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A DRUG NAME: TOPOTECAN

SYNONYM(S): Topotecan Hydrochloride, SKF 104864

COMMON TRADE NAME(S): Hycamtin® (GlaxoSmithKline)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Topotecan is a semi-synthetic analogue of camptothecin, an agent derived from the Oriental yew tree, *Campothecan accuminata*. The cytotoxic effects of the camptothecins are believed to be related to their activity as inhibitors of topoisomerase – I, an enzyme involved in the replication and repair of nuclear DNA. As DNA is replicated in dividing cells, topoisomerase-I acts by binding to super-coiled DNA and causing single-stranded breaks in that DNA. As a result, topoisomerase –I is able to relieve the torsional stresses that are introduced into DNA ahead of the replication complex or 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.

Oral Absorption	42% (oral formulation investigated in early clinical trials)	
Distribution	Topotecan is evenly distributed between blood cells and plasma. Pharmacokinetics are dose proportional	
	Cross blood brain barrier?	Good penetration (varies with different administration schedules)
	PPB	35%
Metabolism	Topotecan undergoes pH-dependent hydrolysis, with the equilibrium favouring the ring-opened hydroxy-acid form at physiologic pH.	
	Active metabolite(s)	Yes
	Inactive metabolite(s)	Yes
Excretion	Topotecan is eliminated primarily in the urine with some elimination via the biliary route.	
	Urine	20-60% (depends on dosing schedule)
	T _{1/2} terminal	2 – 3 hrs

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C INDICATIONS AND STATUS

- * For the treatment of metastatic cancer of the ovary after failure of initial or subsequent therapy Carcinoma of the cervix (in combination with Cisplatin)
- * For the treatment of sensitive (relapsed \geq 60 days after first line chemotherapy) small cell lung cancer after failure of first-line chemotherapy
- * *Health Canada approved indication*

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D ADVERSE EFFECTS

ORGAN SITE	SIDE EFFECT	ONSET	
Dermatologic	Rash (16%; may be severe)	I	E
	Alopecia (49%)		E
Extravasation hazard (refer to Appendix 2)	Minor local reaction	I	
Gastrointestinal	Nausea, Vomiting (64%)	I	
	Anorexia (19%)	I	
	Constipation (29%); obstruction (5%)		E
	Abdominal pain (22%)		E
	Stomatitis (18%)		E
	Diarrhea (32%), typhlitis (rare)		E
Hematologic	<u>Neutropenia</u> (78%-grade 4); Nadir 12 d		E
	<u>Thrombocytopenia</u> (<25 x 10 ⁹ /L: 27%), Nadir 15 days		E
	Bleeding (rare)		E
	Febrile neutropenia (23%, 3% fatal)		E
	Anemia (37% - grade 3 or 4)		E
Hepatic	Elevated liver enzymes/bilirubin (8%)		E
Nervous System	Headache (18%)		E
	Paresthesia (7%)		E
Other	Hypersensitivity (angioedema -rare)		E
	Fever (28%)	I	E
	Pain (23%)		E

D	ADVERSE EFFECTS (continued)		
	ORGAN SITE	SIDE EFFECT	ONSET
	Musculoskeletal	Arthralgia / myalgia (6%)	E
	Respiratory	Dyspnea (22%)	I E
		Cough; pneumonia (SCLC, 15%)	I E
		Interstitial lung disease (rare)	E D

Dose-limiting side effects are underlined.

I = immediate (onset in hours to days); E = early (days to weeks);

D = delayed (weeks to months); L = late (months to years)

Myelosuppression is the dose-limiting toxicity of topotecan, particularly neutropenia, which occurs more frequently and is often more severe than thrombocytopenia. It is dose related, reversible and non-cumulative, but complicated by infection or fever in 23% of patients and 7% of cycles. Neutropenia is more severe in heavily pre-treated patients. Decreased renal function is associated with a lower MTD and more marked neutropenia. It is recommended that topotecan be administered only to patients with adequate bone marrow reserve and is contraindicated in patients with severe renal dysfunction.

