PRODUCT MONOGRAPH

^{Pr}pms-TOPOTECAN

Topotecan hydrochloride for Injection

Topotecan 1 mg per vial and 4 mg per vial,
incorporated as the hydrochloride for reconstitution

Antineoplastic Agent

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Prpms-TOPOTECAN
Topotecan hydrochloride for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous (IV) infusion	Lyophilized powder Topotecan 1 mg or 4 mg per vial, incorporated as the hydrochloride for the reconstitution	Hydrochloric Acid, Mannitol, Sodium Hydroxide, and Tartaric Acid.

INDICATIONS AND CLINICAL USE

Adults
pms-TOPOTECAN (topotecan hydrochloride) is indicated for the treatment of:

- metastatic carcinoma of the ovary after failure of initial or subsequent therapy.
- sensitive small cell lung cancer after failure of first line chemotherapy (defined as recurrence at least 60 days after first line chemotherapy).

Pediatrics
Safety and effectiveness in pediatric patients have not been established, therefore is not recommended for use in this population.

CONTRAINDICATIONS

pms-TOPOTECAN is contraindicated:

- in patients who have a history of hypersensitivity reactions (anaphylactoid reactions) to topotecan or to any of its excipients.
- in patients who are pregnant or breast-feeding.
- in patients who already have severe bone marrow depression prior to starting first course, as evidenced by baseline absolute neutrophils < 1.5x109/L and/or a platelet count of < $100x10^9$/L
- in patients with severe renal impairment (creatinine clearance of < 20 mL/min or < 0.33 mL/sec).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

pms-TOPOTECAN should be prescribed by a qualified health care professional who is experienced in the use of antineoplastic therapy agents.

The following is a clinically significant adverse event:

- **Bone marrow suppression, primarily neutropenia** (see WARNINGS AND PRECAUTIONS, Hematologic)**;**
- **Potentially fatal neutropenic colitis** (see WARNINGS AND PRECAUTIONS, Gastrointestinal)**;**
- **Potentially fatal interstitial lung disease** (see WARNINGS AND PRECAUTIONS, Respiratory)**.**

General

pms-TOPOTECAN should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Bone marrow suppression, primarily neutropenia, is the dose limiting toxicity. Therapy with topotecan hydrochloride should not be given to patients with baseline absolute neutrophil counts of 1.5x109/L or less. In order to monitor the occurrence of bone marrow suppression, frequent peripheral blood cell counts should be performed on all patients receiving pms-TOPOTECAN (see DOSAGE AND ADMINISTRATION)**.**

Inadvertent extravasation with topotecan hydrochloride has been associated only with mild local reactions such as erythema (and bruising).

Caution should be observed when driving or operating machinery if fatigue or asthenia persist.

Selection of Patients In Small Cell Lung Cancer

Clinical studies were conducted in patients with sensitive and refractory small cell lung cancer; a reduced chance for benefit in the refractory patients was noted with response rates ranging from 11-31% for patients with sensitive disease and 2.1 to 7.3% for patients with refractory disease. As the risk for toxicity is similar, the overall benefit/risk is reduced.

The benefit to patients versus the risk of toxicity must be carefully weighed.

Carcinogenesis and Mutagenesis

The carcinogenic potential of topotecan hydrochloride has not been studied. (See Special Populations, Pregnant Women.)

Topotecan hydrochloride has been shown to be genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro*, and mouse bone marrow cells *in vivo*, but is not mutagenic in bacterial cells (*Salmonella typhimurium* and *Escherichia coli*).

Gastrointestinal

Topotecan-induced neutropenia can cause neutropenic colitis (caecitis or typhlitis). 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, the possibility of neutropenic colitis should be considered.

Hematologic

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan. Neutropenia is not cumulative over time. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with topotecan [2% fatalities across all SCLC studies (n = 426 subjects), which includes 3% fatalities in one Phase III SCLC study (n = 107 subjects, Table 4)] (see ADVERSE REACTIONS).

Topotecan hydrochloride should not be administered to patients with baseline absolute neutrophil counts of less than $1.5x10^9$/L. To monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving topotecan hydrochloride. Patients should not be retreated with subsequent courses of topotecan hydrochloride until neutrophils recover to a level > $1x10^9$/L, platelets recover to a level > $100x10^9$/L and hemoglobin recovers to 90 g/L, using transfusion if necessary.

Neutropenia

Grade 4 neutropenia (< 0.5x109/L) occurred in 78% of patients and 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 1.3%.

Topotecan-induced neutropenia can cause neutropenic colitis (see WARNINGS AND PRECAUTIONS, Gastrointestinal).

In the case of severe neutropenia (< $0.5x10^9$/L for 7 days or more) during a course of topotecan hydrochloride, a reduction in dose of 0.25 mg/m^2 for subsequent courses of therapy is recommended (see DOSAGE AND ADMINISTRATION).

Thrombocytopenia

Grade 4 thrombocytopenia (< $25x10^9$/L) 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

Severe anemia (Grade 3/4, < 80 g/L) 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

Topotecan hydrochloride should only be administered in patients with adequate bone marrow reserves including baseline absolute neutrophil counts of at least $1.5x10^9$/L and platelet count at

least $100x10^9$/L. Frequent monitoring of blood counts should be instituted during treatment with topotecan hydrochloride (see DOSAGE AND ADMINISTRATION).

Respiratory

Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see ADVERSE REACTIONS). 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. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

Special Populations

Pregnant Women:

Topotecan hydrochloride may cause fetal harm when administered to a pregnant woman. Topotecan was shown to cause embryonic and fetal lethality when given to rats (0.59 mg/m^2) and rabbits (1.25 mg/m^2) at doses less than the human clinical intravenous dose (1.5 mg/m^2). At maternally toxic doses (0.59 mg/m^2), topotecan caused malformations, primarily of the eye, brain, skull, and vertebrae. This drug is contraindicated during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with topotecan hydrochloride and to inform the treating physician immediately should this occur.

Nursing Women:

pms-TOPOTECAN is contraindicated during breast-feeding (see CONTRAINDICATIONS).

Pediatrics:

Safety and effectiveness of topotecan in pediatric patients have not been established, and therefore is not indicated for use in this population.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Data in the following section are based on the combined experience of 453 patients with metastatic ovarian carcinoma, and 426 patients with small cell lung cancer, treated with topotecan hydrochloride. Table 1 lists the principal hematologic toxicities and Table 2 lists non-hematologic toxicities occurring in at least 15% of patients.

