These records are from CDER's historical file of information previously disclosed under the Freedom of Information Act (FOIA) for this drug approval and are being posted as is. They have not been previously posted on Drugs@FDA because of the quality (e.g., readability) of some of the records. The documents were redacted before amendments to FOIA required that the volume of redacted information be identified and/or the FOIA exemption be cited. These are the best available copies.

NDA20-671

NDA 20-671

Ap Ltr
Proposed LBL9
MOR
Exclusivity Summ.
Ped. Pts
Clin. Pharm + Bio
Pharm/Tox

Stat
Micro
Chem
E.A. + Fonsi
FDA Corres
memos
Co. Corres
ODAC mins +
Slides 2/24/96

AP Ltr
Draft LBLG

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-671

MAY 28 1996

SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

Attention: Richard Swenson, Ph.D.
Associate Director, U.S. Regulatory Affairs

Dear Dr. Swenson:

Please refer to your December 21, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hycamtin™ (topotecan hydrochloride) 4 mg for Injection.

We acknowledge receipt of your amendment dated May 10, 1996.

This new drug application provides for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-671. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments to:

1) provide updated survival and other efficacy data for studies 39, 34, and 33.

2) assure that the DMF holder, will provide FDA a copy of the English translation of the master production record of in a reasonable time. The record needs to be reviewed and found acceptable by the Agency before production of new batches of commences in . (enough lead time should be allowed for necessary revisions, if any).

3) for the annual stability study of future batches of topotecan drug substance under long term storage conditions, follow the same study protocol as described in the NDA for the stability study of the validation batches.

Please submit the above information to the NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Debra Catterson, R.Ph.
Project Manager
(301) 827-1544

Sincerely yours,

Robert Temple 5/28/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-671
HFD-150/Div. files
HFD-150/CSO/D.Catterson
HFD-150/SHirschfeld
HFD-150/YHsieh
HFD-150/WMcGuinn
HFD-860/PZannikos
HFD-710/VBerger
HFD-710/GChi
HFD-2/M.Lumpkin
HFD-101/L.Carter
HFD-101/L.Carter (with labeling)
HFD-810/C.Hoiberg
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) - for all NDAs and supplements for adverse reaction changes.
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)
HFD-021/J.Treacy (with labeling)
HFR-MA100

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r/d Initials:
/DPease/5.28.96
/SHirschfeld/5.28.96
/RJustice/5.28.96
/YHsieh/5.28.96
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/WMcGuinn/5.28.96
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/ARahman/5.28.96
/VBerger/5.28.96
/CGnecco/5.28.96
/CHoiberg/5.28.96

APPROVAL [with Phase 4 Commitments]

XX:L1

Prescribing Information

HYCAMTIN™

brand of 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 1500 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

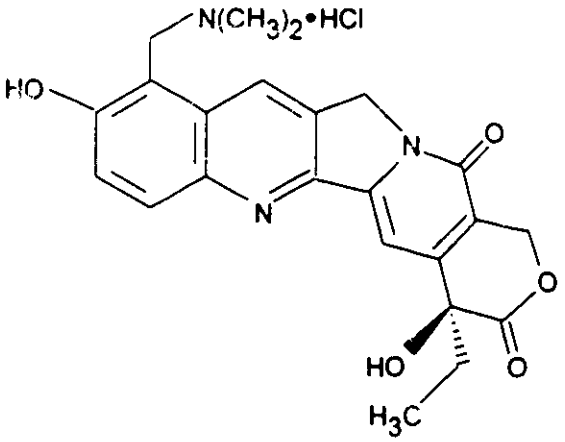
Hycamtin (topotecan hydrochloride) is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity.

Hycamtin (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.

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 $\leq$ 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 that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway.

In humans, about 30 % of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination (see Special Populations).

Special Populations

Gender: The overall mean topotecan plasma clearance in male patients was approximately 24 % higher than 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, common in the elderly, is a more important determinant of topotecan clearance.

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} 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 three 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 - 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 dihydropyridine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo*.

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 - 90 % decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

CLINICAL STUDIES:

Hycamtin (topotecan hydrochloride) was studied in four clinical trials of 452 patients with metastatic ovarian carcinoma. All patients had disease that had recurred on , or was unresponsive to, a platinum-containing regimen. Patients in these four 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 one of a 21-day course.

Two of the studies, involving 223 patients given topotecan, are mature enough for evaluation (although survival results are incomplete). Hycamtin was compared with paclitaxel in a randomized trial involving 112 patients treated with Hycamtin (1.5

mg/m^2/d x 5 days starting on day one 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 one 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 (measured from the time of documented response), and time to progression are shown in Table 1.

Table 1. Efficacy of Hycamtin vs Paclitaxel in Ovarian Cancer

Parameter	*Hycamtin* (n=112)	Paclitaxel (n=114)
Complete Response Rate	5.4%	3.5%
Partial Response Rate	14.3%	8.8%
Overall Response Rate	19.6%	12.3%
95% CI	12.8-28.2 %	6.9-19.7%
(p-value)	(0.0918)	
Response Duration (weeks)		
Median	22.2	12.0
Range	5.1+ to 31.6+	4.8+ to 21.0+
hazard-ratio (Hycamtin:paclitaxel)	0.276	
(p-value)	(0.065)	
Time to Progression (weeks)		
Median	23.1	14.0
Range	0.7+ to 62.1+	0.1 to 30.9
hazard-ratio (Hycamtin:paclitaxel)	0.578	
(p-value)	(0.002)	

+value corresponds to a censored event; i.e., patient had not yet progressed

The calculation for duration of response was based on the interval between best response and time to progression, not from time of enrollment nor from time of initial response to time to progression.

The time to response was longer with Hycamtin compared to paclitaxel with a mean of 10 weeks (range 5.4- 31.6) vs 7 weeks (range 4.8 - 9.4). Consequently, the efficacy of Hycamtin may be decreased if patients are withdrawn from treatment prematurely.

In the crossover phase, in patients who did not respond to treatment on the initial arm of the trial, 5 of 53 (9.4%) patients who received Hycamtin after paclitaxel had a partial response and 1 of 37 (2.7%) patients who received paclitaxel after Hycamtin had a complete response.

Hycamtin was active in 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 four partial responders on the paclitaxel arm, for a response rate of 7%.

The adverse reaction profile for paclitaxel in this study was consistent with the product's approved labeling; the adverse reaction profile for Hycamtin in this study was consistent

with that obse. ved in all 452 patients from the four ovarian cancer clinical trials (see ADVERSE REACTIONS).

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 one prior platinum-containing regimen. The response rate was 14% (95% CI =7.9% to 20.9%). The median duration of response was 18 weeks (range 5-42 weeks). The time to progression was 8.4 weeks (range: 0.7 to 72.1 weeks).

INDICATIONS AND USAGE

Hycamtin (topotecan hydrochloride) is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

CONTRAINDICATIONS

Hycamtin is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan.

Neutropenia: Severe (grade 4, <500 cells/mm^3) neutropenia was most common during course 1 of treatment (60% of patients) and occurred in 40% of all courses. The nadir neutrophil count occurred at a median of 11 days. Prophylactic G-CSF was given in 27%

of courses after the first cycle. Therapy-related sepsis or febrile neutropenia occurred in 26% of patients and sepsis was fatal in 0.8%.

Thrombocytopenia: Grade 4 thrombocytopenia (<25,000/mm^3) occurred in 26% of patients and in 9% of courses, with a median duration of 5 days and platelet nadir at a median of 15 days. There were no episodes of serious bleeding. Platelet transfusions were given to 13% of patients and in 4% of courses.

Anemia: Severe anemia (grade 3/4, <8gm/dL) occurred in 40% of patients and in 16% of courses. Median nadir was at Day 15. Transfusions were needed in 56% of patients and in 23% of courses.

Monitoring of Bone Marrow Function: Hycamtin should only be administered in patients with adequate bone marrow reserves, including baseline neutrophil counts of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with Hycamtin. Patients should not be treated with subsequent courses of Hycamtin until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3 and hemoglobin levels recover to 9.0 mg/dL, (with transfusion if necessary). Severe myelotoxicity has been reported when Hycamtin is used in combination with cisplatin (see Drug Interactions)

Pregnancy: Hycamtin may cause fetal harm when administered to a pregnant woman. The effects of topotecan on pregnant women have not been studied. If topotecan is used during a patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming pregnant. Topotecan caused embryonic and fetal death in rats and rabbits. In rabbits, a dose of 0.32 mg/kg/d (about twice the clinical dose on a mg/m^2 basis) on days six through twenty of gestation caused fetal resorption. This dose caused significant maternal toxicity. In the rat, a dose of 0.23 mg/kg/d (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day six caused fetal resorption, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/d (about half the clinical dose on a mg/m^2 basis) given to rats on days six 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), scull and vertebrae.

PRECAUTIONS

General: Inadvertent extravasation with Hycamtin has been associated with only mild local reactions such as erythema and bruising.

Hematology: Monitoring of bone marrow function is essential (see **WARNINGS** and **DOSAGE AND ADMINSTRATION)**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity testing of topotecan has not been performed. Topotecan, however, is known to be genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

Drug Interactions:

Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should not be initiated until day 6 of the course of therapy, 24 hours after completion of treatment with Hycamtin [1].

Myelosuppression was more severe when Hycamtin was given in combination with cisplatin in Phase 1 studies. In a reported study on concomitant administration of cisplatin 50 mg/m^2 and Hycamtin at a dose of 1.25 mg/m^2 /day x 5 days, one of three patients having neutropenia for 12 days and a second patient died with neutropenic sepsis. There are no adequate data to define a safe and effective regimen for Hycamtin and cisplatin in combination.

Pregnancy: Pregnancy Category D. (See WARNINGS section.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving Hycamtin (see CONTRAINDICATIONS).

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

ADVERSE REACTIONS

Data in the following section are based on the experience of 452 patients with metastatic ovarian carcinoma treated with Hycamtin. Table 2 lists the principal hematologic toxicities and Table 3 lists non-hematologic toxicities occurring in at least 19% of patients.

Table 2: Summary of Hematologic Adverse Events in Patients Receiving Hycamtin

Hematologic Adverse Events	Patients n=452 % Incidence	Courses n=2375 % Incidence
Neutropenia		
<1,500 cells/mm^3	98	78
<500 cells/mm^3	81	40
Leukopenia		
<3,000 cells/mm^3	98	77
<1,000 cells/mm^3	32	11
Thrombocytopenia		
<75,000/mm^3	63	39
<25,000/mm^3	26	9
Anemia		
<10 g/dL	95	76
<8 g/dL	40	16
Sepsis or fever/infection with Grade 4 neutropenia	26	7
Platelet transfusions	13	4
RBC transfusions	56	23

Table 3: Summary of Non-hematologic Adverse Events in Patients Receiving Hycamtin

Non-hematologic Adverse Events	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	n=452 Patients	n=2375 Courses	n=452 Patients	n=2375 Courses	n=452 Patients	n=2375 Courses
Gastrointestinal						
Nausea	77	50	10	3	<1	<1
Vomiting	58	26	6	3	3	<1
Diarrhea	42	19	4	1	<1	<1
Constipation	39	18	2	<1	1	<1
Abdominal Pain	33	13	4	<1	2	<1
Stomatitis	24	9	2	<1	<1	<1
Anorexia	19	8	2	<1	0	0
Body as a Whole						
Fatigue	37	25	6	2	0	0
Fever	34	13	1	<1	<1	<1
Asthenia	21	10	3	<1	1	<1
Skin/Appendages Alopecia	59	62	NA	NA	NA	NA

Premedications were not routinely used in these clinical studies.

Table 4 shows the grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/paclitaxel comparator trial (including adverse events in patients who crossed over to the alternative treatment).

Table 4 Comparative Toxicity Profiles

	Hycamtin		Paclitaxel	
Adverse Event	**Pts**	**Courses**	**Pts**	**Courses**
	n= 165	n= 731	n= 151	n=676
Hematologic Grade 3/4	%	%	%	%
Grade 4 neutropenia (< 500 cells/mL)	80.0	38.2	19.9	8.7
Grade 3/4 Anemia (Hgb < 8g/dL)	40.6	25.3	18.5	17.2
Grade 4 Thrombocytopenia (< 25 000 plts/mL)	21.8	7.0	0.7	0.1
Fever/Grade 4 neutropenia	21.2	5.7	4.0	0.9
Documented Sepsis	5.5	1.2	1.3	0.3
Death related to Sepsis	1.8	0.4	0.0	0.0
Non-hematologic Grade 3/4				
Gastrointestinal				
Nausea	10.3	3.6	3.4	0.7
Vomiting	9.1	2.3	4.0	0.9
Constipation	4.9	1.2		0
Diarrhea	5.5	1.5	0.7	0.2
Abdominal pain	6.1	2.6	5.4	1.3
Intestinal Obstruction	4.8	1.6		0
Stomatitis	1.8	0.4	0.7	0.2
Constitutional				
Fatigue	6.7	2.2	4.7	1.8
Fever	6.7	1.5	1.3	0.3
Dyspnea	6.1	2.3	4.0	1.0
Neuromuscular				
Arthralgia	1.2	0.4	2.0	0.4
Asthenia	5.5	1.4	4.0	1.6
Myalgia	0	0	2.7	1.5
Pain	1.8	0.6	1.3	0.6
Paresthesia	1.2	0.4	0	0

Hematologic: (See WARNINGS)

Gastrointestinal: The incidence of nausea was 77% (10% grade 3/4) and vomiting occurred in 58% (9% grade 3/4) of patients (See Table 3). The prophylactic use of anti-emetics was not routine in patients treated with Hycamtin. Forty-two % of patients had diarrhea (5% grade 3/4) , 39% constipation (3% grade 3/4) and 33% had abdominal pain (6% grade 3/4).

Skin/Appendages: Total alopecia (Grade 2) occurred in 42% of patients.

Central and Peripheral Nervous System: Headache (21%) was the most frequently reported neurologic toxicity. Paresthesia occurred in 9% of patients but was generally Grade 1.

Liver/Biliary: Grade 1 transient elevations in SGOT/AST and SGPT/ALT occurred in 5% of patients. Greater elevations, grade 3/4 , occurred in <1%. Grade 3/4 elevated bilirubin occurred in <3% of patients.

Respiratory: Dyspnea (20%); Grade 3/4 dyspnea (4%).

OVERDOSAGE

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

The LD_{10} in mice receiving single intravenous infusions of Hycamtin was 75 mg/m^2 (CI 95%: 47 to 97).

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of Hycamtin, patients must have a baseline neutrophil count of >1500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended dose of Hycamtin (topotecan hydrochloride) 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. A minimum of four courses is recommended because median time to response in three clinical trials was 9 to 12 weeks. In the event of severe neutropenia during any course, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. Alternatively, in the event of severe neutropenia, G-CSF may be administered following the subsequent course (before resorting to dose reduction) starting from Day 6 of the course (24 hours after completion of topotecan administration).

Adjustment of Dose in Special Populations

Hepatic Impairment: No dosage adjustment appears to be required for treating patients with impaired hepatic function (plasma bilirubin >1.5 to <10 mg/dL).

Renal Functional Impairment: No dosage adjustment appears to be required for treating patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20 to 39

mL/min). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

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

PREPARATION FOR ADMINISTRATION

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

Preparation for Intravenous Administration:

Each Hycamtin 4 mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of Hycamtin (topotecan hydrochloride) are stable until the date indicated on the package when stored between 20° and 25°C (68° and 77°F) and protected from

light in the original package. Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of Hycamtin diluted for infusion are stable at approximately 20° to 25 °C (68° to 77°F) and ambient lighting conditions for 24 hours.

HOW SUPPLIED

NDC 0007-4201-05: Hycamtin (topotecan hydrochloride) for Injection is supplied in 4 mg (free base) single-dose vials, in packages of 5 vials.

Storage: Store the vials protected from light in the original cartons at controlled room temperature between 20° and 25°C (68° and 77°F).

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES:

1. Rowinsky, 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;14:1224-1235.

2. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402

3..AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253(11):1590-1592.

4. National Study Commission on Cytotoxic Exposure-recommendations for handling cytotoxic agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences. 179 Longwood Avenue, Boston, Massachusetts, 02115

5 Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Austr 1983;1:426-428.

6.Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept./Oct. 258-263.

7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hos Pharm 1990; 47:1033-1049.

8. OSHA Work-Practice guidelines for personnel dealing with cytotoxic(antineoplastic) drugs. Am J Hosp Pharm 1986; 43:1193-1204.

DATE OF ISSUANCE (MONTH, YEAR)

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SmithKline Beecham Pharmaceuticals

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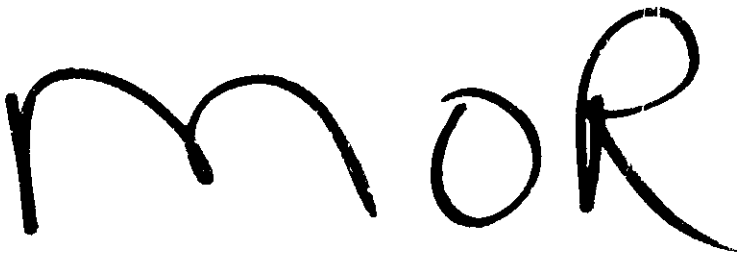

MEDICAL REVIEW OF NDA 20-671: Hycamtin® (Topotecan)

APPLICANT: Smith Kline Beecham

REVIEWING MEDICAL OFFICER: Steven Hirschfeld, MD., Ph.D.

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1.0 GENERAL INFORMATION 4

2.0 INTRODUCTION 5

3.0 DESCRIPTION OF CLINICAL DATA SOURCES 8

4.0 REGULATORY HISTORY 9

5.0 LIST OF INDS AND NDAS 12

6.0 CONTROLLED CLINICAL STUDY 039 13

6.1 Study Design and Objectives 13

6.2 Overview of Demographics, Treatment and Efficacy Results 18

6.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables 24

6.4 Adverse Experience and Safety Data 29

6.5 Reviewer's Conclusion 41

7.0 NONCOMPARATOR CLINICAL STUDY 031 41

7.1 Study Design and Objectives 41

7.2 Overview of Demographics, Treatment and Efficacy Results 45

7.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables 52

7.4 Adverse Experience and Safety Results 54

7.5 Reviewer's Conclusion 61

8.0 SUMMARY OF EFFICACY IN OVARIAN CANCER STUDIES 61

10.0 FOUR MONTH SAFETY UPDATE 82

10.1 Background 82

10.2 Drug-related Adverse Events 84

10.3 Serious Adverse Events 87

10.4 Adverse Events Leading to Treatment Withdrawal 90

10.5 Deaths 92

10.6 Clinical Laboratory Data 96

10.7 Sponsor's Conclusions 96

11.0 REVIEWER'S CONCLUSIONS 96

12.0 ODAC MEETING, APRIL 19, 1996 98

13.0 PRODUCT LABELLING COMMENTS 99

14.0 RECOMMENDED REGULATORY ACTION 122

15.0 DEFICIENCY LIST 123

1.0 GENERAL INFORMATION

Drug Name:	Hycamtin® (topotecan)
Applicant:	Smith Kline Beecham
NDA Submission Date:	December 21, 1995
Electronic Data Files Installed:	January 26, 1996
Pharmacologic Category.	Topoisomerase I inhibitor
Proposed Indication:	Ovarian cancer second line therapy
30-Day Meeting:	January 21, 1996
45-Day Meeting:	February 5, 1996
Safety Update:	April 30, 1996
ODAC Meeting:	April 19, 1996

2.0 INTRODUCTION

Ovarian Cancer

Ovarian cancer is potentially one of the most treatable gynecological malignancies since most tumors are sensitive to anticancer therapy; however, due to difficulties in detecting disease in the population most at risk, most women present with advanced or disseminated disease and it is the leading cause of death among women with gynecological malignancies. Ovarian cancer comprises about 4% of the total annual cases of cancer in the United States, with approximately 21,000 new cases. In 1992, about 13,000 women died from the disease, which is about 6% of all cancer deaths among women and 1% of all deaths. The peak incidence of the disease is highest in white women in their sixties, and only between 10 and 15 % of cases affect women who are less than 50 or premenopausal. The incidence is significantly lower outside industrial countries, and has been linked to a high fat diet, although speculation exists concerning environmental pollutants gaining access to the genital tract. There is an association between exposure to asbestos and talc and the development of ovarian cancer.

There is a decrease in the risk for women who are multiparous, with one or two pregnancies giving reducing the risk by about 50% and three or more reducing the risk to 33% compared to women who are nulliparous. The use of oral contraceptives can also reduce the risk by about 25%. The inference from these observations is that continuous ovulation is a risk factor. There is an association with breast cancer in that women who have had breast cancer have a twofold increase in the risk for ovarian cancer and women with ovarian cancer have a three to four fold increase in the risk for breast cancer.

Classification of ovarian tumors depends upon the probable tissue of origin. Most ovarian tumors develop from the surface of the ovary, and are of the epithelial type. In the North America and Europe, the incidence is from 85 to 90%. The remainder are derived from germ or stromal cells. In women under 40 years of age, epithelial types are uncommon and in women under 30, the histology is primarily germ cell. The epithelial ovarian cancers can be grouped in eight histologic types. The majority or about 75% are serous type, followed by mucinous, endometrioid, clear cell, mixed type, Brenner, and undifferentiated. The last category consists of unclassified cells such as mesotheliomas.

The tumor develops typically on the surface of the organ and is clinically silent. The peritoneum can function as a partially immunoprivileged site, and this may

account for the fact that local spread is by surface shedding, lymphatics, and rarely, hematogenously.

Ovarian tumor cells lose the capacity to be growth inhibited by transforming growth factor beta, which normally functions as an autocrine regulator of normal ovarian epithelium. Ovarian tumors exhibit other features of growth dysregulation by producing macrophage colony stimulating factor (M-CSF) and the *fms* oncogene product, which is a receptor for M-CSF. About 30% of tumors also produce the *HER-2/neu* oncogene, which can function as an epidermal growth factor receptor and is associated with a poor prognosis.

Many tissues, but particularly the coelemic epithelial cells of the ovary produce a glycoprotein termed CA -125. Serum levels of this molecule can be used to monitor disease response or progression; however, in practice it lacks the sensitivity and specificity to be a unique tumor marker. In the context of a post menopausal woman with a pelvic mass, levels of CA-125 above 35 U/ml are 80% predictive for a malignancy and levels above 95 U/ml are greater than 95% predictive.

The diagnosis ultimately depends upon tissue obtained during a staging laporatomy, and if the histology is positive for malignancy, cytoreductive surgery is usually performed during the same procedure. This is the primary modality of treatment. The greater the extent of tissue removal, the better the prognosis and the better the response to subsequent therapy.

The International Federation of Gynecology and Obstetrics (FIGO) in 1987 and 1988 defined four stages of primary carcinoma of the ovary. In Stage I disease carcinoma is limited to the ovaries. Stage II disease is defined as carcinoma involving one or both ovaries with pelvic extension. In Stage III disease tumor has spread to involve the peritoneum outside the true pelvis and/or the retroperitoneal or inguinal nodes. Ovarian carcinoma with disseminated metastases including parenchymal liver metastases constitutes Stage IV disease.

Patients with Stage III and IV disease are treated with systemic chemotherapy. Historically, single agent studies using DNA alkylators such as melphalan, cyclophosphamide, chlorambucil and thiotepa have shown response rates of 30 to 65 % with median survival of 10 to 14 months. Other classes of cytotoxic drugs such as antimetbolites, antibiotics, plant alkaloids and cis- and carboplatin have shown activity and response rates from 25 to 50%. Since the first demonstrations of superiority in complete response rates and disease free

survival in 1978 with combination regimens, current practice is to follow cytoreductive surgery with combination systemic chemotherapy based on a cis- or carboplatin regimen in combination with either cyclophosphamide or paclitaxel for 6 cycles. Therapy results in complete response rates of about 30 to 35% and overall response rates of about 80%. The probability of remission depends upon the amount of residual disease. Median survival in several studies is about 2 years, and 5 year survival is 20-25 %.

Despite the best available chemotherapy, most patients with advanced ovarian cancer will die of their disease. Furthermore, the patients with ovarian cancer refractory to platinum based regimens have response rates less than 10-20% to second-line therapy. The group of patients with recurrent ovarian carcinoma (relapse at least six months after achieving a complete response) is quite heterogeneous. Reinduction with a platinum based regimen is the therapy of choice, with response rates in the range of 20-50%.

Topotecan - Background And Therapeutic Rationale

Topotecan (SK&F 104864) is a semisynthetic analog of the alkaloid camptothecin, which incorporates a stable basic side-chain at the 9-position of the A-ring of 10-hydroxycamptothecin, and retains the S-configuration at the chiral carbon-20. The basic side-chain affords water solubility to the compound without requiring hydrolysis of the E ring lactone, which is required for biologic activity.

Camptothecin was initially isolated from the stemwood of the tree *Captotheca acuminata*, and showed activity against murine leukemia. In entered clinical trials in 1970, but had secondary effects of severe myelosuppresion, alopecia and hemorrhagic cystitis.

Like camptothecin, topotecan is a specific inhibitor of topoisomerase-I, forming a covalent bond with the enzyme via the E ring lactone. Inhibition of this enzyme results in lethal DNA damage during the course of DNA replication. Topoisomerase-I has been demonstrated to be intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Binding to and inactivation of topoisomerase I prevents reannealing of the strands of DNA. Inhibitors of topoisomerases are unique in that they do not cause cytotoxicity by depleting the product of their target enzymes, but by producing DNA damage by interfering with topoisomerase function. Therefore, drug activity is directly proportional to target enzyme level rather than inversely proportional to target enzyme level, which is the case for

many cytotoxic enzyme inhibitors. Topoisomerase-I activity is not linked to proliferation rate and similar enzyme activities can be detected in slowly proliferating or quiescent cells. Thus, topotecan has the potential for activity against human solid tumors that tend to proliferate slowly and are generally refractory to most of the established anticancer drugs. In contrast to camptothecin, the absence of a hydrolyzed E ring whose conformation is pH dependent (acidic pH favoring the lactone and neutral pH favoring the inactive carboxylate), may account for the decreased hemorrhagic cystitis.

3.0 DESCRIPTION OF CLINICAL DATA SOURCES

Volume 1.1 of the December 21, 1995 submission contains the index to the application, proposed text of the labeling for topotecan, and summaries of the chemistry, manufacturing, and controls, the nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, the clinical data summary, a discussion of the proposed benefit/risk relationship, and the proposed post marketing studies. The volumes devoted to the clinical section are volumes 1.34 to 1.149 and the case report forms are in volume 1.241. The volumes devoted to the clinical section are summarized below.

Clinical Pharmacology	1.34
Controlled Studies:	
034 Open Multicenter Phase II Study-Advanced Epithelial Ovarian Cancer	1.73 to 1.84
039 Open-Label Multicenter Randomized Phase III Study of Topotecan versus Paclitaxel- Advanced Epithelial ovarian Cancer	1.40 to 1.66
Other Studies	
004 Phase I Continuous 24 hour infusion	1.35
005 Phase I daily times 5-Solid tumors	1.36
097 Phase I Study in Cancer Patients with Hepatic or Renal Dysfunction	1.38
047 Single dose oral bioavailability	1.39
012 Open Phase II daily times 5 every 21 days-Advanced Epithelial Ovarian Cancer	1.67
033 Open Multicenter Phase II of daily times 5 every 21 days in Patients with Advanced Epithelial Ovarian Cancer who failed prior chemotherapy with paclitaxel and either cisplatin or carboplatin	1.85
051 Open Phase II continuous 21 day infusion every 28 days in Patients with Advanced Epithelial	1.123

An electronic submission was provided in which the NDA summary, the technical summaries, and several sections of the complete NDA were included for viewing using Folio Views, a Windows- based text retrieval system. The complete submission was available for viewing as scanned images using TIM Smart View, a Windows-based image viewer. On February 5, 1996, partial data files from the two controlled trials, 034 and 039, were made available as SAS for Windows files on diskettes, and on February 12 more complete data was made available on CD-ROM . Additional data files as floppy disks were provided on March 5, 1996 and March 15, 1996. Smith Kline Beecham provided the review team with two external CD-ROM readers to access these files.

4.0 REGULATORY HISTORY

This section is quoted from the NDA.

Background

Initial Phase I studies with topotecan evaluated a number of different dosing schedules including single infusion, daily infusion and continuous infusion regimens. Objective tumor responses were seen in Phase I studies that evaluated a 30 minute infusion schedule given on five consecutive days every three weeks. There was concurrence on the maximum tolerated dose on this regimen at 1.5 mg/m2/day. These clinical data, together with pre-clinical evidence that more prolonged exposure of tumors or tumor cells to topotecan would enhance activity, lead to this schedule being evaluated further in Phase II studies in preference to single administration schedules.

An early SB sponsored Phase II, single institution study (012), confirmed that topotecan was active in patients with platinum resistant ovarian carcinoma. An objective response rate of 13% was seen in 30 patients who had received no more than two prior regimens. More than 80% of the patients in this study were platinum resistant. A larger Phase II study (034) was subsequently initiated in Europe in patients failing a single platinum based regimen and it was decided that an initial filing for this indication would be targeted.

Two further studies in patients with metastatic ovarian cancer who had failed first-line therapy were agreed with the FDA. One study (039) was to be a randomized, comparative study with paclitaxel and the other (033) a study in patients who had failed a combination of paclitaxel and cisplatin or carboplatin. These studies were discussed at the end of Phase II meeting described in the next section.

End of Phase II Meeting, 11 May 1993

The plans for development of topotecan in ovarian cancer patients were discussed at an End of Phase II meeting with FDA held on 11 May 1993. At this meeting the recommendations of FDA were accepted by SB including comments on a proposed randomized, comparative Phase II/III study of topotecan against paclitaxel (study 039), in which it was suggested that patients be allowed to switch from their randomized therapy to the alternate treatment. An additional study was recommended by FDA of topotecan in patients who had failed a first-line combination of paclitaxel and cisplatin or carboplatin (study 033). The latter study was influenced by the anticipated presentation of data from a study of paclitaxel and cisplatin in the first-line therapy of ovarian cancer. It was agreed that combined European and US trials would be acceptable. Communication subsequent to the End of Phase II meeting related mainly to the randomized, comparative study 039. There were no substantial issues on study 033.

Subsequent communication on 3 June 1993 from SB and 29 June 1993 attempted to clarify some items including the re-treatment criteria for patients in the randomized study (study 039). FDA stated they imposed no requirement with respect to equal neutrophil counts prior to re-treatment with topotecan and paclitaxel, but that allowing a lower threshold for retreatment with topotecan would have to be justified with clinical data.

On 1 March 1994, FDA made comments following review of Protocol 039. Comments included a statement that FDA would prefer that SB use the same re-treatment criteria for neutrophil count in both arms of the study. In addition concerns about country differences in the use of G-CSF were made and comments were made on the power of the study. SB responded on 25 May 1994 that there was justification for the re-treatment value based on experience with topotecan and that SB was not aware of the full database upon which the dosing recommendations of paclitaxel were based. SB stated they could not control the use of G-CSF across countries in this international study. To address the comments on the power of the study, the statements by FDA made at the End of Phase II meeting were re-stated, namely, study 039 was not designed for formal statistical comparison between treatment arms. Subsequent correspondence by

FDA on 11 July 1994 acknowledged SB's position on the above issues but recommended that stratification by center would be one way of addressing differences in use of G-CSF. On the 28 July 1994 SB responded that stratification by center would be impractical and that SB felt the use of G-CSF in this study would be minimal.

On 26 October 1994 a letter received from FDA raised an unresolved issue on the date of closure of study 039 and restated a preference for stratification by center. To resolve these issues it was agreed that at the end of a teleconference to discuss a different indication, discussion would continue on the unresolved issues with study 039. At the teleconference on 9 November 1994 it was agreed that study 039 would close for analysis 20 weeks following the enrollment of the last patient. This would allow the last patient to receive six courses of therapy if there were no substantial dose delays. It was agreed that given the number of strata already in the study (16), the number of centers (>30) and the status of the study, which was more than half enrolled, it was impractical to stratify. Additional comments included FDA emphasis of the importance of the data following cross-over from paclitaxel to topotecan, which could support a favorable labeling claim. A short discussion on the slow recruitment to study 033 followed, and it was agreed that patients failing second-line therapy who had received both a platinum containing regimen and paclitaxel would be allowed into the study. The study plan would be to enroll 50 patients failing first-line and 50 patients failing second-line paclitaxel/platinum therapy. The only previous issue that had arisen on this study was the assessment of patient benefit, which had been addressed by the inclusion of a quality of life questionnaire.

Pre-NDA Meeting, 8 September 1995

At this meeting no major issues were identified on the proposed format of the clinical section of the topotecan NDA.

FDA requested that SB include an analysis of data that included all patients randomized to treatment for study 039, in addition to the SB defined intent to treat analysis, which included all patients receiving at least one dose of topotecan. It was noted that this would only be possible for response rate, since patients would not have time to event variables. Brief narratives would be included in the study reports for the patients who were randomized but not treated.

SB agreed to include a co-variate analysis of time to event variables (eg a Cox Regression analysis), and to provide graphic displays of Quality of Life data. Data on quality of life would include observed scores and change from baseline to end of best response.

It was agreed that it would be inappropriate to pool efficacy results across studies in the planned Integrated Analysis of Efficacy.

Immediately following this meeting a presentation of the planned CANDA was made. The following agreements were made:

The topotecan NDA would consist of paper copy and electronic portions. Certain electronic portions (case report forms, case report tabulations and selected patient listings such as laboratory data output) would be presented to FDA as electronic data only, provided this was acceptable to the Division. The Consumer Safety Officer, was to inform SB if electronic submission of CRF's, CRT's and other listings were acceptable. The FDA review clock would start when both paper and electronic portions were available and staff had been trained to use the SB CANDA.

5.0 LIST OF IND'S AND NDA'S

Note: This section is quoted from the NDA

IND Topotecan hydrochloride (SK&F S-104864-A) for injection has been investigated clinically worldwide, including the United States, under IND granted to SmithKline Beecham Pharmaceuticals and was initiated on

2 March 1989.

IND Topotecan hydrochloride (SK&F S-104864-A) for oral use has been investigated clinically in the United States and Europe under IND that was granted to SmithKline Beecham Pharmaceuticals and was initiated on

18 August 1993.

IND Topotecan hydrochloride for injection has been investigated clinically worldwide, including the United States, under IND that was granted to the U.S. National Cancer Institute and was initiated on 28 March 1990.

IND Topotecan hydrochloride for injection will be investigated clinically in the United States under IND that was granted to Steven A. Miles, MD., Associate Professor of Medicine, University of California at Los Angeles CARE Center and was initiated on 30 November 1995.

The first marketing applications for topotecan hydrochloride will be submitted December, 1995, in the United States and other countries, including the United Kingdom, France, Italy, Australia and South Africa.

Based on topotecan's pleiotropic antitumor activity, a number of Phase II studies have been initiated and are ongoing.

6.0 CONTROLLED CLINICAL STUDY 039

For the following four sections, all quotations from the sponsor NDA will appear in regular type. All comments from the reviewer will appear in bold type.

6.1 Study Design and Objectives

Study Title

An Open-Label, Multicenter, Randomized, Phase III Study of Topotecan HCl as Single Agent, Second-Line Therapy (Administered Intravenously as Five Daily Doses Every 21 Days) Versus Taxol (Administered as a Three Hour Infusion Every 21 Days) in Women With Advanced Epithelial Ovarian Carcinoma (Study SKF 104864/039).

Investigators and Centers

Sixty-one investigators from both North America and Europe participated in the study. Thirty-seven investigators entered 90 patients into the alternate treatment Phase of the study. The number of patients in each country are displayed in the table on the next page.

COUNTRY	# of Patients
Austria	3
Belgium	5
Canada	2
France	30
Germany	4
Italy	15
Netherlands	25
Poland	13
Spain	8
Sweden	9
Switzerland	5
United Kingdom	62
USA	45

Publications

There were no publications at the time of issue of this report.

Study Dates

For the randomized Phase of the study, the first patient received study medication on 7 February 1994. The last patient was randomized on 31 January 1995. For the alternate treatment Phase of the study, the first patient received alternate study medication on 25 April 1994. Clinical cutoff was 20 June 1995. All treatment courses completed by that date were included in this report.

Objectives

Primary Objectives

The primary objectives of the study were:

- To evaluate the response rate, response duration, and time to progression , in women with advanced epithelial ovarian carcinoma randomized to treatment with topotecan administered as five daily 30 minute infusions every 21 days or paclitaxel administered as a 3-hour infusion every 21 days in patients who have failed one platinum-based chemotherapeutic regimen (cisplatin or carboplatin).

- To evaluate the qualitative and quantitative toxicities of topotecan and paclitaxel administered on these schedules.

Secondary Objectives

The secondary objectives of the study were:

- To evaluate time to response and survival in patients with advanced epithelial ovarian carcinoma treated with topotecan or paclitaxel administered on these schedules.

- To evaluate the effect on the Quality of Life of patients treated with topotecan and paclitaxel on these schedules.

- To evaluate the population pharmacokinetics of topotecan administered as a 30-minute infusion for five consecutive days every 21 days.

Study Design

Protocol 039 was an open, multicenter, randomized, stratified, Phase III study to evaluate the efficacy and toxicity of topotecan versus paclitaxel for the treatment of patients with advanced epithelial ovarian carcinoma who failed one platinum-based chemotherapeutic regimen. Eligible patients with measurable bidimensional disease were randomized to treatment with topotecan administered as five daily 30-minute infusions every 21 days or paclitaxel administered as a 3-hour infusion every 21 days. Patients who progressed or whose best response was stable disease after 6 courses on one regimen were eligible to be switched to the other regimen.

Protocol Amendments

Amendment 1 (9 December 1993): Protocol Synopsis and Section 4.2 (Inclusion Criteria): the requirement of FIGO Stage III or Stage IV was changed to metastatic disease since most patients would not be restaged at entry into the study. Additional changes to Section 4.2 (Inclusion Criteria) included the following: the requirement of a skin lesion diameter was changed from >2 cm to > 0.5 cm since a skin lesion can be easily measured and response to therapy evaluated; addition of a scale to be noted with all forms of lesion measurement so that the lesion diameters could be easily measured; hormonal therapy within 4 weeks of study was for conditions other than ovarian carcinoma; change of the

representation of units for WBC, neutrophils, and platelets from international units to reflect American practice; the addition of "or creatinine clearance of >60 ml/min" to the requirement of creatinine >1.5 mg/dL. Modifications to Section 4.3 (Exclusion Criteria) included modification for allowance of hormonal therapy for conditions other than ovarian carcinoma (e.g. menopause). Section 5.2 (Screening Evaluation): the requirement to document FIGO Stage was eliminated. Modifications to Section 5.3 (Treatment Courses) included: addition of creatinine clearance to be performed if creatinine was >1.5 mg/dL; requirement to perform blood chemistries prior to next course only if the day 15 results reflected clinically significant deterioration from baseline values; the representation of units for WBC, neutrophils, and platelets to reflect American standards; the exception of grade 3 or 4 vomiting for dose reduction was removed since it would be unwarranted to treat the patient at day 21 in the event of grade 3 or 4 vomiting.

Amendment 2 (31 May 1994): Section 4.1 Number of Patients was modified to include details of the randomization procedure. Sections 5.3.1 Procedure for Dose Modification of Topotecan and 5.3.2 Procedure for Dose Modification of Taxol were changed such that the same neutrophil criteria (neutrophils < 500/mm^3 associated with fever/infection or lasting >7 days) were used for both topotecan and Taxol regarding the requirement for the use of G-CSF to manage grade 4 neutropenia. Section 5.3.5.1 Blood Sampling was changed based on additional stability data allowing blood samples for pharmacokinetic sampling to be stored for up to one month at <-20° C. In Section 7.6.2 reporting Serious Adverse Experience(s) Dr. Colin Broom was added as medical monitor. In Section 9.1 Criteria For Efficacy the primary criteria for efficacy were changed to the response rate, response duration, and time to progression and secondary criterion was changed to the Quality of Life to agree with Sections 2.1 and 2.2. Section 9.3.1 Comparison of Interest was changed to include a statement for the time of closure of the data base for analysis. Section 9.4 Efficacy Analyses was clarified with respect to the specific statistical methodology to be used for analyzing all major study endpoints.

Modification 1 (12 September 1994): Appendix N Procedure for Randomization was corrected as the schematic was incorrect.

Amendment 3 (20 February 1995): Time to response and survival were added as secondary objectives/efficacy criteria to the Synopsis, Section 2.2 Objectives: Secondary and Section 9.1 Criteria for Efficacy. Section 9.3.1 Comparison of Interest was changed to specify the cut-off date for the collection of new clinical data to be included in the primary analyses (20 weeks after the date of enrollment of the last randomized patient).

Modification 2 (5 April 1995): Dr. Ian Hudson replaced Dr. Michael McDonald as the clinical trial monitor in the United Kingdom.

Ethics

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki as amended in Hong Kong (1989). The protocol and statement of informed consent were approved by an Institutional Review Board or Ethics Committee prior to each center's initiation. Written informed consent was obtained from each patient prior to entry into the study. Case report forms were provided for each patient's data to be recorded. Primary: response rate, response duration, time to progression, and qualitative and quantitative toxicities of topotecan and paclitaxel.

Study Population

The target enrollment was one hundred evaluable patients per arm. All patients were to have bidimensionally measurable disease and have failed one platinum-based chemotherapeutic regimen. Two hundred thirty-five patients were randomized. Nine patients (5 randomized to topotecan and 4 randomized to paclitaxel) did not receive study medication. Thus, the intent-to-treat population consisted of 112 patients randomized to topotecan and 114 patients randomized to paclitaxel.

Treatment and Administration

Eligible patients were randomized to receive topotecan 1.5 mg/m^2/day as a 30-minute infusion for 5 consecutive days every 21 days or paclitaxel 175 mg/m^2/day as a 3 hour infusion every 21 days. The initial dose could be increased or decreased according to toxicity. For patients with neutropenia, G-CSF was to be administered before a reduction in dose was considered. Patients were premedicated prior to paclitaxel administration according to the manufacturer's labeling in order to prevent severe hypersensitivity reactions. Paclitaxel was obtained through commercial sources. Topotecan was from batches U-93056 and U-94036.

Evaluation Criteria

The primary efficacy parameters were:

Response rate, response duration (defined as the elapsed time from first documented response until the first documented disease progression) and time to progression.

The secondary efficacy parameters were:

Time to response, survival, and quality of life (assessed by repeated administration of the EORTC QLQ-C30 questionnaire).

Safety Parameters

Qualitative and quantitative hematologic and non-hematological toxicities were evaluated. Serious adverse experiences, deaths, changes in vital signs, ECG results, body weight changes and non-hematological laboratory assessments were also tabulated.