Neutropenic colitis (typhlitis/caecitis) have been reported in clinical trials. For patients who present with cough, fever, dyspnea and/or hypoxia suggestive of interstitial lung disease (ILD), treatment should be interrupted and patients should be managed accordingly. If ILD is diagnosed, topotecan should be discontinued.

Alopecia and **gastrointestinal disturbances** were the most common adverse effects related to the administration of topotecan. Prophylactic use of antiemetics was not routine in patients treated with topotecan. Most of the non-hematologic toxicities are mild to moderate in severity and not dose-limiting.

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E DOSING

Adults:

Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9/L$, a platelet count of $\geq 100 \times 10^9/L$, and a hemoglobin level of ≥ 90 g/L.

Intravenous Infusion:

Single agent: Topotecan $1.5\text{mg}/\text{m}^2$ over 30 minutes on days 1 to 5; q 21 days.

A minimum of 4 courses is recommended.

In combination: Topotecan dose adjustment is suggested. Refer to specific regimen for details.

Dosage with toxicity :

Do not retreat until neutrophils $\geq 1 \times 10^9/L$; platelets $\geq 100 \times 10^9/L$, and hemoglobin ≥ 90 g/L (after transfusion if necessary)

E

DOSING (continued)

Worst Toxicity Previous Cycle	Action ¹
Grade 4 neutropenia \geq 7 days	Reduce dose by 0.25mg/m ² OR Use G-CSF with next cycle
Febrile neutropenia	
Cycle delay for hematologic toxicity	
Platelets \leq 25 x 10 ⁹ /L	Reduce dose by 0.25mg/m ²
Grade 3 GI or organ toxicity	
Grade 4 GI or organ toxicity	Discontinue
1. Do not retreat until toxicity \leq grade 2 and ANC \geq 1.0 X 10 ⁹ /L and platelet count \geq 100 X 10 ⁹ /L.	

Dosage in renal impairment:

Creatinine Clearance (mL/min)

40-60
20-39
<20

Adjusted dose

No Change
0.75mg/m²
CONTRAINDICATED

Dosage in hepatic impairment: No dosage adjustment is required for treating patients with bilirubin < 171 μ mol/L. Total topotecan clearance in patients with hepatic impairment only decreased by about 10%, as compared to the control group of patients.

Elderly patients: No dosage adjustment needed other than for renal function as above

Children: Safety and efficacy have not been established. Preliminary data suggest pharmacokinetics similar to adults.

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ADMINISTRATION GUIDELINES (see [Appendix 3a](#))

- Mix in 50mL-100mL minibag (NS or D5W); infuse over 30 minutes.
- Final concentration should be 20 mcg - 500 mcg/mL.

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G SPECIAL PRECAUTIONS

Topotecan is **contraindicated** in patients with hypersensitivity reactions to topotecan or any of its other ingredients, in patients who already have severe bone marrow depression prior to starting the first course (neutrophils $< 1.5 \times 10^9/L$ and/or a platelets $< 100 \times 10^9/L$), and in patients with severe renal impairment (CrCl < 20 mL/min). Use with caution in patients with risk factors for pneumonitis.

The long-term **carcinogenic** potential of topotecan has not been studied. Topotecan is genotoxic, fetotoxic and teratogenic; therefore it is contraindicated in **pregnancy** and **lactation**. Adequate contraception must be used by both sexes, during treatment and for at least 6 months after topotecan cessation.

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H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cisplatin when given on day 1	Severity of myelosuppression increases	Additive	Avoid
G-CSF (concomitant)	Prolong duration of neutropenia		If G-CSF is to be used, it should not be initiated until day 6 of the course of therapy.
Cucurmin (Turmeric)	May reduce effect of topotecan	Inhibits topotecan induced apoptosis	Avoid concomitant use
Phenytoin	Decreased effect of topotecan	Increases clearance of Topotecan	Avoid or may need to increase topotecan dose

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I RECOMMENDED CLINICAL MONITORING**Recommended Clinical Monitoring****Suggested Clinical Monitoring**

- Baseline and regular CBC – counts must be assessed prior to each cycle.
- Clinical toxicity assessment of GI, dermatologic, infection, bleeding and pulmonary effects. Grade toxicity using the current [NCI Common Toxicity Criteria Version](#)
- Baseline and regular hepatic and renal function tests

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