Table 1: Summary of Hematologic Adverse Events in Patients Receiving Topotecan hydrochloride

	Patients N = 879	Courses N = 4124
Hematologic Adverse Events	**% Incidence**	**% Incidence**
Neutropenia		
$< 1.5x10^9$/L	97	81
$< 0.5x10^9$/L	78	39

	Patients N = 879	Courses N = 4124
Hematologic Adverse Events	**% Incidence**	**% Incidence**
Leukopenia		
$< 3x10^9/L$	97	80
$< 1x10^9/L$	32	11
Thrombocytopenia		
$< 75x10^9/L$	69	42
$< 25x10^9/L$	27	9
Anemia		
< 100 g/L	89	71
< 80 g/L	37	14
Sepsis or fever/infection with Grade 4 neutropenia	23	7
Platelet transfusions	15	4
RBC transfusions	52	22

Table 2: Summary of Non-hematologic Adverse Events in Patients Receiving Topotecan hydrochloride

Non-hematologic Adverse Events	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	n=879 Patients	n=4124 Courses	n=879 Patients	n=4124 Courses	n=879 Patients	n=4124 Courses
Gastrointestinal						
Nausea	64	42	7	2	1	<1
Vomiting	45	22	4	1	1	<1
Diarrhea	32	14	3	1	1	<1
Constipation	29	15	2	1	1	<1
Abdominal Pain	22	10	2	1	2	<1
Stomatitis	18	8	1	<1	<1	<1
Anorexia	19	9	2	1	<1	<1
Body as a Whole						
Fatigue	29	22	5	2	0	0
Fever	28	11	1	<1	<1	<1
Pain*	23	11	2	1	1	<1
Asthenia	25	13	4	1	2	<1
Skin/Appendages						
Alopecia	49	54	N/A	N/A	N/A	N/A
Rash**	16	6	1	<1	0	0
Respiratory System						
Dyspnea	22	11	5	2	3	1
Coughing	15	7	1	<1	0	0
CNS/ Peripheral Nervous System						
Headache	18	7	1	<1	<1	0

*Pain includes body pain, back pain and skeletal pain.

**Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption and rash maculo-papular.

Hematologic:
(See WARNINGS AND PRECAUTIONS)

Gastrointestinal:
The prophylactic use of anti-emetics was not routine in patients treated with topotecan hydrochloride. Gastrointestinal effects were usually mild at the recommended dose level. The incidence of nausea was 64% (8% Grade 3/4) and vomiting occurred in 45% (6% Grade 3/4) of patients (see Table 2).

Thirty-two percent of patients had diarrhea (4% Grade 3/4), 29% constipation (2% Grade 3/4) and 22% had abdominal pain (4% Grade 3/4). Grade 3/4 abdominal pain was 6% in ovarian cancer patients and 2% in small cell lung cancer patients.

After IV administration of topotecan hydrochloride, drug-related diarrhea (Grade 1/2) was 10% in patients greater than 65 years of age (see DOSAGE AND ADMINISTRATION).

Skin / Appendages
Total alopecia (Grade 2) occurred in 31% of patients.

Central and Peripheral Nervous System
Headache (18%) was the most frequently reported neurologic toxicity. Paresthesia occurred in 7% of patients, but was generally Grade 1.

Liver / Biliary
Grade 1 transient elevations in hepatic enzymes (8%); Grade 3/4 elevated Bilirubin occurred in < 2% of patients.

Respiratory
The incidence of Grade 3/4 dyspnea was 3.8% in ovarian cancer patients and 12.2% in small cell lung cancer patients. Table 3 shows the Grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/paclitaxel comparator trial. Table 4 shows the Grade 3/4 hematologic and major non-hematologic adverse events in the topotecan / CAV comparator trial in small cell lung cancer.

Note: All grading scales are based on National Cancer Institute criteria.

Table 3: Comparative Toxicity Profiles for Ovarian Cancer Patients Randomized to Receive Topotecan hydrochloride or Paclitaxel

Adverse Event	Topotecan hydrochloride		Paclitaxel	
	Patients n=112 %	Courses n=597 %	Patients n=114 %	Courses n=589 %
Hematologic Grade 3/4				
Grade 4 neutropenia ($<0.5x10^9$/L)	80.2	35.8	21.4	8.6

Adverse Event	Topotecan hydrochloride		Paclitaxel	
	Patients n=112 %	Courses n=597 %	Patients n=114 %	Courses n=589 %
Grade 3/4 Anemia (Hgb <80 g/L)	41.4	16.1	6.3	1.9
Grade 4 Thrombocytopenia ($<25x10^9$/L)	27.0	10.0	2.7	0.5
Fever/Grade 4 neutropenia	23.2	6.0	4.0	1.0
Documented Sepsis	4.5	0.8	1.8	0.3
Death related to Sepsis	1.8	N/A	0	N/A
Non-hematologic Grade 3/4				
Gastrointestinal				
Abdominal pain	5.4	1.3	3.5	0.9
Constipation	5.4	1.0	0.0	0.0
Diarrhea	6.3	1.9	0.9	0.2
Intestinal Obstruction	4.5	1.0	4.4	0.8
Nausea	9.8	2.7	1.8	0.3
Stomatitis	0.9	0.2	0.9	0.2
Vomiting	9.9	1.9	2.7	0.5
Constitutional				
Anorexia	3.6	0.8	0.0	0.0
Dyspnea	6.3	1.8	5.4	1.2
Fatigue	7.1	1.8	6.1	2.2
Malaise	1.8	0.5	1.8	0.3
Neuromuscular				
Arthralgia	0.9	0.2	2.6	0.5
Asthenia	5.4	1.6	2.6	1.0
Headache	0.9	0.2	1.8	0.8
Myalgia	0.0	0.0	2.6	1.5
Pain*	4.5	1.0	7.0	2.2
Chest Pain	1.8	0.3	0.9	0.3
Skin and Appendages				
Rash**	0	0	0.9	0.2
Liver/Biliary				
Increased Hepatic Enzymes+	0.9	0.2	0.9	0.2