Statistical Methods

This was not a true crossover study, data collected during the randomized and alternate phases were treated independently. Patients were stratified according to platinum sensitivity, baseline ascites and age. Efficacy analyses were performed for the Intent-to-Treat population (ITT) for both the randomized and alternate phases of the study and a Protocol-Defined population (PP) subset which excluded patients with a documented protocol violation for the randomized phase. Objective response was compared between treatment groups using Pearson's uncorrected chi-square statistic. The null hypothesis of no difference between treatment regimens was tested at a nominal 5% type I error rate against a two-tailed alternative. Traditional survival methods were employed to summarize the time to event variables. Kaplan-Meier estimates were obtained for each endpoint and presented in lifetable format with four week intervals. Time to Event outcomes were also compared between treatments by the Cox regression model.

Qualitative and quantitative results were summarized for hematological toxicities relating to white blood cells, neutrophils, platelets and hemoglobin. Qualitative data were summarized by course and by patient and included time to onset and duration of grade 4 toxicities (grade 3 and 4 for anemia). Quantitative assessments of hematological toxicities included calculation of absolute nadirs, percentage change from baseline and day of occurrence of nadirs. Non-hematological toxicities were summarized within patient and within course.

6.2 Overview of Demographics, Treatment and Efficacy Results

Patient Disposition and Key Demographic Data

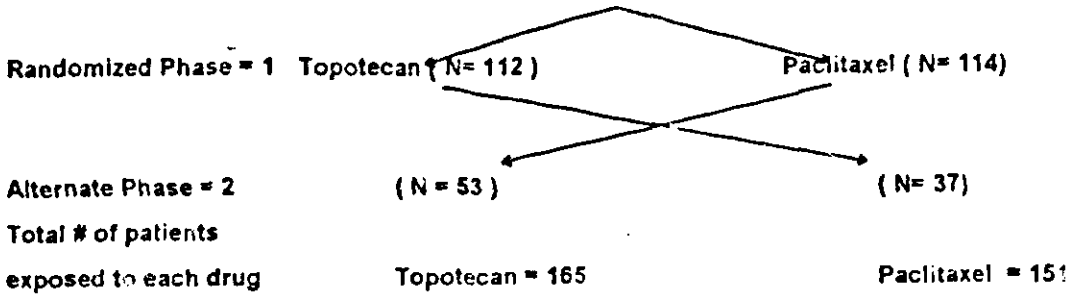
Patient demographics are provided in the table on the next page.

For both topotecan and paclitaxel malignant serous tumors were the most frequently occurring tumor type (52%); the number of patients with at least one tumor ≥5 cm in diameter at baseline was similar (49% and 54%, respectively). The median performance status was 1 with the similar proportion of patients assessed as PS 2 at baseline (18% and 15%, respectively). Fifty-four percent of topotecan treated and 52% of paclitaxel treated patients were refractory or had relapsed within six months of completing first-line therapy.

Intent to Treat	Topotecan	Paclitaxel
Demographic Characteristics	(N = 112)	(N = 114)
Age (years)	n (%)	n (%)
18-40	3 (2.7)	3 (2.6)
41-64	71 (63.4)	75 (65.8)
> 65	38 (33.9)	36 (31.6)
Mean	59.2	58.3
Range		
Race		
Caucasian	112 (100.0)	106 (93.0)
Black	0 (0.0)	5 (4.4)
Hispanic	0 (0.0)	3 (2.6)
Weight (kgs)		
Mean	65.0	67.6
Range		
Body Surface Area (m2)		
Mean	1.7	1.7
Range		

Number of Patients on each Arm :

Randomization



The number (%) of patients completed or withdrawn from the study is giver in the table below.

Number of Patients	Topotecan		Paclitaxel	
	n	(%)	n	(%)
Completed Treatment	71	(63.4)	87	(76.3)
Premature Discontinuations	25	(22.3)	16	(14.0)
Ongoing	16	(14.3)	11	(9.6)
Switched to Alternate Therapy	37	(33.0)	53	(46.5)
Evaluated for Safety	112	(100.0)	114	(100.0)
Evaluated for ITT	112	(100.0)	114	(100.0)

Withdrawal Reasons

Seventy-one (63.4%) of the 112 patients treated with topotecan and 87 (76.3%) of the 114 patients treated with paclitaxel completed the study. Twelve patients (10.7%) who received topotecan were withdrawn for adverse experiences compared with 8/114 (7%) of patients who received paclitaxel. Patients who were withdrawn from the study for adverse experiences are discussed in section 6.6. Patients whose data was incomplete at the time of clinical cutoff (20 June 1995) are represented as "ongoing".

Number (%) of Randomized Patients who Completed the Study or were Withdrawn by the Reason for Study Withdrawal

Study Conclusion	Topotecan	Paclitaxel
	(n=112)	(n=114)
Reason	n (%)	n (%)
COMPLETED STUDY	71 (63.4)	87 (76.3)
Adverse Experience	12 (10.7)	8 (7.0)
Protocol Violation	1 (0.9)	1* (0.9)
Lost to follow-up	2 (1.8)	2 (1.8)
Other**	10 (8.9)	5 (4.4)
Total Withdrawn	25 (22.3)	16 (14.0)
Ongoing	16 (14.3)	11 (9.6)
Switched to Alternate Phase	37 (33.0)	53 (46.5)

*errata: patient completed six courses of randomized paclitaxel and was withdrawn due to protocol violation after course 1 of alternate therapy

** comprised primarily of patient request or refusal

Protocol Violations

A total of 16 patients for topotecan and 9 patients for paclitaxel were in violation of the protocol, and were excluded from the per protocol analysis of efficacy. The most frequent reason for protocol violation in both treatment groups was lack of assessment beyond five days after completing a treatment course.

Number of Patients (%) and Reason for Protocol Violation by Randomized Treatment

Study Medication	Topotecan	Paclitaxel
Total Patients	n = 112	n = 114
Protocol Violation Reason	n (%)	n (%)
Not assessed beyond 5 days	11 (9.8)	6 (5.3)
Did not have required measurable disease	2 (1.8)	1 (0.9)
Indicator lesion in field of prior radiation	1 (0.9)	1 (0.9)
Entered with Second Primary Cancer	1 (0.9)	
More than one prior chemo. regimen	1 (0.9)	
Did not have required performance status		2 (1.8)
Total Number with Any Violation	16 (14.3)	9* (7.9)

*patient violated for performance status of 3 and lack of assessment beyond 5 days

in patients treated with topotecan, 5 of the 11 patients not assessed beyond 5 days were withdrawn for adverse experiences 4 patients progressed after less than 2 courses of therapy 1 patient was lost to follow-up; and 1 patient refused further treatment

In patients treated with paclitaxel, 6 patients were not assessed beyond 5 days. Three patients were withdrawn for adverse experiences), 2 patients

progressed after 1 course of therapy, and 1 patient was lost to follow-up.

Courses Administered

A total of 502/555 (90%) topotecan courses were administered at 1.5 mg/m^2/day and 538/550 (98%) paclitaxel courses were administered at 175 mg/m^2/day. The median number of courses administered was 5 for both treatment groups. Dose modifications for all patients and courses are given in the table below.

Number of Courses Administered

	Topotecan	Paclitaxel
Randomized Phase	**555**	**550**
Alternate Phase	**176**	**126**
Total	**731**	**676**

Dose Modifications

Study Drug	Topotecan		Paclitaxel	
Total Patients/Courses	112	555	114	550
Patients/Courses > 1	96	443	108	436
	n (%)	n (%)	n (%)	n (%)
Delays After Course 1 Patients/Courses	57 (59.4)	90 (20.3)	18 (16.7)	24 (5.5)
Reductions After Course 1 Patients/Courses	13 (13.5)	17 (3.8)	5 (4.6)	5 (1.1)
Escalations After Course 1 Patients/Courses	3 (3.1)	3 (0.7)	0 (0.0)	0 (0.0)

*Calculations of dose delays, reductions or escalations as percent did not include initial courses.

6.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables

All objective responses claimed by the investigators underwent independent radiological review. The applicant's assessment of response rate for the intent-to-treat population is tabulated below.

Population	Intent to Treat	
Study Drug	Topotecan	Paclitaxel
Patient #	112	114
	n (%)	n (%)
CR	5 (4.5)	3 (2.6)
PR	18 (16.1)	15 (13.2)
SD	33 (29.5)	38 (33.3)
PD	39 (34.8)	56 (49.1)
NE	17 (15.2)	5 (4.4)

The reviewer's assessment of the best response for all patients randomized to study medication is tabulated below.

039	CR	PR	Total
Topotecan	**6 (5.4%)**	**16 (14.3%)**	**22 (19.6%)**
Paclitaxel	**(3.5%)**	**10 (8. 8%)**	**14 (12.3%)**

Time to response was calculated using the day the patient achieved the best response. Duration of response was calculated by the following criteria :

- Any patient that had a new lesion, whether or not the sum of the products of all lesions showed a decrease over the previous measurement was considered to have progression

- Any patient that had a 25 % increase in the sum of the products of all lesions over the previous best minimum was considered to have progression. For example, if a patient had a sum of products of 50, then decreased to 24, the first measurement that was greater than 30 (25 % of 24) would be considered the day of progression.

As shown in the table below, the applicant's median time to response was 9.0 weeks for topotecan and 6.0 weeks for paclitaxel. The hazard ratio (topotecan:paclitaxel) for time to response was 0.476 (p=0.0409). The median duration of response was 32.1 weeks for topotecan and 19.7 weeks for paclitaxel. The hazard ratio (T:P) was 0.416 (p=0.2218).

Time to Response

TTR (wks)	n=23	n=15
Median	9.0	6.0
Range		
Hazard Ratio (Topo/Paclitaxel)		0.476
p value	0.0409*	

Response Duration

RD (wks)	n=23	n=15
Median	32.1	19.7
Range		
Hazard Ratio (Topo/Paclitaxel)		0.416
p value	0.2218	

As is shown in the table on the next page, the applicant's median time to progression in the intent-to-treat population was 23.1 weeks for topotecan and 14.0 weeks for paclitaxel. The hazard ratio (T:P) was 0.578 (p=0.0021).

Time to Progression

TTP (wks)	n=112	n=114
Median	23.1	14.0
Range		
Hazard Ratio (Topo/Paclitaxel)		0.578
p value	.0021*	

At the time of the clinical cutoff for this study, approximately 80% of the patients were still alive, with the number of patients who had died similar for both treatments (25 topotecan treated patients and 22 paclitaxel treated patients). The applicant's median survival time was 61.3 weeks for topotecan and 42.6 weeks for paclitaxel. The hazard ratio (T:P) was 1.210 (p=0.5153).

Survival

Survival (wks)	n=112	n=114
Median	61.3	42.6
Range		
Hazard Ratio (Topo/Paclitaxel)		1.210
p value	.0.5153	

Quality of life assessed by the EORTC QLQ-C30 questionnaire did not indicate substantial changes from baseline or differences between treatment groups

The small sample size in this randomized comparative study precluded definitive conclusions regarding the relative efficacy of topotecan and paclitaxel. However, the three primary efficacy parameters indicated that patients randomized to topotecan experienced a higher response rate, longer response duration and a longer time to progression than those receiving paclitaxel. These results **suggest** that the efficacy of topotecan is **equal to or possibly greater** than that of the recently approved paclitaxel schedule used in this study, **and warrants further investigation.**

Alternate Treatment

As discussed previously, patients who progressed or had stable disease on randomized treatment were given the option to switch to alternate treatment. Responses were seen in five (9%) of the patients switched to topotecan (all partial response) and in one (3%) of those switched to paclitaxel (complete response). The median duration of response for topotecan was 17.6 weeks (range 6.1 to 17.6 weeks) and for paclitaxel was undefined. As a majority of patients in each treatment group (topotecan 81%; paclitaxel 86%) were alive at the time of the cut-off for inclusion in the analysis, median survival is not reported here.

The results for the primary efficacy variables and the additional, secondary efficacy variable, time to response, are presented on the next page.

Best Response and Time to Event Results for Patients in the Intent-to-Treat Population Switched to Alternate Treatment in Study 039

Response Variable	Topotecan n=53	Paclitaxel n=37
Responders		
Complete response	0	1 (2.7%)
Partial response	5 (9.4%)	0
Total responders	5 (9.4%)	1 (2.7%)
95% CI	(3.1, 20.7)	(0.1, 14.2)
Non-responders		
Stable disease	8 (15.1%)	10 (27.0%)
Progression	26 (49.1%)	16 (43.2%)
Not evaluable	4 (26.4%)	10 (27.0%)
Total non-responders	48 (90.6%)	36 (97.3%)
Duration of response (weeks)	n=5	n=1
Median	17.6	undefined
Range		
Time to progression (weeks)	n=53	n=37
Median	8.7	8.9
Range		
Time to response (weeks)	n=5	n=1
Median	6.1	3.0
Range		

* Value corresponds to a censored event

Analysis of changes in quality of life parameters between baseline and the end of best response revealed a decrease (improvement) in the median score for nausea/vomiting with topotecan and decreases (improvement) in the median scores for fatigue and pain with paclitaxel . The quality of life score was also improved on paclitaxel.

Quality of Life - Changes from Baseline to End of Best Response by Factor Median and Range at each Assessment in Patients who Received Alternate Treatment

Study Drug	Alternate Topotecan		Alternate Paclitaxel	
QOL Parameter	n	median range	n	median range
Appetite Loss	33	0 0	21	0.0
Cognitive Function	30	0.0	20	0.0
Constipation	33	0.0	21	0.0
Diarrhea	34	0 0	21	0.0
Dyspnea	33	0 0	21	0 0
Emotional Function	30	0.0	20	8.0
Fatigue	34	0.0	21	-11.0
Financial Impact	9	0.0	20	0.0
Nausea/Vomiting	34	-16.0	21	0.0
Pain	34	0.0	21	-17.0.
Physical Function	30	0.0	21	0.0
Quality of Life	29	0.0	20	16.0
Role Function	30	0.0	21	0.0
Social Function	30	0.0	20	0.0
Sleep Disturbance	34	0.0	20	0.0

Data source: SKF 104864-A/039 Table 16; Appendix 12.6A

6.4 Adverse Experience and Safety Data

Hematologic Toxicity

The percentage of patients and courses with grade 3/4 hematologic toxicity was calculated and then tabulated for leukopenia, neutropenia, thrombocytopenia, and anemia For each patient all laboratory values were first standardized to the same units, then for each day a differential and

Grade 3&4 Anemia

	Totals	Patients	% Patients	Courses	% Courses
Total Hgb measurements	5132	226		1711	
Topo Hgb measurements	2904	165		890	
Taxol Hgb measurements	2228	150		821	
Total Hgb< 8	761	80	35.4%	301	17.6%
Topo Hgb<8	463	67	40.6%	185	20.8%
Taxol Hgb< 8	298	28	18.7%	116	14.1%

Transfusions

Trial 039				
Platelets	Patients	% Patients	Courses	% Courses
Topo	16	9.7%	36	4.9%
Taxol	0	0%	0	0%
RBC				
Topo	91	55.2%	215	29.4%
Taxol	22	14.6%	33	4.9%

Grade 4 Lymphocytopenia

	Totals	Patients	% Patients	Courses	% Courses
Total ALC measurements	5334	226		1710	
Topo ALC measurements	3014	165		889	
Taxol ALC measurements	2320	150		821	
Total ALC < 500	336	92	40.7%	221	12.92%
Topo ALC < 500	218	62	37.6%	135	15.19%
Taxol ALC < 500	118	45	30.0%	86	10.48%

Hematologic toxicities were more prevalent in the topotecan group compared to the paclitaxel group. Although severe hematologic toxicity was associated with topotecan treatment, toxicity resolved within a week in approximately 70% of treatment courses. Additionally, continued courses of therapy did not demonstrate evidence of cumulative toxicity. Median nadir values and day of nadir occurrence remained relatively constant throughout the study.N

Neutropenia Duration in Days

	Topotecan	Paclitaxel
# > 6 days	162	27
Median	5.00	6.00
Mean	5.56	5.68
Std.Dev.	12.19	2.49
Min.	1	1
Max.	219	15
# of courses	391	66

Fever > 38.0° C

	Mean	Std. dev.	Min	Max	# of patients	# of courses
Total	17.10	15.55	1	118	54	74
Topo	8.51	17.80	1	118	42	55
Taxol	3.10	3.30	1	12	15	19

NB Some patients got both drugs and were febrile with each

Fever Duration

	Mean	Std. Dev.	Min	Max	# of patients	# of courses
Total	5.28	11.05	1	118	75	133
Topo	6.43	13.10	1	118	56	93
Taxol	2.85	3.73	1	19	26	40

NB Some patients got both drugs and were febrile with each

Documented Fever and Neutropenia

	Mean	Std. dev.	Min	Max	# of patients	# of courses
Total	8.15	4.90	2	24	40	48
Topo	8.00	5.10	2	24	35	42
Taxol	9.00	3.30	5	15	6	6

NB Some patients got both drugs and were febrile with each

Documented Sepsis

			Sepsis		Septic Deaths	
	# of patients	# of courses	# of deaths	% of pts	% of courses	% of pts	% of courses
Total	11	11	3	4.87%	0.78%	2.65%	0.43%
Topo	9	9	3	5.45%	1.23%	1.8%	0.82%
Taxol	2	2	0	1.3%	0.30%	0.0%	0.0%

Systemic antibiotics were used by 58% of patients in 21% of topotecan courses. Suspected or documented infection was proximate to grade 4 neutropenia in a total of 25% of patients and 7% of courses, with an additional 5% of patients and 1% of courses being associated with sepsis. Six patients treated with topotecan during the randomized phase and 11 patients during either the randomized phase or the alternate phase developed sepsis. The sepsis was considered related to topotecan therapy in 5 of the 6 initial instances, and resulted in the death of 3 patients. Systemic antibiotics were used by 33% of patients in 11% of paclitaxel courses. Suspected or documented infection was proximate to grade 4 neutropenia in a total of 4% of patients and 1% of courses with an additional 2% of patients and 0.4% of courses associated with sepsis. Two patients treated with paclitaxel developed sepsis, which was considered related to therapy in one of the patients. Neither patient died due to sepsis.

In order to maintain a 21 day dosing schedule for both treatment groups, prophylactic G-CSF administration was allowed after course 1 of therapy in either treatment group. Prophylactic G-CSF was administered in 23% of topotecan courses and in <1% of paclitaxel courses. Other supportive measures, (treatment G-CSF and RBC transfusions) did not increase with increasing courses of therapy.

Duration of Fever and Neutropenia in days

	Fever > 38° C. per course						Fever and Neutropenia per course						Sepsis	
	Topo	Mean	Std. dev.	Min	Max		Topo	Mean	Std. dev.	Min	Max		Topo	
1	25	5.76	5.09	1	24	1	25	8.38	5.28	2	24	1	5	
2	10	5.38	5.1	1	16	2	8	8.22	5.78	2	16	2	2	
3	7	5	5.42	1	13	3	2	4.5	2.12	3	6	3	1	
4	4	2	1.41	1	3	4	1	4		4	4	4		
5	5	31.2	48.82	1	118	5	2	9.33	1.15	8	10	5		
6	2	5.5	4.95	2	9	6	1	2		2	2	6		
												9	1	
	Taxol	Mean	Std. dev.	Min	Max		Taxol	Mean	Std. dev.	Min	Max		Taxol	
1	6	3.5	4.23	1	12	1	2	9.67	4.04	5	12	1	2	
2	3	4	4.24	1	7	2	2	7	0	7	7	2		
3	3	3.67	3.79	1	8	3	1	15		15	15	3		
4	2	1	0	1	1	4	1	9		9	9	4		
5	4	2		2	2	5						5		
6	1					6						6		

Non-Hematologic Toxicity

Non-hematologic adverse experiences were reported in 112/112 (100%) of patients who received topotecan and in 113/114 (99%) of patients who received paclitaxel (see table below). The majority of non-hematologic adverse experiences reported in both treatment groups were mild. Nausea and vomiting, fatigue, stomatitis and fever were reported more frequently for patients who received topotecan, while alopecia (grade 2), abdominal pain, arthralgia, paresthesia, myalgia, skeletal pain and neuropathy were reported more frequently for patients who received paclitaxel.

Study 039 Paclitaxel Non-Hematologic Adverse Events by Course

					Grade									
Adverse Event by Courses	Total	% of Total Courses	Unk	%	1	%	2	%	3	%	4	per cent	SAE	%
ALOPECIA	668	98.82			118	17.46	549	81.21	1	0.15			1	0.67
PARESTHESIA	182	26.92	9	1.33	141	20.86	32	4.73						
NAUSEA	162	23.96	1	0.15	123	18.20	33	4.88	5	0.74			5	3.36
ARTHRALGIA	146	21.60	5	0.74	78	11.54	60	8.88	3	0.44			3	2.01
FATIGUE	145	21.45	32	4.73	77	11.39	24	3.55	12	1.78			12	8.05
ABDOMINAL PAIN	140	20.71	7	1.04	74	10.95	50	7.40	8	1.18	1	0.15	9	6.04
MYALGIA	128	18.93	3	0.44	68	10.06	47	6.95	10	1.48			10	6.71
VOMITING	111	16.42			77	11.39	26	4.14	5	0.74	1	0.15	6	4.03
CONSTIPATION	108	15.98	23	3.40	63	9.32	22	3.25						
DIARRHEA	102	15.09			81	11.98	20	2.96	1	0.15			1	0.67
PAIN	96	14.20	7	1.04	38	5.62	47	6.95	4	0.59			4	2.68
NEUROPATHY PERIPHERAL	87	12.87	3	0.44	72	10.65	11	1.63	1	0.15			1	0.67
ASTHENIA	86	12.72	17	2.51	36	5.33	22	3.25	11	1.63			11	7.38
DYSPNEA	85	12.57	3	0.44	52	7.69	23	3.40	6	0.89	1	0.15	7	4.70
FLUSHING	79	11.69	13	1.92	52	7.69	14	2.07						
SKELETAL PAIN	55	8.14	4	0.59	28	4.14	12	1.78	11	1.63			11	7.38
HEADACHE	53	7.84	3	0.44	32	4.73	13	1.92	5	0.74			5	3.36
BACK PAIN	48	7.10	4	0.59	25	3.70	17	2.51	2	0.30			2	1.34
HEMATURIA	47	6.95			40	5.92	7	1.04						

Study 039 Paclitaxel Non-Hematologic Adverse Events by Patients

			Grade											
Adverse Event	Total	% of total courses	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	142	95.30			15	10.07	126	84.56	1	0.67			1	0.67
NAUSEA	70	46.98	1	0.67	44	29.53	20	13.42	5	3.36			5	3.36
ABDOMINAL PAIN	60	40.27	4	2.68	24	16.11	24	16.11	7	4.70	1	0.67	8	5.37
DIARRHEA	57	38.26			38	25.50	18	12.08	1	0.67			1	0.67
CONSTIPATION	53	35.57	11	7.38	27	18.12	15	10.07						
ARTHRALGIA	48	32.21	1	0.67	20	13.42	24	16.11	3	2.01			3	2.01
VOMITING	48	32.21			24	16.11	18	12.08	5	3.36	1	0.67	6	4.03
PARESTHESIA	46	30.87	1	0.67	33	22.15	12	8.05						
FATIGUE	45	30.20	8	5.37	18	12.08	12	8.05	7	4.70			7	4.70
MYALGIA	40	26.85	1	0.67	15	10.07	20	13.42	4	2.68			4	2.68
PAIN	30	20.13	2	1.34	13	8.72	13	8.72	2	1.34			2	1.34
DYSPNEA	29	19.46			15	10.07	8	5.37	5	3.36	1	0.67	6	4.03
ASTHENIA	26	17.45	2	1.34	9	6.04	9	6.04	6	4.03			6	4.03
FEVER	26	17.45	1	0.67	10	6.71	13	8.72	2	1.34			2	1.34
FLUSHING	26	17.45	6	4.03	16	10.74	4	2.68						
STOMATITIS	26	17.45	3	2.01	13	8.72	9	6.04	1	0.67			1	0.67
BACK PAIN	22	14.77	2	1.34	10	6.71	8	5.37	2	1.34			2	1.34
HEADACHE	22	14.77			12	8.05	8	5.37	2	1.34			2	1.34
HEMATURIA	22	14.77			19	12.75	3	2.01						
ANOREXIA	21	14.09			8	5.37	12	8.05	1	0.67			1	0.67
NEUROPATHY PERIPHERAL	21	14.09			15	10.07	5	3.36	1	0.67			1	0.67
SKELETAL PAIN	20	13.42			9	6.04	5	3.36	6	4.03			6	4.03
DYSPEPSIA	17	11.41	4	2.68	7	4.70	6	4.03						
COUGHING	16	10.74	1	0.67	11	7.38	4	2.68						
MALAISE	15	10.07			4	2.68	9	6.04	2	1.34			2	1.34

Study 039 Topotecan Non-Hematologic Adverse Events by Course

			Grade											
Adverse Event by Courses	Total	% of total courses	Unk	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	621	84.95	1	0.14	202	27.63	418	57.18						
NAUSEA	432	59.10	2	0.27	301	41.18	103	14.09	25	3.42	1	0.14	26	15.76
VOMITING	258	35.29	1	0.14	157	21.48	83	11.35	11	1.50	6	0.82	17	10.30
FATIGUE	253	34.61	60	8.21	78	10.67	99	13.54	16	2.19			16	9.70
CONSTIPATION	182	24.90	28	3.83	86	11.76	59	8.07	8	1.09	1	0.14	9	5.45
DIARRHEA	148	20.25	2	0.27	96	13.13	39	5.34	10	1.37	1	0.14	11	6.67
ABDOMINAL PAIN	125	17.10	6	0.82	65	8.89	35	4.79	17	2.33	2	0.27	19	11.52
DYSPNEA	113	15.46	7	0.96	47	6.43	42	5.75	9	1.23	8	1.09	17	10.30
ASTHENIA	110	15.05	13	1.78	34	4.65	53	7.25	8	1.09	2	0.27	10	6.06
FEVER	100	13.68	2	0.27	42	5.75	45	6.16	5	0.68	6	0.82	11	6.67
STOMATITIS	72	9.85	2	0.27	46	6.29	21	2.87	3	0.41			3	1.82
HEADACHE	64	8.76	5	0.68	29	3.97	27	3.69	3	0.41			3	1.82
ANOREXIA	62	8.48	6	0.82	27	3.69	25	3.42	4	0.55			4	2.42
MALAISE	49	6.70	1	0.14	13	1.78	27	3.69	7	0.96	1	0.14	8	4.85
PAIN	49	6.70	5	0.68	31	4.24	9	1.23	4	0.55			4	2.42
HEMATURIA	45	6.16			41	5.61	2	0.27			2	0.27	2	1.21
DEPRESSION	43	5.88	6	0.82	25	3.42	10	1.37	2	0.27			2	1.21
PARESTHESIA	42	5.75	3	0.41	35	4.79	4	0.55						
BACK PAIN	41	5.61	3	0.41	26	3.56	10	1.37	1	0.14	1	0.14	2	1.21
ANXIETY	39	5.34	5	0.68	24	3.28	9	1.23	1	0.14			1	0.61
RASH	38	5.20	4	0.55	21	2.87	13	1.78						

Study 039 Topotecan Non-Hematologic Adverse Events by Patients

			Grade											
Adverse Event by Topotecan Patient	Total	% of total courses	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	141	85.45	1	0.61	29	17.58	111	67.27						
NAUSEA	131	79.39			67	40.61	47	28.48	16	9.70	1	0.61	17	10.3
VOMITING	98	59.39			40	24.24	43	26.06	10	6.06	5	3.03	15	9.09
CONSTIPATION	68	41.21	9	5.45	26	15.76	25	15.15	7	4.24	1	0.61	8	4.85
FATIGUE	67	40.61	13	7.88	18	10.91	25	15.15	11	6.67			11	6.67
DIARRHEA	65	39.39			39	23.64	17	10.30	8	4.85	1	0.61	9	5.45
FEVER	56	33.94	2	1.21	12	7.27	31	18.79	5	3.03	6	3.64	11	6.67
ABDOMINAL PAIN	52	31.52	3	1.82	23	13.94	16	9.70	8	4.85	2	1.21	10	6.06
STOMATITIS	41	24.85	2	1.21	16	10.91	18	10.91	3	1.82			3	1.82
DYSPNEA	37	22.42	3	1.82	13	7.88	11	6.67	6	3.64	4	2.42	10	6.06
ASTHENIA	36	21.82	3	1.82	8	4.85	16	9.70	7	4.24	2	1.21	9	5.45
ANOREXIA	28	16.97	2	1.21	10	6.06	12	7.27	4	2.42			4	2.42
HEADACHE	28	16.97	2	1.21	14	8.48	9	5.45	3	1.82			3	1.82
BACK PAIN	24	14.55	1	0.61	13	7.88	8	4.85	1	0.61	1	0.61	2	1.21
PAIN	22	13.33	2	1.21	9	5.45	8	4.85	3	1.82			3	1.82
MALAISE	21	12.73			4	2.42	11	6.67	5	3.03	1	0.61	6	3.64
RASH	21	12.73	3	1.82	9	5.45	9	5.45						
URINARY TRACT INFECTION	21	12.73					18	10.91	2	1.21	1	0.61	3	1.82
DYSPEPSIA	20	12.12	3	1.82	10	6.06	7	4.24						
COUGHING	19	11.52	6	3.64	10	6.06	2	1.21	1	0.61			1	0.61
PARESTHESIA	19	11.52	2	1.21	15	9.09	2	1.21						
HEMATURIA	18	10.91			16	9.70	1	0.61			1	0.61	1	0.61

Treatment was administered on schedule or within two days of schedule in 77% of topotecan courses and in 92% of paclitaxel courses, with delays beyond a week occurring in 5% and 3% of courses, respectively. Thirteen of the 112 topotecan patients (12%) were dose-reduced compared with 5/114 (4%) of

patients treated with paclitaxel. The most frequent reasons for dose reductions in patients treated with topotecan were hematologic, and were non-hematologic for patients treated with paclitaxel.

Deaths

Of 112 patients randomized to topotecan, 11 patients died within 30 days of receiving topotecan (seven patients died due to progressive disease, two patients died due to sepsis associated with hematologic toxicity and two patients died due to other causes: adult respiratory distress syndrome and pulmonary embolism). Nine patients died greater than 30 days after completing topotecan therapy all due to progressive disease with the exception of one patient who died due to cardiopulmonary arrest five months post therapy. Of 114 patients randomized to paclitaxel, four patients died within 30 days of receiving paclitaxel (three patients died due to progressive disease and one patient died due to what was suspected to be a massive pulmonary embolism). Eight patients died greater than 30 days after completing paclitaxel due to progressive disease.

Serious Adverse Experiences

Of 112 patients randomized to topotecan, 55 (49%) experienced serious adverse experiences. The most frequently reported serious adverse experiences were hematologic toxicities associated with sequelae. Of 114 patients randomized to paclitaxel, 35 (31%) patients experienced serious adverse experiences. The most frequently reported serious adverse experiences were intestinal obstruction and abdominal pain. One paclitaxel treated patient developed an acute hypersensitivity reaction.

Withdrawals Due to Adverse Experiences

Twelve of 112 patients (11%) treated with topotecan and 8/114 (7%) of patients treated with paclitaxel were withdrawn from the study due to adverse experiences.

Non-Hematologic Laboratory Toxicities of Clinical Concern

There were no discernible clinically important trends in laboratory parameters during repeated courses of therapy for topotecan or paclitaxel.

Vital Signs of Clinical Concern and ECG Results

In both treatment groups, few measurements were out of the normal range. Approximately 90% of patients in both treatment groups entered the study with

normal ECG results. There was no evidence of clinically important cardiotoxicity with topotecan or paclitaxel therapy.

Summary of Changes in Body Weight

The mean patient body weight on the first day of therapy, at the end of study, and the mean percent change in body weight were similar for both treatment groups.

Number of Non-Hematologic Adverse Events

All Adverse Events

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses
Topo	25.11	23.00	1	202	4118	164	99.4 %	710
Taxol	25.70	18.20	1	86	3854	149	98.6 %	671

Adverse Events = 3

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses
Topo	2.62	2.35	1	15	215	82	50.0%	130
Taxol	2.84	2.25	1	10	159	56	37.6%	102

Adverse Events = 4

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses
Topo	1.53	1.08	1	6	55	36	22.0%	45
Taxol	1.18	0.60	1	3	13	11	7.4%	11

6.5 Reviewer's Conclusion

Topotecan showed a response rate that was as good as or perhaps better than paclitaxel in patients with ovarian cancer who had been previously treated with a platinum containing regimen. Time to progression data showed a significant difference in the proportion of patients who progressed on paclitaxel compared to topotecan at the time of study closure. The toxicity of topotecan was primarily hematologic and 9 patients in the randomized phase of the study had sepsis. Non- hematologic toxicities were common, although in most cases tolerable and manageable.

7.0 NONCOMPARATOR CLINICAL STUDY 034

7.1 Study Design and Objectives

Title

An open, multicenter, Phase II study of intravenous topotecan, given as 5 daily doses every 21 days, in advanced epithelial ovarian cancer (Study Number 104864/034)

Investigators and Centers

Twenty-six investigators in nine countries

Publication

None at issue

Study Dates

The first patient received study medication on 31 May 1993 and the last patient was enrolled on 18 March 1994. The cut-off date for inclusion of data in this study report was 28 February 1995. At this time three patients were continuing in the study and the last of these patients to enter the study had completed treatment course 10. For these three patients, data for completed courses are included in the study report.

Objectives

Primary: to evaluate the response rate and response duration of advanced epithelial ovarian carcinoma treated with topotecan administered as five daily infusions every 21 days in patients who have failed platinum-based chemotherapy.

Secondary: to evaluate the qualitative and quantitative toxicities of topotecan administered on this schedule.

Study Design

This was an open-label study to evaluate the efficacy and toxicity of topotecan for the treatment of patients with advanced ovarian carcinoma who had failed one or two prior chemotherapy regimens which con ned a platinum-based cytotoxic agent. Topotecan was administered intravenously over 30 minutes for five consecutive days, every 21 days. The initial dose was 1.5 mg/m^2/day. Following each treatment course, the dose was to be decreased by 0.25 mg/m^2/day to a minimum of 1.0 mg/m^2/day if:

a. the patient experienced grade 4 granulocytopenia or grade 3-4 thrombocytopenia lasting >6 days or associated with clinical sequelae, or

b. the patient experienced grade 2 non-hematologic toxicity (except nausea, vomiting or alopecia),

c. the patient experienced toxicity that required a delay in the next treatment course beyond two weeks.

If the patient experienced grade 4 granulocytopenia or grade 3-4 thrombocytopenia lasting >14 days, or grade 3-4 non-hematologic toxicity, the dose was to be decreased by 0.5 mg/m^2/day.

If the patient experienced no toxicity > grade 1, the dose was to be escalated by 0.25 mg/m^2/day (each course) to a maximum dose of 3.0 mg/m^2/day.

Clinical and laboratory parameters were to be assessed for disease response and toxicity.

A total of 40 evaluable patients were to be accrued in two stages using the Gehan design. Fourteen patients were to be entered in the first stage. If none of them exhibited a complete or partial response, the study was to be terminated. If at least one of the first 14 patients exhibited a response, the study was to continue to a total of 40 evaluable patients.

Protocol Amendments

Revision 1, 24 January 1992: Course Day 1 laboratory data collection instructions were changed so that hematology and blood chemistries were not required if the most recent values were normal and were taken within seven

days. This change was made because a review of prior data showed that when abnormalities in these parameters had occurred, they were evident by day 15 of each course.

Inclusion criteria (3.2.2) were changed from "age between 18 and 75 years" to "age at least 18 years old"; from "hemoglobin >10.0 g/dL" to " hemoglobin >9.0 g/dL"; "life expectancy >8 weeks" to "life expectancy >3 months."

Two exclusion criteria (3.2.3) were added: "History of allergic reactions to chemically related compounds." and "Patients with child bearing potential, not practicing adequate contraception."

An additional phrase was added to Screening Evaluation (3.3.2), bullet 1: "and any residual toxicity related to prior therapies."

Procedure for Dose Modification (3.3.4), Hematologic Toxicity was changed from

"-Grade 3-4 associated with fever/infection: Reduce single infusion dose for next treatment cycle by 0.25 mg/m^2/day

-Grade 3-4 not associated with fever/infection: No dose reduction" to

"Granulocyte Nadir

Grade 4 associated with fever/infection or lasting 7-14 days; Reduce single infusion dose by 0.25 mg/m^2/day

Grade 4 lasting > 14 days; Reduce single infusion dose by 0.50 mg/m^2/day

Grade 4 not associated with fever/infection or lasting < 7 days; No dose reduction:

Platelet Nadir

Grade 3-4 associated with bleeding or lasting 7-14 days; Reduce single infusion dose by 0.25 mg/m^2/day

Grade 3-4 lasting > 14 days; Reduce single infusion dose by 0.50 mg/m2/day"

Same section (3.3.4) "maximum infusion dose is 2.5 mg/m^2/day" was changed to "maximum infusion dose is 3.0 mg/m^2/day." Added the paragraph "If a patient has toxicity that requires a delay in the next treatment cycle of more than 2 weeks, the single infusion dose for the next treatment cycle will be decreased by 0.25 mg/m^2 and if on the lowest dose, the patient will be withdrawn from the study."

Amendment 1, 20 February 1992: The medical monitor was changed from M. Jennifer Hardin, M.D., to Bruce Wallin, M.D.

These changes had no significant impact on the results of the study.

Study Population

Female patients (aged >18 years) with advanced epithelial ovarian cancer who had failed first-line therapy with one regimen containing cisplatin or carboplatin, were to be entered into the study until 100 evaluable patients had been accrued. One hundred and eleven patients were entered into the study and, of these, 92 fulfilled the criteria for inclusion in the per protocol population.

Treatment and Administration

Topotecan was given as a 30-minute intravenous infusion on five consecutive days every 21 days. The initial dose was 1.5 mg/m^2/day but subsequently this could be increased or decreased by 0.25 mg/m^2/day, within the range mg/m^2/day (in patients with neutropenia, granulocyte-colony stimulating factor was to be administered before a reduction in dose was considered). Treatment could be delayed on a weekly basis, depending upon toxicity. The number of courses of treatment given was dependent upon disease response. The topotecan preparation was from batches numbered U-91024-J7AA and U-93056.

Evaluation Criteria

Efficacy Parameters: The primary efficacy endpoints were overall (best) response rate and response duration. Secondary endpoints were time to response, time to progression and survival.

Safety Parameters: Qualitative and quantitative toxicities were assessed by recording adverse experiences, with toxicity grades where appropriate, physical examinations, ECGs and clinical laboratory tests.

Statistical Methods

Efficacy results were summarized and two-tailed 95% confidence intervals were calculated for overall topotecan response (best response) rates. Best response was cross-classified with age, response to previous therapy, baseline disease status and CA-125 response. Mean and median cumulative dose and dose intensity were calculated for patients in each response category.

Time to event data were summarized by traditional survival methods and presented in standard life tables, summary tables and graphically, with Kaplan Meier estimates for each week of 'survival'.

Qualitative and quantitative results were summarized for hematological toxicities relating to white blood cells, neutrophils, platelets and hemoglobin. Qualitative data were summarized by course and by patient and included time to onset and

duration of grade 4 toxicities (grade 3 and 4 for anemia). Quantitative assessments of hematological toxicities included calculation of absolute nadirs, percentage change from baseline and day of occurrence of nadirs. Non-hematological toxicities were summarized within patient and within course.

7.2 Overview of Demographics, Treatment and Efficacy Results

Patient Demographics

One hundred and eleven patients were entered into the study by 26 investigators in nine countries. The number of patients in each country who entered the study, completed the study and were eligible for inclusion in the per protocol population are shown in the table below.

	Status		
Country	Entered	Completed	Per Protocol
Belgium	7	6	6
France	22	16	15
Germany	12	9	10
Italy	25	23	22
Netherlands	20	18	16
South Africa	1	1	1
Spain	6	5	6
Switzerland	2	0	2
United Kingdom	16	12	14

Patient Disposition is shown in the following table.

Patient Disposition Trial 034

	Number of patients:
Entered	111
Completed treatment	90
Withdrawn	18
Ongoing	3
Evaluated for intent-to-treat	111
Evaluated for per protocol	92
Evaluated for safety	111

The reasons for exclusion of patients from the per protocol population are provided in the Protocol Violations section. The main reasons for excluding patients from the per protocol population were that patients had received more than one prior regimen of chemotherapy or that the indicator lesions were in the field of prior radiotherapy. The primary reason for withdrawal of patients from the study was adverse experiences.

Demographic data are shown below for the intent-to-treat population. All patients were Caucasian except for one black and one patient for whom race was not stated.

Demographic Characteristics Trial 034

Demographic Characteristic	Intent-to Treat (n=111)
Age (years)	
≤ 40	6 (5.4)
41-64	75 (67.6)
≥65	30 (27.0)
Mean	57.3
Range	
Race	
Black	1 (0.9)
Caucasian	109 (98.2)
Not specified	1 (0.9)
Body weight (kg)	
Mean	66.7
Range	
Body surface area (m2)	
Mean	1.69
Range	

Number of Patients Present at Each Phase (or Visit)

All of the 111 patients who entered the study underwent the first course of treatment with topotecan. Nearly half of the patients (53/111) had at least five courses of treatment but less than 10 patients received more than 10 courses.). The median number of courses of treatment received was four (range).

Withdrawal Reason

Of the 111 patients who entered the study, 90 (81.1%) completed active treatment. A total of 18 patients (16.2%) withdrew and the most frequent reason for withdrawal, in 10 patients, was the occurrence of adverse experiences. Three patients were continuing in the study at the time of the cut-off.

Number of patients at each treatment course

Course	Number of patients
1	111
2	104
3	79
4	69
5	53
6	44
7	27
8	23
9	11
10	10
11-17	?5

Number (%) of patients who completed the study or were withdrawn, by reason for study withdrawal

Reason for study conclusion	# (%) patients
Completed active treatment*	90 (81.1)
Withdrawal reason**	
Adverse experiences	10 (9.0)
Lost to follow-up	6 (5.4)
Protocol violation, including non-compliance	1 (0.9)
Other	1 (0.9)
Total withdrawn	18 (16.2)
Ongoing	3 (2.7)
Total	111 (100)

* A patient was considered to have completed active treatment unless she was withdrawn because of adverse experiences or protocol violation, or was lost to follow-up and did not fulfill the criteria for efficacy evaluability. The following were also considered to have completed active treatment: patients who withdrew for any reason but fulfilled the criteria for efficacy evaluability patients for whom lack of efficacy (including progressive disease or disease stable for 8 weeks) was given as the reason for withdrawal; and those for whom the investigator checked the completion box in the CRF and gave no other reason for conclusion ** Patients who died are included as withdrawals due to adverse experiences if death was due to an adverse experience which was not associated with progressive disease

Protocol Violations

The numbers of patients who violated the protocol and were excluded from the per protocol population, together with the reasons for violation, are shown in the following table:

Number (%) of patients who were protocol violations and reasons for violation and exclusion from the per protocol population

Reason for protocol violation	# (%) of patients*
Two prior regimens of chemotherapy	7 (6.3)
Indicator lesion in field of prior radiotherapy	5 (4.5)
Not assessed beyond 5 days	3 (2.7)
Did not have required measurable disease	3 (2.7)
Received hormonal treatment for cancer**	1 (0.9)
Did not have required performance status	1 (0.9)
Protocol violation; patient withdrawn	1 (0.9)
Surgery within previous 28 days	1 (0.9)
Concomitant malignancy	1 (0.9)
CT scan too early	1 (0.9)
Total number of patients who violated the protocol	19 (17.1)

A patient may have more than one reason for protocol violation. ** Hormonal treatment for cancer was not specified in the protocol as a violation but it was considered that such treatment may affect the assessments of efficacy. One patient received hormonal treatment for cancer and also had an indicator lesion in the field of prior radiotherapy and was therefore excluded from the per protocol population.

