HY:LXX

PRESCRIBING INFORMATION

HYCAMTIN®

(topotecan hydrochloride)

For Injection

FOR INTRAVENOUS USE

WARNING

HYCAMTIN (topotecan hydrochloride) for Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Therapy with HYCAMTIN should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection and death, frequent peripheral blood cell counts should be performed on all patients receiving HYCAMTIN.

DESCRIPTION

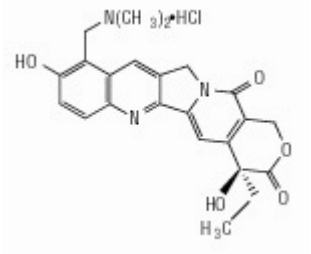
HYCAMTIN (topotecan hydrochloride) is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity.

HYCAMTIN 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.

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 monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5$•HCl and a molecular weight of 457.9.

Topotecan hydrochloride has the following structural formula:



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

CLINICAL PHARMACOLOGY

Mechanism of Action: Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

Pharmacokinetics: The pharmacokinetics of topotecan have been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30-minute infusion. Topotecan exhibits multiexponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

Metabolism and Elimination: 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.

Renal clearance is an important determinant of topotecan elimination (see Special Populations: Renal Impairment).

In a mass balance/excretion study in 4 patients with solid tumors, the overall recovery of total topotecan and its N-desmethyl metabolite in urine and feces over 9 days averaged 73.4 ± 2.3% of the administered IV dose. Mean values of 50.8 ± 2.9% as total topotecan and 3.1 ± 1.0% as N-desmethyl topotecan were excreted in the urine following IV administration. Fecal elimination of total topotecan accounted for 17.9 ± 3.6% while fecal elimination of N-desmethyl topotecan was 1.7 ±0.6%. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine. These metabolites, topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide, were less than 2% of the administered dose.

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

Geriatrics: Topotecan pharmacokinetics have not been specifically studied in an elderly population, but population pharmacokinetic analysis in female patients did not identify age as a significant factor. Decreased renal clearance, which is common in the elderly, is a more important determinant of topotecan clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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

Renal Impairment: In patients with mild renal impairment (creatinine clearance of 40 to 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to

39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Mean half-life, estimated in 3 renally impaired patients, was about 5.0 hours. Dosage adjustment is recommended for these patients (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2.0 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Pharmacokinetic studies of the interaction of topotecan with concomitantly administered medications have not been formally investigated. In vitro inhibition studies using marker substrates known to be metabolized by human P450 CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

Administration of cisplatin (60 or 75 mg/m^2 on Day 1) before topotecan (0.75 mg/m^2/day on Days 1-5 in 9 patients with ovarian cancer had no significant effect on the C_{max} and AUC of total topotecan.

Topotecan 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 before topotecan 0.3 mg/m^2 IV daily on days 2-6. Topotecan had no effect on dose-normalized (60 mg/m^2) C_{max} values of free platimun 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 before topotecan 0.75 mg/m^2 IV daily on days 1-5.

No pharmacokinetic data are available following topotecan (0.75 mg/m^2/day for 3 consecutive days) and cisplatin (50 mg/m^2/day on day 1) in patients with cervical cancer.

Pharmacodynamics: The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases with increasing topotecan dose or topotecan AUC. When topotecan is administered at a dose of 1.5 mg/m^2/day for 5 days, an 80% to 90% decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

CLINICAL STUDIES

Ovarian Cancer: HYCAMTIN 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 studies 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 study was a randomized trial of 112 patients treated with HYCAMTIN (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 study therapy, or who progressed, could be given the alternative treatment.

Response rates, response duration, and time to progression are shown in Table 1.

Table 1. Efficacy of HYCAMTIN Versus Paclitaxel in Ovarian Cancer

Parameter	HYCAMTIN (n = 112)	Paclitaxel (n = 114)
Complete response rate	5%	3%
Partial response rate	16%	11%
Overall response rate	21%	14%
95% Confidence interval	13 to 28%	8 to 20%
(p-value)	(0.20)	
Response duration* (weeks)	n = 23	n = 16
Median	25.9	21.6
95% Confidence interval	22.1 to 32.9	16.0 to 34.0
hazard-ratio (HYCAMTIN:paclitaxel)	0.78	
(p-value)	(0.48)	
Time to progression (weeks)		
Median	18.9	14.7
95% Confidence interval	12.1 to 23.6	11.9 to 18.3
hazard-ratio (HYCAMTIN:paclitaxel)	0.76	
(p-value)	(0.07)	
Survival (weeks)		
Median	63.0	53.0
95% Confidence interval	46.6 to 71.9	42.3 to 68.7
hazard-ratio (HYCAMTIN:paclitaxel)	0.97	
(p-value)	(0.87)	

* 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 HYCAMTIN compared to 6.0 weeks (range 2.4 to 18.1) with paclitaxel. Consequently, the efficacy of HYCAMTIN may not be achieved if patients are withdrawn from treatment prematurely.

In the crossover phase, 8 of 61 (13%) patients who received HYCAMTIN after paclitaxel had a partial response and 5 of 49 (10%) patients who received paclitaxel after HYCAMTIN had a response (2 complete responses).

HYCAMTIN 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 study, there were no complete responders and 4 partial responders on the paclitaxel arm, for a response rate of 7%.

HYCAMTIN 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).

Small Cell Lung Cancer: HYCAMTIN was studied in 426 patients with recurrent or progressive small cell lung cancer in 1 randomized, comparative study and in 3 single-arm studies.

Randomized Comparative Study: In a randomized, comparative, Phase 3 trial, 107 patients were treated with HYCAMTIN (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 ≥60 days after completion of first-line therapy). A total of 77% of patients treated with HYCAMTIN 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 2.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.