*Pain includes body pain, skeletal pain, and back pain

**Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and rash maculo-papular.

+Increased hepatic enzymes includes Increased SGOT/AST, Increased SGPT/ALT and Increased Hepatic Enzymes

Table 4: Comparative Toxicity Profiles for Small Cell Lung Cancer Patients Randomized to Receive Topotecan hydrochloride or CAV

Adverse Event	Topotecan hydrochloride		CAV	
	Patients n=107 %	Courses n=446 %	Patients n=104 %	Courses n=359 %
Hematologic Grade 3/4				
Grade 4 neutropenia ($<0.5x10^9$/L)	70	38	72	51
Grade 3/4 Anemia (Hgb <80 g/L)	42	18	20	7
Grade 4 Thrombocytopenia ($<25x10^9$/L)	29	10	5	1
Fever/Grade 4 neutropenia	28	9	26	13
Documented Sepsis	5	1	5	1
Death related to Sepsis	3	N/A	1	N/A
Non-hematologic Grade 3/4				
Gastrointestinal				
Abdominal pain	6	1	4	2
Constipation	1	<1	0	0
Diarrhea	1	<1	0	0
Nausea	8	2	6	2
Stomatitis	2	<1	1	<1
Vomiting	3	<1	3	1
Constitutional				
Anorexia	3	1	4	2
Dyspnea	9	5	14	7
Fatigue	6	4	10	3
Neuromuscular				
Asthenia	9	4	7	2
Headache	0	0	2	<1
Pain*	5	2	7	4
Respiratory System				
Pneumonia	8	2	6	2
Coughing	2	1	0.0	0
Skin/Appendages				
Rash**	1	<1	1	<1
Liver/Biliary				
Increased Hepatic Enzymes+	1	<1	0	0

*Pain includes body pain, skeletal pain, and back pain
** Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and rash maculo-papular.
+Increased hepatic enzymes includes Increased SGOT/AST, Increased SGPT/ALT and Increased Hepatic Enzymes

Premedications were not routinely used in patients randomized to topotecan hydrochloride, while patients receiving CAV received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor type 2 blockers.

Post market Adverse Drug Reactions

Reports of adverse events in patients taking topotecan hydrochloride after market introduction include the following:

Body as a Whole:	allergic manifestations, angioedema, anaphylactoid reactions, extravasation*, pancytopenia
Gastrointestinal:	abdominal pain**
Hematologic:	severe bleeding (in association with thrombocytopenia)
Respiratory, Thoracic and Mediastinal Disorders:	interstitial lung disease
Skin / Appendages:	severe dermatitis, severe pruritus

*Reactions associated with extravasation have been mild and have not generally required specific therapy.

**Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see WARNINGS and PRECAUTIONS).

DRUG INTERACTIONS

There are no adequate data to define a safe and effective regimen for topotecan hydrochloride in combination with other cytotoxic agents. Preliminary studies combining topotecan hydrochloride with platinum-containing agents (e.g., cisplatin or carboplatin) suggest a sequence- dependent interaction whereby greater myelosuppression is seen when the platinum-containing agent is given on day 1 compared to day 5 of the topotecan hydrochloride dosing. If pms-TOPOTECAN is administered in combination with other cytotoxic agents, dose reduction may be necessary.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Initial Dose:
Prior to administration of the first course of pms-TOPOTECAN (topotecan hydrochloride), patients must have:

- a baseline absolute neutrophil count of $\geq 1.5 \times 10^9$/L
- a platelet count of $\geq 100 \times 10^9$/L
- a hemoglobin level of ≥ 90 g/L

Recommended Dose and Dosage Adjustment

Initial Dose
The recommended dose of pms-TOPOTECAN is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day one of a 21-day course. Because median time to response in three ovarian cancer clinical trials was 9 to 12 weeks and median time to

response in four small cell lung cancer trials was 5 to 7 weeks, a minimum of 4 courses of pms-TOPOTECAN is recommended.

Subsequent doses
pms-TOPOTECAN should not be re-administered unless the absolute neutrophil count is more than or equal to $1x10^9$/L, the platelet count is more than or equal to $100x10^9$/L, and the hemoglobin level is more than or equal to 90 g/L (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medications (e.g., G-CSF) or to dose reduces to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (absolute neutrophil count less than $0.5x10^9$/L) for 7 days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m^2/day to 1.25 mg/m^2/day (or subsequently down to 1.0 mg/m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below $25x10^9$/L.

Routine pre-medication for the prevention of non-hematological adverse events is not required with pms-TOPOTECAN.

Hepatic Impairment
No dosage adjustment is required for treating patients with hepatic impairment (plasma bilirubin > 1.5 to < 10 mg/dL or (SI units) > 25.7 to < 171 mcmol/L).

Renally impaired patients
No dosage adjustment is required for patients with mild renal impairment (CrCl 40 to 60 mL/min or 0.67 to 1 mL/sec). Dosage adjustment to 0.75 mg/m^2/day is recommended for patients with moderate renal impairment (CrCl 20 to 39 mL/min or 0.33 to 0.65 mL/sec). Advice on dosing of topotecan for patients with moderate renal impairment (creatinine clearance of 20 to 39 mL/min) is based on studies involving patients with advanced cancer. Treatment with pms-TOPOTECAN in patients with severe renal impairment (CrCl < 20 mL/min or 0.33 mL/sec) is not recommended (see CONTRAINDICATIONS).

Neutropenia
In the case of severe neutropenia (< $0.5x10^9$/L for 7 days or more) during a course of pms-TOPOTECAN, a reduction in dose of 0.25 mg/m^2 for subsequent courses of therapy is recommended (see WARNINGS AND PRECAUTIONS, Neutropenia)

Use in Children
Insufficient data are available in pediatric patients to provide a dosage recommendation (see PRECAUTIONS AND WARNINGS).

Use in the Elderly
No dosage adjustment appears to be needed in the elderly, other than adjustments related to renal function.

After IV administration of topotecan, drug-related diarrhea (Grade 1/2) was 10% in patients greater than 65 years of age (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Gastrointestinal). Patients over the age of 65 should be closely monitored for diarrhea and treated accordingly.

Dosage in Combination with Cytotoxic Agents
Dose adjustment may be necessary if pms-TOPOTECAN is administered in combination with other cytotoxic agents (see DRUG INTERACTIONS).