In addition to the patients who were considered protocol violations, there were a number of patients who were classified as conduct of study deviations for whom the deviation was not considered sufficient to warrant exclusion of the patient from the per protocol population. The numbers of patients who deviated from the protocol and the reasons for deviation and inclusion are summarized on the next page.

Number of patients who deviated from the protocol and reasons for deviation and inclusion in the per protocol population.

Study deviation	Reason for inclusion	# of patients
Surgery within 28 days	Surgery insignificant	4
Radiotherapy	Other assessable lesions/ years since radiotherapy	4
Abnormal laboratory values	Unlikely to affect assessment	4
Dose modification incorrect/irregular dosing	Considered acceptable	3
Chemotherapy within 28 days	Laboratory results satisfactory	2
5-8 day treatment delays because of holidays	Considered acceptable	2
No measurable lesion at baseline	Measurable lesion day 8	1
Radiophosphorus installation	Not clinically significant	1
Abdominal tumor pain*	No evidence of secondary	1
Baseline CT scan day 8	Considered acceptable	1
Prophylactic G-CSF course 1	Considered acceptable	1
Total number of patients who deviated from the protocol		24

* Identified while screening data for patients with concomitant malignancies; however, review of data on the CRF showed no evidence of a secondary tumor in this patient

Efficacy Results

Response to topotecan did not appear to be related to response to previous therapy, baseline disease status and CA-125 response. However, a response was seen in two patients who had not responded to first-line therapy. All patients aged <40 years were non-responders. Mean and median cumulative dose and dose intensity were similar for patients in each response category.

A summary of the applicant's results for objective response, time to response from the start of treatment, response duration from the time of first documented response, time to progression from the start of treatment and survival from the start of treatment are provided below for the intent-to-treat population.

Response Variable		# Patients (%)
		n=111
Complete Response	1	(0.9%)
Partial Response	15	(13.5%)
Total Responses	16	(14.4%)
Stable Disease	25	(22.5%)
Progression	68	(61.3%)
Not Done	2	(1.8%)
Duration of Response	n=16	
Median (weeks)	16.3	
Range (weeks)		
Time to Response	n=16	
Median (weeks)	10.4	
Range (weeks)		
Time to Progression	n=111	
Median (weeks)	11.3	
Range (weeks)		
Survival Time	n=111	
Median (weeks)	52.4	
Range		

7.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables

Time to response was calculated using the day the patient achieved the best response. Duration of response was calculated by the following criteria :

- Any patient that had a new lesion, whether or not the sum of the products of all lesions showed a decrease over the previous measurement was considered to have progression

- Any patient that had a 25 % increase in the sum of the products of all lesions over the previous best minimum was considered to have progression. For example, if a patient had a sum of products of 50, then decreased to 24, the first measurement that was greater than 30 (25 % of 24) would be considered the day of progression.

Time to progression was calculated using the same criteria.

Objective Responses: CR 1 (0.9%) PR 14 (12.6 %)

Total Responses: 15 (13.5%)

Time to Response in Days

N		Mean	S.D.		Min	Max
1	CR	62.00	0.00		62	62
14	PR	104.36	57.76	38	225	
15	Total	101.53	56.72	38	225	

Response Duration in Days

Mean	S.D.	Min	Max
95.00	27.39	63	126

Using these criteria, a set of 69 were selected for determining the time to progression and establishing a Kaplan-Meier time to event and a proportions plot.

Time to Progression in weeks

Median	8.43
Mean	10.00
Minimum	3
Maximum	24

7.4 Adverse Experience and Safety Results

Hematological Toxicity

Dose delays and reductions were required due to hematological toxicity in 14.5% and 3.9% of courses, respectively, and in 1.6% and 1.1% of courses, respectively, due to non-hematological toxicity. Most dose delays and reductions occurred in early courses, particularly courses 2 and 3.

The predominant hematological toxicity seen with topotecan was neutropenia, with grade 3 and 4 toxicity occurring in 97.3% of patients (108/111) and 69.1% of courses (374/541). The median time to onset of grade 4 neutropenia was 9 days from the start of treatment (range days) and the median duration was 7 days (range days). Prophylactic or treatment G-CSF was given to 26.1% of patients (29/111) in 20.5% of courses (113/552). Infection or fever >grade 2 or febrile neutropenia was reported in a total of 34.2% of patients (38/111) and 11.2% of courses (62/552) and infection or fever >grade 2 or febrile neutropenia proximate to grade 4 neutropenia in a total of 16.2% of patients 18/111) in 4.3% of courses (24/552). Systemic antibiotic treatment, including prophylactic use, was given to 40.5 % of patients in 13.9 % of courses and there were no reports of sepsis.

Platelet transfusions were given to 7.2% of patients in 2.4% of courses.

Anemia (at least grade 1) was reported in all patients during topotecan treatment and grade 3 and 4 anemia occurred in 31.5% of patients (35/111) and 11.1% of courses (61/548). Median time to onset of grade 3 and 4 anemia was 12 days (range days) and median duration was 7 days (range days). The proportion of courses with grade 3 and 4 anemia was lower for patients who did not have anemia at baseline (7.3% of courses; 34/464) than for patients who had

anemia at baseline (hemoglobin value < 11 g/dL at any time prior to first dose; 32.1%; 27/84). Red cell transfusions were given to 54.1% of patients in 20.7% of courses.

There was no evidence of an increase in incidence of grades 3 and 4 hematological toxicities with increasing numbers of courses of treatment, suggesting a lack of cumulative toxicity, although the median duration of grade 4 neutropenia tended to be longer after course 8 (8.5 to 13 days) than in earlier courses (7 days). Interpretation of these data is complicated, however, by the small number of patients in later courses.

Grade 4 Neutropenia

	Total	Patients	% Patients	Courses	% Courses
Total ANC measurements	2214	111		552	
Total ANC <500	320	88	79.3	221	40.0%

Fever, Duration, and Febrile Neutropenia

Fever > 38.0 C Duration in Days

Mean	Std. dev.	Min	Max	# of patients	per cent of all patients	# of courses	per cent of all courses	Total Measurements
3.27	3.17	1	12	21	19.8 %	30	5.43%	66

Documented Fever and Neutropenia Duration in days

Mean	Std. dev.	Min	Max	# of patients	per cent of all patients	# of courses	per cent of all courses	Total Measurements
4.44	4.03	1	15	18	16.2 %	28	5.07%	32

Fever and Fever and Neutropenia by Course

Course Fever > 38° C. per course

	Total	Mean	Std. dev.	Min	Max
1	12	3.69	3.84	1	12
2	5	3.50	2.08	1	6
3	5	3.40	3.21	1	9
4	3	1.50	0.58	1	2
5	3	5.00	5.66	1	9
6					

Course Fever and Neutropenia per course

	Total	Mean
1	12	5.46
2	8	6.42
3	4	5.29
4	3	1.75
5	1	1
6	1	5

Thrombocytopenia

	Total	# Patients	% Patients	Courses	% Courses
Total Plt measurements	2143	111		552	
Platelets <25,000	52	16	14.4%	21	3.80%

Grade 3,4 Anemia

		# Patients	% Patients	Courses	% Courses
Total # Hgb measurements	2164	111		552	
Total Hgb <8	581	51	34.0%	183	33.2%

Lymphocytopenia

	Total	Patients	% Patients	Courses	% Courses
Total ALC measurements	5334	111		552	
Total ALC < 500	102	34	30.63%	77	13.95%

Non-Hematologic Toxicity

Alopecia was the most commonly occurring adverse experience in 82% of patients (91/111) and, in 57.7% (64/111), the alopecia was grade 2. The next most frequent adverse experiences were nausea (75.7% of patients; 84/111), vomiting (54.1% of patients; 60/111) and diarrhea (43.2% of patients 48/111). These were also most frequently reported as related/possibly related to topotecan. The most common grade 3 and 4 toxicities reported as related/possibly related to topotecan were vomiting (5.4% of patients; 6/111), hyperbilirubinemia and nausea (both 4.5% of patients; 5/111). The profile of adverse experiences in course 1 was similar to that overall.

Adverse Events by Course

Course	Unknown	1	2	3	4	9	Sum	Patients
1	134	298	128	31	4	2	597	111
2	133	290	112	35	10	3	583	104
3	106	207	94	15	1	2	425	79
4	85	167	87	10		3	352	69
5	72	133	73	8	1	3	290	53
6	68	97	71	4		1	241	44
7	35	67	4[illegible]	4		1	150	27
8	32	56	37	3			128	23
9	11	22	13				46	11
10	12	14	11				37	10
11	7	12	2				21	5
12	1	7	4	1			13	4
13	5	8	1				14	3
14	2	9	1				12	3
15	2	11	2				15	3
16	2	4	2				8	2
17	2	2	1				5	1

Study 034 Non-hematologic Adverse Events by Number of Courses

					Grade									
Adverse Event by Courses	Total	% of total course	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	497	90.04	1	0.18	212	38.41	284	51.45						
NAUSEA	248	44.93	1	0.18	184	33.33	53	9.60	10	1.81			10	6.71
VOMITING	138	25.00	1	0.18	90	16.30	40	7.25	7	1.27			7	4.70
DIARRHEA	95	17.21	1	0.18	71	12.86	14	2.54	6	1.09	3	0.54	9	6.04
ABDOMINAL PAIN	93	16.85	17	3.08	57	10.33	16	2.90	3	0.54			3	2.01
FATIGUE	91	16.49	86	15.6			5	0.91						
CONSTIPATION	82	14.86	79	14.3	3	0.54								
STOMATITIS	78	14.13	2	0.36	47	8.51	26	4.71	2	0.36	1	0.18	3	2.01
ASTHENIA	72	13.04	66	12.0	2	0.36	2	0.36	2	0.36			2	1.34
HEADACHE	68	12.32	7	1.27	47	8.51	12	2.17	2	0.36			2	1.34
PHOSPHATASE ALKALINE INCREASED	68	12.32	1	0.18	64	11.59	3	0.54						
HEMATURIA	67	12.14	1	0.18	62	11.23	4	0.72						
HYPERGLYCEMIA	65	11.78	2	0.36	53	9.60	4	0.72	5	0.91			5	3.36
FEVER	61	11.05	4	0.72	24	4.35	31	5.62	2	0.36			2	1.34
ANOREXIA	42	7.61	8	1.45	20	3.62	13	2.36	1	0.18			1	0.67
PARESTHESIA	35	6.34	6	1.09	22	3.99	5	0.91	2	0.36			2	1.34
ALBUMINURIA	34	6.16	1	0.18	32	5.80	1	0.18						
DYSPNEA	34	6.16			11	1.99	16	2.90	7	1.27			7	4.70
HYPOKALEMIA	33	5.98			25	4.53	8	1.45						
SGPT INCREASED	33	5.98			25	4.53	7	1.27	1	0.18			1	0.67
DYSPEPSIA	31	5.62	9	1.63	17	3.08	5	0.91						
HYPOMAGNESEMIA	29	5.25			17	3.08	9	1.63	1	0.18			1	0.67
HYPOPHOSPHATEMIA	29	5.25	29	5.25										

Study 034 Non-hematologic Adverse Events by Number of Patients

Adverse Event by Patient	Total	%	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	93	83.78			28	25.23	65	58.56						
NAUSEA	84	75.68	1	0.90	45	40.54	32	28.83	6	5.41			6	4.03
VOMITING	60	54.05	1	0.90	32	28.83	21	18.92	6	5.41			6	4.03
DIARRHEA	49	44.14	1	0.90	33	29.73	9	8.11	4	3.60	2	1.80	6	4.03
CONSTIPATION	40	36.04	38	34.23	2	1.80								
ABDOMINAL PAIN	39	35.14	5	4.50	21	18.92	10	9.01	3	2.70			3	2.01
FEVER	35	31.53	3	2.70	11	9.91	19	17.12	2	1.80			2	1.34
FATIGUE	33	29.73	30	27.03			3	2.70						
STOMATITIS	33	29.73	1	0.90	19	17.12	10	9.0	2	1.80	1	0.90		2.01
HEADACHE	30	27.03	5	4.50	16	14.41	8	7.21	1	0.90			1	0.67
ASTHENIA	25	22.52	22	19.82	1	0.90			2	1.80			2	1.34
PHOSPHATASE ALKALINE INCREASED	25	22.52			22	19.82	3	2.70						
HEMATURIA	23	20.72			20	18.02	3	2.70						
HYPERGLYCEMI	21	18.92	1	0.90	14	12.61	3	2.70	2	1.80			2	1.34
ANOREXIA	19	17.12	3	2.70	7	6.31	8	7.21	1	0.90			1	0.67
HYPOMAGNESEMIA	19	17.12			10	9.01	7	6.31	1	0.90			1	0.67
DYSPNEA	17	15.3			6	5.41	6	5.41	5	4.50			5	3.36
HYPOKALEMIA	17	15.32			11	9.91	6	5.41						
SGPT INCREASED	17	15.32			11	9.91	5	4.50	1	0.90			1	0.67
ALBUMINURIA	16	14.41			15	13.51	1	0.90						
ALBUMIN GLOBULIN RATIO ABNORMAL	14	12.61	14	12.61										
COUGHING	14	12.61	4	3.60	6	5.41	2	1.80	2	1.80			2	1.34
DYSPEPSIA	14	12.61	4	3.60	7	6.31	3	2.70						
HYPONATREMIA	13	11.71			6	5.41	5	4.50	1	0.90			1	0.67
ANEMIA	12	10.81	2	1.80	1	0.90	2	1.80	7	6.31			7	4.70
BILIRUBINEMIA	12	10.81			2	1.80	3	2.70	5	4.50	2	1.80	7	4.70
HYPOCALCEMIA	12	10.81	1	0.90	6	5.41	2	1.80	1	0.90			1	0.67
PARESTHESIA	12	10.81	3	2.70	7	6.31	1	0.90	1	0.90			1	0.67
SGOT INCREASED	12	10.81			11	9.91			1	0.90			1	0.67

Non-Hematologic Adverse Events per Patient

	Mean	Stdev	Min	Max	Sum	# of patients	# of courses
Total	26.46	18.04	2	85	2937	111	551

Adverse Events = Grade 3

	Mean	Stdev	Min	Max	Sum	# of patients	per cent	# of courses	per cent
Total	2.58	1.97	1	10	111	42	37.8%	43	7.8%

Adverse Events = Grade 4

	Mean	Stdev	Min	Max	Sum	# of patients	per cent	# of courses	per cent
Total	1.78	1.09	1	4	16	8	7.2%	9	1.6%

Serious Adverse Experiences and Deaths

Anemia (8.1% of patients; 9/111) was the most frequently occurring serious adverse experience followed by granulocytopenia, intestinal obstruction and thrombocytopenia (all 6.3% of patients; 7/111) Hematological toxicities were the most common serious adverse experiences that were reported as related/possibly related to topotecan, ranging in incidence from 5.4% (6/111) to 7.2% (8/111) of patients.

By the cut-off date for inclusion in this report, a total of 28 (25.2%) patients had died, eight (7.2%) within 30 days of the last dose of topotecan. In all but four cases the cause of death was progressive disease. For three patients, who died within 30 days of topotecan treatment, the causes of death were febrile aplasia, myocardial infarction/cardiac arrest and thromboembolism. For the fourth patient, who died 103 days after treatment, the reason was not provided.

Withdrawals Due to Adverse Experiences

Ten patients (9.0%; 10/111) withdrew from the study due to adverse

thrombocytopenia (3.6% of patients; 4/111), anemia and cardiac arrest (each 1.8% of patients; 2/111). The remainder were single occurrences.

Vital Signs and ECGs

There were no changes of note in vital signs following topotecan treatment. Worsening of ECG findings was seen in four patients (5.3%) at the end of course 1 and two other patients (3.1%) at the end of the study. There was no evidence to suggest a topotecan effect on ECG's. No consistent changes were seen, and, in most cases where changes occurred, other factors such as significant medical history or concomitant metabolic disturbances were likely to have contributed.

Laboratory Tests

The most frequently occurring laboratory values of clinical concern (grade 3 or 4 toxicities) were hyperbilirubinemia in 6.3% of patients (7/111) and 2.0% of courses (11/537) and hyperglycemia in 3.7% of patients (4/108) and 1.3% of courses (7/524). The initial onset of grade 3 or 4 hyperbilirubinemia or hyperglycemia tended to be in early courses but there was no consistency in the pattern or magnitude of abnormal values and in a majority of patients values had returned to grade 0 to 2 by the last course.

7.5 Reviewer's Conclusion

This study has shown that topotecan, given as five daily intravenous infusions every 21 days, is active in patients with ovarian cancer who had failed treatment with one platinum-based chemotherapeutic regimen. The response rate was similar to that seen for historical controls in comparable multicenter studies. The main toxicity was hematological, predominantly neutropenia, but this was generally not associated with significant clinical sequelae and topotecan was well-tolerated with respect to non-hematological toxicities.

8.0 Integrated Summary of Efficacy in Ovarian Cancer Studies

The results of studies 039 and 034, supported by 033 and 012 (not reviewed) demonstrate the efficacy of topotecan in the treatment of recurrent ovarian cancer. Study 039 was the only comparative study conducted.

In all four of these studies, 445 patients received at least one dose of topotecan. The demographic characteristics of patients in these four studies

were similar although the baseline disease characteristics of platinum sensitivity, time to progression from first-line therapy and tumor bulk were most favorable for patients in study 039 and less favorable for patients in study 034. The population of patients on study 033 and 012 were also a poor prognosis group with more than 80% of patients being considered platinum resistant.

At the time of the 20 June 1995 clinical cut-off, 87/112 (78%) and 92/114 (81%) of patients treated with topotecan and paclitaxel, respectively, were alive. The estimated survival in patients treated with topotecan was a median of 61.3 weeks compared to 42.6 weeks on paclitaxel. Comparison of survival between treatment groups was not significant. Since the majority of patients were still alive at the time of the analysis, longer follow up is required to determine if the statistically significant difference in time to progression will translate into significantly improved survival with topotecan.

In the alternate arm of study 039, a total of 53 patients switched treatment to receive topotecan versus 37 patients who switched to receive paclitaxel. Five patients (9%) in the alternate topotecan group achieved a partial response and one patient (3%) in the alternate paclitaxel group achieved a complete response. A number of patients remain on treatment so it is too early to draw further conclusions from this component of the study.

Study 034 was non-comparative and was intended to assess the efficacy of topotecan versus historical controls. The efficacy endpoints assessed were response rate median time to response (10.4 weeks), median response duration (16.3 weeks), median time to progression (11.3 weeks) and estimated median survival (52.4 weeks). These results indicated that topotecan, used as a single agent, is comparable in terms of efficacy when compared to historical controls particularly the large, multicenter, European-Canadian study with paclitaxel which compared four different schedules of paclitaxel in patients failing first or second-line therapy [9, 10]. The response rate for the four schedules used ranged from %. When paclitaxel was administered at a dose of 175 mg/m2 and infused over 3 hours, the response rate was 14.6%, similar to the response rate reported for this schedule in study 039.

The efficacy results reported in study 034 were less impressive than those observed in study 03 This may in part be explained by the poorer prognosis of patients recruited into study 034, particularly with regard to the important baseline characteristic of platinum sensitivity. In study 034, 66% of patients were in the poor prognosis group with platinum resistant disease (defined as having no response or having relapsed within six months of prior therapy). This

respond or had relapsed within six months of prior therapy following the 175 mg/m^2 dose in the European-Canadian study In addition, more patients were less likely to respond due to bulky disease in study 034, with the greatest tumor diameter being in excess of 5 cm in 61% of patients compared to 50% in the topotecan arm of study 039. The corresponding figure in the European-Canadian study following the 175 mg/m^2 dose study was 68%

Study 033 was also non-comparative and was intended to determine if patients who had failed prior chemotherapy including both platinum and paclitaxel would respond to topotecan. The data from this study are considered to be interim since many patients received insufficient courses to expect a response. However, responses to topotecan treatment have been observed after failing first- and second-line chemotherapy. This patient population can also be considered a poor prognosis group, with 81% of patients being resistant to prior platinum therapy

Study 012 was a fourth, supportive and non-comparative study. The results seen in this initial study in platinum resistant disease were consistent with the other three studies.

Quality of life parameters measured in study 039 and study 033 did not indicate substantial changes when the assessment at baseline and end of best response were compared.

Since the design of studies 039, 034, 033 and 012 were similar, it was possible to review the results for the overall patient population. The efficacy results between studies are consistent. Differences in efficacy seen between studies were likely due to differences in baseline disease characteristics.

The results also support the selection of the starting dose for topotecan (1.5 mg/m^2/day) and the schedule (daily times five, repeated every 21 days). Dose intensity was maintained using this schedule. G-CSF was used to maintain dose intensity in 19% of all courses administered.

In conclusion, topotecan at the dose and schedule used in the four studies, is effective in the treatment of recurrent ovarian cancer. The results in the failed platinum population and failed platinum and paclitaxel population also suggest there is a lack of cross-resistance between topotecan and platinum or paclitaxel. The small sample size in the randomized comparative study 039, precludes

9.0 Integrated Summary of Safety

The Integrated Safety Summary presents safety data from 12 studies sponsored by SB that have interim or final reports. A total of 774 patients received at least one dose of topotecan in these studies, including a total of 445 patients from four studies in recurrent ovarian cancer. A further 14 SB sponsored studies which are either ongoing or recently closed to recruitment have not yet been reported. All serious adverse events, withdrawals and deaths are included for the 502 patients in these unreported studies. For all ongoing studies a clinical cut-off date of 20th June 1995 was applied.

Phase I studies:

Four Phase I studies of intravenous topotecan are reported. These studies enrolled 131 patients with solid tumors. One study (005) used the daily times five regimen of study drug, one used the daily times five regimen plus a single dose of cisplatin at each course (017), while the others used different regimens.

Phase II/III studies in ovarian cancer:

There are four reported studies in ovarian cancer, each used a starting dose level of 1.5 mg/m2/day given as a 30-minute infusion for five consecutive days every 21 days (referred to as the "daily times five" regimen). All patients had advanced ovarian cancer and had failed at least one previous platinum containing regimen. Study 039 was a multicenter, randomized, comparative study versus paclitaxel in which patients who progressed or whose best response was stable disease after 6 courses on the randomized arm could be switched to the other treatment (alternate) arm. Study 034 was a non-comparative, multicenter study in patients failing one prior regimen. Study 033 was a multicenter, non-comparator study in patients who had failed one prior therapy with a platinum/paclitaxel combination or who had failed two prior regimens which must have included platinum and paclitaxel. Study 012 was an early phase II single institution study in patients failing no more than two prior regimens. In total 445 patients, including those given topotecan in the alternate phase of study 039, were treated with at least one dose of topotecan. Data from these studies have been combined, and since these data are the most relevant for the indication they are discussed in greatest detail. Data from the single comparative study 039 are also presented separately in detail.

Phase II Breast Cancer Studies

One reported study (013) utilized the daily times five regimen in 20 patients. A further study (030) included 18 patients with advanced breast cancer, and used a single 24-hour infusion of 22.5 mg/m2 repeated every 21 days.

Two studies conducted by the EORTC are presented as interim reports, both used the daily times five regimen. One study (011) was in 59 previously untreated patients with colorectal cancer, and the other (014) was in 101 previously treated patients with small cell lung cancer.

Other Studies

There are 13 ongoing topotecan clinical studies using the intravenous route of administration and one additional ongoing phase I study investigating an oral dosage form of topotecan. The intravenous studies include the daily times five regimen, a 21-day continuous infusion every 28 days, and one other study evaluating a weekly 24-hour continuous infusion regimen. A total of 502 patients were enrolled in these studies at the clinical cut-off date.

Further studies have been sponsored by the National Cancer Institute (NCI). These have not been fully reported, but all publications have been referred to as safety data from other sources. One NCI sponsored study of patients with hepatic and renal impairment has been summarized in the ISS Item 8, Section g (Report SK&F 104864A/097).

Overall Extent of Exposure

The 12 reported clinical studies involved 774 patients and a total of 3351 courses of topotecan. The majority of patients were treated with the daily times five regimen in which a daily 30-minute intravenous infusion of topotecan administered on five consecutive days constituted a treatment course. The scheduled interval between treatment courses was 21 days. In the studies using this regimen, 3090 topotecan treatment courses were administered to 688 patients.

The reported studies include four Phase I studies (004, 005, 010 and 017; total 131 patients), four Phase II/III studies of ovarian cancer (012, 033, 034 and 039; total 445 patients), two Phase II studies of breast cancer patients (013, 030; total 38 patients), one EORTC Phase II study in patients with colorectal cancer (011; 59 patients) and one EORTC Phase II study in patients with small cell lung cancer (014E; 101 patients.

In the four Phase II/III ovarian cancer studies, 445 patients received a total of 2019 topotecan courses, of which 1673 courses (82.8%) were administered at the starting dose of 1.5 mg/m2/day. Retreatment commenced within five days of the scheduled start dates for 1206 (76.6%) of 1574 courses after the first course. The dose level was reduced in just 100 (6.4%) of 1574 courses after the first course. Overall in the four ovarian cancer studies, topotecan patients received a median of 4 courses per patient (range 1-33), a median dose intensity of 2.39 mg/m2/week and a median cumulative dose of 30 mg/m2. Data are presented on nine subset populations of the ovarian cancer patients based upon their demographic and baseline characteristics. Of the 2019 courses, 1293 courses (64.0%) were administered to 284 patients (63.8%) who were between 41 and 64 years old. In these studies, the use of G-CSF was permitted after a patient's

first topotecan course, before dose level reduction in order to maint dose intensity, if neutropenia or sequelae of neutropenia would have been the sole reason for a dose reduction. G-CSF was used prophylactically in 388/2019 (19.2%) of treatment courses.

One of the four ovarian cancer studies was a randomized Phase II/III study (Study 039)comparing topotecan treatment of 112 patients for a total 555 courses with paclitaxel treatment of 114 patients for a total of 550 courses. The topotecan patients had a median of 5 courses per patient (range ., a median dose intensity of 2.3 mg/m2/week and a median cumulative dose of 37.5 mg/m2. The paclitaxel patients had a median of 5 courses per patient (range ., a median dose intensity of 56.3 mg/m2/week and a median cumulative dose of 875 mg/m2.

In addition to the 12 reported studies, there are 13 ongoing topotecan clinical studies using the intravenous route of administration, and one ongoing study investigating an oral dosage form of topotecan. Of the ongoing studies, five are using the daily times five regimen, seven studies are using a regimen in which topotecan is administered as a 21-day continuous infusion every 28 days, and one other study is evaluating a weekly 24-hour continuous infusion regimen. A total of 502 patients were enrolled in these studies at the clinical cut-off date, these patients received at least one dose of topotecan, but no further data is available on overall extent of exposure.

Demographics

The population described in this section consists of the 774 patients that were treated in the 12 reported clinical studies described in Section 2, four Phase I and eight Phase II/III studies. These include 668 patients treated with topotecan on the daily times five regimen.

The Phase I studies (Studies 004, 005, 010, and 017) involved 131 patients of whom 92 (70.2%) were male. The mean age of the patients was 59.0 (range , years. One hundred and twelve patients (85.5%) had a performance status £ 1. Seventy-nine patients (60.3%) had prior chemotherapy and 93 patients (71.0%) had prior surgical treatment of their cancer.

In four studies of ovarian cancer, three Phase II (Studies 012, 033 and 034) and one Phase III (Study 039), there were 445 patients, all of whom were pretreated. The patients' mean age was 57.6 (range years, and 339 patients (76.2%) had a performance status £ 1. Two hundred and sixty-one patients (58.7%) had a histopathologic diagnosis of malignant serous tumor. In 341 patients (76.6%) the tumor histologic grade was £ grade 3. The maximum lesion diameter was < 5 cm in 201 patients (45.2%) and was > 5 cm but < 10 cm in 199 patients (44.7%). Liver metastases were known to present at baseline in 289 patients (65.0%). Creatinine test results were within normal limits in 398 (89.4%) patients. Baseline anemia was recorded for 128 of the ovarian cancer

patients (29%) in the four studies. The majority of patients, 292 (65.6%), had only one prior treatment regimen, and only 13 patients (2.9%) had more than two prior chemotherapy regimens. Two hundred and sixty-one patients (58.7%) had achieved either a complete response or a partial response to first-line therapy and 85 patients (19.1%) had stable disease as their best response to first-line chemotherapy.

Overall, the demographic characteristics of the ovarian cancer patients in the randomized phase of the comparator study of topotecan and paclitaxel (Study 039) were similar to the characteristics of patients in the pooled population of 445 patients in the four ovarian studies, described above. Of 226 total patients, 112 were randomized to the topotecan arm and are included in the pooled population; 114 patients were randomized to the paclitaxel arm. In baseline comparison of prior platinum therapy, the randomized phase of the comparator study had a higher proportion of patients who were late relapse (46.4%) than did the pooled population of patients in the four studies (30.8%). In the randomized phase of the comparator study, a complete response or a partial response to first-line chemotherapy had been achieved by 64.3% of patients, compared to 58.7% of the pooled population of patients in the four ovarian studies.

In two Phase II breast cancer studies (Studies 013 and 030) there were 38 patients, mean age 58.4 (range ') years, of whom 26 had a reported performance status £ 1. All patients had prior chemotherapy, 36 patients had prior radiation therapy and 35 patients had prior surgical treatment of their breast cancer.

Two Phase II studies conducted by the EORTC-ECTG (SB Studies 011 and 014E) enrolled a total of 160 patients, but reported data on 151 evaluable patients, 95 male and 56 female, median age 59 (range 34 to 75) years. One hundred and thirty-two (87.4%) patients had a performance status £ 1. One of the studies (Study 011) involved 57 evaluable colorectal cancer patients of whom 52 (91.2%) had prior surgical treatment and only two patients (3.5%) had prior chemotherapy. The other study (Study 014E) was an investigation in 94 evaluable small cell lung cancer patients, all of whom had prior chemotherapy; 49 patients (52.1%) entered the study with disease classified as refractory to prior chemotherapy and 45 patients (47.9%) had disease classified as sensitive to prior chemotherapy.

Adverse Experiences in Clinical Trials

All toxicities were reported as grades according to the modified Common Toxicity Criteria (CTC) of the National Cancer Institute. Hematologic and non-hematologic toxicities were examined for the 131 patients in four Phase I and for the 445 patients in three Phase II and one Phase III study which assessed topotecan 1.5 mg/m2 daily times five regimen in patients with advanced ovarian carcinoma. In the Phase III study in patients with recurrent ovarian cancer, topotecan was compared with paclitaxel given at a dose of 175 mg/m2 over three hours. Additionally, toxicities were examined in two EORTC Phase II

studies using topotecan daily times five regimen in 57 patients with colorectal cancer and in 94 patients with small cell lung cancer.

Hematologic Toxicities

White blood cell, neutrophil, platelet and hemoglobin counts were evaluated to assess the hematologic toxicity of topotecan. The severity of toxicities was presented by CTC grade, and the incidence of toxicity by patients and by course was tabulated. Time to onset and duration of severe toxicity, hematologic nadir, and infective complications were also examined.

In Phase I studies, dose limiting toxicities were neutropenia or leukopenia in three of the studies, and neutropenia and thrombocytopenia in the fourth study. infective complications resulting from hematologic toxicities were infrequent in all four Phase I studies.

In the ovarian cancer studies 039, 034, and 033, hematologic criteria for treatment initiation included neutrophils > 1,500/mm3, platelets > 100,000/mm3 and hemoglobin > 9 g/dL. Retreatment criteria for subsequent courses were the same except that neutrophils > 1,000/mm3 were recommended for topotecan.

In the combined ovarian population of 445 patients, hematologic toxicities observed with topotecan daily times five regimen were reversible, non-cumulative and manageable, and infrequently led to serious sequelae. Grade 4 neutropenia was the most frequently reported toxicity, experienced by 79% of patients and associated with 42% of courses administered, and as expected was most prevalent during course 1 of therapy before dose reduction or G-CSF use were instituted. Grade 4 thrombocytopenia was experienced by 23% of patients in 9% of courses. Grade 3 or grade 4 anemia was experienced by 37% of patients in 15% of courses.

Day of ophil nadir occurred earlier with additional courses of therapy (but remaine istant for platelets and hemoglobin). This was probably related to the less severe depression of the neutrophil nadir subsequent to course one, due to a proportion of patients receiving dose reductions and G-CSF in these later courses. Median duration of severe toxicity was one week or less; grade 4 neutropenia lasting longer than one week was associated with 12% of total courses administered. There was no clear evidence of cumulative toxicity associated with topotecan therapy, as evidenced by the lack of progressively lower hematologic nadirs. Sequelae of hematologic toxicities were infrequent, particularly after course one of therapy. Suspected or documented infections proximate to grade 4 neutropenia were associated with 6.5% of courses, with sepsis reported in a further 1.1% of courses. Topotecan induced myelosuppression was considered related to the death of three patients (0.7%).

INTEGRATED SAFETY DATA IN OVARIAN CANCER STUDIES SUBMITTED TO FDA

Neutropenia

Total ANC measurements	5271	Patients	276			Courses	1441	
Total ANC< 500	727	Patients	220	% All Pts.	79.7%	Courses	500	34.7%

Duration in Days

	039 All	Topo	Taxol	034	Cumulative
Mean	5.58	5.56	5.68	6.34	5.73
Std.Dev.	11.32	12.19	2.49	10.48	11.85
Min.	1	1	1	1	1
Max.	219	219	15	109	219
# of courses	457	391	66	105	496

Anemia

Total Hgb measurements	5068	Patients	276			Courses	1442	
Total Hgb< 8	879	Patients	79	% All Pts.	28.6%	Courses	299	20.7%

Thrombocytopenia

Total Plt measurements	5015	Patients	276			Courses	1442	
Total Plt < 25	126	Patients	52	% All Pts.	18.8%	Courses	72	4.99%

Lymphopenia

Total ALC measurements	8348	Patients	276			Courses	1441	
Total ALC < 500	320	Patients	96	% All Pts.	34.78%	Courses	212	14.71%

Adverse Experiences in Clinical Trials

All toxicities were reported as grades according to the modified Common Toxicity Criteria (CTC) of the National Cancer Institute. Hematologic and non-hematologic toxicities were examined for 131 patients in four Phase I MTD studies which assessed several dosing regimens in various tumor types, and for 445 patients in three Phase II and one Phase III study which assessed topotecan 1.5 mg/m2 daily times five regimen in patients with advanced ovarian carcinoma. In the Phase III study in patients with recurrent ovarian cancer, topotecan daily times five regimen was compared with paclitaxel given at a dose of 175 mg/m2 over three hours. Additionally, toxicities were examined in two EORTC Phase II studies using topotecan daily times five regimen in 57 patients with colorectal cancer and in 94 patients with small cell lung cancer.

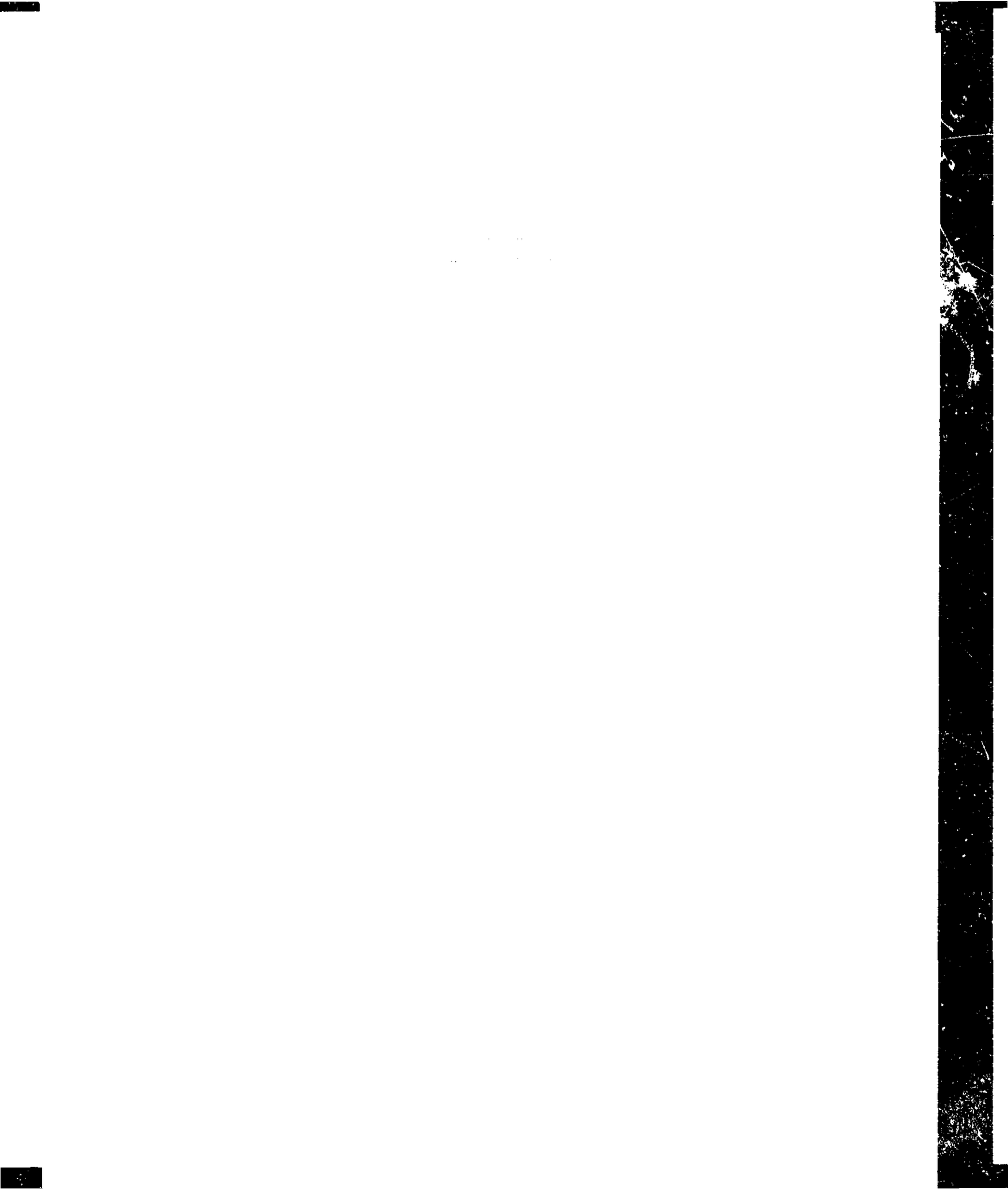
Hematologic Toxicities

White blood cell, neutrophil, platelet and hemoglobin counts were evaluated to assess the hematologic toxicity of topotecan. The severity of toxicities was presented by CTC grade, and the incidence of toxicity by patients and by course was tabulated. Time to onset and duration of severe toxicity, hematologic nadir, and infective complications were also examined.

In Phase I studies, dose limiting toxicities were neutropenia or leukopenia in three of the studies, and neutropenia and thrombocytopenia in the fourth study. Infective complications resulting from hematologic toxicities were infrequent in all four Phase I studies.

In the combined ovarian population of 445 patients, hematologic toxicities observed with topotecan daily times five regimen were reversible, non-cumulative and manageable, and infrequently led to serious sequelae. Grade 4 neutropenia was the most frequently reported toxicity, experienced by 79% of patients and associated with 42% of courses administered, and was most prevalent during course 1 of therapy before dose reductions or G-CSF use was instituted. Grade 4 thrombocytopenia was experienced by 23% of patients in 9% of courses. Grade 3 or grade 4 anemia was experienced by 37% of patients in 15% of courses.

Day of neutrophil nadir occurred earlier with additional courses of therapy, but remained constant for platelets and hemoglobin. This was probably related to the less severe depression of the neutrophil nadir subsequent to course one, due to a proportion of patients receiving dose reductions and G-CSF in these later courses. Median duration of severe toxicity was one week or less; grade 4 neutropenia lasting longer than one week was associated with 12% of total courses administered. There was no clear evidence of cumulative toxicity associated with topotecan therapy, as evidenced by the lack of progressively



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NDA 20-671

AP Ltr
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Ped. Pts
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ODAC mins +
Slides 2/24/96

AP Ltr
Draft LBLG

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-671

MAY 28 1996

SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

Attention: Richard Swenson, Ph.D.
Associate Director, U.S. Regulatory Affairs

Dear Dr. Swenson:

Please refer to your December 21, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hycamtin™ (topotecan hydrochloride) 4 mg for Injection.

We acknowledge receipt of your amendment dated May 10, 1996.

This new drug application provides for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-671. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments to:

1) provide updated survival and other efficacy data for studies 39, 34, and 33.

2) assure that the DMF holder, will provide FDA a copy of the English translation of the master production record of in a reasonable time. The record needs to be reviewed and found acceptable by the Agency before production of new batches of commences in . (enough lead time should be allowed for necessary revisions, if any).

3) for the annual stability study of future batches of topotecan drug substance under long term storage conditions, follow the same study protocol as described in the NDA for the stability study of the validation batches.

Please submit the above information to the NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Debra Catterson, R.Ph.
Project Manager
(301) 827-1544

Sincerely yours,

Robert Temple 5/28/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-671
HFD-150/Div. files
HFD-150/CSO/D.Catterson
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HFD-150/YHsieh
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HFD-021/J.Treacy (with labeling)
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APPROVAL [with Phase 4 Commitments]

XX:L1

Prescribing Information

HYCAMTIN™

brand of 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 1500 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

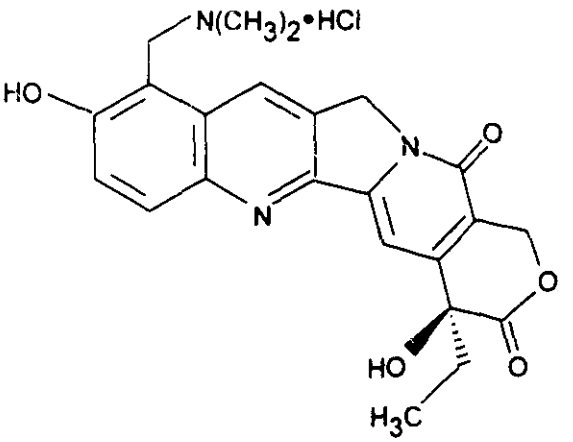
Hycamtin (topotecan hydrochloride) is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity.

Hycamtin (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.

