximately 24% higher than that in female patients, largely reflecting difference in body size.

Age: 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 (2.4), Use in Specific Populations (8.5)]*.

Renal Impairment: In patients with mild renal impairment (Clcr = 40 to 60 mL/min), plasma clearance of topotecan lactone was decreased by 33% compared with patients with normal renal function (Clcr greater than 60 mL/min). In patients with moderate renal impairment (Clcr = 20 to 39 mL/min), plasma clearance of topotecan lactone was reduced by 65% compared with patients with normal renal function. Dosage adjustment is recommended for patients with moderate renal impairment. No dosage adjustment is required in patients with mild renal impairment *[see Dosage and Administration (2.4), Use in Specific Populations (8.6)]*.

Hepatic Impairment: Plasma clearance of topotecan lactone in patients with hepatic impairment serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased by 33% compared with patients with normal hepatic function (serum bilirubin levels less than 1.7 mg/dL).

Drug Interactions
Effects of Topotecan on Drug-Metabolizing Enzymes: In vitro inhibition studies using marker substrates for 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.

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 (0.3 mg/m^2 IV daily on Days 2 to 6) 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. Topotecan (0.75 mg/m^2 IV daily on Days 1 to 5) 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.

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 0.25 times 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
Topotecan hydrochloride 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 topotecan hydrochloride (1.5 mg/m^2/day × 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. The efficacy outcome measures were response rate, response duration, and time to progression.

The results of the trial did not show statistically significant improvements in response rates, response duration, time to progression, and overall survival as shown in Table 4.

Table 4. Efficacy of Topotecan Hydrochloride versus Paclitaxel in Ovarian Cancer

Parameter	Topotecan Hydrochloride (n = 112)	Paclitaxel (n = 114)
Overall response rate (95% CI) Complete response rate Partial response rate	21% (13% to 28%) 5% 16%	14% (8% to 20%) 3% 11%
Response duration[a] (months) Median (95% CI)	6.0 (5.1 to 7.6)	5.0 (3.7 to 7.8)
Time to progression (months) Median (95% CI) HR (Topotecan hydrochloride: paclitaxel) (95% CI)	4.4 (2.8 to 5.4) 0.76 (0.57 to 1.02)	3.4 (2.7 to 4.2)
Survival (months) Median (95% CI) HR (Topotecan hydrochloride: paclitaxel) (95% CI)	14.5 (10.7 to 16.5) 0.97 (0.71 to 1.34)	12.2 (9.7 to 15.8)

HR = hazard-ratio; CI = confidence interval.

[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 topotecan hydrochloride compared with 6.0 weeks (range: 2.4 to 18.1) with paclitaxel. In the crossover phase, 8 of 61 (13%) patients who received topotecan hydrochloride after paclitaxel had a partial response and 5 of 49 (10%) patients who received paclitaxel after topotecan hydrochloride had a response (2 complete responses).

Topotecan hydrochloride 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%.

Topotecan hydrochloride 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
Topotecan hydrochloride 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 topotecan hydrochloride (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 greater than or equal to 60 days after completion of first-line therapy). A total of 77% of patients treated with topotecan hydrochloride and 79% of patients treated with CAV received platinum/etoposide with or without other agents as first-line chemotherapy. The efficacy outcome measures were response rate and duration of response.

The results of the trial did not show statistically significant improvements in response rates, response duration, time to progression, and overall survival as shown in Table 5.

Table 5. Efficacy of Topotecan Hydrochloride versus CAV (cyclophosphamide-doxorubicin-vincristine) in Small Cell Lung Cancer Patients Sensitive to First-Line Chemotherapy

Parameter	Topotecan Hydrochloride (n = 107)	CAV (n = 104)
Overall response rate (95% CI) Complete response rate	24% (16% to 32%)	18% (11% to 26%)
Partial response rate	0%	1%
Response duration[a] (months)	24%	17%
Median (95% CI)	3.3 (3.0 to 4.1)	3.5 (3.0 to 5.3)
Time to progression (months) Median (95% CI) HR (Topotecan hydrochloride:CAV) (95% CI)	3.1 (2.6 to 4.1) 0.92 (0.69 to 1.22)	2.8 (2.5 to 3.2)
Survival (months) Median (95% CI) HR (Topotecan hydrochloride:CAV) (95% CI)	5.8 (4.7 to 6.8) 1.04 (0.78 to 1.39)	5.7 (5.0 to 7.0)

HR = hazard-ratio; CI = confidence interval.

[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 hydrochloride 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 hydrochloride or who received CAV are presented in Table 6. 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 6. Percentage of Patients with Symptom Improvement[a]: Topotecan Hydrochloride versus CAV in Patients with Small Cell Lung Cancer

Symptom	Topotecan Hydrochloride (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.

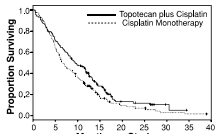
[b] Number of patients with baseline and at least 1 post-baseline assessment.

Single-Arm Trials
Topotecan hydrochloride 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 greater than or equal to 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 topotecan hydrochloride (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 topotecan hydrochloride 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 topotecan hydrochloride 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 Topotecan Hydrochloride plus Cisplatin versus Cisplatin Monotherapy in Cervical Cancer Patients



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

15 REFERENCES
1. "OSHA Hazardous Drugs." *OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.*

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Topotecan hydrochloride for injection is supplied as a sterile, lyophilized, buffered, light yellow to greenish powder. Topotecan hydrochloride for injection is supplied as follows:

Product No.	NDC No.	Strength	
760210	63323-762-10	4 mg (free base) per vial	Single dose vial, packaged individually.
760217	63323-762-17	4 mg (free base) per vial	Single dose vial, in packages of 5.

The container closure is not made with natural rubber latex.

16.2 Storage and Handling
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light; product is light-sensitive. Retain in carton. Handle and dispose of topotecan hydrochloride for injection consistent with recommendations for the handling and disposal of hazardous drugs[1].

17 PATIENT COUNSELING INFORMATION

- **Bone Marrow Suppression**
  Inform patients that topotecan hydrochloride decreases blood cell counts such as white blood cells, platelets, and red blood cells. Advise patients to notify their healthcare provider promptly for fever, other signs of infection (e.g., chills, cough, or burning pain on urination), or bleeding. Inform patients that frequent blood tests will be performed while taking topotecan hydrochloride to monitor for the occurrence of bone marrow suppression.
- **Embryofetal Toxicity**
  Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected during treatment with topotecan hydrochloride. Advise females of reproductive potential to use effective contraception during treatment and for 1 month after the last dose of topotecan hydrochloride. Advise males with a female sexual partner of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of topotecan hydrochloride *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.
- **Lactation**
  Advise nursing mothers to discontinue breastfeeding during treatment with topotecan hydrochloride *[see Use in Specific Populations (8.2)]*.
- **Infertility**
  Advise male and female patients of the potential risk for impaired fertility and possible family planning options *[see Use in Specific Populations (8.3)]*.
- **Asthenia and Fatigue**
  Advise patients that topotecan hydrochloride may cause asthenia or fatigue. These symptoms may impair the ability to safely drive or operate machinery.

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