Administration
pms-TOPOTECAN is a cytotoxic anticancer drug. As with other potentially toxic compounds, pms-TOPOTECAN should be prepared under a vertical laminar flow hood while wearing gloves and protective clothing. If pms-TOPOTECAN solution contacts the skin; wash the skin immediately and thoroughly with soap and water. If pms-TOPOTECAN contacts mucous membranes, flush thoroughly with water.

Preparation for Intravenous Administration:
Each pms-TOPOTECAN 1mg vial is reconstituted with 1.1 mL Sterile Water for Injection, giving a final concentration of 1 mg/mL. Each pms-TOPOTECAN 4 mg vial is reconstituted with 4 mL Sterile Water for Injection, giving a final concentration of 1 mg/mL.

Then the appropriate volume of the reconstituted solution is further diluted to an infusion concentration of 20 – 500 mcg/mL in 50 to 100 mL of either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Since the vials contain no preservative, it is recommended that the product be used immediately after reconstitution. If not used immediately the reconstituted product should be stored in a refrigerator, for up to 24 hours.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity and particulate matter, discoloration and leakage prior to administration, whenever solution and container permit.

OVERDOSAGE

There is no known antidote for overdosage with topotecan hydrochloride. Further management should be as clinically indicated. Overdoses (from 1.1 fold up to 10 fold of the prescribed dose) have been reported in patients being treated with intravenous topotecan**.** The primary complication of overdosage is bone marrow suppression. The observed signs and symptoms for overdose are consistent with the known adverse reactions associated with topotecan (see ADVERSE REACTIONS). In addition, elevated hepatic enzymes, mucositis, fatal hemorrhagic necrotizing colitis, hypotension and tachycardia have been reported following overdose. In a phase I study, one patient was incorrectly dosed at 35 mg/m^2 during course 9 of therapy and experienced hematologic toxicity associated with this increased dose.

The LD_{10} Rate in mice receiving single intravenous infusions of topotecan hydrochloride was 74.85 mg/m^2 (CI 95%: 47.22 to 97.41).

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Topotecan hydrochloride inhibits topoisomerase-I, an enzyme that functions in DNA replication to relieve the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilizing the covalent complex of enzyme and strand-cleaved DNA, which is an intermediate of the catalytic mechanism, thereby inducing breaks in the protein-associated DNA single-strands, resulting in cell death.

Pharmacodynamics

The dose-limiting toxicity for topotecan is leukopenia. The relationship between decreased white blood count and either topotecan or total topotecan AUC can be described by a Sigmoid E_{max} Model.

Pharmacokinetics

Following intravenous administration of topotecan at doses of 0.5 to 1.5 mg/m^2 as a 30-minute infusion daily for 5 days, topotecan demonstrated a clearance of 1030 mL/min with a plasma half-life of 2 to 3 hours.

Comparison of pharmacokinetic parameters did not suggest any change in pharmacokinetics over the dosing period. Area under the curve increased approximately in proportion to the increase in dose.

Distribution:

Topotecan has a volume of distribution of 130 L. Binding of topotecan to plasma proteins is about 35%. Topotecan is evenly distributed between blood cells and plasma.

Metabolism:

Topotecan undergoes pH dependent hydrolysis, with the equilibrium favoring the ring-opened hydroxy-acid form at physiologic pH.

Excretion:

The renal clearance of topotecan could not be measured in humans due to the effect of urine pH on interconversion, although measurement of total topotecan (the lactone ring and the ring-opened hydroxy acid) in urine suggests that a variable fraction of the dose (generally 20 to 60%) is excreted in urine. Topotecan has also been measured in human bile samples indicating that topotecan is excreted by both biliary and urinary routes in humans.

Special Populations and Conditions

Pediatrics:
The pharmacokinetics of topotecan were studied in 12 pediatric patients treated with topotecan at doses between 2.0 and 7.5 mg/m^2 as a 24-hour continuous infusion. Mean plasma clearance was 28.3 L/h/m^2 with a range of 18.1 to 44.2 L/h/m^2. These values are similar to plasma clearance values seen in adults (approx. 36 L/h/m^2) who received 24-hour topotecan infusions.

Geriatrics:
Topotecan pharmacokinetics has not been specifically investigated in elderly patients. However, a population pharmacokinetic analysis in female patients did not identify age as a significant factor. Renal clearance is likely to be a more important determinant of topotecan clearance than age in this patient population.

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

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

Hepatic Insufficiency:
Based on clinical data and total topotecan pharmacokinetics, no dosage adjustment is required in patients with hepatic impairment (serum bilirubin < 10 mg/dL or 171 mcmol/L). Plasma clearance in patients with hepatic impairment decreased to about 67% when compared with a control group of patients. Topotecan half-life was increased by about 30%, but no change in volume of distribution was observed. Total topotecan clearance in patients with hepatic impairment only decreased by about 10% compared with the control group of patients.

Renal Insufficiency:
Plasma clearance of topotecan in patients with mild renal impairment (creatinine clearance [CrCl] of 40 to 60 mL/min or 0.67 to 1 mL/sec) decreased to about 67% compared with control patients. Volume of distribution was slightly decreased and thus half-life only increased by 14%.

In patients with moderate renal impairment (CrCl of 20 to 39 mL/min or 0.33 to 0.65 mL/sec), topotecan plasma clearance was reduced to 34% of the value in control patients. Volume of distribution also decreased by about 25%, which resulted in an increase in mean half-life from 1.9 hours to 4.9 hours. Total topotecan clearance also decreased by 57% in patients with moderate renal impairment and by 17% in patients with mild renal impairment. Based on clinical data and on total topotecan pharmacokinetics, no dosage adjustment is required for patients with mild renal impairment (CrCl 40 to 60 mL/min or 0.67 to 1 mL/sec). Dosage adjustment to 0.75 mg/m^2/day is recommended for patients with moderate renal impairment. Topotecan hydrochloride is not recommended for patients with a creatinine clearance of < 20 mL/min (0.33 mL/min).

STORAGE AND STABILITY

Unopened vials of pms-TOPOTECAN are stable until the date indicated on the package when stored between 15ºC and 30ºC and protected from light in the original package.

Reconstituted Solutions:
Vials which have been reconstituted with Water for Injection are stable for up to 24 hours when refrigerated at 5ºC or stored at 30ºC.