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 $pH \leq 4$ the lactone is exclusively present whereas the ring-opened hydroxy-acid form predominates at physiologic pH. *In vitro* studies in human liver microsomes indicate that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway.

In humans, about 30 % of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination (see Special Populations).

Special Populations

Gender: The overall mean topotecan plasma clearance in male patients was approximately 24 % higher than 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, common in the elderly, is a more important determinant of topotecan clearance.

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} 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 three 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 - 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 dihydropyridine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo*.

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 - 90 % decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

CLINICAL STUDIES:

Hycamtin (topotecan hydrochloride) was studied in four clinical trials of 452 patients with metastatic ovarian carcinoma. All patients had disease that had recurred on , or was unresponsive to, a platinum-containing regimen. Patients in these four 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 one of a 21-day course.

Two of the studies, involving 223 patients given topotecan, are mature enough for evaluation (although survival results are incomplete). Hycamtin was compared with paclitaxel in a randomized trial involving 112 patients treated with Hycamtin (1.5

$mg/m^2/d$ x 5 days starting on day one 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 one 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 (measured from the time of documented response), and time to progression are shown in Table 1.

Table 1. Efficacy of Hycamtin vs Paclitaxel in Ovarian Cancer

Parameter	*Hycamtin* (n=112)	Paclitaxel (n=114)
Complete Response Rate	5.4%	3.5%
Partial Response Rate	14.3%	8.8%
Overall Response Rate	19.6%	12.3%
95% CI	12.8-28.2 %	6.9-19.7%
(p-value)	(0.0918)	
Response Duration (weeks)		
Median	22.2	12.0
Range	5.1+ to 31.6+	4.8+ to 21.0+
hazard-ratio (Hycamtin:paclitaxel)	0.276	
(p-value)	(0.065)	
Time to Progression (weeks)		
Median	23.1	14.0
Range	0.7+ to 62.1+	0.1 to 30.9
hazard-ratio (Hycamtin:paclitaxel)	0.578	
(p-value)	(0.002)	

+value corresponds to a censored event; i.e., patient had not yet progressed

The calculation for duration of response was based on the interval between best response and time to progression, not from time of enrollment nor from time of initial response to time to progression.

The time to response was longer with Hycamtin compared to paclitaxel with a mean of 10 weeks (range 5.4- 31.6) vs 7 weeks (range 4.8 - 9.4). Consequently, the efficacy of Hycamtin may be decreased if patients are withdrawn from treatment prematurely.

In the crossover phase, in patients who did not respond to treatment on the initial arm of the trial, 5 of 53 (9.4%) patients who received Hycamtin after paclitaxel had a partial response and 1 of 37 (2.7%) patients who received paclitaxel after Hycamtin had a complete response.

Hycamtin was active in 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 four partial responders on the paclitaxel arm, for a response rate of 7%.

The adverse reaction profile for paclitaxel in this study was consistent with the product's approved labeling; the adverse reaction profile for Hycamtin in this study was consistent

with that obser ed in all 452 patients from the four ovarian cancer clinical trials (see ADVERSE REACTIONS).

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 one prior platinum-containing regimen. The response rate was 14% (95% CI =7.9% to 20.9%). The median duration of response was 18 weeks (range 5-42 weeks). The time to progression was 8.4 weeks (range: 0.7 to 72.1 weeks).

INDICATIONS AND USAGE

Hycamtin (topotecan hydrochloride) is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

CONTRAINDICATIONS

Hycamtin is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan.

Neutropenia: Severe (grade 4, <500 cells/mm^3) neutropenia was most common during course 1 of treatment (60% of patients) and occurred in 40% of all courses. The nadir neutrophil count occurred at a median of 11 days. Prophylactic G-CSF was given in 27%

of courses after the first cycle. Therapy-related sepsis or febrile neutropenia occurred in 26% of patients and sepsis was fatal in 0.8%.

Thrombocytopenia: Grade 4 thrombocytopenia (<25,000/mm^3) occurred in 26% of patients and in 9% of courses, with a median duration of 5 days and platelet nadir at a median of 15 days. There were no episodes of serious bleeding. Platelet transfusions were given to 13% of patients and in 4% of courses.

Anemia: Severe anemia (grade 3/4, <8gm/dL) occurred in 40% of patients and in 16% of courses. Median nadir was at Day 15. Transfusions were needed in 56% of patients and in 23% of courses.

Monitoring of Bone Marrow Function: Hycamtin should only be administered in patients with adequate bone marrow reserves, including baseline neutrophil counts of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with Hycamtin. Patients should not be treated with subsequent courses of Hycamtin until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3 and hemoglobin levels recover to 9.0 mg/dL, (with transfusion if necessary). Severe myelotoxicity has been reported when Hycamtin is used in combination with cisplatin (see Drug Interactions)

Pregnancy: Hycamtin may cause fetal harm when administered to a pregnant woman. The effects of topotecan on pregnant women have not been studied. If topotecan is used during a patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming pregnant. Topotecan caused embryonic and fetal death in rats and rabbits. In rabbits, a dose of 0.32 mg/kg/d (about twice the clinical dose on a mg/m^2 basis) on days six through twenty of gestation caused fetal resorption. This dose caused significant maternal toxicity. In the rat, a dose of 0.23 mg/kg/d (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day six caused fetal resorption, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/d (about half the clinical dose on a mg/m^2 basis) given to rats on days six 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), scull and vertebrae.

PRECAUTIONS

General: Inadvertent extravasation with Hycamtin has been associated with only mild local reactions such as erythema and bruising.

Hematology: Monitoring of bone marrow function is essential (see **WARNINGS** and **DOSAGE AND ADMINSTRATION)**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity testing of topotecan has not been performed. Topotecan, however, is known to be genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

Drug Interactions:

Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should not be initiated until day 6 of the course of therapy, 24 hours after completion of treatment with Hycamtin [1].

Myelosuppression was more severe when Hycamtin was given in combination with cisplatin in Phase 1 studies. In a reported study on concomitant administration of cisplatin 50 mg/m^2 and Hycamtin at a dose of 1.25 mg/m^2/day x 5 days, one of three patients having neutropenia for 12 days and a second patient died with neutropenic sepsis. There are no adequate data to define a safe and effective regimen for Hycamtin and cisplatin in combination.

Pregnancy: Pregnancy Category D. (See WARNINGS section.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving Hycamtin (see CONTRAINDICATIONS).

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

ADVERSE REACTIONS

Data in the following section are based on the experience of 452 patients with metastatic ovarian carcinoma treated with Hycamtin. Table 2 lists the principal hematologic toxicities and Table 3 lists non-hematologic toxicities occurring in at least 19% of patients.

Table 2: Summary of Hematologic Adverse Events in Patients Receiving Hycamtin

Hematologic Adverse Events	Patients n=452 % Incidence	Courses n=2375 % Incidence
Neutropenia		
<1,500 cells/mm^3	98	78
<500 cells/mm^3	81	40
Leukopenia		
<3,000 cells/mm^3	98	77
<1,000 cells/mm^3	32	11
Thrombocytopenia		
<75,000/mm^3	63	39
<25,000/mm^3	26	9
Anemia		
<10 g/dL	95	76
<8 g/dL	40	16
Sepsis or fever/infection with Grade 4 neutropenia	26	7
Platelet transfusions	13	4
RBC transfusions	56	23

Table 3: Summary of Non-hematologic Adverse Events in Patients Receiving Hycamtin

Non-hematologic Adverse Events	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	n=452 Patients	n=2375 Courses	n=452 Patients	n=2375 Courses	n=452 Patients	n=2375 Courses
Gastrointestinal						
Nausea	77	50	10	3	<1	<1
Vomiting	58	26	6	3	3	<1
Diarrhea	42	19	4	1	<1	<1
Constipation	39	18	2	<1	1	<1
Abdominal Pain	33	13	4	<1	2	<1
Stomatitis	24	9	2	<1	<1	<1
Anorexia	19	8	2	<1	0	0
Body as a Whole						
Fatigue	37	25	6	2	0	0
Fever	34	13	1	<1	<1	<1
Asthenia	21	10	3	<1	1	<1
Skin/Appendages Alopecia	59	62	NA	NA	NA	NA

Premedications were not routinely used in these clinical studies.

Table 4 shows the grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/paclitaxel comparator trial (including adverse events in patients who crossed over to the alternative treatment).

Table 4 Comparative Toxicity Profiles

	Hycamtin		Paclitaxel	
Adverse Event	**Pts**	**Courses**	**Pts**	**Courses**
	n= 165	n= 731	n= 151	n=676
Hematologic Grade 3/4	%	%	%	%
Grade 4 neutropenia (< 500 cells/mL)	80.0	38.2	19.9	8.7
Grade 3/4 Anemia (Hgb < 8g/dL)	40.6	25.3	18.5	17.2
Grade 4 Thrombocytopenia (< 25 000 plts/mL)	21.8	7.0	0.7	0.1
Fever/Grade 4 neutropenia	21.2	5.7	4.0	0.9
Documented Sepsis	5.5	1.2	1.3	0.3
Death related to Sepsis	1.8	0.4	0.0	0.0
Non-hematologic Grade 3/4				
Gastrointestinal				
Nausea	10.3	3.6	3.4	0.7
Vomiting	9.1	2.3	4.0	0.9
Constipation	4.9	1.2		0
Diarrhea	5.5	1.5	0.7	0.2
Abdominal pain	6.1	2.6	5.4	1.3
Intestinal Obstruction	4.3	1.6		0
Stomatitis	1.8	0.4	0.7	0.2
Constitutional				
Fatigue	6.7	2.2	4.7	1.8
Fever	6.7	1.5	1.3	0.3
Dyspnea	6.1	2.3	4.0	1.0
Neuromuscular				
Arthralgia	1.2	0.4	2.0	0.4
Asthenia	5.5	1.4	4.0	1.6
Myalgia	0	0	2.7	1.5
Pain	1.8	0.6	1.3	0.6
Paresthesia	1.2	0.4	0	0

Hematologic: (See WARNINGS)

Gastrointestinal: The incidence of nausea was 77% (10% grade 3/4) and vomiting occurred in 58% (9% grade 3/4) of patients (See Table 3). The prophylactic use of anti-emetics was not routine in patients treated with Hycamtin. Forty-two % of patients had diarrhea (5% grade 3/4) , 39% constipation (3% grade 3/4) and 33% had abdominal pain (6% grade 3/4).

Skin/Appendages: Total alopecia (Grade 2) occurred in 42% of patients.

Central and Peripheral Nervous System: Headache (21%) was the most frequently reported neurologic toxicity. Paresthesia occurred in 9% of patients but was generally Grade 1.

Liver/Biliary: Grade 1 transient elevations in SGOT/AST and SGPT/ALT occurred in 5% of patients. Greater elevations, grade 3/4 , occurred in <1%. Grade 3/4 elevated bilirubin occurred in <3% of patients.

Respiratory: Dyspnea (20%); Grade 3/4 dyspnea (4%).

OVERDOSAGE

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

The LD_{10} in mice receiving single intravenous infusions of Hycamtin was 75 mg/m^2 (CI 95%: 47 to 97).

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of Hycamtin, patients must have a baseline neutrophil count of >1500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended dose of Hycamtin (topotecan hydrochloride) 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. A minimum of four courses is recommended because median time to response in three clinical trials was 9 to 12 weeks. In the event of severe neutropenia during any course, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. Alternatively, in the event of severe neutropenia, G-CSF may be administered following the subsequent course (before resorting to dose reduction) starting from Day 6 of the course (24 hours after completion of topotecan administration).

Adjustment of Dose in Special Populations

Hepatic Impairment: No dosage adjustment appears to be required for treating patients with impaired hepatic function (plasma bilirubin >1.5 to <10 mg/dL).

Renal Functional Impairment: No dosage adjustment appears to be required for treating patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20 to 39

mL/min). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

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

PREPARATION FOR ADMINISTRATION

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

Preparation for Intravenous Administration:

Each Hycamtin 4 mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of Hycamtin (topotecan hydrochloride) are stable until the date indicated on the package when stored between 20° and 25°C (68° and 77°F) and protected from

light in the original package. Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of Hycamtin diluted for infusion are stable at approximately 20° to 25 °C (68° to 77°F) and ambient lighting conditions for 24 hours.

HOW SUPPLIED

NDC 0007-4201-05: Hycamtin (topotecan hydrochloride) for Injection is supplied in 4 mg (free base) single dose vials, in packages of 5 vials.

Storage: Store the vials protected from light in the original cartons at controlled room temperature between 20° and 25°C (68° and 77°F).

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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6.Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept./Oct. 258-263.

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8. OSHA Work-Practice guidelines for personnel dealing with cytotoxic(antineoplastic) drugs. Am J Hosp Pharm 1986; 43:1193-1204.

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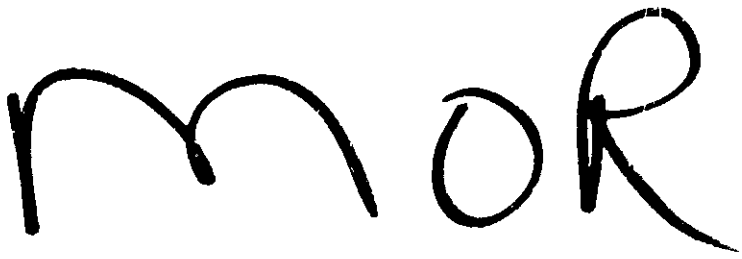
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MEDICAL REVIEW OF NDA 20-671: Hycamtin® (Topotecan)

APPLICANT: Smith Kline Beecham

REVIEWING MEDICAL OFFICER: Steven Hirschfeld, MD., Ph.D.

Draft for ODAC: March 25, 1996

ODAC Meeting: April 19, 1996

Review Completed: May 23, 1996

BEST POSSIBLE COPY

1.0 GENERAL INFORMATION 4

2.0 INTRODUCTION 5

3.0 DESCRIPTION OF CLINICAL DATA SOURCES 8

4.0 REGULATORY HISTORY 9

5.0 LIST OF INDS AND NDAS 12

6.0 CONTROLLED CLINICAL STUDY 039 13

6.1 Study Design and Objectives 13

6.2 Overview of Demographics, Treatment and Efficacy Results 18

6.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables 24

6.4 Adverse Experience and Safety Data 29

6.5 Reviewer's Conclusion 41

7.0 NONCOMPARATOR CLINICAL STUDY 034 41

7.1 Study Design and Objectives 41

7.2 Overview of Demographics, Treatment and Efficacy Results 45

7.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables 52

7.4 Adverse Experience and Safety Results 54

7.5 Reviewer's Conclusion 61

8.0 SUMMARY OF EFFICACY IN OVARIAN CANCER STUDIES 61

10.0 FOUR MONTH SAFETY UPDATE 82

10.1 Background 82

10.2 Drug-related Adverse Events 84

10.3 Serious Adverse Events 87

10.4 Adverse Events Leading to Treatment Withdrawal 90

10.5 Deaths 92

10.6 Clinical Laboratory Data 96

10.7 Sponsor's Conclusions 96

11.0 REVIEWER'S CONCLUSIONS 96

12.0 ODAC MEETING, APRIL 19, 1996 98

13.0 PRODUCT LABELLING COMMENTS 99

14.0 RECOMMENDED REGULATORY ACTION 122

15.0 DEFICIENCY LIST 123

1.0 GENERAL INFORMATION

Drug Name:	Hycamtin® (topotecan)
Applicant:	Smith Kline Beecham
NDA Submission Date:	December 21, 1995
Electronic Data Files Installed:	January 26, 1996
Pharmacologic Category.	Topoisomerase I inhibitor
Proposed Indication:	Ovarian cancer second line therapy
30-Day Meeting:	January 21, 1996
45-Day Meeting:	February 5, 1996
Safety Update:	April 30, 1996
ODAC Meeting:	April 19, 1996

2.0 INTRODUCTION

Ovarian Cancer

Ovarian cancer is potentially one of the most treatable gynecological malignancies since most tumors are sensitive to anticancer therapy; however, due to difficulties in detecting disease in the population most at risk, most women present with advanced or disseminated disease and it is the leading cause of death among women with gynecological malignancies. Ovarian cancer comprises about 4% of the total annual cases of cancer in the United States, with approximately 21,000 new cases. In 1992, about 13,000 women died from the disease, which is about 6% of all cancer deaths among women and 1% of all deaths. The peak incidence of the disease is highest in white women in their sixties, and only between 10 and 15 % of cases affect women who are less than 50 or premenopausal. The incidence is significantly lower outside industrial countries, and has been linked to a high fat diet, although speculation exists concerning environmental pollutants gaining access to the genital tract. There is an association between exposure to asbestos and talc and the development of ovarian cancer.

There is a decrease in the risk for women who are multiparous, with one or two pregnancies giving reducing the risk by about 50% and three or more reducing the risk to 33% compared to women who are nulliparous. The use of oral contraceptives can also reduce the risk by about 25%. The inference from these observations is that continuous ovulation is a risk factor. There is an association with breast cancer in that women who have had breast cancer have a twofold increase in the risk for ovarian cancer and women with ovarian cancer have a three to four fold increase in the risk for breast cancer.

Classification of ovarian tumors depends upon the probable tissue of origin. Most ovarian tumors develop from the surface of the ovary, and are of the epithelial type. In the North America and Europe, the incidence is from 85 to 90%. The remainder are derived from germ or stromal cells. In women under 40 years of age, epithelial types are uncommon and in women under 30, the histology is primarily germ cell. The epithelial ovarian cancers can be grouped in eight histologic types. The majority or about 75% are serous type, followed by mucinous, endometrioid, clear cell, mixed type, Brenner, and undifferentiated. The last category consists of unclassified cells such as mesotheliomas.

The tumor develops typically on the surface of the organ and is clinically silent. The peritoneum can function as a partially immunoprivileged site, and this may

account for the fact that local spread is by surface shedding, lymphatics, and rarely, hematogenously.

Ovarian tumor cells lose the capacity to be growth inhibited by transforming growth factor beta, which normally functions as an autocrine regulator of normal ovarian epithelium. Ovarian tumors exhibit other features of growth dysregulation by producing macrophage colony stimulating factor (M-CSF) and the *fms* oncogene product, which is a receptor for M-CSF. About 30% of tumors also produce the *HER-2/neu* oncogene, which can function as an epidermal growth factor receptor and is associated with a poor prognosis.

Many tissues, but particularly the coelemic epithelial cells of the ovary produce a glycoprctein termed CA -125. Serum levels of this molecule can be used to monitor disease response or progression; however, in practice it lacks the sensitivity and specificity to be a unique tumor marker. In the context of a post menopausal woman with a pelvic mass, levels of CA-125 above 35 U/ml are 80% predictive for a malignancy and levels above 95 U/ml are greater than 95% predictive.

The diagnosis ultimately depends upon tissue obtained during a staging laporatomy, and if the histology is positive for malignancy, cytoreductive surgery is usually performed during the same procedure. This is the primary modality of treatment. The greater the extent of tissue removal, the better the prognosis and the better the response to subsequent therapy.

The International Federation of Gynecology and Obstetrics (FIGO) in 1987 and 1988 defined four stages of primary carcinoma of the ovary. In Stage I disease carcinoma is limited to the ovaries. Stage II disease is defined as carcinoma involving one or both ovaries with pelvic extension. In Stage III disease tumor has spread to involve the peritoneum outside the true pelvis and/or the retroperitoneal or inguinal nodes. Ovarian carcinoma with disseminated metastases including parenchymal liver metastases constitutes Stage IV disease.

Patients with Stage III and IV disease are treated with systemic chemotherapy. Historically, single agent studies using DNA alkylators such as melphalan, cyclophosphamide, chlorambucil and thiotepa have shown response rates of 30 to 65 % with median survival of 10 to 14 months. Other classes of cytotoxic drugs such as antimetbolites, antibiotics, plant alkaloids and cis- and carboplatin have shown activity and response rates from 25 to 50%. Since the first demonstrations of superiority in complete response rates and disease free

survival in 1978 with combination regimens, current practice is to follow cytoreductive surgery with combination systemic chemotherapy based on a cis- or carboplatin regimen in combination with either cyclophosphamide or paclitaxel for 6 cycles. Therapy results in complete response rates of about 30 to 35% and overall response rates of about 80%. The probability of remission depends upon the amount of residual disease. Median survival in several studies is about 2 years, and 5 year survival is 20-25 %.

Despite the best available chemotherapy, most patients with advanced ovarian cancer will die of their disease. Furthermore, the patients with ovarian cancer refractory to platinum based regimens have response rates less than 10-20% to second-line therapy. The group of patients with recurrent ovarian carcinoma (relapse at least six months after achieving a complete response) is quite heterogeneous. Reinduction with a platinum based regimen is the therapy of choice, with response rates in the range of 20-50%.

Topotecan - Background And Therapeutic Rationale

Topotecan (SK&F 104864) is a semisynthetic analog of the alkaloid camptothecin, which incorporates a stable basic side-chain at the 9-position of the A-ring of 10-hydroxycamptothecin, and retains the S-configuration at the chiral carbon-20. The basic side-chain affords water solubility to the compound without requiring hydrolysis of the E ring lactone, which is required for biologic activity.

Camptothecin was initially isolated from the stemwood of the tree *Captotheca acuminata*, and showed activity against murine leukemia. In entered clinical trials in 1970, but had secondary effects of severe myelosuppresion, alopecia and hemorrhagic cystitis.

Like camptothecin, topotecan is a specific inhibitor of topoisomerase-I, forming a covalent bond with the enzyme via the E ring lactone. Inhibition of this enzyme results in lethal DNA damage during the course of DNA replication. Topoisomerase-I has been demonstrated to be intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Binding to and inactivation of topoisomerase I prevents reannealing of the strands of DNA. Inhibitors of topoisomerases are unique in that they do not cause cytotoxicity by depleting the product of their target enzymes, but by producing DNA damage by interfering with topoisomerase function. Therefore, drug activity is directly proportional to target enzyme level rather than inversely proportional to target enzyme level, which is the case for

many cytotoxic enzyme inhibitors. Topoisomerase-I activity is not linked to proliferation rate and similar enzyme activities can be detected in slowly proliferating or quiescent cells. Thus, topotecan has the potential for activity against human solid tumors that tend to proliferate slowly and are generally refractory to most of the established anticancer drugs. In contrast to camptothecin, the absence of a hydrolyzed E ring whose conformation is pH dependent (acidic pH favoring the lactone and neutral pH favoring the inactive carboxylate), may account for the decreased hemorrhagic cystitis.

3.0 DESCRIPTION OF CLINICAL DATA SOURCES

Volume 1.1 of the December 21, 1995 submission contains the index to the application, proposed text of the labeling for topotecan, and summaries of the chemistry, manufacturing, and controls, the nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, the clinical data summary, a discussion of the proposed benefit/risk relationship, and the proposed post marketing studies. The volumes devoted to the clinical section are volumes 1.34 to 1.149 and the case report forms are in volume 1.241. The volumes devoted to the clinical section are summarized below.

Clinical Pharmacology	1.34
Controlled Studies:	
034 Open Multicenter Phase II Study-Advanced Epithelial Ovarian Cancer	1.73 to 1.84
039 Open-Label Multicenter Randomized Phase III Study of Topotecan versus Paclitaxel- Advanced Epithelial ovarian Cancer	1.40 to 1.66
Other Studies	
004 Phase I Continuous 24 hour infusion	1.35
005 Phase I daily times 5-Solid tumors	1.36
097 Phase I Study in Cancer Patients with Hepatic or Renal Dysfunction	1.38
047 Single dose oral bioavailability	1.39
012 Open Phase II daily times 5 every 21 days-Advanced Epithelial Ovarian Cancer	1.67
033 Open Multicenter Phase II of daily times 5 every 21 days in Patients with Advanced Epithelial Ovarian Cancer who failed prior chemotherapy with paclitaxel and either cisplatin or carboplatin	1.85
051 Open Phase II continuous 21 day infusion every 28 days in Patients with Advanced Epithelial	1.123

An electronic submission was provided in which the NDA summary, the technical summaries, and several sections of the complete NDA were included for viewing using Folio Views, a Windows- based text retrieval system. The complete submission was available for viewing as scanned images using TIM Smart View, a Windows-based image viewer. On February 5, 1996, partial data files from the two controlled trials, 034 and 039, were made available as SAS for Windows files on diskettes, and on February 12 more complete data was made available on CD-ROM . Additional data files as floppy disks were provided on March 5, 1996 and March 15, 1996. Smith Kline Beecham provided the review team with two external CD-ROM readers to access these files.

4.0 REGULATORY HISTORY

This section is quoted from the NDA.

Background

Initial Phase I studies with topotecan evaluated a number of different dosing schedules including single infusion, daily infusion and continuous infusion regimens. Objective tumor responses were seen in Phase I studies that evaluated a 30 minute infusion schedule given on five consecutive days every three weeks. There was concurrence on the maximum tolerated dose on this regimen at 1.5 mg/m2/day. These clinical data, together with pre-clinical evidence that more prolonged exposure of tumors or tumor cells to topotecan would enhance activity, lead to this schedule being evaluated further in Phase II studies in preference to single administration schedules.

An early SB sponsored Phase II, single institution study (012) confirmed that topotecan was active in patients with platinum resistant ovarian carcinoma. An objective response rate of 13% was seen in 30 patients who had received no more than two prior regimens. More than 80% of the patients in this study were platinum resistant. A larger Phase II study (034) was subsequently initiated in Europe in patients failing a single platinum based regimen and it was decided that an initial filing for this indication would be targeted.

Two further studies in patients with metastatic ovarian cancer who had failed first-line therapy were agreed with the FDA. One study (039) was to be a randomized, comparative study with paclitaxel and the other (033) a study in patients who had failed a combination of paclitaxel and cisplatin or carboplatin. These studies were discussed at the end of Phase II meeting described in the next section.

End of Phase II Meeting, 11 May 1993

The plans for development of topotecan in ovarian cancer patients were discussed at an End of Phase II meeting with FDA held on 11 May 1993. At this meeting the recommendations of FDA were accepted by SB including comments on a proposed randomized, comparative Phase II/III study of topotecan against paclitaxel (study 039), in which it was suggested that patients be allowed to switch from their randomized therapy to the alternate treatment. An additional study was recommended by FDA of topotecan in patients who had failed a first-line combination of paclitaxel and cisplatin or carboplatin (study 033). The latter study was influenced by the anticipated presentation of data from a study of paclitaxel and cisplatin in the first-line therapy of ovarian cancer. It was agreed that combined European and US trials would be acceptable. Communication subsequent to the End of Phase II meeting related mainly to the randomized, comparative study 039. There were no substantial issues on study 033.

Subsequent communication on 3 June 1993 from SB and 29 June 1993 attempted to clarify some items including the re-treatment criteria for patients in the randomized study (study 039). FDA stated they imposed no requirement with respect to equal neutrophil counts prior to re-treatment with topotecan and paclitaxel, but that allowing a lower threshold for retreatment with topotecan would have to be justified with clinical data.

On 1 March 1994, FDA made comments following review of Protocol 039. Comments included a statement that FDA would prefer that SB use the same re-treatment criteria for neutrophil count in both arms of the study. In addition concerns about country differences in the use of G-CSF were made and comments were made on the power of the study. SB responded on 25 May 1994 that there was justification for the re-treatment value based on experience with topotecan and that SB was not aware of the full database upon which the dosing recommendations of paclitaxel were based. SB stated they could not control the use of G-CSF across countries in this international study. To address the comments on the power of the study, the statements by FDA made at the End of Phase II meeting were re-stated, namely, study 039 was not designed for formal statistical comparison between treatment arms. Subsequent correspondence by

FDA on 11 July 1994 acknowledged SB's position on the above issues but recommended that stratification by center would be one way of addressing differences in use of G-CSF. On the 28 July 1994 SB responded that stratification by center would be impractical and that SB felt the use of G-CSF in this study would be minimal.

On 26 October 1994 a letter received from FDA raised an unresolved issue on the date of closure of study 039 and restated a preference for stratification by center. To resolve these issues it was agreed that at the end of a teleconference to discuss a different indication, discussion would continue on the unresolved issues with study 039. At the teleconference on 9 November 1994 it was agreed that study 039 would close for analysis 20 weeks following the enrollment of the last patient. This would allow the last patient to receive six courses of therapy if there were no substantial dose delays. It was agreed that given the number of strata already in the study (16), the number of centers (>30) and the status of the study, which was more than half enrolled, it was impractical to stratify. Additional comments included FDA emphasis of the importance of the data following cross-over from paclitaxel to topotecan, which could support a favorable labeling claim. A short discussion on the slow recruitment to study 033 followed, and it was agreed that patients failing second-line therapy who had received both a platinum containing regimen and paclitaxel would be allowed into the study. The study plan would be to enroll 50 patients failing first-line and 50 patients failing second-line paclitaxel/platinum therapy. The only previous issue that had arisen on this study was the assessment of patient benefit, which had been addressed by the inclusion of a quality of life questionnaire.

Pre-NDA Meeting, 8 September 1995

At this meeting no major issues were identified on the proposed format of the clinical section of the topotecan NDA.

FDA requested that SB include an analysis of data that included all patients randomized to treatment for study 039, in addition to the SB defined intent to treat analysis, which included all patients receiving at least one dose of topotecan. It was noted that this would only be possible for response rate, since patients would not have time to event variables. Brief narratives would be included in the study reports for the patients who were randomized but not treated.

SB agreed to include a co-variate analysis of time to event variables (eg a Cox Regression analysis), and to provide graphic displays of Quality of Life data Data on quality of life would include observed scores and change from baseline to end of best response.

It was agreed that it would be inappropriate to pool efficacy results across studies in the planned Integrated Analysis of Efficacy.

Immediately following this meeting a presentation of the planned CANDA was made. The following agreements were made:

The topotecan NDA would consist of paper copy and electronic portions. Certain electronic portions (case report forms, case report tabulations and selected patient listings such as laboratory data output) would be presented to FDA as electronic data only, provided this was acceptable to the Division. The Consumer Safety Officer, was to inform SB if electronic submission of CRF's, CRT's and other listings were acceptable. The FDA review clock would start when both paper and electronic portions were available and staff had been trained to use the SB CANDA.

5.0 LIST OF IND'S AND NDA'S

Note: This section is quoted from the NDA

IND Topotecan hydrochloride (SK&F S-104864-A) for injection has been investigated clinically worldwide, including the United States, under IND granted to SmithKline Beecham Pharmaceuticals and was initiated on 2 March 1989.

IND Topotecan hydrochloride (SK&F S-104864-A) for oral use has been investigated clinically in the United States and Europe under IND that was granted to SmithKline Beecham Pharmaceuticals and was initiated on 18 August 1993.

IND Topotecan hydrochloride for injection has been investigated clinically worldwide, including the United States, under IND that was granted to the U.S. National Cancer Institute and was initiated on 28 March 1990.

IND Topotecan hydrochloride for injection will be investigated clinically in the United States under IND that was granted to Steven A. Miles, MD., Associate Professor of Medicine, University of California at Los Angeles CARE Center and was initiated on 30 November 1995.

The first marketing applications for topotecan hydrochloride will be submitted December, 1995, in the United States and other countries, including the United Kingdom, France, Italy, Australia and South Africa.

Based on topotecan's pleiotropic antitumor activity, a number of Phase II studies have been initiated and are ongoing.

6.0 CONTROLLED CLINICAL STUDY 039

For the following four sections, all quotations from the sponsor NDA will appear in regular type. All comments from the reviewer will appear in bold type.

6.1 Study Design and Objectives

Study Title

An Open-Label, Multicenter, Randomized, Phase III Study of Topotecan HCl as Single Agent, Second-Line Therapy (Administered Intravenously as Five Daily Doses Every 21 Days) Versus Taxol (Administered as a Three Hour Infusion Every 21 Days) in Women With Advanced Epithelial Ovarian Carcinoma (Study SKF 104864/039).

Investigators and Centers

Sixty-one investigators from both North America and Europe participated in the study. Thirty-seven investigators entered 90 patients into the alternate treatment Phase of the study. The number of patients in each country are displayed in the table on the next page.

COUNTRY	# of Patients
Austria	3
Belgium	5
Canada	2
France	30
Germany	4
Italy	15
Netherlands	25
Poland	13
Spain	8
Sweden	9
Switzerland	5
United Kingdom	62
USA	45

Publications

There were no publications at the time of issue of this report.

Study Dates

For the randomized Phase of the study, the first patient received study medication on 7 February 1994. The last patient was randomized on 31 January 1995. For the alternate treatment Phase of the study, the first patient received alternate study medication on 25 April 1994. Clinical cutoff was 20 June 1995. All treatment courses completed by that date were included in this report.

Objectives

Primary Objectives

The primary objectives of the study were:

- To evaluate the response rate, response duration, and time to progression , in women with advanced epithelial ovarian carcinoma randomized to treatment with topotecan administered as five daily 30 minute infusions every 21 days or paclitaxel administered as a 3-hour infusion every 21 days in patients who have failed one platinum-based chemotherapeutic regimen (cisplatin or carboplatin).
- To evaluate the qualitative and quantitative toxicities of topotecan and paclitaxel administered on these schedules.

Secondary Objectives

The secondary objectives of the study were:

- To evaluate time to response and survival in patients with advanced epithelial ovarian carcinoma treated with topotecan or paclitaxel administered on these schedules.
- To evaluate the effect on the Quality of Life of patients treated with topotecan and paclitaxel on these schedules.
- To evaluate the population pharmacokinetics of topotecan administered as a 30-minute infusion for five consecutive days every 21 days.

Study Design

Protocol 039 was an open, multicenter, randomized, stratified, Phase III study to evaluate the efficacy and toxicity of topotecan versus paclitaxel for the treatment of patients with advanced epithelial ovarian carcinoma who failed one platinum-based chemotherapeutic regimen. Eligible patients with measurable bidimensional disease were randomized to treatment with topotecan administered as five daily 30-minute infusions every 21 days or paclitaxel administered as a 3-hour infusion every 21 days. Patients who progressed or whose best response was stable disease after 6 courses on one regimen were eligible to be switched to the other regimen.

Protocol Amendments

Amendment 1 (9 December 1993): Protocol Synopsis and Section 4.2 (Inclusion Criteria): the requirement of FIGO Stage III or Stage IV was changed to metastatic disease since most patients would not be restaged at entry into the study. Additional changes to Section 4.2 (Inclusion Criteria) included the following: the requirement of a skin lesion diameter was changed from >2 cm to > 0.5 cm since a skin lesion can be easily measured and response to therapy evaluated; addition of a scale to be noted with all forms of lesion measurement so that the lesion diameters could be easily measured; hormonal therapy within 4 weeks of study was for conditions other than ovarian carcinoma; change of the

representation of units for WBC, neutrophils, and platelets from international units to reflect American practice; the addition of "or creatinine clearance of >60 ml/min" to the requirement of creatinine >1.5 mg/dL. Modifications to Section 4.3 (Exclusion Criteria) included modification for allowance of hormonal therapy for conditions other than ovarian carcinoma (e.g. menopause). Section 5.2 (Screening Evaluation): the requirement to document FIGO Stage was eliminated. Modifications to Section 5.3 (Treatment Courses) included: addition of creatinine clearance to be performed if creatinine was >1.5 mg/dL; requirement to perform blood chemistries prior to next course only if the day 15 results reflected clinically significant deterioration from baseline values; the representation of units for WBC, neutrophils, and platelets to reflect American standards; the exception of grade 3 or 4 vomiting for dose reduction was removed since it would be unwarranted to treat the patient at day 21 in the event of grade 3 or 4 vomiting.

Amendment 2 (31 May 1994): Section 4.1 Number of Patients was modified to include details of the randomization procedure. Sections 5.3.1 Procedure for Dose Modification of Topotecan and 5.3.2 Procedure for Dose Modification of Taxol were changed such that the same neutrophil criteria (neutrophils < 500/mm^3 associated with fever/infection or lasting >7 days) were used for both topotecan and Taxol regarding the requirement for the use of G-CSF to manage grade 4 neutropenia. Section 5.3.5.1 Blood Sampling was changed based on additional stability data allowing blood samples for pharmacokinetic sampling to be stored for up to one month at <-20° C. In Section 7.6.2 reporting Serious Adverse Experience(s) Dr. Colin Broom was added as medical monitor. In Section 9.1 Criteria For Efficacy the primary criteria for efficacy were changed to the response rate, response duration, and time to progression and secondary criterion was changed to the Quality of Life to agree with Sections 2.1 and 2.2. Section 9.3.1 Comparison of Interest was changed to include a statement for the time of closure of the data base for analysis. Section 9.4 Efficacy Analyses was clarified with respect to the specific statistical methodology to be used for analyzing all major study endpoints.

Modification 1 (12 September 1994): Appendix N Procedure for Randomization was corrected as the schematic was incorrect.

Amendment 3 (20 February 1995): Time to response and survival were added as secondary objectives/efficacy criteria to the Synopsis, Section 2.2 Objectives: Secondary and Section 9.1 Criteria for Efficacy. Section 9.3.1 Comparison of Interest was changed to specify the cut-off date for the collection of new clinical data to be included in the primary analyses (20 weeks after the date of enrollment of the last randomized patient).

Modification 2 (5 April 1995): Dr. Ian Hudson replaced Dr. Michael McDonald as the clinical trial monitor in the United Kingdom.

Ethics

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki as amended in Hong Kong (1989). The protocol and statement of informed consent were approved by an Institutional Review Board or Ethics Committee prior to each center's initiation. Written informed consent was obtained from each patient prior to entry into the study. Case report forms were provided for each patient's data to be recorded. Primary: response rate, response duration, time to progression, and qualitative and quantitative toxicities of topotecan and paclitaxel.

Study Population

The target enrollment was one hundred evaluable patients per arm. All patients were to have bidimensionally measurable disease and have failed one platinum-based chemotherapeutic regimen. Two hundred thirty-five patients were randomized. Nine patients (5 randomized to topotecan and 4 randomized to paclitaxel) did not receive study medication. Thus, the intent-to-treat population consisted of 112 patients randomized to topotecan and 114 patients randomized to paclitaxel.

Treatment and Administration

Eligible patients were randomized to receive topotecan 1.5 mg/m^2/day as a 30-minute infusion for 5 consecutive days every 21 days or paclitaxel 175 mg/m^2/day as a 3 hour infusion every 21 days. The initial dose could be increased or decreased according to toxicity. For patients with neutropenia, G-CSF was to be administered before a reduction in dose was considered. Patients were premedicated prior to paclitaxel administration according to the manufacturer's labeling in order to prevent severe hypersensitivity reactions. Paclitaxel was obtained through commercial sources. Topotecan was from batches U-93056 and U-94036.

Evaluation Criteria

The primary efficacy parameters were:

Response rate, response duration (defined as the elapsed time from first documented response until the first documented disease progression) and time to progression.

The secondary efficacy parameters were:

Time to response, survival, and quality of life (assessed by repeated administration of the EORTC QLQ-C30 questionnaire).

Safety Parameters

Qualitative and quantitative hematologic and non-hematological toxicities were evaluated. Serious adverse experiences, deaths, changes in vital signs, ECG results, body weight changes and non-hematological laboratory assessments were also tabulated.

Statistical Methods

This was not a true crossover study, data collected during the randomized and alternate phases were treated independently. Patients were stratified according to platinum sensitivity, baseline ascites and age. Efficacy analyses were performed for the Intent-to-Treat population (ITT) for both the randomized and alternate phases of the study and a Protocol-Defined population (PP) subset which excluded patients with a documented protocol violation for the randomized phase. Objective response was compared between treatment groups using Pearson's uncorrected chi-square statistic. The null hypothesis of no difference between treatment regimens was tested at a nominal 5% type I error rate against a two-tailed alternative. Traditional survival methods were employed to summarize the time to event variables. Kaplan-Meier estimates were obtained for each endpoint and presented in lifetable format with four week intervals. Time to Event outcomes were also compared between treatments by the Cox regression model.

Qualitative and quantitative results were summarized for hematological toxicities relating to white blood cells, neutrophils, platelets and hemoglobin. Qualitative data were summarized by course and by patient and included time to onset and duration of grade 4 toxicities (grade 3 and 4 for anemia). Quantitative assessments of hematological toxicities included calculation of absolute nadirs, percentage change from baseline and day of occurrence of nadirs. Non-hematological toxicities were summarized within patient and within course.

6.2 Overview of Demographics, Treatment and Efficacy Results

Patient Disposition and Key Demographic Data

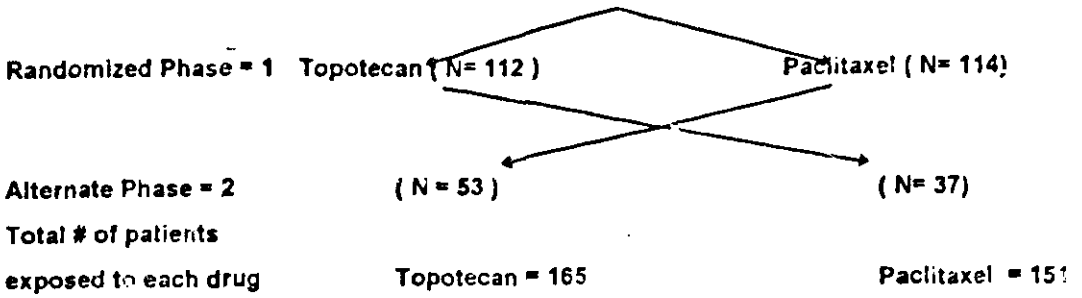
Patient demographics are provided in the table on the next page.

For both topotecan and paclitaxel malignant serous tumors were the most frequently occurring tumor type (52%); the number of patients with at least one tumor ≥5 cm in diameter at baseline was similar (49% and 54%, respectively). The median performance status was 1 with the similar proportion of patients assessed as PS 2 at baseline (18% and 15%, respectively). Fifty-four percent of topotecan treated and 52% of paclitaxel treated patients were refractory or had relapsed within six months of completing first-line therapy.

Intent to Treat	Topotecan	Paclitaxel
Demographic Characteristics	(N = 112)	(N = 114)
Age (years)	n (%)	n (%)
18-40	3 (2.7)	3 (2.6)
41-64	71 (63.4)	75 (65.8)
> 65	38 (33.9)	36 (31.6)
Mean	59.2	58.3
Range		
Race		
Caucasian	112 (100.0)	106 (93.0)
Black	0 (0.0)	5 (4.4)
Hispanic	0 (0.0)	3 (2.6)
Weight (kgs)		
Mean	65.0	67.6
Range		
Body Surface Area (m2)		
Mean	1.7	1.7
Range		

Number of Patients on each Arm :

Randomization



The number (%) of patients completed or withdrawn from the study is giver in the table below.