However, since the vials contain no preservative, it is recommended that the product should be used immediately after reconstitution. If not used immediately, the reconstituted solution should be stored in a refrigerator and discarded after 24 hours.

Diluted solutions:
Reconstituted vials of pms-TOPOTECAN diluted for infusion are stable for up to 24 hours at approximately 20ºC to 25ºC and ambient lighting conditions. If not used immediately, the diluted solution should be stored in a refrigerator in line with good pharmaceutical practice. Refrigerate if not used immediately. Discard unused portion after 24 hours.

SPECIAL HANDLING INSTRUCTIONS

Handling and Disposal:
Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-TOPOTECAN For Injection

1 mg:
Each sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base and the following non-medicinal ingredients: mannitol and tartaric acid. Hydrochloric acid and sodium hydroxide may be used to adjust to a pH of 3. The solution pH ranges from 2.5 to 3.5. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion. pms-TOPOTECAN for injection is supplied in a 1 mg (free base) single-dose vial, in a package of 1 vial.

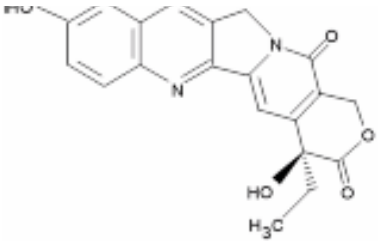
4 mg:
Each sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base and the following non-medicinal ingredients: mannitol and tartaric acid. Hydrochloric acid and sodium hydroxide may be used to adjust to a pH of 3. The solution pH ranges from 2.5 to 3.5. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by

intravenous infusion. pms-TOPOTECAN for injection is supplied in a 4 mg (free base) single-dose vial, in a package of 1 vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Topotecan hydrochloride
Chemical name:	(S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H- pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3, 14-(4H,12H)-dione monohydrochloride.
Molecular formula:	$C_{23}H_{23}N_3O_5$•HCl
Molecular mass:	457.9 g/mol
Structural formula:	

Physicochemical properties:

Description:	Topotecan hydrochloride is a yellow to yellow orange powder.
Solubility:	It is soluble in water
Melting Point:	Melts with decomposition at 213ºC to 218ºC.

CLINICAL TRIALS

Ovarian Cancer

Study Demographics and Trial Design:
Topotecan hydrochloride was studied in four clinical trials of 453 patients with metastatic ovarian carcinoma.

Patients in these four studies received an initial dose of 1.5 mg/m^2 given by intravenous infusion over 30 minutes for the first five consecutive days of a 21-day course.

In a randomized Phase III study, topotecan hydrochloride was compared with paclitaxel in patients with recurrent ovarian cancer who had failed initial treatment with a platinum containing regimen. This study treated 112 patients with topotecan hydrochloride (1.5 mg/m^2/day for the first 5 consecutive days of a 21-day course) and 114 patients with paclitaxel (175 mg/m^2 over 3 hours on day one of a 21-day course).

Response rates, response duration (measured from the time of documented response), time to progression, time to response and survival for the comparative study are provided in Table 5.

Study results:
Patients receiving topotecan hydrochloride achieved a higher response rate (21% vs. 14%, p=0.196) than those receiving paclitaxel; a longer duration of response (median of 26 vs. 22 weeks, Hazard-ratio = 0.778, p=0.476); a longer time to progression (median of 19 vs. 15 weeks, Hazard-ratio=0.764, p=0.0718); and a longer estimated median survival (63 vs. 53 weeks, Hazard-ratio=0.986, p=0.9315).

However, the median time to response was longer with topotecan hydrochloride compared to paclitaxel: median of 8 vs. 6 weeks (Hazard-ratio=0.615, p=0.1465). Consequently there is a risk of underestimating the expected efficacy of topotecan hydrochloride if patients are withdrawn from treatment prematurely (see DOSAGE AND ADMINISTRATION).

Table 5: Comparative Efficacy Parameters of topotecan hydrochloride vs. paclitaxel in Ovarian Cancer

Parameter	Topotecan hydrochloride (n=112)	Paclitaxel (n=114)
Complete Response Rate (%) Partial Response Rate (%) Overall Response Rate (%) 95% CI	4.5 16.1 20.5 (13.1, 28.0)	2.6 11.4 14.0 (7.7, 20.4)
(p-value)	(0.196)	
Response Duration (weeks) Median 95% CI	 26* (22.1, 32.9)	 22* (16.0, 34.6)
Hazard-ratio (p-value)	0.778 (0.476)	
Time to Progression (weeks) Median 95% CI	 19 (12.1, 23.6)	 15 (11.9, 18.3)

Parameter	Topotecan hydrochloride (n=112)	Paclitaxel (n=114)
Hazard-ratio (p-value)	0.764 (0.0718)	
Time to Response (weeks) Median Range	 8.0* 3.1 to 19.0	 6.0* 2.4 to 12.3
Hazard-ratio (p-value)	0.615 (0.1465)	
Survival (weeks) Median Range	 63 0.7 to 122.1	 53 0.6 to 129.9
Hazard-ratio (p-value)	0.97 (0.87)	

* topotecan (n=23) paclitaxel (n=16)

Patients who failed on the initial arm of this study were allowed to switch to the alternate treatment. Eight of 61 (13.1%) patients who received topotecan hydrochloride after paclitaxel responded. Five of 49 (10.2%) patients who received paclitaxel after topotecan hydrochloride responded.

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 seven partial responses were seen in 60 patients, for a response rate of 13%. In the same study, there were no complete responders and only four partial responders on the paclitaxel arm, for a response rate of 7%.

Topotecan hydrochloride remained active in patients who did not respond to or eventually failed paclitaxel, as shown by the responders in this trial and the trial in platinum and paclitaxel failures (see below).

The safety profile for paclitaxel in this study was consistent with the products monograph; the safety profile for topotecan hydrochloride in this study was consistent with that observed in all 453 patients from the four ovarian clinical trials (see ADVERSE REACTIONS).

The three additional studies were open-label and non-comparative in design. The first study enrolled 111 patients with recurrent ovarian cancer who had failed one prior platinum-containing regimen. The response rate was 14% (95% CI: =7.9 - 20.9%). The median duration of response was 16 weeks (range: 4.6 to 41.9 weeks). The time to progression was 11 weeks (range: 0.7 to 72.1 weeks). The median survival was 52 weeks (range: 1.4 to 72.3 weeks).

A second open study enrolled 139 patients with recurrent ovarian cancer who had failed one (62 patients) or two (77 patients) prior regimens containing platinum and paclitaxel. The response rates in this study for evaluable patients were 12.9% and 16.9%, respectively. Median response duration was 18.1 weeks. Median time to progression was 12 weeks (range: 0.6 - 52.7 weeks). Median survival was 51.3 weeks for patients failing first-line therapy.

The third open study enrolled 30 patients with recurrent ovarian cancer who had failed one or two prior platinum-containing regimens. The response rate was 13% (95% CI: =3.8 - 30.7%). The median duration of response was 28 weeks (range: 16 - 59 weeks).

Small Cell Lung Cancer

Study Demographics and Trial Design:

Topotecan hydrochloride was studied in 426 patients with recurrent or progressive small cell lung cancer in one randomized Phase III, comparative study and in three non-randomized, Phase II studies.

In a randomized, Phase III, comparative trial, 107 patients were treated with topotecan hydrochloride (1.5 mg/m^2/day x 5 days starting on day one of a 21-day course) and 104 patients were treated with CAV (1000 mg/m^2 cyclophosphamide, 45 mg/m^2 doxorubicin, 2 mg vincristine administered sequentially on day one 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 hydrochloride 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 6.

Table 6: Efficacy of topotecan hydrochloride vs. CAV (cyclophosphamide-doxorubicin- vincristine) in Small Cell Lung Cancer Patients Sensitive to First-Line Chemotherapy

Parameter	Topotecan hydrochloride (n=107)	CAV (n=104)
Complete Response Rate Partial Response Rate Overall Response Rate 95% Confidence Interval*	0.0% 24.3% 24.3% 16.17 to 32.43%	1.0% 17.3% 18.3% 10.84 to 25.7%
(p-value)	(0.285)	
Response Duration (weeks) Median 95% Confidence Interval	n=26 14.4 13.1 to 18.0	n=19 15.3 13.1 to 23.1
Hazard-ratio (topotecan hydrochloride : CAV) (p-value)	1.42 (0.30)	
Time to Progression (weeks) Median 95% Confidence Interval	 13.3 11.4 to 16.4	 12.3 11.0 to 14.1
Hazard-ratio (topotecan hydrochloride: CAV) (p-value)	0.92 (0.55)	
Survival (weeks) Median 95% Confidence Interval	 25.0 20.6 to 29.6	 24.7 21.7 to 30.3
Hazard-ratio (topotecan hydrochloride: CAV) (p-value)	1.04 (0.80)	

The calculation for duration of response was based on the interval between first response and time to progression.
* 95% confidence interval for the difference in the rate of response (6.0%) was -6.0 to 18%

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

Palliation of disease-related symptoms was greater in patients who received topotecan hydrochloride than in patients who received CAV. These clinically important improvements occurred at a higher rate in 8 of 9 symptoms in patients treated with topotecan hydrochloride. Symptom improvement was statistically significant in 5 of 9 symptoms. These data are presented in Table 7.

Patients treated with topotecan hydrochloride also experienced a longer time to worsening in 7 of 9 disease-related symptoms (shortness of breath, anorexia, interference with daily activity, cough, insomnia, hoarseness and fatigue). Time to worsening of chest pain and hemoptysis were similar for both treatment groups. Statistically significant differences in the length of time to worsening of shortness of breath (p=0.046) and anorexia (p=0.003) were noted, with the topotecan hydrochloride group worsening at a slower rate.

Table 7: Percentage of Patients with Symptom Improvement+: topotecan hydrochloride versus CAV in Patients with Small Cell Lung Cancer

Symptom	topotecan hydrochloride (n=107)		CAV (n=104)		Pearson chi-square p-value
	n++	(%)	n++	(%)	
Shortness of Breath	**68**	(27.9)	**61**	(6.6)	0.002
Interference with Daily Activity	**67**	(26.9)	**63**	(11.1)	0.023
Fatigue	**70**	(22.9)	**65**	(9.2)	0.032
Hoarseness	**40**	(32.5)	**38**	(13.2)	0.043
Cough	**69**	(24.6)	**61**	(14.8)	0.160
Insomnia	**57**	(33.3)	**53**	(18.9)	0.085
Anorexia	**56**	(32.1)	**57**	(15.8)	0.042
Chest Pain	**44**	(25.0)	**41**	(17.1)	0.371
Hemoptysis	**15**	(26.7)	**12**	(33.3)	0.706

+ defined as improvement sustained over at least 2 courses compared to baseline
++ Number of patients with baseline and at least one post-baseline assessment.

Topotecan hydrochloride (1.5 mg/m^2/day x 5 days starting on day one of a 21-day course) was also studied in three open-label, non-comparative trials in 319 patients with recurrent or progressive small cell lung cancer after treatment with first-line chemotherapy. In all three 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).

In one study, the median response rate was 15.4% for sensitive (n=52) and 2.1% for refractory patients (n=47). Median time to response was 6.1 weeks (sensitive) and 5.4 weeks (refractory). The median duration of response was 23.1 weeks (sensitive) and 24.9 weeks (refractory). Median time to progression was 13.1 weeks (sensitive) and 9.6 weeks (refractory). Median survival time was 28.3 weeks (sensitive) and 21.4 weeks (refractory). Disease-related symptoms resolved or improved versus baseline in 20% of patients (n=65), remained unchanged in 60%, or worsened in 20%.

In an EORTC (European Organization for Research and Treatment of Cancer) Study, the median response rate was 31.1% for sensitive (n=45) and 7.3% for refractory patients (n=55). Median time to response was 7 weeks for sensitive and 5.6 weeks for refractory patients. The median duration of response was 20.7 weeks (sensitive) and 30.7 weeks (refractory). Median time to progression was 17.7 weeks (sensitive) and 8.3 weeks (refractory). Median survival was 35.6 weeks (sensitive) and 20.9 weeks (refractory).

In a third study, the median response rate was 11.3% for sensitive (n=71) and 2.1% for refractory patients (n=48). Median time to response was 5.6 weeks (sensitive) and 5.7 weeks (refractory). The median duration of response was 21.9 weeks (sensitive) and 22.0 weeks (refractory). Median time to progression was 10.3 weeks (sensitive) and 6.4 weeks (refractory). Median survival time was 26.4 weeks (sensitive) and 15.9 weeks (refractory).