Number of Patients	Topotecan		Paclitaxel	
	n	(%)	n	(%)
Completed Treatment	71	(63.4)	87	(76.3)
Premature Discontinuations	25	(22.3)	16	(14.0)
Ongoing	16	(14.3)	11	(9.6)
Switched to Alternate Therapy	37	(33.0)	53	(46.5)
Evaluated for Safety	112	(100.0)	114	(100.0)
Evaluated for ITT	112	(100.0)	114	(100.0)

Withdrawal Reasons

Seventy-one (63.4%) of the 112 patients treated with topotecan and 87 (76.3%) of the 114 patients treated with paclitaxel completed the study. Twelve patients (10.7%) who received topotecan were withdrawn for adverse experiences compared with 8/114 (7%) of patients who received paclitaxel. Patients who were withdrawn from the study for adverse experiences are discussed in section 6.6. Patients whose data was incomplete at the time of clinical cutoff (20 June 1995) are represented as "ongoing".

Number (%) of Randomized Patients who Completed the Study or were Withdrawn by the Reason for Study Withdrawal

Study Conclusion	Topotecan	Paclitaxel
	(n=112)	(n=114)
Reason	n (%)	n (%)
COMPLETED STUDY	71 (63.4)	87 (76.3)
Adverse Experience	12 (10.7)	8 (7.0)
Protocol Violation	1 (0.9)	1* (0.9)
Lost to follow-up	2 (1.8)	2 (1.8)
Other**	10 (8.9)	5 (4.4)
Total Withdrawn	25 (22.3)	16 (14.0)
Ongoing	16 (14.3)	11 (9.6)
Switched to Alternate Phase	37 (33.0)	53 (46.5)

*errata: patient completed six courses of randomized paclitaxel and was withdrawn due to protocol violation after course 1 of alternate therapy

** comprised primarily of patient request or refusal

Protocol Violations

A total of 16 patients for topotecan and 9 patients for paclitaxel were in violation of the protocol, and were excluded from the per protocol analysis of efficacy. The most frequent reason for protocol violation in both treatment groups was lack of assessment beyond five days after completing a treatment course.

Number of Patients (%) and Reason for Protocol Violation by Randomized Treatment

Study Medication	Topotecan	Paclitaxel
Total Patients	n = 112	n = 114
Protocol Violation Reason	n (%)	n (%)
Not assessed beyond 5 days	11 (9.8)	6 (5.3)
Did not have required measurable disease	2 (1.8)	1 (0.9)
Indicator lesion in field of prior radiation	1 (0.9)	1 (0.9)
Entered with Second Primary Cancer	1 (0.9)	
More than one prior chemo. regimen	1 (0.9)	
Did not have required performance status		2 (1.8)
Total Number with Any Violation	16 (14.3)	9* (7.9)

*patient violated for performance status of 3 and lack of assessment beyond 5 days

in patients treated with topotecan, 5 of the 11 patients not assessed beyond 5 days were withdrawn for adverse experiences 4 patients progressed after less than 2 courses of therapy 1 patient was lost to follow-up; and 1 patient refused further treatment

In patients treated with paclitaxel, 6 patients were not assessed beyond 5 days. Three patients were withdrawn for adverse experiences), 2 patients

progressed after 1 course of therapy, and 1 patient was lost to follow-up.

Courses Administered

A total of 502/555 (90%) topotecan courses were administered at 1.5 mg/m^2/day and 538/550 (98%) paclitaxel courses were administered at 175 mg/m^2/day. The median number of courses administered was 5 for both treatment groups. Dose modifications for all patients and courses are given in the table below.

Number of Courses Administered

	Topotecan	Paclitaxel
Randomized Phase	**555**	**550**
Alternate Phase	**176**	**126**
Total	**731**	**676**

Dose Modifications

Study Drug	Topotecan		Paclitaxel	
Total Patients/Courses	112	555	114	550
Patients/Courses > 1	96	443	108	436
	n (%)	n (%)	n (%)	n (%)
Delays After Course 1 Patients/Courses	57 (59.4)	90 (20.3)	18 (16.7)	24 (5.5)
Reductions After Course 1 Patients/Courses	13 (13.5)	17 (3.8)	5 (4.6)	5 (1.1)
Escalations After Course 1 Patients/Courses	3 (3.1)	3 (0.7)	0 (0.0)	0 (0.0)

*Calculations of dose delays, reductions or escalations as percent did not include initial courses.

6.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables

All objective responses claimed by the investigators underwent independent radiological review. The applicant's assessment of response rate for the intent-to-treat population is tabulated below.

Population	Intent to Treat	
Study Drug	Topotecan	Paclitaxel
Patient #	112	114
	n (%)	n (%)
CR	5 (4.5)	3 (2.6)
PR	18 (16.1)	15 (13.2)
SD	33 (29.5)	38 (33.3)
PD	39 (34.8)	56 (49.1)
NE	17 (15.2)	5 (4.4)

The reviewer's assessment of the best response for all patients randomized to study medication is tabulated below.

039	CR	PR	Total
Topotecan	6 (5.4%)	16 (14.3%)	22 (19.6%)
Paclitaxel	(3.5%) 10 (8. 8%)		14 (12.3%)

Time to response was calculated using the day the patient achieved the best response. Duration of response was calculated by the following criteria :

- Any patient that had a new lesion, whether or not the sum of the products of all lesions showed a decrease over the previous measurement was considered to have progression

- Any patient that had a 25 % increase in the sum of the products of all lesions over the previous best minimum was considered to have progression. For example, if a patient had a sum of products of 50, then decreased to 24, the first measurement that was greater than 30 (25 % of 24) would be considered the day of progression.

As shown in the table below, the applicant's median time to response was 9.0 weeks for topotecan and 6.0 weeks for paclitaxel. The hazard ratio (topotecan:paclitaxel) for time to response was 0.476 (p=0.0409). The median duration of response was 32.1 weeks for topotecan and 19.7 weeks for paclitaxel. The hazard ratio (T:P) was 0.416 (p=0.2218).

Time to Response

TTR (wks)	n=23	n=15
Median	9.0	6.0
Range		
Hazard Ratio (Topo/Paclitaxel)		0.476
p value	0.0409*	

Response Duration

RD (wks)	n=23	n=15
Median	32.1	19.7
Range		
Hazard Ratio (Topo/Paclitaxel)		0.416
p value	0.2218	

As is shown in the table on the next page, the applicant's median time to progression in the intent-to-treat population was 23.1 weeks for topotecan and 14.0 weeks for paclitaxel. The hazard ratio (T:P) was 0.578 (p=0.0021).

Time to Progression

TTP (wks)	n=112	n=114
Median	23.1	14.0
Range		
Hazard Ratio (Topo/Paclitaxel)		0.578
p value	.0021*	

At the time of the clinical cutoff for this study, approximately 80% of the patients were still alive, with the number of patients who had died similar for both treatments (25 topotecan treated patients and 22 paclitaxel treated patients). The applicant's median survival time was 61.3 weeks for topotecan and 42.6 weeks for paclitaxel. The hazard ratio (T:P) was 1.210 (p=0.5153).

Survival

Survival (wks)	n=112	n=114
Median	61.3	42.6
Range		
Hazard Ratio (Topo/Paclitaxel)		1.210
p value	.0.5153	

Quality of life assessed by the EORTC QLQ-C30 questionnaire did not indicate substantial changes from baseline or differences between treatment groups

The small sample size in this randomized comparative study precluded definitive conclusions regarding the relative efficacy of topotecan and paclitaxel. However, the three primary efficacy parameters indicated that patients randomized to topotecan experienced a higher response rate, longer response duration and a longer time to progression than those receiving paclitaxel. These results suggest that the efficacy of topotecan is equal to or possibly greater than that of the recently approved paclitaxel schedule used in this study, and warrants further investigation.

Alternate Treatment

As discussed previously, patients who progressed or had stable disease on randomized treatment were given the option to switch to alternate treatment. Responses were seen in five (9%) of the patients switched to topotecan (all partial response) and in one (3%) of those switched to paclitaxel (complete response). The median duration of response for topotecan was 17.6 weeks (range 6.1 to 17.6 weeks) and for paclitaxel was undefined. As a majority of patients in each treatment group (topotecan 81%; paclitaxel 86%) were alive at the time of the cut-off for inclusion in the analysis, median survival is not reported here.

The results for the primary efficacy variables and the additional, secondary efficacy variable, time to response, are presented on the next page.

Best Response and Time to Event Results for Patients in the Intent-to-Treat Population Switched to Alternate Treatment in Study 039

Response Variable	Topotecan n=53	Paclitaxel n=37
Responders		
Complete response	0	1 (2.7%)
Partial response	5 (9.4%)	0
Total responders	5 (9.4%)	1 (2.7%)
95% CI	(3.1, 20.7)	(0.1, 14.2)
Non-responders		
Stable disease	8 (15.1%)	10 (27.0%)
Progression	26 (49.1%)	16 (43.2%)
Not evaluable	4 (26.4%)	10 (27.0%)
Total non-responders	48 (90.6%)	36 (97.3%)
Duration of response (weeks)	n=5	n=1
Median	17.6	undefined
Range		
Time to progression (weeks)	n=53	n=37
Median	8.7	8.9
Range		
Time to response (weeks)	n=5	n=1
Median	6.1	3.0
Range		

* Value corresponds to a censored event

Analysis of changes in quality of life parameters between baseline and the end of best response revealed a decrease (improvement) in the median score for nausea/vomiting with topotecan and decreases (improvement) in the median scores for fatigue and pain with paclitaxel . The quality of life score was also improved on paclitaxel.

Quality of Life - Changes from Baseline to End of Best Response by Factor Median and Range at each Assessment in Patients who Received Alternate Treatment

Study Drug	Alternate Topotecan		Alternate Paclitaxel	
QOL Parameter	n	median range	n	median range
Appetite Loss	33	0.0	21	0.0
Cognitive Function	30	0.0	20	0.0
Constipation	33	0.0	21	0.0
Diarrhea	34	0.0	21	0.0
Dyspnea	33	0.0	21	0.0
Emotional Function	30	0.0	20	8.0
Fatigue	34	0.0	21	-11.0
Financial Impact	9	0.0	20	0.0
Nausea/Vomiting	34	-16.0	21	0.0
Pain	34	0.0	21	-17.0
Physical Function	30	0.0	21	3.0
Quality of Life	29	0.0	20	16.0
Role Function	30	0.0	21	0.0
Social Function	30	0.0	20	0.0
Sleep Disturbance	34	0.0	20	0.0

Data source: SKF 104864-A/039 Table 16; Appendix 12.6A

6.4 Adverse Experience and Safety Data

Hematologic Toxicity

The percentage of patients and courses with grade 3/4 hematologic toxicity was calculated and then tabulated for leukopenia, neutropenia, thrombocytopenia, and anemia. For each patient all laboratory values were first standardized to the same units, then for each day a differential and

Grade 3&4 Anemia

	Totals	Patients	% Patients	Courses	% Courses
Total Hgb measurements	5132	226		1711	
Topo Hgb measurements	2904	165		890	
Taxol Hgb measurements	2228	150		821	
Total Hgb< 8	761	80	35.4%	301	17.6%
Topo Hgb<8	463	67	40.6%	185	20.8%
Taxol Hgb< 8	298	28	18.7%	116	14.1%

Transfusions

Trial 039				
Platelets	Patients	% Patients	Courses	% Courses
Topo	16	9.7%	36	4.9%
Taxol	0	0%	0	0%
RBC				
Topo	91	55.2%	215	29.4%
Taxol	22	14.6%	33	4.9%

Grade 4 Lymphocytopenia

	Totals	Patients	% Patients	Courses	% Courses
Total ALC measurements	5334	226		1710	
Topo ALC measurements	3014	165		889	
Taxol ALC measurements	2320	150		821	
Total ALC < 500	336	92	40.7%	221	12.92%
Topo ALC < 500	218	62	37.6%	135	15.19%
Taxol ALC < 500	118	45	30.0%	86	10.48%

Hematologic toxicities were more prevalent in the topotecan group compared to the paclitaxel group. Although severe hematologic toxicity was associated with topotecan treatment, toxicity resolved within a week in approximately 70% of treatment courses. Additionally, continued courses of therapy did not demonstrate evidence of cumulative toxicity. Median nadir values and day of nadir occurrence remained relatively constant throughout the study.N

Neutropenia Duration in Days

	Topotecan	Paclitaxel
# > 6 days	162	27
Median	5.00	6.00
Mean	5.56	5.68
Std.Dev.	12.19	2.49
Min.	1	1
Max.	219	15
# of courses	391	66

Fever > 38.0° C

	Mean	Std. dev.	Min	Max	# of patients	# of courses
Total	17.10	15.55	1	118	54	74
Topo	8.51	17.80	1	118	42	55
Taxol	3.10	3.30	1	12	15	19

NB Some patients got both drugs and were febrile with each

Fever Duration

	Mean	Std. Dev.	Min	Max	# of patients	# of courses
Total	5.28	11.05	1	118	75	133
Topo	6.43	13.10	1	118	56	93
Taxol	2.85	3.73	1	19	26	40

NB Some patients got both drugs and were febrile with each

Documented Fever and Neutropenia

	Mean	Std. dev.	Min	Max	# of patients	# of courses
Total	8.15	4.90	2	24	40	48
Topo	8.00	5.10	2	24	35	42
Taxol	9.00	3.30	5	15	6	6

NB Some patients got both drugs and were febrile with each

Documented Sepsis

			Sepsis			Septic Deaths	
	# of patients	# of courses	# of deaths	% of pts	% of courses	% of pts	% of courses
Total	11	11	3	4.87%	0.78%	2.65%	0.43%
Topo	9	9	3	5.45%	1.23%	1.8%	0.82%
Taxol	2	2	0	1.3%	0.30%	0.0%	0.0%

Systemic antibiotics were used by 58% of patients in 21% of topotecan courses. Suspected or documented infection was proximate to grade 4 neutropenia in a total of 25% of patients and 7% of courses, with an additional 5% of patients and 1% of courses being associated with sepsis. Six patients treated with topotecan during the randomized phase and 11 patients during either the randomized phase or the alternate phase developed sepsis. The sepsis was considered related to topotecan therapy in 5 of the 6 initial instances, and resulted in the death of 3 patients. Systemic antibiotics were used by 33% of patients in 11% of paclitaxel courses. Suspected or documented infection was proximate to grade 4 neutropenia in a total of 4% of patients and 1% of courses with an additional 2% of patients and 0.4% of courses associated with sepsis. Two patients treated with paclitaxel developed sepsis, which was considered related to therapy in one of the patients. Neither patient died due to sepsis.

In order to maintain a 21 day dosing schedule for both treatment groups, prophylactic G-CSF administration was allowed after course 1 of therapy in either treatment group. Prophylactic G-CSF was administered in 23% of topotecan courses and in <1% of paclitaxel courses. Other supportive measures, (treatment G-CSF and RBC transfusions) did not increase with increasing courses of therapy.

Duration of Fever and Neutropenia in days

	Fever > 38° C. per course						Fever and Neutropenia per course						Sepsis	
	Topo	Mean	Std. dev.	Min	Max		Topo	Mean	Std. dev.	Min	Max		Topo	
1	25	5.76	5.09	1	24	1	25	8.38	5.28	2	24	1	5	
2	10	5.38	5.1	1	16	2	8	8.22	5.78	2	16	2	2	
3	7	5	5.42	1	13	3	2	4.5	2.12	3	6	3	1	
4	4	2	1.41	1	3	4	1	4		4	4	4		
5	5	31.2	48.82	1	118	5	2	9.33	1.15	8	10	5		
6	2	5.5	4.95	2	9	6	1	2		2	2	6		
												9	1	
	Taxol	Mean	Std. dev.	Min	Max		Taxol	Mean	Std. dev.	Min	Max		Taxol	
1	6	3.5	4.23	1	12	1	2	9.67	4.04	5	12	1	2	
2	3	4	4.24	1	7	2	2	7	0	7	7	2		
3	3	3.67	3.79	1	8	3	1	15		15	15	3		
4	2	1	0	1	1	4	1	9		9	9	4		
5	4	2		2	2	5						5		
6	1					6						6		

Non-Hematologic Toxicity

Non-hematologic adverse experiences were reported in 112/112 (100%) of patients who received topotecan and in 113/114 (99%) of patients who received paclitaxel (see table below). The majority of non-hematologic adverse experiences reported in both treatment groups were mild. Nausea and vomiting, fatigue, stomatitis and fever were reported more frequently for patients who received topotecan, while alopecia (grade 2), abdominal pain, arthralgia, paresthesia, myalgia, skeletal pain and neuropathy were reported more frequently for patients who received paclitaxel.

Study 039 Paclitaxel Non-Hematologic Adverse Events by Course

					Grade									
Adverse Event by Courses	Total	% of Total Courses	Unk	%	1	%	2	%	3	%	4	per cent	SAE	%
ALOPECIA	668	98.82			118	17.46	549	81.21	1	0.15			1	0.67
PARESTHESIA	182	26.92	9	1.33	141	20.86	32	4.73						
NAUSEA	162	23.96	1	0.15	123	18.20	33	4.88	5	0.74			5	3.36
ARTHRALGIA	146	21.60	5	0.74	78	11.54	60	8.88	3	0.44			3	2.01
FATIGUE	145	21.45	32	4.73	77	11.39	24	3.55	12	1.78			12	8.05
ABDOMINAL PAIN	140	20.71	7	1.04	74	10.95	50	7.40	8	1.18	1	0.15	9	6.04
MYALGIA	128	18.93	3	0.44	68	10.06	47	6.95	10	1.48			10	6.71
VOMITING	111	16.42			77	11.39	28	4.14	5	0.74	1	0.15	6	4.03
CONSTIPATION	108	15.98	23	3.40	63	9.32	22	3.25						
DIARRHEA	102	15.09			81	11.98	20	2.96	1	0.15			1	0.67
PAIN	96	14.20	7	1.04	38	5.62	47	6.95	4	0.59			4	2.68
NEUROPATHY PERIPHERAL	87	12.87	3	0.44	72	10.65	11	1.63	1	0.15			1	0.67
ASTHENIA	86	12.72	17	2.51	36	5.33	22	3.25	11	1.63			11	7.38
DYSPNEA	85	12.57	3	0.44	52	7.69	23	3.40	6	0.89	1	0.15	7	4.70
FLUSHING	79	11.69	13	1.92	52	7.69	14	2.07						
SKELETAL PAIN	55	8.14	4	0.59	28	4.14	12	1.78	11	1.63			11	7.38
HEADACHE	53	7.84	3	0.44	32	4.73	13	1.92	5	0.74			5	3.36
BACK PAIN	48	7.10	4	0.59	25	3.70	17	2.51	2	0.30			2	1.34
HEMATURIA	47	6.95			40	5.92	7	1.04						

Study 039 Paclitaxel Non-Hematologic Adverse Events by Patients

					Grade									
Adverse Event	Total	% of total courses	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	142	95.30			15	10.07	126	84.56	1	0.67			1	0.67
NAUSEA	70	46.98	1	0.67	44	29.53	20	13.42	5	3.36			5	3.36
ABDOMINAL PAIN	60	40.27	4	2.68	24	16.11	24	16.11	7	4.70	1	0.67	8	5.37
DIARRHEA	57	38.26			38	25.50	18	12.08	1	0.67			1	0.67
CONSTIPATION	53	35.57	11	7.38	27	18.12	15	10.07						
ARTHRALGIA	48	32.21	1	0.67	20	13.42	24	16.11	3	2.01			3	2.01
VOMITING	48	32.21			24	16.11	18	12.08	5	3.36	1	0.67	6	4.03
PARESTHESIA	46	30.87	1	0.67	33	22.15	12	8.05						
FATIGUE	45	30.20	8	5.37	18	12.08	12	8.05	7	4.70			7	4.70
MYALGIA	40	26.85	1	0.67	15	10.07	20	13.42	4	2.68			4	2.68
PAIN	30	20.13	2	1.34	13	8.72	13	8.72	2	1.34			2	1.34
DYSPNEA	29	19.46			15	10.07	8	5.37	5	3.36	1	0.67	6	4.03
ASTHENIA	26	17.45	2	1.34	9	6.04	9	6.04	6	4.03			6	4.03
FEVER	26	17.45	1	0.67	10	6.71	13	8.72	2	1.34			2	1.34
FLUSHING	26	17.45	6	4.03	16	10.74	4	2.68						
STOMATITIS	26	17.45	3	2.01	13	8.72	9	6.04	1	0.67			1	0.67
BACK PAIN	22	14.77	2	1.34	10	6.71	8	5.37	2	1.34			2	1.34
HEADACHE	22	14.77			12	8.05	8	5.37	2	1.34			2	1.34
HEMATURIA	22	14.77			19	12.75	3	2.01						
ANOREXIA	21	14.09			8	5.37	12	8.05	1	0.67			1	0.67
NEUROPATHY PERIPHERAL	21	14.09			15	10.07	5	3.36	1	0.67			1	0.67
SKELETAL PAIN	20	13.42			9	6.04	5	3.36	6	4.03			6	4.03
DYSPEPSIA	17	11.41	4	2.68	7	4.70	6	4.03						
COUGHING	16	10.74	1	0.67	11	7.38	4	2.68						
MALAISE	15	10.07			4	2.68	9	6.04	2	1.34			2	1.34

Study 039 Topotecan Non-Hematologic Adverse Events by Course

			Grade											
Adverse Event by Courses	Total	% of total courses	Unk	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	621	84.95	1	0.14	202	27.63	418	57.18						
NAUSEA	432	59.10	2	0.27	301	41.18	103	14.09	25	3.42	1	0.14	26	15.76
VOMITING	258	35.29	1	0.14	157	21.48	83	11.35	11	1.50	6	0.82	17	10.30
FATIGUE	253	34.61	60	8.21	78	10.67	99	13.54	16	2.19			16	9.70
CONSTIPATION	182	24.90	28	3.83	86	11.76	59	8.07	8	1.09	1	0.14	9	5.45
DIARRHEA	148	20.25	2	0.27	96	13.13	39	5.34	10	1.37	1	0.14	11	6.67
ABDOMINAL PAIN	125	17.10	6	0.82	65	8.89	35	4.79	17	2.33	2	0.27	19	11.52
DYSPNEA	113	15.46	7	0.96	47	6.43	42	5.75	9	1.23	8	1.09	17	10.30
ASTHENIA	110	15.05	13	1.78	34	4.65	53	7.25	8	1.09	2	0.27	10	6.06
FEVER	100	13.68	2	0.27	42	5.75	45	6.16	5	0.68	6	0.82	11	6.67
STOMATITIS	72	9.85	2	0.27	46	6.29	21	2.87	3	0.41			3	1.82
HEADACHE	64	8.76	5	0.68	29	3.97	27	3.69	3	0.41			3	1.82
ANOREXIA	62	8.48	6	0.82	27	3.69	25	3.42	4	0.55			4	2.42
MALAISE	49	6.70	1	0.14	13	1.78	27	3.69	7	0.96	1	0.14	8	4.85
PAIN	49	6.70	5	0.68	31	4.24	9	1.23	4	0.55			4	2.42
HEMATURIA	45	6.16			41	5.61	2	0.27			2	0.27	2	1.21
DEPRESSION	43	5.88	6	0.82	25	3.42	10	1.37	2	0.27			2	1.21
PARESTHESIA	42	5.75	3	0.41	35	4.79	4	0.55						
BACK PAIN	41	5.61	3	0.41	26	3.56	10	1.37	1	0.14	1	0.14	2	1.21
ANXIETY	39	5.34	5	0.68	24	3.28	9	1.23	1	0.14			1	0.61
RASH	38	5.20	4	0.55	21	2.87	13	1.78						

Study 039 Topotecan Non-Hematologic Adverse Events by Patients

					Grade									
Adverse Event by Topotecan Patient	Total	% of total courses	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	141	85.45	1	0.61	29	17.58	111	67.27						
NAUSEA	131	79.39			67	40.61	47	28.48	16	9.70	1	0.61	17	10.3
VOMITING	98	59.39			40	24.24	43	26.06	10	6.06	5	3.03	15	9.09
CONSTIPATION	68	41.21	9	5.45	26	15.76	25	15.15	7	4.24	1	0.61	8	4.85
FATIGUE	67	40.61	13	7.88	18	10.91	25	15.15	11	6.67			11	6.67
DIARRHEA	65	39.39			39	23.64	17	10.30	8	4.85	1	0.61	9	5.45
FEVER	56	33.94	2	1.21	12	7.27	31	18.79	5	3.03	6	3.64	11	6.67
ABDOMINAL PAIN	52	31.52	3	1.82	23	13.94	16	9.70	8	4.85	2	1.21	10	6.06
STOMATITIS	41	24.85	2	1.21	18	10.91	18	10.91	3	1.82			3	1.82
DYSPNEA	37	22.42	3	1.82	13	7.88	11	6.67	6	3.64	4	2.42	10	6.06
ASTHENIA	36	21.82	3	1.82	8	4.85	16	9.70	7	4.24	2	1.21	9	5.45
ANOREXIA	28	16.97	2	1.21	10	6.06	12	7.27	4	2.42			4	2.42
HEADACHE	28	16.97	2	1.21	14	8.48	9	5.45	3	1.82			3	1.82
BACK PAIN	24	14.55	1	0.61	13	7.88	8	4.85	1	0.61	1	0.61	2	1.21
PAIN	22	13.33	2	1.21	9	5.45	8	4.85	3	1.82			3	1.82
MALAISE	21	12.73			4	2.42	11	6.67	5	3.03	1	0.61	6	3.64
RASH	21	12.73	3	1.82	9	5.45	9	5.45						
URINARY TRACT INFECTION	21	12.73					13	10.91	2	1.21	1	0.61	3	1.82
DYSPEPSIA	20	12.12	3	1.82	10	6.06	7	4.24						
COUGHING	19	11.52	6	3.64	10	6.06	2	1.21	1	0.61			1	0.61
PARESTHESIA	19	11.52	2	1.21	15	9.09	2	1.21						
HEMATURIA	18	10.91			16	9.70	1	0.61			1	0.61	1	0.61

Treatment was administered on schedule or within two days of schedule in 77% of topotecan courses and in 92% of paclitaxel courses, with delays beyond a week occurring in 5% and 3% of courses, respectively. Thirteen of the 112 topotecan patients (12%) were dose-reduced compared with 5/114 (4%) of

patients treated with paclitaxel. The most frequent reasons for dose reductions in patients treated with topotecan were hematologic, and were non-hematologic for patients treated with paclitaxel.

Deaths

Of 112 patients randomized to topotecan, 11 patients died within 30 days of receiving topotecan (seven patients died due to progressive disease, two patients died due to sepsis associated with hematologic toxicity and two patients died due to other causes: adult respiratory distress syndrome and pulmonary embolism). Nine patients died greater than 30 days after completing topotecan therapy all due to progressive disease with the exception of one patient who died due to cardiopulmonary arrest five months post therapy. Of 114 patients randomized to paclitaxel, four patients died within 30 days of receiving paclitaxel (three patients died due to progressive disease and one patient died due to what was suspected to be a massive pulmonary embolism). Eight patients died greater than 30 days after completing paclitaxel due to progressive disease.

Serious Adverse Experiences

Of 112 patients randomized to topotecan, 55 (49%) experienced serious adverse experiences. The most frequently reported serious adverse experiences were hematologic toxicities associated with sequelae. Of 114 patients randomized to paclitaxel, 35 (31%) patients experienced serious adverse experiences. The most frequently reported serious adverse experiences were intestinal obstruction and abdominal pain. One paclitaxel treated patient developed an acute hypersensitivity reaction.

Withdrawals Due to Adverse Experiences

Twelve of 112 patients (11%) treated with topotecan and 8/114 (7%) of patients treated with paclitaxel were withdrawn from the study due to adverse experiences.

Non-Hematologic Laboratory Toxicities of Clinical Concern

There were no discernible clinically important trends in laboratory parameters during repeated courses of therapy for topotecan or paclitaxel.

Vital Signs of Clinical Concern and ECG Results

In both treatment groups, few measurements were out of the normal range. Approximately 90% of patients in both treatment groups entered the study with

normal ECG results. There was no evidence of clinically important cardiotoxicity with topotecan or paclitaxel therapy.

Summary of Changes in Body Weight

The mean patient body weight on the first day of therapy, at the end of study, and the mean percent change in body weight were similar for both treatment groups.

Number of Non-Hematologic Adverse Events

All Adverse Events

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses
Topo	25.11	23.00	1	202	4118	164	99.4 %	710
Taxol	25.70	18.20	1	86	3854	149	98.6 %	671

Adverse Events = 3

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses
Topo	2.62	2.35	1	15	215	82	50.0%	130
Taxol	2.84	2.25	1	10	159	56	37.6%	102

Adverse Events = 4

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses
Topo	1.53	1.08	1	6	55	36	22.0%	45
Taxol	1.18	0.60	1	3	13	11	7.4%	11

6.5 Reviewer's Conclusion

Topotecan showed a response rate that was as good as or perhaps better than paclitaxel in patients with ovarian cancer who had been previously treated with a platinum containing regimen. Time to progression data showed a significant difference in the proportion of patients who progressed on paclitaxel compared to topotecan at the time of study closure. The toxicity of topotecan was primarily hematologic and 9 patients in the randomized phase of the study had sepsis. Non- hematologic toxicities were common, although in most cases tolerable and manageable.

7.0 NONCOMPARATOR CLINICAL STUDY 034

7.1 Study Design and Objectives

Title

An open, multicenter, Phase II study of intravenous topotecan, given as 5 daily doses every 21 days, in advanced epithelial ovarian cancer (Study Number 104864/034)

Investigators and Centers

Twenty-six investigators in nine countries

Publication

None at issue

Study Dates

The first patient received study medication on 31 May 1993 and the last patient was enrolled on 18 March 1994. The cut-off date for inclusion of data in this study report was 28 February 1995. At this time three patients were continuing in the study and the last of these patients to enter the study had completed treatment course 10. For these three patients, data for completed courses are included in the study report.

Objectives

Primary: to evaluate the response rate and response duration of advanced epithelial ovarian carcinoma treated with topotecan administered as five daily infusions every 21 days in patients who have failed platinum-based chemotherapy.

Secondary: to evaluate the qualitative and quantitative toxicities of topotecan administered on this schedule.

Study Design

This was an open-label study to evaluate the efficacy and toxicity of topotecan for the treatment of patients with advanced ovarian carcinoma who had failed one or two prior chemotherapy regimens which contained a platinum-based cytotoxic agent. Topotecan was administered intravenously over 30 minutes for five consecutive days, every 21 days. The initial dose was 1.5 mg/m^2/day. Following each treatment course, the dose was to be decreased by 0.25 mg/m^2/day to a minimum of 1.0 mg/m^2/day if:

a. the patient experienced grade 4 granulocytopenia or grade 3-4 thrombocytopenia lasting >6 days or associated with clinical sequelae, or

b. the patient experienced grade 2 non-hematologic toxicity (except nausea, vomiting or alopecia),

c. the patient experienced toxicity that required a delay in the next treatment course beyond two weeks.

If the patient experienced grade 4 granulocytopenia or grade 3-4 thrombocytopenia lasting >14 days, or grade 3-4 non-hematologic toxicity, the dose was to be decreased by 0.5 mg/m^2/day.

If the patient experienced no toxicity > grade 1, the dose was to be escalated by 0.25 mg/m^2/day (each course) to a maximum dose of 3.0 mg/m^2/day.

Clinical and laboratory parameters were to be assessed for disease response and toxicity.

A total of 40 evaluable patients were to be accrued in two stages using the Gehan design. Fourteen patients were to be entered in the first stage. If none of them exhibited a complete or partial response, the study was to be terminated. If at least one of the first 14 patients exhibited a response, the study was to continue to a total of 40 evaluable patients.

Protocol Amendments

Revision 1, 24 January 1992: Course Day 1 laboratory data collection instructions were changed so that hematology and blood chemistries were not required if the most recent values were normal and were taken within seven

days. This change was made because a review of prior data showed that when abnormalities in these parameters had occurred, they were evident by day 15 of each course.

Inclusion criteria (3.2.2) were changed from "age between 18 and 75 years" to "age at least 18 years old"; from "hemoglobin >10.0 g/dL" to " hemoglobin >9.0 g/dL", "life expectancy >8 weeks" to "life expectancy >3 months."

Two exclusion criteria (3.2.3) were added: "History of allergic reactions to chemically related compounds." and "Patients with child bearing potential, not practicing adequate contraception."

An additional phrase was added to Screening Evaluation (3.3.2), bullet 1: "and any residual toxicity related to prior therapies."

Procedure for Dose Modification (3.3.4), Hematologic Toxicity was changed from

"-Grade 3-4 associated with fever/infection: Reduce single infusion dose for next treatment cycle by 0.25 mg/m^2/day

-Grade 3-4 not associated with fever/infection: No dose reduction" to

"Granulocyte Nadir

Grade 4 associated with fever/infection or lasting 7-14 days; Reduce single infusion dose by 0.25 mg/m^2/day

Grade 4 lasting > 14 days; Reduce single infusion dose by 0.50 mg/m^2/day

Grade 4 not associated with fever/infection or lasting < 7 days; No dose reduction:

Platelet Nadir

Grade 3-4 associated with bleeding or lasting 7-14 days; Reduce single infusion dose by 0.25 mg/m^2/day

Grade 3-4 lasting > 14 days; Reduce single infusion dose by 0.50 mg/m2/day"

Same section (3.3.4) "maximum infusion dose is 2.5 mg/m^2/day" was changed to "maximum infusion dose is 3.0 mg/m^2/day." Added the paragraph "If a patient has toxicity that requires a delay in the next treatment cycle of more than 2 weeks, the single infusion dose for the next treatment cycle will be decreased by 0.25 mg/m^2 and if on the lowest dose, the patient will be withdrawn from the study."

Amendment 1, 20 February 1992: The medical monitor was changed from M. Jennifer Hardin, M.D., to Bruce Wallin, M.D.

These changes had no significant impact on the results of the study.

Study Population

Female patients (aged >18 years) with advanced epithelial ovarian cancer who had failed first-line therapy with one regimen containing cisplatin or carboplatin, were to be entered into the study until 100 evaluable patients had been accrued. One hundred and eleven patients were entered into the study and, of these, 92 fulfilled the criteria for inclusion in the per protocol population.

Treatment and Administration

Topotecan was given as a 30-minute intravenous infusion on five consecutive days every 21 days. The initial dose was 1.5 mg/m^2/day but subsequently this could be increased or decreased by 0.25 mg/m^2/day, within the range mg/m^2/day (in patients with neutropenia, granulocyte-colony stimulating factor was to be administered before a reduction in dose was considered). Treatment could be delayed on a weekly basis, depending upon toxicity. The number of courses of treatment given was dependent upon disease response. The topotecan preparation was from batches numbered U-91024-J7AA and U-93056.

Evaluation Criteria

Efficacy Parameters: The primary efficacy endpoints were overall (best) response rate and response duration. Secondary endpoints were time to response, time to progression and survival.

Safety Parameters: Qualitative and quantitative toxicities were assessed by recording adverse experiences, with toxicity grades where appropriate, physical examinations, ECGs and clinical laboratory tests.

Statistical Methods

Efficacy results were summarized and two-tailed 95% confidence intervals were calculated for overall topotecan response (best response) rates. Best response was cross-classified with age, response to previous therapy, baseline disease status and CA-125 response. Mean and median cumulative dose and dose intensity were calculated for patients in each response category.

Time to event data were summarized by traditional survival methods and presented in standard life tables, summary tables and graphically, with Kaplan Meier estimates for each week of 'survival'.

Qualitative and quantitative results were summarized for hematological toxicities relating to white blood cells, neutrophils, platelets and hemoglobin. Qualitative data were summarized by course and by patient and included time to onset and

duration of grade 4 toxicities (grade 3 and 4 for anemia). Quantitative assessments of hematological toxicities included calculation of absolute nadirs, percentage change from baseline and day of occurrence of nadirs. Non-hematological toxicities were summarized within patient and within course.

7.2 Overview of Demographics, Treatment and Efficacy Results

Patient Demographics

One hundred and eleven patients were entered into the study by 26 investigators in nine countries. The number of patients in each country who entered the study, completed the study and were eligible for inclusion in the per protocol population are shown in the table below.

Country	Status		
	Entered	Completed	Per Protocol
Belgium	7	6	6
France	22	16	15
Germany	12	9	10
Italy	25	23	22
Netherlands	20	18	16
South Africa	1	1	1
Spain	6	5	6
Switzerland	2	0	2
United Kingdom	16	12	14

Patient Disposition is shown in the **following** table.

Patient Disposition Trial 034

	Number of patients:
Entered	111
Completed treatment	90
Withdrawn	18
Ongoing	3
Evaluated for intent-to-treat	111
Evaluated for per protocol	92
Evaluated for safety	111

The reasons for exclusion of patients from the per protocol population are provided in the Protocol Violations section. The main reasons for excluding patients from the per protocol population were that patients had received more than one prior regimen of chemotherapy or that the indicator lesions were in the field of prior radiotherapy. The primary reason for withdrawal of patients from the study was adverse experiences.

Demographic data are shown below for the intent-to-treat population. All patients were Caucasian except for one black and one patient for whom race was not stated.

Demographic Characteristics Trial 034

Demographic Characteristic	Intent-to Treat (n=111)
Age (years)	
≤ 40	6 (5.4)
41-64	75 (67.6)
≥65	30 (27.0)
Mean	57.3
Range	
Race	
Black	1 (0.9)
Caucasian	109 (98.2)
Not specified	1 (0.9)
Body weight (kg)	
Mean	66.7
Range	
Body surface area (m2)	
Mean	1.69
Range	

Number of Patients Present at Each Phase (or Visit)

All of the 111 patients who entered the study underwent the first course of treatment with topotecan. Nearly half of the patients (53/111) had at least five courses of treatment but less than 10 patients received more than 10 courses.). The median number of courses of treatment received was four (range).

Withdrawal Reason

Of the 111 patients who entered the study, 90 (81.1%) completed active treatment. A total of 18 patients (16.2%) withdrew and the most frequent reason for withdrawal, in 10 patients, was the occurrence of adverse experiences. Three patients were continuing in the study at the time of the cut-off.

Number of patients at each treatment course

Course	Number of patients
1	111
2	104
3	79
4	69
5	53
6	44
7	27
8	23
9	11
10	10
11-17	?5

Number (%) of patients who completed the study or were withdrawn, by reason for study withdrawal

Reason for study conclusion	# (%) patients
Completed active treatment*	90 (81.1)
Withdrawal reason**	
Adverse experiences	10 (9.0)
Lost to follow-up	6 (5.4)
Protocol violation, including non-compliance	1 (0.9)
Other	1 (0.9)
Total withdrawn	18 (16.2)
Ongoing	3 (2.7)
Total	111 (100)

* A patient was considered to have completed active treatment unless she was withdrawn because of adverse experiences or protocol violation, or was lost to follow-up and did not fulfill the criteria for efficacy evaluability. The following were also considered to have completed active treatment: patients who withdrew for any reason but fulfilled the criteria for efficacy evaluability patients for whom lack of efficacy (including progressive disease or disease stable for 8 weeks) was given as the reason for withdrawal; and those for whom the investigator checked the completion box in the CRF and gave no other reason for conclusion ** Patients who died are included as withdrawals due to adverse experiences if death was due to an adverse experience which was not associated with progressive disease

Protocol Violations

The numbers of patients who violated the protocol and were excluded from the per protocol population, together with the reasons for violation, are shown in the following table:

Number (%) of patients who were protocol violations and reasons for violation and exclusion from the per protocol population

Reason for protocol violation	# (%) of patients*
Two prior regimens of chemotherapy	7 (6.3)
Indicator lesion in field of prior radiotherapy	5 (4.5)
Not assessed beyond 5 days	3 (2.7)
Did not have required measurable disease	3 (2.7)
Received hormonal treatment for cancer**	1 (0.9)
Did not have required performance status	1 (0.9)
Protocol violation; patient withdrawn	1 (0.9)
Surgery within previous 28 days	1 (0.9)
Concomitant malignancy	1 (0.9)
CT scan too early	1 (0.9)
Total number of patients who violated the protocol	19 (17.1)

A patient may have more than one reason for protocol violation. ** Hormonal treatment for cancer was not specified in the protocol as a violation but it was considered that such treatment may affect the assessments of efficacy. One patient received hormonal treatment for cancer and also had an indicator lesion in the field of prior radiotherapy and was therefore excluded from the per protocol population.

In addition to the patients who were considered protocol violations, there were a number of patients who were classified as conduct of study deviations for whom the deviation was not considered sufficient to warrant exclusion of the patient from the per protocol population. The numbers of patients who deviated from the protocol and the reasons for deviation and inclusion are summarized on the next page.

Number of patients who deviated from the protocol and reasons for deviation and inclusion in the per protocol population.

Study deviation	Reason for inclusion	# of patients
Surgery within 28 days	Surgery insignificant	4
Radiotherapy	Other assessable lesions/ years since radiotherapy	4
Abnormal laboratory values	Unlikely to affect assessment	4
Dose modification incorrect/irregular dosing	Considered acceptable	3
Chemotherapy within 28 days	Laboratory results satisfactory	2
5-8 day treatment delays because of holidays	Considered acceptable	2
No measurable lesion at baseline	Measurable lesion day 8	1
Radiophosphorus installation	Not clinically significant	1
Abdominal tumor pain*	No evidence of secondary	1
Baseline CT scan day 8	Considered acceptable	1
Prophylactic G-CSF course 1	Considered acceptable	1
Total number of patients who deviated from the protocol		24

* Identified while screening data for patients with concomitant malignancies; however, review of data on the CRF showed no evidence of a secondary tumor in this patient

Efficacy Results

Response to topotecan did not appear to be related to response to previous therapy, baseline disease status and CA-125 response. However, a response was seen in two patients who had not responded to first-line therapy. All patients aged <40 years were non-responders. Mean and median cumulative dose and dose intensity were similar for patients in each response category.

A summary of the applicant's results for objective response, time to response from the start of treatment, response duration from the time of first documented response, time to progression from the start of treatment and survival from the start of treatment are provided below for the intent-to-treat population.

Response Variable		# Patients (%)
		n=111
Complete Response	1	(0.9%)
Partial Response	15	(13.5%)
Total Responses	16	(14.4%)
Stable Disease	25	(22.5%)
Progression	68	(61.3%)
Not Done	2	(1.8%)
Duration of Response	n=16	
Median (weeks)	16.3	
Range (weeks)		
Time to Response	n=16	
Median (weeks)	10.4	
Range (weeks)		
Time to Progression	n=111	
Median (weeks)	11.3	
Range (weeks)		
Survival Time	n=111	
Median (weeks)	52.4	
Range		

7.3 Reviewer's Evaluation of Primary and Secondary Efficacy Variables

Time to response was calculated using the day the patient achieved the best response. Duration of response was calculated by the following criteria :

- Any patient that had a new lesion, whether or not the sum of the products of all lesions showed a decrease over the previous measurement was considered to have progression

- Any patient that had a 25 % increase in the sum of the products of all lesions over the previous best minimum was considered to have progression. For example, if a patient had a sum of products of 50, then decreased to 24, the first measurement that was greater than 30 (25 % of 24) would be considered the day of progression.

Time to progression was calculated using the same criteria.

Objective Responses: CR 1 (0.9%) PR 14 (12.6 %)

Total Responses: 15 (13.5%)

Time to Response in Days

N		Mean	S.D.		Min	Max
1	CR	62.00	0.00		62	62
14	PR	104.36	57.76	38	225	
15	Total	101.53	56.72	38	225	

Response Duration in Days

Mean	S.D.	Min	Max
95.00	27.39	63	126

Using these criteria, a set of 69 were selected for determining the time to progression and establishing a Kaplan-Meier time to event and a proportions plot.

Time to Progression in weeks

Median	8.43
Mean	10.00
Minimum	3
Maximum	24

7.4 Adverse Experience and Safety Results

Hematological Toxicity

Dose delays and reductions were required due to hematological toxicity in 14.5% and 3.9% of courses, respectively, and in 1.6% and 1.1% of courses, respectively, due to non-hematological toxicity. Most dose delays and reductions occurred in early courses, particularly courses 2 and 3.

The predominant hematological toxicity seen with topotecan was neutropenia, with grade 3 and 4 toxicity occurring in 97.3% of patients (108/111) and 69.1% of courses (374/541). The median time to onset of grade 4 neutropenia was 9 days from the start of treatment (range days) and the median duration was 7 days (range days). Prophylactic or treatment G-CSF was given to 26.1% of patients (29/111) in 20.5% of courses (113/552). Infection or fever >grade 2 or febrile neutropenia was reported in a total of 34.2% of patients (38/111) and 11.2% of courses (62/552) and infection or fever >grade 2 or febrile neutropenia proximate to grade 4 neutropenia in a total of 16.2% of patients 18/111) in 4.3% of courses (24/552). Systemic antibiotic treatment, including prophylactic use, was given to 40.5 % of patients in 13.9 % of courses and there were no reports of sepsis.

Platelet transfusions were given to 7.2% of patients in 2.4% of courses.

Anemia (at least grade 1) was reported in all patients during topotecan treatment and grade 3 and 4 anemia occurred in 31.5% of patients (35/111) and 11.1% of courses (61/548). Median time to onset of grade 3 and 4 anemia was 12 days (range days) and median duration was 7 days (range days). The proportion of courses with grade 3 and 4 anemia was lower for patients who did not have anemia at baseline (7.3% of courses, 34/464) than for patients who had

anemia at baseline (hemoglobin value < 11 g/dL at any time prior to first dose; 32.1%; 27/84). Red cell transfusions were given to 54.1% of patients in 20.7% of courses.

There was no evidence of an increase in incidence of grades 3 and 4 hematological toxicities with increasing numbers of courses of treatment, suggesting a lack of cumulative toxicity, although the median duration of grade 4 neutropenia tended to be longer after course 8 (8.5 to 13 days) than in earlier courses (7 days). Interpretation of these data is complicated, however, by the small number of patients in later courses.

Grade 4 Neutropenia

	Total	Patients	% Patients	Courses	% Courses
Total ANC measurements	2214	111		552	
Total ANC <500	320	88	79.3	221	40.0%

Fever, Duration, and Febrile Neutropenia

Fever > 38.0 C Duration in Days

Mean	Std. dev.	Min	Max	# of patients	per cent of all patients	# of courses	per cent of all courses	Total Measurements
3.27	3.17	1	12	21	19.8 %	30	5.43%	66

Documented Fever and Neutropenia Duration in days

Mean	Std. dev.	Min	Max	# of patients	per cent of all patients	# of courses	per cent of all courses	Total Measurements
4.44	4.03	1	15	18	16.2 %	28	5.07%	32

Fever and Fever and Neutropenia by Course

Course Fever > 38° C. per course

	Total	Mean	Std. dev.	Min	Max
1	12	3.69	3.84	1	12
2	5	3.50	2.08	1	6
3	5	3.40	3.21	1	9
4	3	1.50	0.58	1	2
5	3	5.00	5.66	1	9
6					

Course Fever and Neutropenia per course

	Total	Mean
1	12	5.46
2	8	6.42
3	4	5.29
4	3	1.75
5	1	1
6	1	5

Thrombocytopenia

	Total	# Patients	% Patients	Courses	% Courses
Total Plt measurements	2143	111		552	
Platelets <25,000	52	16	14.4%	21	3.80%

Grade 3,4 Anemia

		# Patients	% Patients	Courses	% Courses
Total # Hgb measurements	2164	111		552	
Total Hgb <8	581	51	34.0%	183	33.2%

Lymphocytopenia

	Total	Patients	% Patients	Courses	% Courses
Total ALC measurements	5334	111		552	
Total ALC < 500	102	34	30.63%	77	13.95%

Non-Hematologic Toxicity

Alopecia was the most commonly occurring adverse experience in 82% of patients (91/111) and, in 57.7% (64/111), the alopecia was grade 2. The next most frequent adverse experiences were nausea (75.7% of patients; 84/111), vomiting (54.1% of patients; 60/111) and diarrhea (43.2% of patients 48/111). These were also most frequently reported as related/possibly related to topotecan. The most common grade 3 and 4 toxicities reported as related/possibly related to topotecan were vomiting (5.4% of patients; 6/111) hyperbilirubinemia and nausea (both 4.5% of patients; 5/111). The profile of adverse experiences in course 1 was similar to that overall.

Adverse Events by Course

Course	Unknown	1	2	3	4	9	Sum	Patients
1	134	298	128	31	4	2	597	111
2	133	290	112	35	10	3	583	104
3	106	207	94	15	1	2	425	79
4	85	167	87	10		3	352	69
5	72	133	73	8	1	3	290	53
6	68	97	71	4		[illegible]	241	44
7	35	67	[illegible]	4		1	150	27
8	32	56	37	3			128	23
9	11	22	13				46	11
10	12	14	11				37	10
11	7	12	2				21	5
12	1	7	4	1			13	4
13	5	8	1				14	3
14	2	9	1				12	3
15	2	11	2				15	3
16	2	4	2				8	2
17	2	2	1				5	1

Study 034 Non-hematologic Adverse Events by Number of Courses

Adverse Event by Courses	Total	% of total course	Unk.	%	Grade 1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	497	90.04	1	0.18	212	38.41	284	51.45						
NAUSEA	248	44.93	1	0.18	184	33.33	53	9.60	10	1.81			10	6.71
VOMITING	138	25.00	1	0.18	90	16.30	40	7.25	7	1.27			7	4.70
DIARRHEA	95	17.21	1	0.18	71	12.86	14	2.54	6	1.09	3	0.54	9	6.04
ABDOMINAL PAIN	93	16.85	17	3.08	57	10.33	16	2.90	3	0.54			3	2.01
FATIGUE	91	16.49	86	15.6			5	0.91						
CONSTIPATION	82	14.86	79	14.3	3	0.54								
STOMATITIS	78	14.13	2	0.36	47	8.51	26	4.71	2	0.36	1	0.18	3	2.01
ASTHENIA	72	13.04	66	12.0	2	0.36	2	0.36	2	0.36			2	1.34
HEADACHE	68	12.32	7	1.27	47	8.51	12	2.17	2	0.36			2	1.34
PHOSPHATASE ALKALINE INCREASED	68	12.32	1	0.18	64	11.59	3	0.54						
HEMATURIA	67	12.14	1	0.18	62	11.23	4	0.72						
HYPERGLYCEMIA	65	11.78	2	0.36	53	9.60	4	0.72	5	0.91			5	3.36
FEVER	61	11.05	4	0.72	24	4.35	31	5.62	2	0.36			2	1.34
ANOREXIA	42	7.61	8	1.45	20	3.62	13	2.36	1	0.18			1	0.67
PARESTHESIA	35	6.34	6	1.09	22	3.99	5	0.91	2	0.36			2	1.34
ALBUMINURIA	34	6.16	1	0.18	32	5.80	1	0.18						
DYSPNEA	34	6.16			11	1.99	16	2.90	7	1.27			7	4.70
HYPOKALEMIA	33	5.98			25	4.53	8	1.45						
SGPT INCREASED	33	5.98			25	4.53	7	1.27	1	0.18			1	0.67
DYSPEPSIA	31	5.62	9	1.63	17	3.08	5	0.91						
HYPOMAGNESEMIA	29	5.25			17	3.08	9	1.63	1	0.18			1	0.67
HYPOPHOSPHATEMIA	29	5.25	29	5.25										

Study 034 Non-hematologic Adverse Events by Number of Patients

Adverse Event by Patient	Total	%	Unk.	%	1	%	2	%	3	%	4	%	SAE	%
ALOPECIA	93	83.78			28	25.23	65	58.56						
NAUSEA	84	75.68	1	0.90	45	40.54	32	28.83	6	5.41			6	4.03
VOMITING	60	54.05	1	0.90	32	28.83	21	18.92	6	5.41			6	4.03
DIARRHEA	49	44.14	1	0.90	33	29.73	9	8.11	4	3.60	2	1.80	6	4.03
CONSTIPATION	40	36.04	38	34.23	2	1.80								
ABDOMINAL PAIN	39	35.14	5	4.50	21	18.92	10	9.01	3	2.70			3	2.01
FEVER	35	31.53	3	2.70	11	9.91	19	17.12	2	1.80			2	1.34
FATIGUE	33	29.73	30	27.03			3	2.70						
STOMATITIS	33	29.73	1	0.90	19	17.12	10	9.01	2	1.80	1	0.90	3	2.01
HEADACHE	30	27.03	5	4.50	16	14.41	8	7.21	1	0.90			1	0.67
ASTHENIA	25	22.52	22	19.82	1	0.90			2	1.80			2	1.34
PHOSPHATASE ALKALINE INCREASED	25	22.52			22	19.82	3	2.70						
HEMATURIA	23	20.72			20	18.02	3	2.70						
HYPERGLYCEMI	21	18.92	1	0.90	14	12.61	3	2.70	2	1.80			2	1.34
ANOREXIA	19	17.12	3	2.70	7	6.31	8	7.21	1	0.90			1	0.67
HYPOMAGNESEMIA	19	17.12			10	9.01	7	6.31	1	0.90			1	0.67
DYSPNEA	17	15.32			6	5.41	6	5.41	5	4.50			5	3.36
HYPOKALEMIA	17	15.32			11	9.91	6	5.41						
SGPT INCREASED	17	15.32			11	9.91	5	4.50	1	0.90			1	0.67
ALBUMINURIA	16	14.41			15	13.51	1	0.90						
ALBUMIN GLOBULIN RATIO ABNORMAL	14	12.61	14	12.61										
COUGHING	14	12.61	4	3.60	6	5.41	2	1.80	2	1.80			2	1.34
DYSPEPSIA	14	12.61	4	3.60	7	6.31	3	2.70						
HYPONATREMIA	13	11.71			6	5.41	5	4.50	1	0.90			1	0.67
ANEMIA	12	10.81	2	1.80	1	0.90	2	1.80	7	6.31			7	4.70
BILIRUBINEMIA	12	10.81			2	1.80	3	2.70	5	4.50	2	1.80	7	4.70
HYPOCALCEMIA	12	10.81	1	0.90	6	5.41	2	1.80	1	0.90			1	0.67
PARESTHESIA	12	10.81	3	2.70	7	6.31	1	0.90	1	0.90			1	0.67
SGOT INCREASED	12	10.81			11	9.91			1	0.90			1	0.67

Non-Hematologic Adverse Events per Patient

	Mean	Stdev	Min	Max	Sum	# of patients	# of courses
Total	26.46	18.04	2	85	2937	111	551

Adverse Events = Grade 3

	Mean	Stdev	Min	Max	Sum	# of patients	per cent	# of courses	per cent
Total	2.58	1.97	1	10	111	42	37.8%	43	7.8%

Adverse Events = Grade 4

	Mean	Stdev	Min	Max	Sum	# of patients	per cent	# of courses	per cent
Total	1.78	1.09		4	16	8	7.2%	9	1.6%

Serious Adverse Experiences and Deaths

Anemia (8.1% of patients; 9/111) was the most frequently occurring serious adverse experience followed by granulocytopenia, intestinal obstruction and thrombocytopenia (all 6.3% of patients; 7/111) Hematological toxicities were the most common serious adverse experiences that were reported as related/possibly related to topotecan, ranging in incidence from 5.4% (6/111) to 7.2% (8/111) of patients.

By the cut-off date for inclusion in this report, a total of 28 (25.2%) patients had died, eight (7.2%) within 30 days of the last dose of topotecan. In all but four cases the cause of death was progressive disease. For three patients, who died within 30 days of topotecan treatment, the causes of death were febrile aplasia, myocardial infarction/cardiac arrest and thromboembolism. For the fourth patient, who died 103 days after treatment, the reason was not provided.

Withdrawals Due to Adverse Experiences

Ten patients (9.0%; 10/111) withdrew from the study due to adverse

thrombocytopenia (3.6% of patients; 4/111), anemia and cardiac arrest (each 1.8% of patients; 2/111). The remainder were single occurrences.

Vital Signs and ECGs

There were no changes of note in vital signs following topotecan treatment. Worsening of ECG findings was seen in four patients (5.3%) at the end of course 1 and two other patients (3.1%) at the end of the study. There was no evidence to suggest a topotecan effect on ECG's. No consistent changes were seen, and, in most cases where changes occurred, other factors such as significant medical history or concomitant metabolic disturbances were likely to have contributed.

Laboratory Tests

The most frequently occurring laboratory values of clinical concern (grade 3 or 4 toxicities) were hyperbilirubinemia in 6.3% of patients (7/111) and 2.0% of courses (11/537) and hyperglycemia in 3.7% of patients (4/108) and 1.3% of courses (7/524). The initial onset of grade 3 or 4 hyperbilirubinemia or hyperglycemia tended to be in early courses but there was no consistency in the pattern or magnitude of abnormal values and in a majority of patients values had returned to grade 0 to 2 by the last course.

7.5 Reviewer's Conclusion

This study has shown that topotecan, given as five daily intravenous infusions every 21 days, is active in patients with ovarian cancer who had failed treatment with one platinum-based chemotherapeutic regimen. The response rate was similar to that seen for historical controls in comparable multicenter studies. The main toxicity was hematological, predominantly neutropenia, but this was generally not associated with significant clinical sequelae and topotecan was well-tolerated with respect to non-hematological toxicities.

8.0 Integrated Summary of Efficacy in Ovarian Cancer Studies

The results of studies 039 and 034, supported by 033 and 012 (not reviewed) demonstrate the efficacy of topotecan in the treatment of recurrent ovarian cancer. Study 039 was the only comparative study conducted.

In all four of these studies, 445 patients received at least one dose of topotecan. The demographic characteristics of patients in these four studies

were similar although the baseline disease characteristics of platinum sensitivity, time to progression from first-line therapy and tumor bulk were most favorable for patients in study 039 and less favorable for patients in study 034. The population of patients on study 033 and 012 were also a poor prognosis group with more than 80% of patients being considered platinum resistant.

At the time of the 20 June 1995 clinical cut-off, 87/112 (78%) and 92/114 (81%) of patients treated with topotecan and paclitaxel, respectively, were alive. The estimated survival in patients treated with topotecan was a median of 61.3 weeks compared to 42.6 weeks on paclitaxel. Comparison of survival between treatment groups was not significant. Since the majority of patients were still alive at the time of the analysis, longer follow up is required to determine if the statistically significant difference in time to progression will translate into significantly improved survival with topotecan.

In the alternate arm of study 039, a total of 53 patients switched treatment to receive topotecan versus 37 patients who switched to receive paclitaxel. Five patients (9%) in the alternate topotecan group achieved a partial response and one patient (3%) in the alternate paclitaxel group achieved a complete response. A number of patients remain on treatment so it is too early to draw further conclusions from this component of the study.

Study 034 was non-comparative and was intended to assess the efficacy of topotecan versus historical controls. The efficacy endpoints assessed were response rate median time to response (10.4 weeks), median response duration (16.3 weeks), median time to progression (11.3 weeks) and estimated median survival (52.4 weeks). These results indicated that topotecan, used as a single agent, is comparable in terms of efficacy when compared to historical controls particularly the large, multicenter, European-Canadian study with paclitaxel which compared four different schedules of paclitaxel in patients failing first or second-line therapy [9, 10]. The response rate for the four schedules used ranged from %. When paclitaxel was administered at a dose of 175 mg/m2 and infused over 3 hours, the response rate was 14.6%, similar to the response rate reported for this schedule in study 039.

The efficacy results reported in study 034 were less impressive than those observed in study 0[illegible] This may in part be explained by the poorer prognosis of patients recruited into study 034, particularly with regard to the important baseline characteristic of platinum sensitivity. In study 034, 66% of patients were in the poor prognosis group with platinum resistant disease (defined as having no response or having relapsed within six months of prior therapy). This

respond or had relapsed within six months of prior therapy following the 175 mg/m^2 dose in the European-Canadian study. In addition, more patients were less likely to respond due to bulky disease in study 034, with the greatest tumor diameter being in excess of 5 cm in 61% of patients compared to 50% in the topotecan arm of study 039. The corresponding figure in the European-Canadian study following the 175 mg/m^2 dose study was 68%.

Study 033 was also non-comparative and was intended to determine if patients who had failed prior chemotherapy including both platinum and paclitaxel would respond to topotecan. The data from this study are considered to be interim since many patients received insufficient courses to expect a response. However, responses to topotecan treatment have been observed after failing first- and second-line chemotherapy. This patient population can also be considered a poor prognosis group, with 81% of patients being resistant to prior platinum therapy.

Study 012 was a fourth, supportive and non-comparative study. The results seen in this initial study in platinum resistant disease were consistent with the other three studies.

Quality of life parameters measured in study 039 and study 033 did not indicate substantial changes when the assessment at baseline and end of best response were compared.

Since the design of studies 039, 034, 033 and 012 were similar, it was possible to review the results for the overall patient population. The efficacy results between studies are consistent. Differences in efficacy seen between studies were likely due to differences in baseline disease characteristics.

The results also support the selection of the starting dose for topotecan (1.5 mg/m^2/day) and the schedule (daily times five, repeated every 21 days). Dose intensity was maintained using this schedule. G-CSF was used to maintain dose intensity in 19% of all courses administered.

In conclusion, topotecan at the dose and schedule used in the four studies, is effective in the treatment of recurrent ovarian cancer. The results in the failed platinum population and failed platinum and paclitaxel population also suggest there is a lack of cross-resistance between topotecan and platinum or paclitaxel. The small sample size in the randomized comparative study 039, precludes

9.0 Integrated Summary of Safety

The Integrated Safety Summary presents safety data from 12 studies sponsored by SB that have interim or final reports. A total of 774 patients received at least one dose of topotecan in these studies, including a total of 445 patients from four studies in recurrent ovarian cancer. A further 14 SB sponsored studies which are either ongoing or recently closed to recruitment have not yet been reported. All serious adverse events, withdrawals and deaths are included for the 502 patients in these unreported studies. For all ongoing studies a clinical cut-off date of 20th June 1995 was applied.

Phase I studies:

Four Phase I studies of intravenous topotecan are reported. These studies enrolled 131 patients with solid tumors. One study (005) used the daily times five regimen of study drug, one used the daily times five regimen plus a single dose of cisplatin at each course (017), while the others used different regimens.

Phase II/III studies in ovarian cancer:

There are four reported studies in ovarian cancer, each used a starting dose level of 1.5 mg/m2/day given as a 30-minute infusion for five consecutive days every 21 days (referred to as the "daily times five" regimen). All patients had advanced ovarian cancer and had failed at least one previous platinum containing regimen. Study 039 was a multicenter, randomized, comparative study versus paclitaxel in which patients who progressed or whose best response was stable disease after 6 courses on the randomized arm could be switched to the other treatment (alternate) arm. Study 034 was a non-comparative, multicenter study in patients failing one prior regimen. Study 033 was a multicenter, non-comparator study in patients who had failed one prior therapy with a platinum/paclitaxel combination or who had failed two prior regimens which must have included platinum and paclitaxel. Study 012 was an early phase II single institution study in patients failing no more than two prior regimens. In total 445 patients, including those given topotecan in the alternate phase of study 039, were treated with at least one dose of topotecan. Data from these studies have been combined, and since these data are the most relevant for the indication they are discussed in greatest detail. Data from the single comparative study 039 are also presented separately in detail.

Phase II Breast Cancer Studies

One reported study (013) utilized the daily times five regimen in 20 patients. A further study (030) included 18 patients with advanced breast cancer, and used a single 24-hour infusion of 22.5 mg/m2 repeated every 21 days.

Two studies conducted by the EORTC are presented as interim reports, both used the daily times five regimen. One study (011) was in 59 previously untreated patients with colorectal cancer, and the other (014) was in 101 previously treated patients with small cell lung cancer.

Other Studies

There are 13 ongoing topotecan clinical studies using the intravenous route of administration and one additional ongoing phase I study investigating an oral dosage form of topotecan. The intravenous studies include the daily times five regimen, a 21-day continuous infusion every 28 days, and one other study evaluating a weekly 24-hour continuous infusion regimen. A total of 502 patients were enrolled in these studies at the clinical cut-off date.

Further studies have been sponsored by the National Cancer Institute (NCI). These have not been fully reported, but all publications have been referred to as safety data from other sources. One NCI sponsored study of patients with hepatic and renal impairment has been summarized in the ISS Item 8, Section g (Report SK&F 104864A/097).

Overall Extent of Exposure

The 12 reported clinical studies involved 774 patients and a total of 3351 courses of topotecan. The majority of patients were treated with the daily times five regimen in which a daily 30-minute intravenous infusion of topotecan administered on five consecutive days constituted a treatment course. The scheduled interval between treatment courses was 21 days. In the studies using this regimen, 3090 topotecan treatment courses were administered to 688 patients.

The reported studies include four Phase I studies (004, 005, 010 and 017; total 131 patients), four Phase II/III studies of ovarian cancer (012, 033, 034 and 039; total 445 patients), two Phase II studies of breast cancer patients (013, 030; total 38 patients), one EORTC Phase II study in patients with colorectal cancer (011; 59 patients) and one EORTC Phase II study in patients with small cell lung cancer (014E; 101 patients.

In the four Phase II/III ovarian cancer studies, 445 patients received a total of 2019 topotecan courses, of which 1673 courses (82.8%) were administered at the starting dose of 1.5 mg/m2/day. Retreatment commenced within five days of the scheduled start dates for 1206 (76.6%) of 1574 courses after the first course. The dose level was reduced in just 100 (6.4%) of 1574 courses after the first course. Overall in the four ovarian cancer studies, topotecan patients received a median of 4 courses per patient (range 1-33), a median dose intensity of 2.39 mg/m2/week and a median cumulative dose of 30 mg/m2. Data are presented on nine subset populations of the ovarian cancer patients based upon their demographic and baseline characteristics. Of the 2019 courses, 1293 courses (64.0%) were administered to 284 patients (63.8%) who were between 41 and 64 years old. In these studies, the use of G-CSF was permitted after a patient's

first topotecan course, before dose level reduction in order to maint dose intensity, if neutropenia or sequelae of neutropenia would have been the sole reason for a dose reduction. G-CSF was used prophylactically in 388/2019 (19.2%) of treatment courses.

One of the four ovarian cancer studies was a randomized Phase II/III study (Study 039)comparing topotecan treatment of 112 patients for a total 555 courses with paclitaxel treatment of 114 patients for a total of 550 courses. The topotecan patients had a median of 5 courses per patient (range), a median dose intensity of 2.3 mg/m2/week and a median cumulative dose of 37.5 mg/m2. The paclitaxel patients had a median of 5 courses per patient (range), a median dose intensity of 56.3 mg/m2/week and a median cumulative dose of 875 mg/m2.

In addition to the 12 reported studies, there are 13 ongoing topotecan clinical studies using the intravenous route of administration, and one ongoing study investigating an oral dosage form of topotecan. Of the ongoing studies, five are using the daily times five regimen, seven studies are using a regimen in which topotecan is administered as a 21-day continuous infusion every 28 days, and one other study is evaluating a weekly 24-hour continuous infusion regimen. A total of 502 patients were enrolled in these studies at the clinical cut-off date, these patients received at least one dose of topotecan, but no further data is available on overall extent of exposure.

Demographics

The population described in this section consists of the 774 patients that were treated in the 12 reported clinical studies described in Section 2, four Phase I and eight Phase II/III studies. These include 668 patients treated with topotecan on the daily times five regimen.

The Phase I studies (Studies 004, 005, 010, and 017) involved 131 patients of whom 92 (70.2%) were male. The mean age of the patients was 59.0 (range , years. One hundred and twelve patients (85.5%) had a performance status £ 1. Seventy-nine patients (60.3%) had prior chemotherapy and 93 patients (71.0%) had prior surgical treatment of their cancer.

In four studies of ovarian cancer, three Phase II (Studies 012, 033 and 034) and one Phase III (Study 039), there were 445 patients, all of whom were pretreated. The patients' mean age was 57.6 (range years, and 339 patients (76.2%) had a performance status £ 1. Two hundred and sixty-one patients (58.7%) had a histopathologic diagnosis of malignant serous tumor. In 341 patients (76.6%) the tumor histologic grade was £ grade 3. The maximum lesion diameter was < 5 cm in 201 patients (45.2%) and was > 5 cm but < 10 cm in 199 patients (44.7%). Liver metastases were known to present at baseline in 289 patients (65.0%). Creatinine test results were within normal limits in 398

patients (29%) in the four studies. The majority of patients, 292 (65.6%), had only one prior treatment regimen, and only 13 patients (2.9%) had more than two prior chemotherapy regimens. Two hundred and sixty-one patients (58.7%) had achieved either a complete response or a partial response to first-line therapy and 85 patients (19.1%) had stable disease as their best response to first-line chemotherapy.

Overall, the demographic characteristics of the ovarian cancer patients in the randomized phase of the comparator study of topotecan and paclitaxel (Study 039) were similar to the characteristics of patients in the pooled population of 445 patients in the four ovarian studies, described above. Of 226 total patients, 112 were randomized to the topotecan arm and are included in the pooled population; 114 patients were randomized to the paclitaxel arm. In baseline comparison of prior platinum therapy, the randomized phase of the comparator study had a higher proportion of patients who were late relapse (46.4%) than did the pooled population of patients in the four studies (30.8%). In the randomized phase of the comparator study, a complete response or a partial response to first-line chemotherapy had been achieved by 64.3% of patients, compared to 58.7% of the pooled population of patients in the four ovarian studies.

In two Phase II breast cancer studies (Studies 013 and 030) there were 38 patients, mean age 58.4 (range ') years, of whom 26 had a reported performance status £ 1. All patients had prior chemotherapy, 36 patients had prior radiation therapy and 35 patients had prior surgical treatment of their breast cancer.

Two Phase II studies conducted by the EORTC-ECTG (SB Studies 011 and 014E) enrolled a total of 160 patients, but reported data on 151 evaluable patients, 95 male and 56 female, median age 59 (range 34 to 75) years. One hundred and thirty-two (87.4%) patients had a performance status £ 1. One of the studies (Study 011) involved 57 evaluable colorectal cancer patients of whom 52 (91.2%) had prior surgical treatment and only two patients (3.5%) had prior chemotherapy. The other study (Study 014E) was an investigation in 94 evaluable small cell lung cancer patients, all of whom had prior chemotherapy; 49 patients (52.1%) entered the study with disease classified as refractory to prior chemotherapy and 45 patients (47.9%) had disease classified as sensitive to prior chemotherapy.

Adverse Experiences in Clinical Trials

All toxicities were reported as grades according to the modified Common Toxicity Criteria (CTC) of the National Cancer Institute. Hematologic and non-hematologic toxicities were examined for the 131 patients in four Phase I and for the 445 patients in three Phase II and one Phase III study which assessed topotecan 1.5 mg/m2 daily times five regimen in patients with advanced ovarian carcinoma. In the Phase III study in patients with recurrent ovarian cancer, topotecan was compared with paclitaxel given at a dose of 175 mg/m2 over

studies using topotecan daily times five regimen in 57 patients with colorectal cancer and in 94 patients with small cell lung cancer.

Hematologic Toxicities

White blood cell, neutrophil, platelet and hemoglobin counts were evaluated to assess the hematologic toxicity of topotecan. The severity of toxicities was presented by CTC grade, and the incidence of toxicity by patients and by course was tabulated. Time to onset and duration of severe toxicity, hematologic nadir, and infective complications were also examined.

In Phase I studies, dose limiting toxicities were neutropenia or leukopenia in three of the studies, and neutropenia and thrombocytopenia in the fourth study. Infective complications resulting from hematologic toxicities were infrequent in all four Phase I studies.

In the ovarian cancer studies 039, 034, and 033, hematologic criteria for treatment initiation included neutrophils > 1,500/mm3, platelets > 100,000/mm3 and hemoglobin > 9 g/dL. Retreatment criteria for subsequent courses were the same except that neutrophils > 1,000/mm3 were recommended for topotecan.

In the combined ovarian population of 445 patients, hematologic toxicities observed with topotecan daily times five regimen were reversible, non-cumulative and manageable, and infrequently led to serious sequelae. Grade 4 neutropenia was the most frequently reported toxicity, experienced by 79% of patients and associated with 42% of courses administered, and as expected was most prevalent during course 1 of therapy before dose reduction or G-CSF use were instituted. Grade 4 thrombocytopenia was experienced by 23% of patients in 9% of courses. Grade 3 or grade 4 anemia was experienced by 37% of patients in 15% of courses.

Day of r.. ophil nadir occurred earlier with additional courses of therapy (but remained .. stant for platelets and hemoglobin). This was probably related to the less severe depression of the neutrophil nadir subsequent to course one, due to a proportion of patients receiving dose reductions and G-CSF in these later courses. Median duration of severe toxicity was one week or less; grade 4 neutropenia lasting longer than one week was associated with 12% of total courses administered. There was no clear evidence of cumulative toxicity associated with topotecan therapy, as evidenced by the lack of progressively lower hematologic nadirs. Sequelae of hematologic toxicities were infrequent, particularly after course one of therapy. Suspected or documented infections proximate to grade 4 neutropenia were associated with 6.5% of courses, with sepsis reported in a further 1.1% of courses. Topotecan induced myelosuppression was considered related to the death of three patients (0.7%).

INTEGRATED SAFETY DATA IN OVARIAN CANCER STUDIES SUBMITTED TO FDA

Neutropenia

Total ANC measurements	5271	Patients	276			Courses	1441	
Total ANC< 500	727	Patients	220	% All Pts.	79.7%	Courses	500	34.7%

Duration in Days

	039 All	Topo	Taxol	034	Cumulative
Mean	5.58	5.56	5.68	6.34	5.73
Std.Dev.	11.32	12.19	2.49	10.48	11.85
Min.	1	1	1	1	1
Max.	219	219	15	109	219
# of courses	457	391	66	105	496

Anemia

Total Hgb measurements	5068	Patients	276			Courses	1442	
Total Hgb< 8	879	Patients	79	% All Pts.	28.6%	Courses	299	20.7%

Thrombocytopenia

Total Plt measurements	5015	Patients	276			Courses	1442	
Total Plt < 25	126	Patients	52	% All Pts.	18.8%	Courses	72	4.99%

Lymphopenia

Total ALC measurements	8348	Patients	276			Courses	1441	
Total ALC < 500	320	Patients	96	% All Pts.	34.78%	Courses	212	14.71%

Adverse Experiences in Clinical Trials

All toxicities were reported as grades according to the modified Common Toxicity Criteria (CTC) of the National Cancer Institute. Hematologic and non-hematologic toxicities were examined for 131 patients in four Phase I MTD studies which assessed several dosing regimens in various tumor types, and for 445 patients in three Phase II and one Phase III study which assessed topotecan 1.5 mg/m2 daily times five regimen in patients with advanced ovarian carcinoma. In the Phase III study in patients with recurrent ovarian cancer, topotecan daily times five regimen was compared with paclitaxel given at a dose of 175 mg/m2 over three hours. Additionally, toxicities were examined in two EORTC Phase II studies using topotecan daily times five regimen in 57 patients with colorectal cancer and in 94 patients with small cell lung cancer.

Hematologic Toxicities

White blood cell, neutrophil, platelet and hemoglobin counts were evaluated to assess the hematologic toxicity of topotecan. The severity of toxicities was presented by CTC grade, and the incidence of toxicity by patients and by course was tabulated. Time to onset and duration of severe toxicity, hematologic nadir, and infective complications were also examined.

In Phase I studies, dose limiting toxicities were neutropenia or leukopenia in three of the studies, and neutropenia and thrombocytopenia in the fourth study. Infective complications resulting from hematologic toxicities were infrequent in all four Phase I studies.

In the combined ovarian population of 445 patients, hematologic toxicities observed with topotecan daily times five regimen were reversible, non-cumulative and manageable, and infrequently led to serious sequelae. Grade 4 neutropenia was the most frequently reported toxicity, experienced by 79% of patients and associated with 42% of courses administered, and was most prevalent during course 1 of therapy before dose reductions or G-CSF use was instituted. Grade 4 thrombocytopenia was experienced by 23% of patients in 9% of courses. Grade 3 or grade 4 anemia was experienced by 37% of patients in 15% of courses.

Day of neutrophil nadir occurred earlier with additional courses of therapy, but remained constant for platelets and hemoglobin. This was probably related to the less severe depression of the neutrophil nadir subsequent to course one, due to a proportion of patients receiving dose reductions and G-CSF in these later courses. Median duration of severe toxicity was one week or less; grade 4 neutropenia lasting longer than one week was associated with 12% of total courses administered. There was no clear evidence of cumulative toxicity associated with topotecan therapy, as evidenced by the lack of progressively

Suspected or documented infections proximate to grade 4 neutropenia were associated with 6.5% of courses, with sepsis reported in 1.1% of courses. Topotecan induced myelosuppression was considered related to the death of three patients (0.7%).

Hematologic toxicity is summarized below in 445 ovarian patients and 2019 courses following topotecan administration.

Table Grade 3 or 4 Hematologic Toxicities Reported In Patients With Recurrent Ovarian Carcinoma (Studies 012, 033, 034, 039 Randomized, And 039 Alternate)

Topotecan Daily Times 5 Regimen	Patients	Courses
Toxicity	n = 445	n = 2019
G4 Neutropenia	349/439 (79.5)	829/1982 (41.8)
G4 Thrombocytopenia	103/439 (23.4)	173/1997 (8.7)
G3/G4 Anemia	162/440 (36.8)	309/1997 (15.5)
Fever or Infection w/ G4 Neutropenia	92/445 (20.7)	131/2019 (6.5)
Sepsis	21/445 (4.7)	22/2019 (1.1)
Death attributed to Myelosuppression	3/445 (0.7)	--

Interventions for toxicity in the combined ovarian population were relatively infrequent. In 2019 courses of topotecan treatment, prophylactic G-CSF was administered in 19% of courses, and treatment G-CSF was administered in 7% of courses. RBC and platelet transfusions were administered in 23% and 4% of courses, respectively. Systemic antibiotics (including prophylactic and empirical use) were given in 17% of courses.

In the phase III study comparing topotecan daily times five regimen with paclitaxel 175 mg/m2/3 hours, the hematologic toxicity profile of topotecan was similar to the overall ovarian population; the paclitaxel regimen used in that study was less myelosuppressive than the topotecan regimen.

Hematologic toxicity observed with topotecan daily times five regimen in patients with colorectal or small cell lung cancer was qualitatively similar to the toxicity reported in patients with recurrent ovarian cancer. In Study 011, Grade 4 neutropenia was reported in 34% of courses, and grade 4 thrombocytopenia in 0.3% of courses. In Study 014, 47% of courses were associated with grade 4 neutropenia and 11% were associated with grade 4 thrombocytopenia. Sepsis was reported as related to the death of one patient within 30 days of topotecan administration in Study 014.

Non-Hematologic Toxicities

Non-hematologic toxicities reported in Phase I and later trials were represented as WHO preferred terms and assigned a CTC grade. Toxicities reported were relatively mild and consistent across Phase I trials. Patients treated with

topotecan at doses ranging from 0.5 to 1.5 mg/m2 reported frequent incidences of grade 1 and 2 nausea and vomiting and alopecia.

In the combined ovarian population of 445 patients and 2019 courses, non-hematologic toxicities were reported in 99% of patients. The majority of non-hematologic toxicities reported were mild, and consistent with toxicities reported in Phase I trials. In general, these toxicities occurred early and did not interfere with further treatment.

The most frequently reported toxicities were related to the gastrointestinal system, including nausea and vomiting. Prophylactic anti-emetics were not mandated in any studies, accounting for the relatively high incidence, however these toxicities were generally mild and not dose-limiting. Diarrhea of grade 3/4 severity was reported in only 2% of courses. Other frequently reported toxicities included alopecia, fatigue, fever (possibly associated with infection or suspected infection), sepsis and documented infection. These data are summarized below.

Table Non-Hematologic Toxicities Reported In > 20% Of Patients And Severe Non-Hematologic Toxicities Reported In > 2% Of Patients With Recurrent Ovarian Carcinoma (Studies 012, 033, 034, 039 Randomized, And 039 Alternate)

Non-Hematologic Preferred Term	Total G1 - G4 %Patients / % Courses	Total G3 or G4 % Patients / % Courses
Nausea	74.8) / (50.7)	(9.0) / (2.7)
Alopecia	(59.3) / (64.4)	n/a
Vomiting	(55.5) / (27.3)	(7.0) / (1.7)
Diarrhea	(39.3) / (19.0)	(4.9) / (1.2)
Constipation	(37.8) / (19.4)	(3.1) / (0.8)
Fatigue	(36.2) / (24.7)	(5.2) / (1.7)
Fever	(31.9) / (14.0)	(1.6) / (0.3)
Abdominal Pain	(30.1) / (13.1)	(4.5) / (1.3)
Stomatitis	(22.9) / (9.7)	(2.0) / (0.5)
Aesthenia	(18.9) / (10.0)	(3.6) / (1.1)
Dyspnea	(18.7) / (9.0)	(3.6) / (1.2)
Malaise	(9.0) / (3.7)	(2.2) / (0.6)
Intestinal Obstruction	(6.5) / (1.8)	(4.3) / (1.1)
Infection	(6.5) / (2.0)	(2.7) / (0.6)
Sepsis	(4.7) / (1.1)	(3.6) / (0.8)
Hyperbilirubinemia	(3.8) / (1.5)	(2.5) / (0.8)

In the Phase III randomized study, non-hematologic toxicities reported in patients treated with topotecan were similar to the overall ovarian population; GI

toxicities and alopecia were most prevalent, followed by fatigue, fever and asthenia. In patients treated with paclitaxel, GI toxicities were also the most frequently reported, but patients treated with paclitaxel experienced more arthralgia, myalgia, paresthesia and peripheral neuropathy than patients treated with topotecan.

In the Phase II studies of topotecan daily times five regimen in patients with colorectal and small cell lung cancer, non-hematalogic toxicities were similar to the ovarian population, and included frequent reports of nausea, vomiting, fatigue, asthenia, and malaise.

Adverse Event per course	#	per cent
ALOPECIA	1118	77.59%
NAUSEA	680	47.19%
VOMITING	396	27.48%
FATIGUE	344	23.87%
CONSTIPATION	264	18.32%
DIARRHEA	243	16.86%
ABDOMINAL PAIN	218	15.13%
AESTHENIA	182	12.63%
FEVER	162	11.24%
STOMATITIS	150	10.41%
DYSPNEA	147	10.20%
HEADACHE	132	9.16%
HEMATURIA	112	7.77%
ANOREXIA	104	7.22%
PHOSPHATASE ALKALINE INCREASED	102	7.08%
PARESTHESIA	77	5.34%

Adverse Event per patient	#	per cent
ALOPECIA	237	85.87%
NAUSEA	216	78.26%
VOMITING	160	57.97%
DIARRHEA	126	45.65%
CONSTIPATION	120	43.48%
FATIGUE	104	37.68%
ABDOMINAL PAIN	102	36.96%
FEVER	98	35.51%
STOMATITIS	84	30.43%
DYSPNEA	63	22.83%
HEADACHE	63	22.83%

AESTHENIA	62	22.46%
ANOREXIA	52	18.84%
ARTHRALGIA	49	17.75%
PARESTHESIA	47	17.03%
HEMATURIA	44	15.94%
PHOSPHATASE ALKALINE INCREASED	44	15.94%
COUGHING	42	15.22%
PAIN	40	14.49%
DYSPEPSIA	39	14.13%
MYALGIA	39	14.13%
BACK PAIN	38	13.77%
RASH	35	12.68%
UPPER RESP TRACT INFECTION	33	11.96%
URINARY TRACT INFECTION	32	11.59%
HYPOKALEMIA	31	11.23%
ANXIETY	30	10.87%
FLUSHING	30	10.87%
MALAISE	29	10.51%
PRURITUS	29	10.51%
HYPOMAGNESEMIA	27	9.78%
ALBUMINURIA	26	9.42%
INTESTINAL OBSTRUCTION	26	9.42%
SGPT INCREASED	24	8.70%
HYPERGLYCEMIA	23	8.33%
PHARYNGITIS	23	8.33%
ALBUMIN GLOBULIN RATIO ABNORMAL	22	7.97%
DIZZINESS	22	7.97%
BLOOD UREA NITROGEN INCREASED	21	7.61%
INFECTION	21	7.61%
HYPOPHOSPHATEMIA	20	7.25%
SKELETAL PAIN	20	7.25%
NPN INCREASED	19	6.88%
SGOT INCREASED	19	6.88%
ASCITES	18	6.52%
DEPRESSION	18	6.52%
EPISTAXIS	18	6.52%
INSOMNIA	18	6.52%
RASH ERYTHEMATOUS	18	6.52%

TASTE PERVERSION	18	6.52%
EDEMA DEPENDENT	17	6.16%
HYPOCALCEMIA	17	6.16%
HYPONATREMIA	17	6.16%
NEUROPATHY PERIPHERAL	17	6.16%
SOMNOLENCE	17	6.16%
HYPOPROTEINEMIA	16	5.80%
BILIRUBINEMIA	15	5.43%
RHINITIS	15	5.43%
RIGORS	15	5.43%
FLATULENCE	14	5.07%

1.5. Serious Adverse Experiences

The SmithKline Beecham definition of a serious adverse experience is any adverse experience that is fatal, life-threatening, permanently or temporarily disabling or incapacitating, or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition, any experience that the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug is reported as a serious event. Patients who were hospitalized for transfusions were considered to experience a serious adverse event by company definition.

There were a total of 1,276 patients treated with topotecan in Phase I and Phase II/III studies. Serious adverse experiences were reported from the SB Clinical database for two Phase I studies (010 and 017), four Phase II/III ovarian cancer studies (012, 033, 034 and 039) and one breast cancer study (030). Serious adverse experiences from the remaining studies were derived from the SB Adverse Experience Gathering Information System (AEGIS) database.

A total of 131 patients were treated in four intravenous Phase I studies (004, 005, 010, and 017). A total of 149 occurrences of serious adverse experiences were reported in 63 patients (48.1%); 103 related or possibly related occurrences were reported in 50/131 (38.2%) patients. An additional 37 patients were treated in one oral Phase I study (049). A total of 50 occurrences of serious adverse experiences were reported in 18/37 patients (48.6%); 36 occurrences in 12/37 (32.4%) patients were considered related. Hematologic toxicities were the most frequently reported serious adverse experiences in the four intravenous Phase I studies, and non-hematologic toxicities were the most frequently reported serious adverse experiences in the oral Phase I study.