DETAILED PHARMACOLOGY

Pharmacokinetics

Metabolism:
Topotecan undergoes pH dependent hydrolysis, with the equilibrium favoring the ring-opened hydroxy-acid form at physiologic pH. The metabolism of topotecan in humans has not been extensively studied. However in rats and dogs, approximately 4% and 17% of the dose, respectively, was excreted as N-desmethyl derivatives of topotecan and its ring opened hydroxy-acid form. *In vitro* studies in rat, dog and human liver microsomes indicate that the rate of metabolism of topotecan to the N-demethylated metabolite in human microsomes is between that in rat and dog liver microsomes.

No other metabolite of topotecan has been identified. A major route of clearance of topotecan was by hydrolysis of the lactone ring to form the ring-opened hydroxy acid.

Drug Interactions:
When given in combination with cisplatin (cisplatin day 1, topotecan days 1 to 5), the clearance of topotecan was reduced on day 5 compared to day 1 (19.1 L/h/m^2 compared to 21.3 L/h/m^2) (see DRUG INTERACTIONS).

In vitro, topotecan did not inhibit human P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine or xanthine oxidase. Following 14 days of intravenous dosing in rats at doses up to 1.36 mg/m^2 topotecan free base, no inductive effect was observed on P450 enzymes 1A, 2B, 3A and 4A.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

The toxicity of topotecan in animals has been predictive of the toxicity observed thus far in patients, where neutropenia (the most common dose-limiting toxicity) was often associated with thrombocytopenia and anemia.

Carcinogenicity

Carcinogenicity studies are not generally performed with antineoplastic agents and have not been performed for topotecan.

Mutagenicity

Topotecan was not mutagenic in bacterial mutagenicity tests using *Salmonella typhimurium* and *Escherichia coli*. Topotecan was genotoxic in mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and in mouse bone marrow cells *in vivo*. Similar findings have been observed for another topoisomerase I inhibitor, CPT-11.

REFERENCES

1. AMA Council Report. Guidelines for handling parenteral antineoplastics. Journal of the American Medical Association 1985; 253(11):1590-1592.

2. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. American Journal of Hospital Pharmacy 1990; 47(5):1033-1049.

3. Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P et al. Topotecan, A New Active Drug in the Second-Line Treatment of Small-Cell Lung Cancer: A Phase Ii Study in Patients with Refractory and Sensitive Disease. J Clin Oncol 1997; 15(5):2090-2096.

4. Blaney SM, Balis FM, Cole DE, Craig C, Reid JM, Ames MM et al. Pediatric Phase I Trial and Pharmacokinetic Study of Topotecan Administered As A 24- Hour Continuous Infusion. Cancer Res 1993; 53(5):1032-1036.

5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. The Medical journal of Australia 1983; 1(9):426-428.

6. Creemers GJ, Bolis G, Gore M, Scarfone G, Lacave AJ, Guastalla JP et al. Topotecan, An Active Drug in the Second-Line Treatment of Epithelial Ovarian Cancer: Results of A Large European Phase Ii Study. J Clin Oncol 1996; 14(12):3056-3061.

7. Goodwin JE, Shin DD - Neutropenia. E-medicine.com. 2005

8. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from The Mount Sinai Medical Center. CA: a cancer journal for clinicians 1983; 33(5):258-263.

9. Miller AA, Hargis JB, Lilenbaum RC, Fields SZ, Rosner GL, Schilsky RL. Phase I study of topotecan and cisplatin in patients with advanced solid tumors: A cancer and leukemia group B study. J Clin Oncol 1994; 12(12):2743-2750.

10. National Study Commission on Cytotoxic Exposure-recommendations for handling cytotoxic agents.

11. O'Reilly S, Rowinsky EK, Slichenmyer W, Donehower RC, Forastiere AA, Ettinger DS et al. Phase I and Pharmacologic Study of Topotecan in Patients with Impaired Renal Function. J Clin Oncol 1996; 14(12):3062-3073.

12. OSHA. Work-Practice guidelines for personnel dealing with cytotoxic antineoplastic drugs. American Journal of Hospital Pharmacy 1986; 43(5):1193-1204.

13. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs.Superintendent.

14. Rowinsky EK, Kaufmann SH, Baker SD, Grochow LB, Chen T-L, Peereboom D et al. Sequences of topotecan and cisplatin: Phase I, pharmacologic, and *in vitro* studies to examine sequence dependence. J Clin Oncol 1996; 14(12):3074-3084.

15. Rowinsky EK, Grochow LB, Sartorius SE, Bowling MK, Kaufmann SH, Peereboom D et al. Phase I and Pharmacologic Study of High Doses of the Topoisomerase I Inhibitor Topotecan with Granulocyte Colony-Stimulating Factor in Patients with Solid Tumors. J Clin Oncol 1996; 14(4):1224-1235.

16. Talcott JA, Siegel RD, Finberg G, Goldman L. Risk Assessment in Cancer patients with Fever and Neutropenia: A Prospective Two-Center Validation of a Predication Rule. J Clin Oncol. 1992; 10(2): 316-322.

17. Product Monograph, PrHYCAMTIN®, Novartis Canada Inc., Date of revision: July 14, 2015, control number: 185244.

PART III: CONSUMER INFORMATION

[Pr]pms-TOPOTECAN
Topotecan hydrochloride for injection

This leaflet is part III of a three-part "Product Monograph" published when pms-TOPOTECAN (topotecan hydrochloride**)** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-TOPOTECAN**.** Contact your doctor or pharmacist if you have any questions about the drug.

You may want to read this leaflet again. **Please Do Not Throw It Away,** until you have finished your medicine.

ABOUT THIS MEDICATION

What the medication is used for:
pms-TOPOTECAN (topotecan hydrochloride) is used for the treatment of:
- ovarian cancer (metastatic) after failure of initial or subsequent therapy.
- sensitive small cell lung cancer after failure of first line chemotherapy (defined as recurrence at least 60 days after first line chemotherapy).

What it does:
pms-TOPOTECAN helps destroy tumors. It acts on an enzyme (topoisomerase-I) to prevent growth of tumor cells.