A total of 1,108 patients were treated with topotecan in Phase II/III studies. A total of 1,204 occurrences of serious adverse experiences were reported in 434

patients (39.2%); 679 occurrences of related or possibly related serious adverse experiences were reported in 270/1,108 (24.4%). These data are displayed by patient population **below :**

Table : Serious Adverse Experiences For Phase II/III Studies

	Patient Population		Patients with SAEs		Related SAEs*
	n	(%)	n	(%)	
Ovarian Daily x 5	445	189	(42.5)	130	(29.2)
Non-Ovarian Daily x 5	485	163	(33.6)	110	(22.7)
Breast	34	6	(17.6)	4	(11.8)
CIV	144	76	(52.8)	26	(18.1)
Total All Phase II/III Studies	1,108	434	(39.2)	270	(24.4)

*Includes patients with related or possibly related SAEs.

A comparison of the most frequently reported serious adverse experiences in the ovarian daily times five population versus the non-ovarian daily times five population is presented **below**. The percentages of patients with hematologic toxicities were similar in the two populations, with slightly higher percentages of patients that reported anemia, febrile neutropenia and fever in the ovarian population. The percentage of patients with serious gastrointestinal adverse experiences in the ovarian population were at least three times greater than the percentages reported in the non-ovarian population.

Table : Most Frequently Reported* Serious Adverse Experiences In The Ovarian And Non-Ovarian Daily Times Five Populations

Serious Adverse	Patients with SAEs				Patients with Related** SAEs			
Experience by	Ovarian		Non-Ovarian		Ovarian		Non-Ovarian	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Granulocytopenia	43	(9.7)	35	(7.2)	43	(9.7)	34	(7.0)
Thrombocytopenia	37	(8.3)	39	(8.0)	36	(8.1)	38	(7.8)
Anemia	34	(7.6)	23	(4.7)	33	(7.4)	22	(4.5)
Febrile Neutropenia	31	(7.0)	22	(4.5)	28	(6.3	22	(4.5)
Fever	30	(6.7)	12	(2.5)	21	(4.7)	7	(1.4)
Leukopenia	18	(4.0)	20	(4.1)	18	(4.0)	19	(3.9)
Sepsis	17	(3.8)	13	(2.7)	14	(3.1)	9	(1.9)
Vomiting	22	(4.9)	8	(1.6)	12	(2.7)	3	(0.6)
Nausea	15	(3.4)	6	(1.2)	11	(2.5)	3	(0.6)
Diarrhea	13	(2.9)	3	(0.6)	9	(2.0)	1	(0.2)

*>2% patients reporting related or possibly related serious adverse experiences in the ovarian daily x 5 population.

**Includes patients with related or possibly related SAEs.

Integrated Summary of Non-hematologic Adverse Events in Studies 034 and 039

Non-Hematologic Adverse Events per Patient

	Mean	Std. dev.	Min	Max	Sum	# of patients	# of courses
Total	25.78	20.52	1	202	7055	275	1261

Adverse Events =Grade 3

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses	per cent
Total	2.60	2.16	1	15	326	124	45.1%	173	13.7%

Adverse Events = Grade 4

	Mean	Std. dev.	Min	Max	Sum	# of patients	per cent	# of courses	per cent
Total	1.65	1.09	1	6	71	44	16.0%	54	4.3%

Significant Adverse Events Experienced by > 2% of Patients in Ovarian Cancer Patients Studies 034 and 039

Adverse Event	N	%
NAUSEA	23	15.44
VOMITING	21	14.09
DIARRHEA	15	10.07
DYSPNEA	15	10.07
ABDOMINAL PAIN	13	8.72
FEVER	13	8.72
FATIGUE	11	7.38
ASTHENIA	11	7.38
INTESTINAL OBSTRUCTION	11	7.38
BILIRUBINEMIA	9	6.04
CONSTIPATION	8	5.37
ANEMIA	7	4.70

STOMATITIS	6	4.03
MALAISE	6	4.03
ANOREXIA	5	3.36
SEPSIS	5	3.36
EMBOLISM PULMONARY	5	3.36
HEADACHE	4	2.68
PAIN	4	2.68
INFECTION	4	2.68
THROMBOPHLEBITIS DEEP	4	2.68

1.6. Adverse Experiences Leading to Withdrawal

For daily times five ovarian studies, withdrawals data were tabulated from the Study Conclusion page as reconciled with the specific adverse experience(s) leading to withdrawal from the adverse experience page(s) of Case Report Forms. For daily times five (non-ovarian) and other studies, withdrawals data were tabulated solely from the adverse experience page(s) "drug stopped" field of Case Report Forms.

A total of 14/131 (10.7%) patients treated with topotecan in four Phase I intravenous studies (004, 005, 010, 017) were withdrawn due to adverse experiences. An additional 10/34 (29.4%) in a single ongoing Phase I Oral study (049) were also withdrawn due to adverse experiences. In 21 reported/ongoing Phase II/III Studies, the majority of patients were treated on a Daily Times Five Regimen (combined ovarian studies 012, 033, 034, and 039); combined non-ovarian daily times five studies (011, 013, 014 EORTC, 014 SB, 015, 032, 053 and 090). Other Phase II/III regimens include two breast cancer studies (030 and 046) and seven continuous intravenous infusion studies (051, 052, 056, 057, 059, 060 and 061). Of 1060 patients treated in Phase II/III studies for whom data is available, 89/1060 (8.4%) were withdrawn due to adverse experiences.

The most prevalent adverse experiences leading to withdrawal in the Phase I intravenous studies were hematologic toxicities and associated infections. The majority of these toxicities were classified as serious and considered related to topotecan. Of the 14/131 (10.7%) patients withdrawn, 10 were withdrawn due to hematologic toxicity/infective complications including one due to sepsis resulting in death. In the single ongoing Phase I Oral study (049), withdrawals were associated with non-hematologic toxicities, predominantly gastrointestinal.

The most prevalent adverse experiences leading to withdrawal in the Phase II/III studies were also hematologic toxicities and associated infections. In the combined ovarian studies 18/445 (4.0%) patients were withdrawn from study due to hematologic toxicities/infective complications including four patients with infection (one resulting in death), four with sepsis (two resulting in death), and

two with febrile neutropenia. In the non-ovarian daily times five studies 18/438 (4.1%) patients were withdrawn due to hematologic toxicities/infective complications including seven patients with infection including pneumonia (two resulting in death); six with sepsis (five resulting in death) and two with febrile neutropenia (one resulting in death). The number of withdrawals due to adverse experience in the daily times five combined ovarian population and in the daily times five non-ovarian population is summarized below. In the continuous intravenous infusion studies 5/143 (3.5%) patients were withdrawn due to hematologic toxicities/infective complications including one patient with infection, one with sepsis resulting in death and one with febrile neutropenia. Aesthenia comprised a majority of the non-hematologic withdrawals in the daily times five regimen (1.1%), but was less of a factor in the combined ovarian population (0.2%), and was not reported as a reason for withdrawal in Study 039 or the 21-day continuous intravenous infusion regimen.

Table: Patients Withdrawn From Daily Times Five Ovarian And Non-Ovarian Studies

Topotecan Study	Daily Times 5 (Ovarian)		Daily Times 5 (Non-Ovarian)	
	N=445	%	N=438	%
Patients with AEs leading to Withdrawal	35	7.9	39	8.9
Patients Withdrawn for Serious AEs	23	5.2	32	7.4
Patients Withdrawn for Related/Possibly Related AEs	23	5.2	28	6.4

In the randomized Study 039, the primary reason for withdrawal in patients randomized to paclitaxel was related neurotoxicity as opposed to related hematologic toxicities and associated infection in patients randomized to topotecan.

1.7. Deaths

Data is available from the 1,276 patients treated with topotecan in Phase I and Phase II/III studies. Deaths were reported for two Phase I studies (010 and 017), four Phase II/III ovarian studies (012, 033, 034 and 039) and one breast study (030) from data on the SB Clintrials database. Deaths from the remaining studies which included studies not yet reported were derived from the SB Adverse Experience Gathering Information System (AEGIS) database. Deaths were categorized into four categories: Progressive Disease (PD), Hematologic Toxicity (including sequelae, such as infection), Non-hematologic Toxicity, and Other. Patients were categorized into the "Other" category if their death was not associated with progressive disease or toxicity. Patients may have been classified into two categories if there was a contribution from both.

Deaths were reported in 40/131 patients (30.5 %) treated in four intravenous Phase I studies (004, 005, 010, and, 017). An additional 37 patients were treated in one oral Phase I study (049); deaths were reported in six patients (16.2%). Four of the 46 deaths were associated with hematologic toxicity; two were considered related (pneumonia with neutropenia). Two patients' deaths were attributed to both progressive disease and sepsis; one associated with neutropenia and considered related occurred within 30 days of the last dose of study medication. These deaths are summarized below.

Table : Summary Of Deaths Reported In Topotecan Phase I Studies

Study	005	017	010	004	049	Total
Regimen	Daily x 5 q 21 days	Daily x 5 with cisplatin q 21 days	30 min infusion q 21 days	24 hour infusion q 7 days	Oral	
# of Patients	48	15	42	26	37	168
# of Deaths	10 (20.8%)	6 (40.0%)	22 (52.4%)	2 (7.7%)	6 (16.2%)	46 (27.4%)
Deaths < 30 days	9 (18.8%)	2 (13.3%)	1 (2.4%)	1 (3.8%)	4(10.8%)	17 (10.1%)
Prog.Dis.	8 (16.7%)	5 (33.3%)	21 (50.0%)	2 (7.7%)	4 (10.8%)	40 (23.8%)
Hematol.Tox	2 (4.2%)	1 (6.7%)	0 (0.0 %)	0 (0.0 %)	1 (2.7 %)	4 (2.4 %)
Prog.Dis. & Hem.Tox.	0 (0.0 %)	0 (0.0 %)	1 (2.4 %)	0 (0.0 %)	1 (2.7 %)	2 (1.2 %)
Related Deaths	1 (2.1 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	2 (5.4%)	3 (1.8 %)

*Death due to progressive disease and sepsis.

**Death due to progressive disease and sepsis with neutropenia.

A total of 1,108 patients were treated with topotecan in Phase II/III studies; deaths were reported for 335 patients (30.2%). The majority of the deaths were attributed to progressive disease (296/335, 88.4%). Hematologic toxicity was associated with death in 15 patients (1.4 %), and to both progressive disease and hematologic toxicity in three additional patients (0.3%).

Deaths that were reported in Phase II/III studies are summarized below. Related or possibly related deaths were reported in 21/1108 patients (1.9%) treated with topotecan. Twelve of the 21 related deaths were associated with hematologic toxicity; eight due to sepsis with neutropenia, two due to pneumonia with neutropenia and two due to neutropenia. Three additional related/possibly related deaths were due to both progressive disease and hematologic toxicity (pneumonia with neutropenia). One death was due to both progressive disease and possibly related GI bleed from tumor. Four of the deaths, considered possibly related, were due to other reasons (pulmonary embolism, sudden death, myocardial infarction, and ischemic ulcerative bowel syndrome). The reason for death was not provided in one patient treated on a compassionate use study (032); however, relationship to topotecan could not be ruled out.

In patients with ovarian cancer treated with topotecan on the daily times five regimen, death was considered possibly related or related to topotecan treatment in four patients (0.9%); three of the deaths were associated with complications of neutropenia. The incidence (3.3%, 16/485) was higher in patients with other tumor types treated on the same regimen; 15 of 16 related deaths were reported in patients with small cell lung cancer (3.1%). Nine of these deaths were reported in one study (014 SB) which is currently ongoing. The incidence of deaths reported in all other studies is consistent with the ovarian population. It has not been fully determined why there should be such an atypically higher number of deaths in this study, however, adverse prognostic factors in this population may be responsible.

Table : Summary Of Deaths Reported In Topotecan Phase II/III Studies

Regimen	Daily x5 q 21 days OVARIAN	Daily x5 q 21 days NON-OVARIAN	Continuous Infusion Other tumors	Other regimens BREAST	TOTAL
# of Patients	445	485	144	34	1108
# of Deaths	111 (24.9%)	185 (38.1%)	37(25.7%)	2(5.9%)	335(30.2%)
Deaths < 30 days	29 (6.5%)	56 (11.5%)	19 (13.2 %)	2 (5.9 %)	106 (9.6%)
Prog.Dis.	100 (22.5%)	161 (33.2 %)	33 (22.9%)	2 (5.9%)	296 (26.7%)
Hematol.Tox	4 (0.9%)	10 (2.1%)	1 (0.7%)	0 (0.0%)	15 (1.4 %)
Prog.Dis. & Hem.Tox.	0 (0.0%)	3 (0.6 %)*	0 (0.0%)	0 (0.0%)	3 (0.3 %)
Prog. Dis. & other reasons	0 (0.0%)	0 (0.0%)	1 (0.7%)**	0 (0.0%)	1 (0.1 %)
Other reasons+	7 (1.6 %)	11 (2.3 %)	2 (1.4%)	0 (0.0%)	20 (1.8 %)
Related Deaths	4 (0.9 %)	16 (3.3 %)	1 (0.7 %)	0 (0.0%)	21 (1.9 %)

*Deaths due to progressive disease and pneumonia with neutropenia.

**Death due to both progressive disease and GI bleed.

+Other reasons include not specified.

10.0 Four Month Safety Update

10.1 Background

The hematologic and non-hematologic toxicity profile of topotecan was fully evaluated in four Phase II/III studies of ovarian cancer (012, 033, 034 and 039 randomized). Data was presented in the previous Integrated Summary of Safety for 445 patients and 2019 courses up to June 20, 1995. For this present Safety Update, seven additional patients and 356 courses of treatment were available as of the November 20, 1995 clinical cut-off. Therefore, data from 452 patients and 2375 courses have been assessed, representing an increase of 1.6% in the number of patients and an increase of 17.6% in the number of courses.

An update is also provided on serious adverse events, deaths and withdrawals for all studies. Data is provided on a total of 1,408 patients, which represents an addition of 132 patients, or an increase of 10.3%, relative to the 1,276 patients included in the NDA.

Overall Extent of Exposure

There were no major differences between the present Safety Update and the previous Integrated Summary of Safety. A brief comparison of course data from the present Safety Update to that of the previous Integrated Summary of Safety is presented in Table 1 for patients with recurrent ovarian cancer.

Following a treatment course, toxicity grades were reviewed and the dose for the next course was reduced by 0.25 mg/m2/day, delayed or G-CSF used, according to the observed hematologic or non-hematologic toxicity. The single infusion dose could also be escalated by 0.25 mg/m2/day if, during the previous course, there was no toxicity greater than grade 2.

There was a similar number of courses administered at the starting dose of 1.5 mg/m2/day. The percentage of courses delayed or reduced remained constant. For both reporting periods the median number of courses administered was 4 (range 1-33). Presently, the reported dose intensity is 2.37 mg/m2/week as compared 2.39 mg/m2/week in the previous Integrated Summary of Safety.

Table 1: Courses of Topotecan with Dose Delays, Reductions, and G-CSF Administration in Patients with Recurrent Ovarian Cancer

	Data from November 20, 1995 Clinical-Cutoff	Data from June 20, 1995 ClinicalCutoff
Total Number of Courses	n=2375	n=2019
	n (%)	n (%)
Number Courses at 1.5 mg/m2/day	1899 (79 9)	1673 (82.8)
Dose Delays*	440/1923 (22 9)	368/1574 (23 4)
Dose Reductions*	123/1923 (6 4)	100/1574 (6.4)
G-CSF Administered Prophylactically	525 (22 1)	388 (19.2)

* Based on the number of courses after course 1

After the first course of topotecan, retreatment commenced within five days of the scheduled start dates in 77% of courses for both reporting periods. For both the present and previous Safety Summaries, only 5% of courses were delayed by more than 7 days. In the present and previous safety summaries, G-CSF was used prophylactically in 22% and 19% of treatment courses, respectively.

One hundred and twenty five additional non-ovarian patients (enrolled in studies other than ovarian cancer studies 012, 033, 034 and 039), have been exposed to topotecan since the data supplied in the NDA. The number of patients (956) exposed to topotecan using various dosing regimens for their reporting period is presented in Table 2.

Table 2: Number of Non-Ovarian Cancer Patients Exposed to Topotecan

		Safety Update	NDA
		Data from November 20, 1995 Clinical-Cutoff	Data from June 20, 1995 Clinical Cutoff
Clinical Study	Treatment Regimen	Number of Patients	Number of Patients
004, 005, 010, 017	Phase I	131	131
011, 013, 014 (SB/EORTC), 015, 032, 053, 090	Daily Times 5 Days IV q 21 Days (non-ovarian)	534	455
051, 052, 056, 057, 059, 060, 061	21-Day continuous IV q 28 Days	200	144
030, 046	24-Hour Infusion q 7 Days	34	34
049	Oral MTD	57	37

10.2 Drug-related Adverse Events

All toxicities were reported as grades according to the modified Common Toxicity Criteria (CTC) of the National Cancer Institute. Hematologic and non-hematologic toxicities were examined for 452 patients and 2375 courses in three Phase II and one Phase III study which assessed topotecan 1.5 mg/m2 daily times five regimen in patients with advanced ovarian carcinoma.

Hematologic Toxicities

White blood cell, neutrophil, platelet and hemoglobin counts were evaluated to assess the hematologic toxicity of topotecan. The incidence of toxicity by patients and by course was tabulated. Time to onset and duration of severe toxicity, hematologic nadir, and infective complications were also examined.

In the combined ovarian population of 452 patients, hematologic toxicities observed with topotecan daily times five regimen were reversible, non-cumulative and manageable. Severe hematologic toxicities for patients and courses during both reporting periods are summarized in Table 3.

Table 3: Grade 3 or 4 Hematologic Toxicities Reported In Patients With Recurrent Ovarian Carcinoma (Studies 012, 033, 034, 039 Randomized, And 039 Alternate)

	Safety Update		NDA	
	Data from November 20, 1995 Clinical Cutoff		Data from June 20, 1995 Clinical Cutoff	
Topotecan Daily Times 5 Regimen Toxicity	Patients n=452	Courses n=2375	Patients n = 445	Courses n = 2019
G4 Neutropenia	362/446 (81.2)	921/2331 (39.5)	349/439 (79.5)	829/1982 (41.8)
G4 Thrombocytopenia	114/447 (25.5)	201/2345 (8.6)	103/439 (23.4)	173/1997 (8.7)
G3/G4 Anemia	179/447 (40.0)	369/2345 (15.7)	162/440 (36.8)	309/1997 (15.5)
Fever or Infection w/ G4 Neutropenia	96/452 (21.2)	140/2375 (5.9)	92/445 (20.7)	131/2019 (6.5)
Sepsis	23/452 (5.1)	24/2375 (1.0)	21/445 (4.7)	22/2019 (1.1)
Death attributed to Myelosuppression	3/452 (0.7)	-	3/445 (0.7)	-

No major differences were noted in a comparison of hematologic toxicities during both reporting periods. Grade 4 neutropenia was the most frequently reported toxicity. The occurrence rate for patients and courses was similar and was most prevalent during course 1 of therapy before dose reductions or G-CSF use was instituted. Rates of grade 4 thrombocytopenia were also comparable for both reporting periods. Grade 3 or grade 4 anemia was reported by 40% of patients as compared to 37% of patients in the NDA.

The median nadir day for neutrophils, platelets and hemoglobin (Days 11, 15, 15, respectively) was the same as previously reported. Median duration of severe toxicity was, again, reported as one week or less; grade 4 neutropenia lasting longer than one week was associated with approximately 11% (259/2375) as opposed to 12% (248/2019) of total courses administered. Sequelae of hematologic toxicities were infrequent. Suspected or documented infections proximate to grade 4 neutropenia were similar. They are presently associated with 5.9% of courses and previously with 6.5% of courses. The occurrence rate of sepsis remained constant, approximately 1.0% of courses. There were no additional deaths related to myelosuppression reported for the present Update. Topotecan induced myelosuppression was considered related to the death of three patients (0.7%) in the previous Safety Summary.

Interventions for toxicity in the combined ovarian population were relatively infrequent. In 2375 courses of topotecan treatment, prophylactic and treatment G-CSF was administered in 22% and 7% of courses as compared to 19% and 7% (2019 courses). RBC and platelet transfusions were administered in 23% and 4% of courses, respectively. Antibiotic usage did not change considerably. Systemic antibiotics (including prophylactic and empiric use) were given in approximately 18% of courses during both reporting periods. The use of IV antibiotics also remained similar for both reporting periods. This occurred in

approximately 23% of patients and 6% of courses for this reporting period. These data are presented for comparison in Table 4.

Table 4: Antibiotic Usage Reported In Patients With Recurrent Ovarian Carcinoma (Studies 012, 033, 034, 039 Randomized, And 039 Alternate)

Antibiotic Usage	Data from November 20, 1995 Clinical Cutoff (Safety Update)		Data from June 20, 1995 Clinical Cutoff (NDA)	
Topotecan Daily Times 5 Regimen	Patients	Courses	Patients	Courses
	n=452	n=2375	n = 445	n = 2019
Systemic Antibiotics*	229 (50.7)	420 (17.7)	220 (49.4)	379 (18.8)
IV Antibiotics**	103 (22.8)	140 (5.9)	97 (21.8)	122 (6.0)
IV Antibiotics w/Gr2 Fever/Infection or Sepsis**	71 (15.7)	77 (3.2)	67 (15.1)	71 (3.5)

Data Source: Safety Update Appendix 4.2.d and ISS Appendix 4.2.d.1

*Slight differences in systemic antibiotic use are due to the inclusion of patients and courses from Protocol 012 in the Safety Update. This protocol was not included in the total count for the NDA.

**Does not include Protocol 012 as route of administration was not collected.

Non-Hematologic Toxicities

Non-hematologic toxicities reported in Phase II/III were represented as WHO preferred terms and assigned a CTC grade.

In the combined ovarian population of 452 patients and 2375 courses, non-hematologic toxicities were reported in 99% of patients. The majority of non-hematologic toxicities were of mild or moderate intensity, and the reported rates of occurrence were consistent with those reported in the previously submitted Integrated Safety Summary.

The most frequently reported toxicities were related to the gastrointestinal system, including nausea and vomiting. Prophylactic anti-emetics were not mandated in any studies, which may have contributed to the relatively high incidence, however these toxicities were generally mild or moderate and not dose-limiting. The occurrence rate of grade 3/4 diarrhea remained unchanged, being reported in approximately 1% of courses. A comparison of other frequently reported toxicities to that which had been previously reported is summarized in Table 5.

Table 5: Non-Hematologic Toxicities Reported In > 20% Of Patients And Severe Non-Hematologic Toxicities Reported In > 2% Of Patients With Recurrent Ovarian Carcinoma (Studies 012, 033, 034, 039 Randomized, And 039 Alternate)

	Data from November 20, 1995 Clinical Cutoff Safety Update		Data from June 20, 1995 Clinical Cutoff NDA	
Non-Hematologic Toxicity (Preferred Term)	Total G1-G4 Percent Pts / Crs	Total G3 or G4 Percent Pts / Crs	Total G1-G4 Percent Pts / Crs	Total G3 or G4 Percent Pts /Crs
Nausea	(77.2) / (50.4)	(10.4) / (2.7)	(74.8) / (50.7)	(9.0) / (2.7)
Alopecia	(58.8) / (61.6)	n/a	(59.3) / (64.4)	n/a
Vomiting	(57.5) / (26.4)	(8.6) / (1.9)	(55.5) / (27.3)	(7.0) / (1.7)
Diarrhea	(41.8) / (18.8)	(5.3) / (1.2)	(39.3) / (19.0)	(4.9) / (1.2)
Constipation	(38.9) / (18.4)	(3.3) / (1.0)	(37.8) / (19.4)	(3.1) / (0.8)
Fatigue	(37.4) / (24.7)	(5.5) / (1.6)	(36.2) / (24.7)	(5.2) / (1.7)
Fever	(33.6) / (13.2)	(1.8) / (0.3)	(31.9) / (14.0)	(1.6) / (0.3)
Abdominal Pain	(33.2) / (13.4)	(5.5) / (1.3)	(30.1) / (13.1)	(4.5) / (1.3)
Stomatitis	(23.5) / (9.1)	(2.2) / (0.5)	(22.9) / (9.7)	(2.0) / (0.5)
Asthenia	(21.0) / (9.6)	(4.0) / (1.1)	(18.9) / (10.0)	(3.6) / (1.1)
Headache	(20.6) / (7.7)	(1.3) / (0.4)	(19.3) / (7.7)	(1.1) / (0.3)
Dyspnea	(19.9) / (9.0)	(3.8) / (1.1)	(18.7) / (9.0)	(3.6) / (1.2)
Urinary Tract Infection	(15.0) / (4.6)	(2.0) / (0.5)	(13.3) / (4.7)	(1.6) / (0.4)
Pain	(12.8) / (5.9)	(2.2) / (0.7)	(11.2) / (5.8)	(2.0) / (0.7)
Malaise	(10.2) / (4.3)	(2.4) / (0.6)	(9.0) / (3.7)	(2.2) / (0.6)
Intestinal Obstruction	(7.3) / (1.8)	(4.9) / (1.1)	(6.5) / (1.8)	(4.3) / (1.1)
Infection	(7.3) / (1.9)	(3.1) / (0.6)	(6.5) / (2.0)	(2.7) / (0.6)
Sepsis	(5.1) / (1.0)	(3.8) / (0.8)	(4.7) / (1.1)	(3.6) / (0.8)
Bilirubinemia	(4.0) / (1.3)	(2.7) / (0.7)	(3.8) / (1.5)	(2.5) / (0.8)
Thrombophlebitis Deep	(2.7) / (0.7)	(2.0) / (0.5)	(2.2) / (0.7)	(1.8) / (0.5)

10.3 Serious Adverse Events

The SmithKline Beecham definition of a serious adverse experience is any adverse experience that is fatal, life-threatening, permanently or temporarily disabling or incapacitating, or results in hospitalization, prolongs a hospital stay or is associated with congenital abnormality, cancer or overdose (either accidental or intentional). In addition, any experience that the investigator regards as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug is reported as a serious event. Patients who were hospitalized for transfusions were considered to experience a serious adverse event by company definition.

Serious adverse experiences were reported from the SB Clintrial database for the safety update as were four intravenous Phase I studies (004, 005, 010, 017),

four Phase II/III ovarian cancer studies (012, 033, 034 and 039) and one breast cancer study (030) for the NDA. The remaining studies in the NDA were reported from the SB Adverse Experience Gathering Information System (AEGIS) database.

A total of 131 patients were treated in four intravenous Phase I studies (004, 005, 010, and 017). There is no additional data to report for these studies. Since June 20, 1995, 20 additional patients were treated with topotecan in the oral Phase I study (049), bringing the total treated to 57. A total of 71 occurrences of serious adverse experiences were reported in 24/57 patients (42.1%) as compared to 50 occurrences that were reported in 18/37 patients (48.6%) in the NDA. Forty-six occurrences in 15/57 patients (26.3%) were considered related or possibly related to topotecan as compared to 36 occurrences in 12/37 (32.4%) patients in the NDA. Non-hematologic toxicities were the most frequently reported serious adverse experiences in the oral Phase I study.

For the safety update, a total of 1,220 patients were treated with topotecan in Phase II/III studies as of November 20, 1995 as compared to 1,108 that were treated as of June 20, 1995 and presented in the NDA. A total of 1,518 occurrences of serious adverse experiences were reported in 503 patients (42.1%) as compared to 1,204 occurrences reported in 434/1,108 (39.2%) patients in the NDA. There was no additional data provided for the breast studies (030 and 046). These data are displayed by patient population in Table 6.

Table 6: Serious Adverse Experiences For Phase II/III Studies

Patient Population	Safety Update		NDA	Patients with SAE's		
	Total Patients Nov 20, 95	Add'l Patients	Total Patients Jun 20 95	Safety Update Nov 20, 95 n (%)	Safety Update Add'l Patients	NDA Jun 20, 95 n (%)
Ovarian Daily x 5	452	7	445	202 (44.7)	13	189 (42.5)
Non-Ovarian Daily x 5	534	49	485	200 (37.5)	37	163 (33.6)
Breast	34	0	34	6 (17.6)	0	6 (17.6)
CIV	200	56	144	95 (47.5)	19	76 (52.8)
Total Phase II/III Studies	1,220	112	1,108	503 (41.2)	69	434 (39.2)

There were 812 occurrences of related or possibly related serious adverse experiences reported in 300/1,220 (24.6%) patients as compared to 679 occurrences of related or possibly related occurrences that were reported in

270/1,108 (24.2%) patients in the NDA. These data are displayed by patient population in Table 7.

Table 7: Related or Possibly Related Serious Adverse Experiences For Phase II/III Studies

Patient Population	Safety Update		NDA	Patients with Related SAEs*		
	Total Patients Nov 20, 95	Add'l Patients	Total Patients Jun 20, 95	Safety Update Nov 20, 95 n (%)	Add'l Patients	NDA Jun 20, 95 n (%)
Ovarian Daily x 5	452	7	445	138 (30.5)	8	130 (29.2)
Non-Ovarian Daily x 5	534	49	485	124 (23.2)	14	110 (22.7)
Breast	34	0	34	4 (11.8)	0	4 (11.8)
CTV	200	56	144	34 (17.0)	8	26 (18.1)
Total Phase II/III Studies	1,220	112	1,108	306 (24.6)	30	270 (24.4)

*Includes patients with related or possibly related SAEs.

A comparison of the most frequently reported serious adverse experiences in the ovarian daily times five population versus the non-ovarian daily times five population is presented in Table 8. The percentages of patients with hematologic toxicities were similar in the two populations, with slightly higher percentages of patients that reported anemia, febrile neutropenia and fever in the ovarian population. The percentage of patients with serious gastrointestinal adverse experiences in the ovarian population were at least two times greater than the percentages reported in the non-ovarian population.

Table 8: Most Frequently Reported* Serious Adverse Experiences In The Ovarian And Non-Ovarian Daily Times Five Populations

Serious Adverse Experience by Preferred Term	Patients With SAEs				Patients with Related** SAEs			
	Ovarian		Non-Ovarian		Ovarian		Non-Ovarian	
	n	(%)	n	(%)	n	(%)	n	(%)
Granulocytopenia	44	(9.7)	41	(7.7)	44	(9.7)	41	(7.7)
Thrombocytopenia	40	(8.8)	43	(8.1)	39	(8.6)	41	(7.7)
Anemia	37	(8.2)	26	(4.9)	36	(8.0)	24	(4.5)
Febrile Neutropenia	33	(7.3)	29	(5.4)	30	(6.6)	26	(4.9)
Fever	32	(7.1)	28	(5.2)	20	(4.4)	15	(2.8)
Leukopenia	17	(3.8)	22	(4.1)	17	(3.8)	22	(4.1)
Sepsis	19	(4.2)	18	(3.4)	14	(3.1)	14	(2.6)
Vomiting	25	(5.5)	11	(2.1)	14	(3.1)	4	(0.7)
Nausea	16	(3.5)	8	(1.5)	13	(2.9)	4	(0.7)
Diarrhea	15	(3.3)	6	(1.1)	10	(2.2)	4	(0.7)

*>2% patients reporting related or possibly related serious adverse experiences in the ovarian daily x 5 population.

**Includes patients with related or possibly related SAEs.

10.4 Adverse Events Leading to Treatment Withdrawal

Withdrawals data were tabulated from the termination record, (reason for withdrawal module) as reconciled with the specific adverse experience(s) leading to withdrawal from the "drug stopped" field of the adverse experience page(s) of Case Report Forms, and were reported from the SB Clintrial database.

The NDA included data available from 1225 patients treated with topotecan in Phase I and Phase II/III studies. In the NDA, withdrawals were reported for patients in five Phase I studies (004, 005, 010, 017, and 049) and in 21 Phase II/III studies (daily times five ovarian studies 012, 033, 034, and 039; non-ovarian daily times five studies 011, 013 014 EORTC, 014 SB, 015, 032, 053, and 090; continuous intravenous infusion studies 051, 052, 056, 057, 059, 060, and 061 and breast studies 030 and 046). For this safety update, data is available for 1408 patients treated with topotecan in Phase I and Phase II/III studies.

A total of 188 patients were treated with topotecan in Phase I studies, 131 of whom participated in intravenous (IV) studies 004, 005, 010, and 017. No additional data is presented for these IV studies. Although 23 additional patients (57 patients, total) have been treated with topotecan in Phase I Study 049 (oral

regimen) since the NDA, no additional patients were withdrawn due to adverse experiences.

In 21 reported/ongoing Phase II/III Studies, a total of 1220 patients were treated with topotecan as of November 20,1995, as compared to 1060 patients reported in the NDA. The majority of these patients were treated on a Daily Times Five Regimen. Of the 1220 patients treated, 96 (7.9%) were withdrawn due to adverse experiences, as compared to 89/1060 (8.4%) in the NDA. The number of withdrawals due to adverse experiences in the daily times 5 combined ovarian, daily times five non-ovarian, and continuous intravenous infusion (CIV) populations is summarized in Table 9. No additional data is presented for breast studies 030 and 046.

Table 9: Numbers Of Patients (%) Withdrawn From Daily Times Five Ovarian, Non-Ovarian and 21-Day CIV Studies

Topotecan Study	Daily x 5 Ovarian				Daily x 5 Non-Ovarian				21-Day CIV			
	Safety Update		NDA		Safety Update		NDA		Safety Update		NDA	
Clinical Cut-Off	Nov 20, 95		Jun 20, 95		Nov 20, 95		Jun 20, 95		Nov 20, 95		Jun 20, 95	
Total Patients	452	%	445	%	534	%	438	%	200	%	143	%
Patients with AEs leading to Withdrawal	35	7.7	35	7.9	42	7.9	39	8.9	15	7.5	11	7.7
Patients Withdrawn for Serious AEs	25	5.5	23	5.2	34	6.4	32	7.4	11	5.5	7	4.9
Patients Withdrawn for Related/Possibly Related AEs	24	5.3	23	5.2	29	5.4	28	6.4	5	2.5	5	3.5

The most prevalent adverse experiences leading to withdrawal in the Phase II/III studies remains hematologic toxicities and associated infections. The percentage of patients withdrawn due to hematologic toxicities/infective complications is comparable to that reported in the NDA. In the combined ovarian studies, the number of withdrawals due to hematologic toxicities/infectious complications remained the same (4.0%), as in the NDA. In the non-ovarian daily times five studies, 3.7% (20/534 patients) were withdrawn due to hematologic toxicities/infective complications, as compared to 4.1% (18/438) in the NDA. In the continuous intravenous infusion (CIV) studies, 3.0% (6/200) were withdrawn due to hematologic toxicities/infective complications, as compared to 3.5% (5/143) reported in the NDA. Asthenia, again, comprised a majority of the non-hematologic withdrawals in the daily times five regimen (0.9%, as compared to 1.1% in the NDA), but was less of a factor (unchanged) in

the combined ovarian population (0.2%), and was not reported as a reason for withdrawal on 21-day CIV regimen.

10.5 Deaths

The NDA included data available from 1,276 patients treated with topotecan in Phase I and Phase II/III studies. Deaths were reported for two Phase I studies (010 and 017), four Phase II/III ovarian studies (012, 033, 034 and 039) and one breast study (030). For this safety update, data is available for 1,408 patients treated with topotecan in Phase I and Phase II/III studies as of November 20, 1995. No additional deaths were recorded for the four intravenous Phase I studies (004, 005, 010 and 017) or the two intravenous Phase II studies in breast cancer (030 and 046). Additional deaths were recorded for the oral Phase I study (049), four Phase II/III ovarian studies (012, 033, 034 and 039), Phase II non-ovarian studies utilizing the daily times five regimen (011, 013, 014E, 014SB, 015, 032, 053 and 090) and for the 21-day continuous intravenous infusion studies in various tumor types (051, 052, 056, 057, 059, 060 and 061). All data on additional deaths is reported from the SB Clintrials database. Data for deaths reported in the NDA was reported from the AEGIS safety database. Deaths were categorized into four categories: Progressive Disease (PD), Hematologic Toxicity (including sequelae, such as infection), Non-hematologic Toxicity, and Other. Patients were categorized into the "Other" category if their death was not associated with progressive disease or toxicity. Patients may have been classified into two categories if there was a contribution from both.

An additional 20 patients were treated in the oral Phase I study (049); two additional deaths, both due to progressive disease, were reported. Overall, 8/57 (14.0%) patients died. The deaths reported for Phase I studies are summarized in Table 10.

Table 10: Summary Of Deaths Reported In Topotecan Phase I Study 049: Summary Of New Deaths

Study	049 -Oral regimen		
	Safety Update November 20, 1995 Data	New Data	NDA June 20, 1995 Data
Patients	57	20	37
Deaths	8 (14.0%)	2	6 (16.2%)
Deaths ≤ 30 Days	3 (5.3%)	(1)*	4 (10.8%)
PD	6 (10.5%)	2	4 (10.8%)
Hem. Tox.	1 (1.8%)	0	1 (2.7%)
PD & Hem. Tox.	1 (1.8%)	0	1 (2.7%)**
Related Deaths	2 (3.5%)	0	2 (5.4%)

*Date of death for Patient (cause: progressive disease) was corrected from 23 days from last dose to 31 days from last dose.

**Death due to progressive disease and sepsis with neutropenia.

Data Source: Safety Update Appendix 7.1.2.4.a

Table 10 Continued: Summary Of Deaths Reported In Topotecan Phase I Studies - Data Unchanged

Study	005	017	010	004
Regimen	Daily x5 q 21 days	Daily x 5 w/Cisplatin q 21 days	30-min infusion q 21 days	24-hour infusion q weekly
Patients	48	15	42	26
Deaths	10 (20.8%)	6 (40.0%)	22 (52.4%)	2 (7.7%)
Deaths ≤ 30 Days	9 (18.8%)	2 (13.3%)	1 (2.4%)	1 (3.8%)
PD	8 (16.7%)	5 (33.3%)	21 (50.0%)	2 (7.7%)
Hem. Tox.	2 (4.2%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
PD & Hem. Tox.	0 (0.0%)	0 (0.0%)	1 (2.4%)*	0 (0.0%)
Related Deaths	1 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*Death due to progressive disease and sepsis.

For this safety update, an additional 112 patients were treated with topotecan in Phase II/III studies for a total of 1,220 patients. An additional 312 deaths were reported. The majority of the newly reported deaths were attributed to progressive disease (284/312, 91.0%). There were two new deaths recorded due to hematologic toxicity (neutropenia and sepsis) and were considered to be related to treatment with topotecan.

In the NDA, a total of 1,108 patients were treated with topotecan in Phase II/III studies and death was reported for 335 patients (30.2%). The majority of the deaths were attributed to progressive disease (296/335, 88.4%). Hematologic toxicity was associated with death in 15 patients (1.4 %), and to both progressive disease and hematologic toxicity in three additional patients (0.3%).

For the overall population of 1,220 patients in the safety update to the NDA, death has been recorded for 647 patients (53.0%). Similarly to the data submitted in the NDA, the majority of the deaths were attributed to progressive disease (583/647, 90.1%). Hematologic toxicity was associated with death in 14 patients (1.1%) and to both progressive disease and hematologic toxicity in three patients (0.2%). The number of deaths associated with hematologic toxicity is less (14 patients) than reported previously in the NDA because the reason for death was reclassified for three patients in the non-ovarian Phase II studies (See Section 7.2.2.).

Deaths that were reported in Phase II/III studies are summarized in Table 11.

Table 11: Summary Of New Deaths Reported In Topotecan Phase II/III Studies

Study	Ovarian Daily x 5 Regimen		
	Safety Update November 20, 1995 Data	New Data	NDA June 20, 1995 Data
No. Patients	452	7	445
Deaths	189 (41.8%)	78	111 (24.9%)
Deaths ≤ 30 Days	32 (7.1%)	3	29 (6.5%)
PD	177 (39.2%)	77	100 (22.5%)
Hem. Tox.	4 (0.8%)	0	4 (0.9%)
Non-hem. Tox	0 (0.0%)	0	0 (0.0%)
PD & Hem. Tox.	0 (0.0%)	0	0 (0.0%)
PD & Other	0 (0.0%)	0	0 (0.0%)
Other Reasons+	8 (1.8%)	1	7 (1.6%)
Related Deaths	4 (0.8%)	0	4 (0.9%)

+Other reasons include not specified.

Table 11 Continued: Summary Of New Deaths Reported In Topotecan Phase II/III Studies

Study	Non-Ovarian Daily x 5 Regimen		
	Safety Update November 20, 1995 Data	New Data	NDA June 20, 1995 Data
No. Patients	534	49	485
Deaths	358 (67.0%)	173	185 (38.1%)
Deaths ≤ 30 Days	68 (12.7%)	12	56 (11.5%)
PD	313 (58.6%)	152	161 (33.2%)
Hem. Tox.	8 (1.5%)	1	10 (2.1%)
Non-hem. Tox	1 (0.2%)	1	0 (0.0%)
PD & Hem. Tox.	3 (0.6%)**	0	3 (0.6%)**
PD & Other	0 (0.0%)	0	0 (0.0%)
Other Reasons+	33 (6.2%)	22	11 (2.3%)
Related Deaths	17 (3.2%)	1	16 (3.3%)

*One new death reported (Patient , though number is less than before due to reclassification of reason for death for Patient : other, Patient . non-hematologic, and Patient . progressive disease .

**Deaths due to progressive disease and pneumonia with neutropenia.

+Other reasons include not specified.

Table 11 Continued: Summary Of Deaths Reported In Other Topotecan Phase II/III Studies - No Change in Data

Study	Other Regimens/ Breast Cancer
No.Patients	34
Deaths	2 (5.9%)
Deaths ≤ 30 Days	2 (5.9%)
PD	2 (5.9%)
Hem. Tox.	0 (0.0%)
PD & Hem. Tox.	0 (0.0%)
PD & Other	0 (0.0%)
Other Reasons+	0 (0.0%)
Related Deaths	0 (0.0%)

*Other reasons include not specified.

Two of the newly reported deaths were considered to be related or possibly related to topotecan. Both deaths were due to hematologic toxicity (neutropenia and sepsis). One patient was being treated with topotecan on the daily times five regimen in a non-ovarian study (small cell lung cancer: Patient The other patient was being treated with topotecan on a 21-

day continuous intravenous infusion study (Patient For the overall patient population, related or possibly related deaths were reported in 23/1220 patients (1.9%) treated with topotecan. Fourteen of the 23 related deaths were associated with hematologic toxicity; ten due to sepsis with neutropenia, two due to pneumonia with neutropenia, and two due to neutropenia. The previous listing for Phase II/III studies was 21/1108 or 1.9%.

10.6 Clinical Laboratory Data

At the cut-off date for this update, there have been no clinically significant trends in mean hepatic biochemistry, renal function or other laboratory results in women with ovarian cancer that have been treated with topotecan. Hematology data were summarized in the section on adverse events, and are notable for Grade 4 neutropenia in 81% of patients, Grade 4 thrombocytopenia in 25.5 % of patients and Grade 3 and Grade 4 anemia in 40% of patients.