When it should not be used:
Do not take pms-TOPOTECAN if:
- you are hypersensitive (allergic) to topotecan or any of the other ingredients of pms-TOPOTECAN.
- you are pregnant or breast-feeding.
- you have severe kidney disease.
- results of your last blood test show that you are not able to receive pms-TOPOTECAN (severe bone marrow depression). Your doctor will tell you.

What the medicinal ingredient is:
The medicinal ingredient is topotecan hydrochloride.

What the nonmedicinal ingredients are:
The nonmedicinal ingredients consist of Hydrochloric Acid, Mannitol, Sodium Hydroxide, and Tartaric Acid.

What dosage forms it comes in:
pms-TOPOTECAN for injection is supplied as sterile powder in single-dose vials. Each vial contains 1 mg or 4 mg of topotecan. Before infusion the powder needs to be reconstituted and diluted.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

pms-TOPOTECAN should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Possible serious side effect includes:
- **a decrease in the number of cells produced in your bone marrow (bone marrow suppression), especially a type of white blood cells called neutrophils (neutropenia).**
- **Bowel inflammation which may cause severe pain in your abdomen, with fever and a decrease in white blood cells which can potentially be fatal (neutropenic colitis).**
- **Lung inflammation which may cause severe coughing, shortness of breath and fever which can potentially be fatal (interstitial lung disease).**

BEFORE you use pms-TOPOTECAN talk to your doctor or pharmacist if:
- you are hypersensitive (allergic) to topotecan or any of the other ingredients of pms-TOPOTECAN.
- you are pregnant or breast-feeding.
- results of your last blood test show that you are not able to receive pms-TOPOTECAN, your doctor will tell you.
- you have kidney disease.

Use of this medicine during Pregnancy and Breast Feeding
You should not be given pms-TOPOTECAN if you are pregnant or think you are pregnant.

Nursing Mothers
Do not breast-feed if you are receiving pms-TOPOTECAN. You should not restart breast-feeding until the doctor tells you it is safe.

Use in Children
Use in children is not recommended as safety and effectiveness have not been established.

Effect on ability to drive and use machinery
pms-TOPOTECAN may make you feel tired. Do not drive or operate any tools or machines if you feel tired or weak.

INTERACTIONS WITH THIS MEDICATION

It is important that your doctor know about all your medications so that you get the best possible treatment. Tell your doctor about all the medicines you are taking including those you have bought without a prescription.

PROPER USE OF THIS MEDICATION

Usual dose:
The dose of pms-TOPOTECAN which you will receive will be based on your body size (surface area) and the results of blood tests carried out before treatment.

The recommended dose of pms-TOPOTECAN is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day one of a 21-day course. Prior to administration, pms-TOPOTECAN powder must be dissolved with water. The pms-TOPOTECAN solution will be diluted further using either Sodium Chloride solution or Dextrose solution. A minimum of four courses of pms-TOPOTECAN is recommended.

Insufficient data are available in children to provide a dosage recommendation.

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

Overdose:

If you think you have been given too much pms-TOPOTECAN, contact your healthcare professional, hospital emergency department or regional Poison Control Centre right away, even if you do not have any symptoms.

Accidental overdosage may result in low blood pressure, fast heart rate and bleeding of the bowel.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, pms-TOPOTECAN can have side effects. The most common side effects with pms-TOPOTECAN are:

- a temporary reduction in the amount of new blood cells produced by your body, particularly of a type of white blood cell which is important for your body to prevent and fight off an infection. In approximately 1 in 20 patients a serious infection is caught during treatment which can be fatal. If at any time during treatment you feel unwell or develop a temperature you should contact your doctor immediately.
- you may become temporarily anemic and tired or take longer for a minor injury to stop bleeding. The reduction in the amount of blood cells (lasts for only a few days), starting from approximately day 8 of each treatment cycle and lasting for about a week. In most cases the level of blood cells return to normal in time for the next cycle of treatment.

Other possible side effects are:
- nausea (feeling sick or queasy or having the urge to throw up)
- vomiting (throwing up)
- diarrhea (frequent and watery bowel movements)
- fever
- hair loss
- stomach pain
- constipation
- swelling and pain of the mouth, tongue or gums
- fatigue (tiredness)
- weakness
- anorexia (weight loss and loss of appetite)
- feeling unwell
- headache
- coughing
- shortness of breath
- yellow skin (jaundice)
- rash
- itching sensation
- mild pain and inflammation at the site of injection.

Severe allergic reactions have been reported rarely.
- lung inflammation (interstitial lung disease) has been reported rarely. Signs include difficulty in breathing, severe cough and fever.

Several of these effects may occur during your treatment. If you notice any of these, or any other effects not mentioned in this leaflet between courses or when you leave hospital/after treatment has finished, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Side Effect/Symptom	Talk with your Doctor immediately
Very Common	Any sign of fever or infection, or any unexpected bruising or bleeding.	X
Common	Serious infection; local symptoms such as sore throat or urinary problems (for example, a burning sensation when urinating, which may be caused by a urinary infection).	X
Uncommon	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate, and collapse	X
Rare	Severe bleeding.	X
	Severe abdominal pain, fever and diarrhea (rarely with blood). These could be signs of bowel inflammation (colitis)	X
	Severe cough, shortness of breath, fever (interstitial lung disease). You are at increased risk if you have had radiation treatment to your lungs, or have previously taken medicines that caused lung damage.	X

This is not a complete list of side effects. For any unexpected effects while taking pms-TOPOTECAN contact your doctor or pharmacist.

HOW TO STORE IT

Unopened vials of pms-TOPOTECAN are stable until the date indicated on the package when stored between 15 ºC and 30ºC and protected from light in the original package.

Reconstituted Solutions
Vials which have been reconstituted with Water for Injection are stable for up to 24 hours when refrigerated at 5ºC or stored at 30ºC.

However, since the vials contain no preservative, it is recommended that the product should be used immediately after reconstitution. If not used immediately, the reconstituted solution should be stored in a refrigerator and discarded after 24 hours.

Diluted solutions
Reconstituted vials of pms-TOPOTECAN diluted for infusion are stable for up to 24 hours at approximately 20 ºC to 25ºC and ambient lighting conditions. If not used immediately, the diluted solution should be stored in a refrigerator in line with good pharmaceutical practice.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

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