10.7 Sponsor's Conclusions

There has been no change in the overall safety profile of topotecan between the NDA submission and this safety update. The main toxicity is hematologic, which is predictable, non-cumulative and manageable. Non-hematologic toxicity is generally mild or moderate, with no unusual or difficult to manage toxicities.

11.0 Reviewer's Conclusions

Efficacy Concerns

Only a minority of patients responded in either of the pivotal studies, the better response being 20% in study 039. Of the responders, 6 had a complete response, and these patients all had small tumor burdens and relatively long times since the previous course of chemotherapy when compared to the other patients in the study. The response for paclitaxel in the same randomized study was 12%. In a statistical model, body size, age, number of lesions, and days since last therapy all were significant factors in predicting response. Topotecan had a comparable rate of response as measured by lesion size and time to progression as paclitaxel did in several published studies in similar clinical settings as the study patient population.

Safety Concerns

The primary toxicities both in frequency and severity were hematologic. Most pronounced was neutropenia and 80% of patients and 35% of courses had

Grade 4 toxicity for an average duration of slightly less than 6 days. Twenty one % of all patients had documented fever and neutropenia, and in study 039, 6 % of patients treated with topotecan had documented sepsis. There were 3 probable deaths related to sepsis, although the data reported across a larger patient population shows a lower incidence than in 039, which may reflect characteristics of the selected population. Not reflected in the current study, but a literature report cautions that concomitant administration of topotecan and filgastrim (G-CSF) can prolong the duration of neutropenia.

Anemia of Grade 3/4 (29% of patients, 21 % of courses), thrombocytopenia of Grade 4 (19% of patients and 5% of courses) and lymphopenia of Grade 4 (35% of patients and 15% of courses) were also common.

The non-hematologic toxicities were common, and generally tolerable with 80% of patients experiencing some Grade 3/4 events. The most common non-hematologic toxicities were alopecia, nausea ,vomiting, diarrhea constipation, fatigue, abdominal pain, fever, stomatitis, dyspnea, headache, and asthenia in over 20% of patients. The most common SAE's were nausea, vomiting, diarrhea, dyspnea, abdominal pain, fever, fatigue, asthenia, intestinal obstruction, and bilirubinemia in > 5 % of patients.

Risk Benefit Assessment

Based on the results of the two submitted studies and on inferences from the literature, topotecan appears to be as effective or more effective than currently available second line therapy for ovarian cancer. The toxicities are commensurate with other cytotoxic agents, although special cares must be exercised for carefully monitoring patients for hematologic toxicity and especially concomitant fever and infection. A statistical model to predict response and risk for fever and neutropenia or sepsis shows that age, body size, days since last chemotherapy and number of lesions all impact on the result, although in opposite directions. In general an older, smaller person with a greater than average for the study population number of days since last chemotherapy and a lesser than average for the study population number of lesions will have the greatest likelihood of responding and the least likelihood of experiencing a neutropenic infection. Since the two probabilities move in opposite directions, the less likely a patient is to respond, the more likely she is to experience infection and neutropenia. Removing the factor of number of lesions decreases the sensitivity of the model by 10%, but it can still be potentially useful for analysis of future studies. For further details see the statistical report.

In summary, topotecan represents an alternative to current salvage therapy for ovarian cancer with risks that are commensurate with other treatment options.

12.0 Oncologic Drug Advisory Committee Meeting, April 19, 1996

The following four questions were voted upon by the committee:

Question 1. Is study 039 an adequate and well-controlled study that supports the approval of topotecan for the treatment of women with recurrent ovarian cancer after first-line therapy with cisplatin or carboplatin ? The committee voted 8 yes to 0 no.

Question 2. IF study 034 is considered to be historically controlled (patient as her own control or results of other studies), is it and adequate and well-controlled study that supports the approval of topotecan for the treatment of women with recurrent ovarian cancer after the first-line therapy with cisplatin or carboplatin ? There was some discussion led by Dr. Richard Gelber that the committee should not consider a historically controlled trial by itself as sufficient, and that in the context of the 039 trial, the data from 034 could be supportive of the approval, but alone it should not be considered as adequate and well-controlled. The vote was 7 yes and Dr. Gelber no.

Question 3. Is the toxicity profile of topotecan acceptable for patients with recurrent ovarian cancer ? There was some discussion as to whether the hematologic toxicity, which was recognized as severe and potentially life threatening by the members of the committee, should be treated by adding G-CSF or other growth factor support or if dose reduction is preferable. The consensus was that since there were data that showed that dose intensity could not be increased by using G-CSF, and that the possibility of other toxicities such as anemia still remain, it would be preferable to recommend dose reduction to decrease toxicity when indicated. The vote was 8 yes and 0 no.

Question 4. Should topotecan be approved " for the treatment of patients with metastatic carcinoma of the ovary after failure of initial of subsequent therapy " or should approval be limited to women with metastatic ovarian cancer after failure of initial platinum therapy ? The discussion centered on what should be considered initial or subsequent therapy, and several discussants noted that initial therapy is often surgery, and subsequent therapy may involve radiation. The question was rephrased to approval for treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy. The vote was unanimous, 8 yes and 0 no.

...uct Labelling Comments

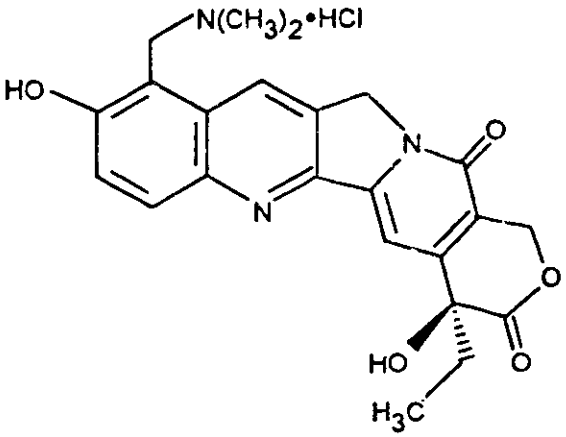
Sponsor Version	FDA Version
XX:L1	XX:L1
Prescribing Information	**Prescribing Information**
HYCAMTIN™	**HYCAMTIN™**
brand of topotecan hydrochloride for Injection (for intravenous use)	brand of topotecan hydrochloride for Injection (for intravenous use)
	ADDITION OF BOXED WARNING
	WARNING Hycamtin (topotecan 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 1500 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, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Hycamtin.
	ADDITIONAL CHANGES HAVE BEEN MADE BY BIOPHARMACEUTICS AND TOXICOLOGY WHICH ARE NOT REFLECTED IN THIS TEXT
DESCRIPTION	**DESCRIPTION**
Hycamtin (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	Hycamtin (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 consist of 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.

Topotecan hydrochloride is a semi-synthetic product with antitumor 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 monohydrochloride.

Topotecan hydrochloride has the following structural formula:



Topotecan hydrochloride is a yellow to yellow-orange powder with the molecular formula $C_{23}H_{23}N_3O_5$.HCl and a molecular weight of 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

CLINICAL PHARMACOLOGY

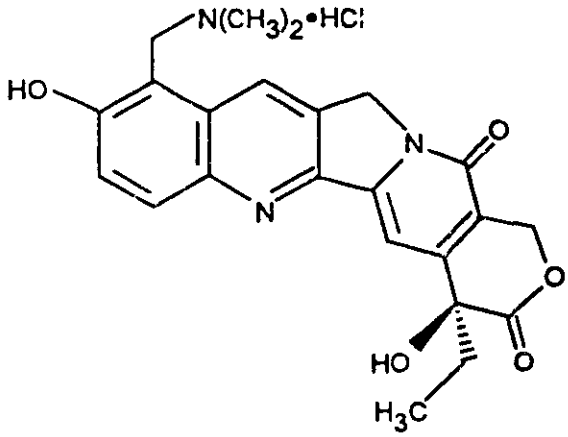
Topotecan hydrochloride is a novel chemotherapeutic agent that inhibits topoisomerase-I, an enzyme that functions in DNA replication to relieve the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilizing the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism. By inhibiting

to yellow-green and is intended for administration by intravenous infusion.

Inactive ingredients consist of 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.

Topotecan hydrochloride is a semi-synthetic product with antitumor 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 monohydrochloride.

Topotecan hydrochloride has the following structural formula:



Topotecan hydrochloride is a yellow to yellow-orange powder with the molecular formula $C_{23}H_{23}N_3O_5$.HCl and a molecular weight of 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

REWORDING FOR CLARITY

CLINICAL PHARMACOLOGY

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. Current research suggests that the cytotoxicity of topotecan is due to double strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex

topoisomerase-I, topotecan induces breaks in the protein-associated DNA single-strands, resulting in cell death.

formed by topotecan, topoisomerase I and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

THIS SECTION HAS BEEN RE-EDITED BY BIOPHARMACEUTICS

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.

Pharmacokinetics

The pharmacokinetics of topotecan has been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30 minute infusion daily for 5 days. Topotecan exhibited multiexponential pharmacokinetics. The terminal half-life was 2 to 3 hours. Mean topotecan clearance ranged from 500 to 1800 mL/min. Area under the curve increased approximately in proportion to the increase in dose. Following the administration of topotecan as a 1.5 mg/m^2 dose given as a 30 minute infusion, a peak plasma level of 35 ng/mL is typically obtained with a corresponding AUC of 60 ng*hr/mL.

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. The binding of topotecan to plasma proteins is 35%. Topotecan is evenly distributed between blood cells and plasma.

Distribution. Topotecan steady-state volume of distribution ranges from 25 to 120 L/m^2. Binding of topotecan to plasma proteins is 35 %..

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 studied. However in rats and dogs, approximately 4% and 17% of the dose, respectively, was excreted as N-desmethy 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

Metabolism: Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety. At pH $\leq$ 4 the lactone is exclusively present whereas the ring-opened hydroxy-acid form predominates at physiologic pH. This reaction constitutes a major route by which topotecan is inactivated. *In vitro* studies in rat, dog, and human liver microsomes indicate that metabolism of topotecan to a N-demethylated metabolite represents a minor metabolic pathway.

has been identified. A major route of clearance of topotecan was by hydrolysis of the lactone ring to form the ring-opened hydroxy acid.

Excretion: 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

Pediatric: 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.[1] 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.

Gender: Hycamtin is indicated for the treatment of ovarian cancer. It has not been determined whether gender affects the pharmacokinetics of *Hycamtin*.

Geriatrics: Topotecan pharmacokinetics have 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.

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

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

Excretion: In humans, 20 - 60 % of the dose is excreted in the urine. Therefore, renal clearance is likely to be an important determinant of topotecan elimination. Biliary excretion has been observed in one patient. Studies suggest that rats may eliminate as much as 18% of an intravenous topotecan dose by intestinal excretion.

Special Populations

ELIMINATED SINCE THERE ARE NO CURRENT PEDIATRIC INDICATIONS

Gender: The overall mean topotecan plasma clearance in male patients was approximately 24 % higher than in female patients.

Geriatrics: Topotecan pharmacokinetics have 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.

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

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 control patients. Change in half-life was not significant.

14%.

In patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.), 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 (Cl_{cr} 40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment.

In patients with moderate renal impairment (Cl_{cr} 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34 % of the value in control patients. Mean half-life estimated in three renally impaired patients was 5.0 hours. Dosage adjustment is recommended in this subgroup of patients. (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: 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. Based on clinical data and total topotecan pharmacokinetics, no dosage adjustment is required in hepatically impaired patients.

Hepatic Impairment: Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 - 15.0 mg/dL) decreased to about 67 % of the value in control patients. Topotecan half-life increased from 2.0 hours to 2.5 hours. However, these hepatically impaired patients were able to tolerate the usual recommended topotecan dosage regimen (See DOSAGE and ADMINISTRATION).

THE PHRASE P450 HAD THE WORD CYTOCHROME ADDED TO IT

Drug Interactions: Pharmacokinetic studies of the interaction of topotecan with concomitantly administered medications have not been formally investigated. However, *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

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 dihydropyridine dehydrogenase suggested that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo* and cannot be ruled out.

Following 14 days of intravenous dosing in rats at doses up to 1.36 mg/m^2 topotecan free base, no

ELIMINATED SINCE IT IS NOT HELPFUL INFORMATION TO THE AVERAGE

inductive effect was observed on P450 enzymes 1A, 2B, 3A and 4A

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.

CLINICAL STUDIES:

Hycamtin (topotecan hydrochloride) was studied in four clinical trials of 445 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 5 consecutive days, starting on day one of a 21-day course.

In a randomized Phase 3 study, *Hycamtin* was compared with paclitaxel. This study treated 112 patients with *Hycamtin* (1.5 mg/m^2/d x 5 days starting on day one of a 21-day course) and 114 patients with paclitaxel (175 mg/m^2 over 3 hours on day 1 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 1.

Patients receiving *Hycamtin* achieved a higher response rate-21% vs 13%- (p=0.138) than those receiving paclitaxel; a longer duration of response: median of 32 vs. 20 weeks (hazard ratio=0.416; p=0.222); a significantly longer time to progression: median of 23 vs 14 weeks (hazard ratio=0.578; p=0.002); and a longer estimated median survival: 61 vs 43 weeks (hazard ratio=1.210; p=0.515). However, the median time

CLINICIAN

Pharmacodynamics: The dose-limiting toxicity for topotecan is leukopenia. Correlations between decreased white blood cell count and either topotecan dose or topotecan AUC have been demonstrated. When topotecan is administered at a dose of 1.5 mg/m^2/day for 5 days, an 80 - 90 % decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

CLINICAL STUDIES:

Hycamtin (topotecan hydrochloride) was studied in four clinical trials of 452 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 5 consecutive days, starting on day one of a 21-day course.

A DESCRIPTION OF THE PRIOR THERAPY OF THE PATIENTS WAS ADDED

In a randomized Phase 3 study, Hycamtin was compared with paclitaxel. This study treated 112 patients with Hycamtin (1.5 mg/m^2/d x 5 days starting on day one of a 21-day course) and 114 patients with paclitaxel (175 mg/m^2 over 3 hours on day 1 of a 21-day course). **All patients had recurrent disease or did not respond to one prior platinum-containing regimen.**

Response rates, response duration (measured from the time of documented response), time to progression, and time to response for the comparative study are provided in Table 1.

ELIMINATED SINCE THE DATA ARE PRESENTED IN THE FOLLOWING TABLE

SURVIVAL NOT INCLUDED SINCE THE DATA ARE STILL IMMATURE

to response was significantly longer with *Hycamtin* compared to paclitaxel: median of 9 vs 6 weeks (hazard ratio=0.476; p=0.041). Consequently there is a risk of underestimating the expected efficacy of *Hycamtin* if patients are withdrawn from treatment prematurely (see DOSAGE AND ADMINISTRATION).

TABLE REVISED USING FDA CONFIRMED VALUES AND ONLY PRIMARY ENDPOINTS AS DEFINED IN THE STUDY PROTOCOL

Table 1. Comparative Efficacy Parameters of Hycamtin vs paclitaxel in Ovarian Cancer

Parameter	*Hycamtin* (n=112)	Paclitaxel (n=114)
Complete Response Rate	5.4%	3.5%
Partial Response Rate	14.3%	8.8%
Overall Response Rate	19.6%	12.3%
95% CI	12.8-28.2 %	6.9-19.7%
(p-value)	(0.0918)	
Response Duration (weeks)		
Median	22.2	12.0
Range		
hazard-ratio (*Hycamtin*:paclitaxel)	0.276	
(p-value)	(0.065)	
Time to Progression (weeks)		
Median	23.1	14.0
Range		
hazard-ratio (*Hycamtin*:paclitaxel)	0.578	
(p-value)	(0.002)	

*estimate corresponds to a censored event

The calculation for duration of response was based on the interval between best response and time to progression, and not from time of enrollment nor from time of initial response to time to progression.

REPHRASING OF TIME TO RESPONSE STATEMENT AND USING DATA CONFIRMED BY FDA

The time to response was longer with *Hycamtin* compared to paclitaxel: mean of 10 weeks (range 5.4- 31.6) vs 7 (range 4.8 to 9.4) weeks. Consequently there is a risk of not achieving the expected efficacy of *Hycamtin* if patients are withdrawn from treatment prematurely.

REPHRASED FOR PRECISION

Patients who failed on the initial arm of this trial were allowed to switch to the alternate treatment. Five of 53 (9%) patients who received *Hycamtin* after paclitaxel have responded. One of 37 (3%) patients who received paclitaxel after *Hycamtin* responded.

Patients whose disease did not respond to treatment on the initial arm of this trial were allowed to switch to the alternate treatment. Five of 53 (9.4%) patients who received Hycamtin after paclitaxel had a partial response. One of 37 (2.7%) patients who received paclitaxel after Hycamtin had a complete response.

Hycamtin was active in 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%. *Hycamtin* 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).

Hycamtin was active in 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%. Hycamtin remained active in patients who did not respond to ***(ELIMINATE THE PHRASE THAT PATIENTS FAILED)*** paclitaxel, as shown by the responders in this trial. ***ELIMINATED THE REFERENCE TO THE TRIAL ON PACLITAXEL AND PLATINUM BECAUSE THE DATA WERE NEVER PROVIDED***

The safety profile for paclitaxel in this study was consistent with the product's approved labeling; the safety profile for *Hycamtin* in this study was consistent with that observed in all 452 patients from the four ovarian clinical trials (see ADVERSE REACTIONS).

The safety profile for paclitaxel in this study was consistent with the product's approved labeling; the safety profile for Hycamtin in this study was consistent with that observed in all 452 patients from the four ovarian clinical trials (see ADVERSE REACTIONS).

The three additional studies were open-labeled and non-comparative in design. The first of these enrolled 111 patients who had failed one prior platinum-containing regimen. The response rate was 14% (95% CI:=7.9% to 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 72.1 weeks).

ONLY ONE ADDITIONAL STUDY WAS REVIEWED SINCE DATA WAS NEVER PROVIDED FOR THE OTHER STUDIES. THE NUMBERS REFLECT FDA CONFIRMED DATA. THE STUDY WAS NOT SUFFICIENTLY MATURE TO INCLUDE MEANINGFUL SURVIVAL DATA.

An additional study that was open-labeled and non-comparative in design enrolled 111 patients who had **recurrent disease or did not respond** to one prior platinum-containing regimen. The response rate was 14% (95% CI =7.9% to 20.9%). The median duration of response was 18 weeks (95% CI = 12 - ∞). The time to progression was 8.4 weeks (range: 0.7 to 72.1 weeks).

A second open study enrolled 139 patients 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 13% and 14%, respectively. Median response duration was 24 weeks (range: 1.4 - 40.7 weeks). Median time to progression was 12 weeks (range: 0.6 - 52.7 weeks). Median survival was 44 weeks (range: 2.9 - 68.7 weeks) for patients failing first-line therapy.

DATA NEVER SUBMITTED FOR CONFIRMATION

The third open study enrolled 30 patients 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).

INDICATIONS AND USAGE

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Hycamtin (topotecan hydrochloride) is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

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SENTENCE ON PREGANCY WAS DELETED SINCE THAT IS ADDRESSED IN WARNING SECTION

CONTRAINDICATIONS

Hycamtin is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients. *Hycamtin* should not be used in patients who are pregnant or breast-feeding, or those with severe bone marrow depression.

CONTRAINDICATIONS

Hycamtin is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. The nadir for neutrophil count occurred at a median of 11 days, and the nadir for platelet and hemoglobin counts occurred at a median of 15 days. The median duration of Grade 4 neutropenia was 7 days, and of thrombocytopenia was 5 days. The median duration of Grade 3/4 anemia was 7 days. (All grading scales reported are based on National Cancer Institute criteria.) *Hycamtin* should only be administered in patients with adequate bone marrow reserves including baseline neutrophil counts of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of blood counts should be instituted during treatment with *Hycamtin*. Patients should not be treated with subsequent courses of *Hycamtin* until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3 and hemoglobin levels recover to 9.0 mg/deciliter, using transfusion if necessary.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. The nadir for neutrophil count occurred at a median of 11 days, and the nadir for platelet and hemoglobin counts occurred at a median of 15 days. The median duration of Grade 4 neutropenia was 7 days, and of thrombocytopenia was 5 days. The median duration of Grade 3/4 anemia was 7 days. (All grading scales reported are based on National Cancer Institute criteria.) Hycamtin should only be administered in patients with adequate bone marrow reserves including baseline neutrophil counts of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with Hycamtin. Patients should not be treated with subsequent courses of Hycamtin until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3 and hemoglobin levels recover to 9.0 mg/deciliter, using transfusion if necessary.

	Severe myelotoxicity has been reported when *Hycamtin* is used in combination with cisplatin (see Drug Interactions)
Hycamtin may cause fetal harm when administered to a pregnant woman. Topotecan was shown to cause embryonic and fetal lethality when given to rats and rabbits at doses less than the human clinical intravenous dose (1.5 mg/m^2). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with *Hycamtin*.	**Pregnancy:** Hycamtin may cause fetal harm when administered to a pregnant woman. **The effects of topotecan on pregnant women have not been studied. If topotecan is used during a patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming pregnant.** Topotecan caused embryonic and fetal death in rats and rabbits. **In rabbits, a dose of 0.32 mg/kg/d (about twice the clinical dose on a mg/m^2 basis) on days six through twenty of gestation caused fetal resorption. This does caused significant maternal toxicity. In the rat, a dose of 0.23 mg/kg/d (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day six caused fetal resorption, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/d (about half the clinical dose on a mg/m^2 basis.**
PRECAUTIONS	PRECAUTIONS *PARENTHESES ELIMINATED FOR CLARITY*
General: Inadvertent extravasation with *Hycamtin* has been associated only with mild local reactions such as erythema (and bruising).	**General:** Inadvertent extravasation with Hycamtin has been associated only with mild local reactions such as erythema and bruising. *A PARAGRAPH WAS ADDED TO DESCRIBE THE INTERACTION WITH G-CSF ALONG WITH A REFERENCE*
Drug Interactions:	**Drug Interactions:** Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should be initiated on day 6 of the course of therapy, 24 hours after completion of treatment with Hycamtin [1]. *THE TEXT WAS REPHRASED FOR CLARITY AND THE INFORMATION FROM*

THE DOSAGE AND ADMINISTRATION SECTION PERTAINING TO THIS ISSUE WAS ADDED. NO SPECIFIC DOSE RECOMMENDATION IS GIVEN FOR GIVING TOPOTECAN AND CISPLATIN DURING THE SAME COURSE BECAUSE THERE ARE NO PUBLISHED GUIDELINES THAT HAVE BEEN VERIFIED, NOR IS THERE DATA ON FILE TO SUPPORT ANY PARTICULAR DOSE COMBINATION.

In Phase I studies, myelosuppression was more severe when *Hycamtin* was given after cisplatin.

When used concomitantly with platinum compounds, the dose of *Hycamtin* must be reduced due to the observed greater incidence of myelosuppression (see DOSAGE AND ADMINISTRATION), and myelosuppression may require delay of subsequent courses (see WARNINGS).

Myelosuppression was more severe when Hycamtin was given in combination with cisplatin in Phase I studies. In a reported study on concomitant administration of cisplatin 50 mg/m^2 and Hycamtin at a dose of 1.25 mg/m^2/day x 5 days, one of three patients having neutropenia for 12 days and a second patient died with neutropenic sepsis. [2] There are no current guidelines for safe and effective dosing of Hycamtin and cisplatin in combination.

Hematology: *Hycamtin* should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. To monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving *Hycamtin*. Patients should not be retreated with subsequent courses of *Hycamtin* until neutrophils recover to a level >1,000 cells/mm^3; platelets recover to a level >100,000 cells/mm^3 and hemoglobin recovers to 9.0 mg/deciliter, using transfusion if necessary.

Hematology: Hycamtin should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. To monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Hycamtin. Patients should not be retreated with subsequent courses of Hycamtin until neutrophils recover to a level >1,000 cells/mm^3; platelets recover to a level >100,000 cells/mm^3 and hemoglobin recovers to 9.0 mg/deciliter, using transfusion if necessary.

In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of *Hycamtin*, a reduction in dose of 0.25 mg/m^2 for subsequent courses of therapy is recommended. As an alternative, G-CSF may be administered before

In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of Hycamtin, a reduction in dose of 0.25 mg/m^2 for subsequent courses of therapy is recommended. As an alternative, G-CSF may be administered before

reducing the dose, starting from Day 6 of the course (the day after completion of topotecan administration).

reducing the dose , starting on Day 6 of the course (**24 hours** after completion of topotecan administration).

REVISION OF CARCINOGENICITY

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of *Hycamtin* has not been studied. (See WARNINGS section.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogencity tests with topotecan have not been done in laboratory animals. neverthelss, topotecan is genotxic to mammalian cells *inv vitro* and *in vivo*. Topetecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation *in vitro*. It was clastogenic tc mouse bone marrow *in vivo*. Topotecan did not cause mutations in bacterial cells. Some dogs given 0.4 mg/m^2 /d for one month (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day six caused a 75% increase in the number of copora lutea. The mechanism causing this super-ovulation has not been determined.

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

Pregnancy: Pregnancy Category D. (See WARNINGS section.) Topotecan hydrochloride was shown to cause embryo-fetal lethality when given to rats (0.59 mg/m^2) and rabbits (1.25 mg/m^2). At maternally toxic doses (0.59 mg/m^2), topotecan caused malformations, primarily of the eye, brain, skull, and vertebrae.

Pregnancy: Pregnancy Category D. (See WARNINGS section.)

Nursing Mothers: It is not known whether the

Nursing Mothers: It is not known whether the

drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving *Hycamtin* (see CONTRAINDICATIONS).

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

ADVERSE REACTIONS

Data in the following section are based on the experience of 452 patients with metastatic ovarian carcinoma treated with *Hycamtin* in Phase II/III studies.

drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving Hycamtin (see CONTRAINDICATIONS).

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

ADVERSE REACTIONS

Data in the following section are based on the experience of 452 patients with metastatic ovarian carcinoma treated with Hycamtin in Phase II/III studies.

Table 2: Summary of Hematologic Adverse Events in 452 Patients Receiving *Hycamtin*

Hematologic Adverse Events	Patients % Incidence	Courses % Incidence
Neutropenia		
<1,500 cells/mm^3	98	78
<500 cells/mm^3	81	40
Leukopenia		
<3,000 cells/mm^3	98	77
<1,000 cells/mm^3	32	11
Thrombocytopenia		
<75,000/mm^3	63	39
<25,000/mm^3	25	9
Anemia		
<10 g/dL	95	76
<8 g/dL	40	16
Sepsis or fever/infection with Grade 4 neutropenia	26	7
Platelet transfusions	13	4
RBC transfusions	56	23

Table 3: Summary of Non-hematologic Adverse Events in 452 Patients Receiving *Hycamtin*

Non-hematologic Adverse Events	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	All Patients	All Courses	All Patients	All Courses	All Patients	All Courses
Gastrointestinal						
Nausea	77	50	10	3	<1	<1
Vomiting	58	26	6	3	3	<1
Diarrhea	42	19	4	1	<1	<1
Constipation	39	18	2	<1	1	<1
Abdominal Pain	33	13	4	<1	2	<1
Stomatitis	24	9	2	<1	<1	<1
Anorexia	19	8	2	<1	0	0
Body as a Whole						
Fatigue	37	25	6	2	0	0
Fever	34	13	1	<1	<1	<1
Asthenia	21	10	3	<1	1	<1
Skin/Appendages						
Alopecia	59	62	NA	NA	NA	NA

Pre medications were not routinely used in these clinical studies

THE WORD REVERSIBLE WAS DELETED BECAUSE SOME PATIENTS NEVER RECOVERED FROM THEIR NEUTROPENIA

Hematologic: Neutropenia (reversible and non-cumulative over time) was the major dose-limiting toxicity. Severe (< 500 cells/mm^3) neutropenia was most common during course 1 of treatment (60% of patients). It occurred in 40% of total courses and generally resolved within one week. Neutrophil nadirs occurred at a median of 11 days. Prophylactic G-CSF was administered in 22% of courses.

Hematologic: Neutropenia (non-cumulative over time) was the major dose-limiting toxicity. Severe (< 500 cells/mm^3) neutropenia was most common during course 1 of treatment (60% of patients). It occurred in 40% of total courses and generally resolved within one week. Neutrophil nadirs occurred at a median of 11 days. Prophylactic G-CSF was administered in XX% of courses after the first cycle..

	THE INCIDENCE OF PATIENTS WITH ANEMIA WAS ADDED
Therapy-related sepsis associated with death occurred in 0.7% of patients. There were no episodes of serious bleeding. Severe anemia (Grade 3/4) occurred in 16% of courses. Median platelet and hemoglobin nadirs occurred on day 15 of treatment.	Therapy-related sepsis associated with death occurred in 0.7% of patients. There were no episodes of serious bleeding Severe anemia (Grade 3/4) **occurred in 40% of patients and** 16% of courses. Median platelet and hemoglobin nadirs occurred on day 15 of treatment.
	THE INCIDENCE OF NAUSEA , VOMITING, DIARRHEA, CONSTIPATION AND ABDOMINAL PAIN WERE INCLUDED TO MAINTAIN CONSISTENCY IN STRUCTURE AND HIGHLIGHT THE DATA
Gastrointestinal: (See Table 3). Prophylactic anti-emetic use was not routine in patients treated with *Hycamtin*.	**Gastrointestinal:** The incidence of nausea was 77% (Grade 3/4 10%)and vomiting was 58% (Grade 3/4 9%) of patients (See Table 3) although the prophylactic use of anti-emetics was not routine in patients treated with Hycamtin. Forty-two % of patients had diarrhea (Grade 3/4 5%) , 39% constipation (Grade 3/4 3%) and 33% had abdominal pain (Grade 3/4 6%).
Skin/Appendages: Total alopecia (Grade 2) occurred in 42% of patients.	**Skin/Appendages:** Total alopecia (Grade 2) occurred in 42% of patients.
Central and Peripheral Nervous System: Headache (21%) was the most frequently reported neurologic toxicity. Paresthesia was generally Grade 1 (9%).	**Central and Peripheral Nervous System:** Headache (21%) was the most frequently reported neurologic toxicity. Paresthesia was generally Grade 1 (9%).
Liver/Biliary: Grade 1 transient elevations in SGOT/AST and SGPT/ALT (5%); Grade 3/4 elevations (<1%). Grade 3/4 elevated bilirubin (<3%).	**Liver/Biliary:** Grade 1 transient elevations in SGOT/AST and SGPT/ALT (5%); Grade 3/4 elevations (<1%). Grade 3/4 elevated bilirubin (<3%).

Respiratory: Dyspnea (20%); Grade 3/4 dyspnea (4%).

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

OVERDOSAGE

There is no known antidote for overdosage with *Hycamtin*. The primary anticipated complication of overdosage would consist of bone marrow suppression. One patient who received a single 35 mg/m^2 infusion of *Hycamtin* showed increased neutropenia.

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

DOSAGE AND ADMINISTRATION

Respiratory: Dyspnea (20%); Grade 3/4 dyspnea (4%).

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

OVERDOSAGE

There is no known antidote for overdosage with Hycamtin. The primary anticipated complication of overdosage would consist of bone marrow suppression. One patient who received a single 35 mg/m^2 infusion of Hycamtin showed increased neutropenia.

THE NUMBERS WERE REDUCED FROM 4 SIGNIFICANT FIGURES TO TWO.

The LD_{10} rate in mice receiving single intravenous infusions of Hycamtin was 75 mg/m^2 (CI 95%: 47 to 97).

DOSAGE AND ADMINISTRATION

THE PHRASE THAT ROUTINE PRE-MEDICATION IS NOT REQUIRED IGNORES THE PREVIOUS SECTION THAT THE MAJORITY OF PATIENTS EXPERIENCED GASTROINTESTINAL SIDE EFFECTS AND IF NOT PRACTICED MAY LEAD TO UNNECESSARY DISCOMFORT

Prior to administration of the first course of *Hycamtin*, patients must have a baseline neutrophil count of >1500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended dose of Hycamtin (topotecan hydrochloride) 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. A minimum of four courses is recommended because median time to response in three clinical trials was 9 to 12 weeks. In the event of severe neutropenia, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. As an alternative, G-CSF may be administered before reducing the dose, starting from Day 6 of the course (the day after completion of topotecan administration). Routine pre-medication for non-hematological adverse events is not required with *Hycamtin*.

Prior to administration of the first course of Hycamtin, patients must have a baseline neutrophil count of >1500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended dose of Hycamtin (topotecan hydrochloride) 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. A minimum of four courses is recommended because median time to response in three clinical trials was 9 to 12 weeks. In the event of severe neutropenia, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. As an alternative, G-CSF may be administered before reducing the dose, starting from Day 6 of the course (**24 hours after** completion of topotecan administration).

Patients who require concurrent cisplatin (for directions for the administration of cisplatin, refer to the cisplatin prescribing information) and *Hycamtin* may be treated as follows: 75 mg/m^2 of cisplatin administered on day one of each course of therapy, followed by 0.75 mg/m^2 of *Hycamtin* by intravenous infusion over 30 minutes for 5 consecutive days, according to the recommended regimen described above. A reported study recommended topotecan 1.0 mg/m^2/d for 5 consecutive days in combination with cisplatin 50 mg/m^2 on day 1 without G-CSF or cisplatin 75 mg/m^2 on day 1 with G-CSF support.[2]

THIS SECTION WAS MOVED TO A PREVIOUS SECTION DISCUSSING CISPLATIN TO CONSOLIDATE THE INFORMATION

No dosage adjustment is required for treating hepatically impaired patients (plasma bilirubin >1.5 to <10 mg/dL).

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No dosage adjustment is required for patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is

No dosage adjustment is required for patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is

recommended for patients with moderate renal impairment (20 to 39 mL/min). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

Insufficient data are available in pediatric patients to provide a dosage recommendation.

PREPARATION FOR ADMINISTRATION

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

Preparation for Intravenous Administration:

Each *Hycamtin* 4 mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Because the lyophilised dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

recommended for patients with moderate renal impairment (20 to 39 mL/min). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

Insufficient data are available in pediatric patients to provide a dosage recommendation.

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

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Because the lyophilised dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of Hycamtin (topotecan hydrochloride) are stable until the date indicated on the package when stored between 15° and 30° C (59° and 86°F) and protected from light in the original package.

Reconstituted vials are stable for up to 24 hours when refrigerated at 5°C (41°F) or stored at 30°C (86°F). Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of *Hycamtin* diluted for infusion are stable at approximately 20° to 25°C (68° to 77°F) and ambient lighting conditions for 24 hours. If not used immediately, the diluted solution should be stored in a refrigerator in line with good pharmaceutical practice.

HOW SUPPLIED

NDC 0007-4201-05: Hycamtin (topotecan hydrochloride) for Injection is supplied in 4 mg (free base) single-dose vials, in packages of 5.

Storage: Store the vials protected from light in the original cartons between 15° and 30°C (59° and 86°F).

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

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HOW SUPPLIED

NDC 0007-4201-05: Hycamtin (topotecan hydrochloride) for Injection is supplied in 4 mg (free base) single-dose vials, in packages of 5.

Storage: Store the vials protected from light in the original cartons between at controlled room temperature between 20° and 25°C (68° and 77° F).

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

been published.[3-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

been published.[3-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

THE REFERENCE TO PEDIATRIC 24-HOUR INFUSION WAS ELIMINATED AND A REFERENCE TO PROLONGED NEUTROPENIA WITH CONCURRENT G-CSF WAS SUBSTITUTED. ADDITIONAL STANDARD REFERENCES ON SAFE HANDLING OF CYTOTOXIC AGENTS WERE ADDED.

REFERENCES:

1. Blaney, SM et al. Pediatric phase 1 trial and pharmacokinetic study of topotecan administered as a 24-hour continuous infusion. *Cancer Res.* 1993;53:1032-1036.

2. Miller AA, et al. Phase 1 study of topotecan and cisplatin in patients with advanced solid tumors: A Cancer and Leukemia Group B study. *J Clin Oncol* 1994;12: 2743-2750.

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1. Rowinsky, 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;14:1224-1235.

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3. Recommendations for the safe handling of parenteral antineoplastic drugs NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402

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5. National Study Commission on Cytotoxic Exposure-recommendations for handling cytotoxic agents. Available from Louis P. Jeffry, Chairman, National Study Commission on Cytotoxic Exposure. Massachusettss College of Pharmacy and Allied Health Sciences. 179

Longwood Avenue, Boston, Massachusetts, 02115

4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Austr* 1983;1:426-428.

6 Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Austr 1983;1:426-428.

5. Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. *CA-A Cancer Journal for Clinicians* 1983; Sept./Oct. 258-263.

7.Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; Sept./Oct. 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hos Pharm* 1990; 47:1033-1049.

8. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hos Pharm 1990; 47:1033-1049.

7. OSHA Work-Practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. *Am J Hosp Pharm* 1986; 43:1193-1204.

9. OSHA Work-Practice guidelines for personnel dealing with cytotoxic(antineoplastic) drugs. Am J Hosp Pharm 1986; 43:1193-1204.

DATE OF ISSUANCE (MONTH, YEAR)

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Philadelphia, PA 19101

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14.0 Recommended Regulatory Action

On April 19, 1996, the Oncologic Drugs Advisory Committee unanimously recommended approval of topotecan as second line therapy for women with ovarian cancer. This decision was based on an objective response rate of 20.5 % in Trial 039 with 4.5% complete response and an objective response rate of 14.4% in Trial 034 with 1 % complete response. The median duration of response in Trial 039 was 22.2 weeks and in Trial 034 it was 18 weeks. Survival data could not be calculated since the majority of the patients were alive at the time of study closure (June 1995). Follow up survival data should be submitted to the Agency when it becomes available. The safety profile of topotecan was notable for hematologic toxicity with % of patients having Grade 4 neutropenia, 21% of all patients and 6% of all courses had fever and neutropenia, and 0.7% of patients had death from sepsis attributed to topotecan. In addition, anemia of Grade 3/4 (29% of patients, 21 % of courses), thrombocytopenia of Grade 4 (19% of patients and 5% of courses) and lymphopenia of Grade 4 (35% of patients and 15% of courses) were also common. Non-hematologic toxicity was primarily gastro-intestinal with 77% of all patients experiencing nausea and 58% experiencing vomiting. The incidence of Grade 3 or 4 gastro-intestinal toxicity was 10% or less. Based on the data from the Safety Update, 7.7% of ovarian patients on the daily x 5 regimen had adverse events leading to withdrawal. Serious adverse events from all causes leading to withdrawal were in 5.5% of patients. Topotecan related or possibly related withdrawals as characterized by the treating physician occurred in 5.3% of patients, primarily due to hematologic toxicity or associated infection. No dose adjustment is recommended for patients with mild renal impairment and a 50% dose reduction is recommended for patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.). No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Topotecan has not been studied in patients with severe hepatic impairment.

Topotecan given as a daily dose of 1.5 mg/m^2 x 5 days every 21 days should be approved for the treatment of "for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy."

15.0 Deficiency List

The survival data were not complete at the time of submission, and the sponsor should commit to providing the data when it is mature.

Steven Hirschfeld, M.D., Ph.D. May 23, 1996
Medical Officer

Robert Justice, M.D. May 23, 1996
Group Leader

cc: NDA # 20 671
HFD-150/ Division File
HFD-150/ D. Catterson, CSO
HFD-150/ R. Justice, Group Leader
HFD-150/ S. Hirschfeld, MO

Exclusivity Summ.
Ped. Pts

MAY 6 1996

EXCLUSIVITY SUMMARY for NDA # 20-671 SUPPL # —

Trade Name HYCAMTIN™ Generic Name (TOPOTECAN HCL) FOR INJECTION

Applicant Name SMITHKLINE BEECHAM PHARMACEUTICALS HFD- 150

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) —

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # N/A _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) N/A

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/.

If yes, explain: _____

_____

_____

_____

Lisa M Catterson
Signature
Title: Consumer Safety Officer

5/2/96
Date

Robert L Justice, M.D.
Signature of Division Director

5/6/96
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

(4)

DRUG USAGE IN PEDIATRIC PATIENTS

NDA # 20-671 Trade (generic) names HYCAMTIN™ (TOPOTECAN HCL) FOR INJECTION

Check any of the following that apply and explain, as necessary, on a separate sheet:

___ 1. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children (e.g., drugs for angina or Alzheimer's disease).

___ 2. Pediatric studies should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (i.e., there are several similar alternative drugs, for example, contrast agents).

___ a. The applicant has committed to doing such studies as will be required to include a pediatric claim in the labeling.

___ (1) We have approved the protocol(s).
___ (2) The protocol(s) has/have been submitted and is/are under review.
___ (3) Protocol design is under discussion with the applicant.
___ (4) The applicant has not yet submitted a protocol.

___ b. The applicant has not committed to doing such studies.

✓ 4. Pediatric studies designed to provide the information needed to include a pediatric claim are ongoing.

___ 5. Some information on pediatric dosing and safety are included in the draft labeling but without a specific pediatric claim.

(Check the appropriate blanks under #2 to indicate whether further data on effectiveness in pediatric patients will be obtained in Phase 4 studies.)

___ 6. The proposed claim in the draft labeling is specifically directed toward a pediatric illness, e.g., petit mal seizures, otis media, JRA, patent ductus.

___ 7. The dosage form is expected to be used primarily in the pediatric population.

___ a. A specific pediatric claim is included in the labeling.

___ b. The labeling does not include a specific pediatric claim. Check the appropriate blanks under #2 to indicate whether further data on effectiveness in pediatric patients will be obtained in Phase 4 studies.)

LRipper/4-12-90/0247r

cc: ORIGINAL NDA 20-671
HFD-150/DIV FILE
SHIRSCHFELD

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Lisa M. Catterson
Signature of Preparer

5/13/96
Date

5/21/96

cc: Orig NDA
HFD-150/Div File
NDA Action Package

Clin. Pharm

+

Bio

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

SK&F S-104864-A (Topotecan) Submission Date: December 21, 1995
Injection
NDA 20-671
SmithKline Beecham Pharmaceuticals
King of Prussia, PA
Reviewer: Peter N. Zannikos, Pharm.D., Ph.D.
Type of Submission: New Molecular Entity (1P)

SYNOPSIS

The disposition of SK&F 104864 (topotecan) was studied in four phase I clinical trials following various intravenous infusion schedules over a wide range of doses. These trials enrolled both male and female cancer patients. A population approach evaluating **total** (SK&F 104864 and SK&F 105992) topotecan disposition in patients with ovarian carcinoma was also implemented.

The pharmacokinetics of SK&F 104864 has been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30 minute infusion daily for 5 days. SK&F 104864 exhibited multiexponential pharmacokinetics. The terminal half-life was 2 to 3 hours, and mean SK&F 104864 clearance was 1030 mL/min. Area under the curve increased approximately in proportion to the increase in dose. Comparison of pharmacokinetic parameters estimated for Days 1 and 4 did not suggest any change in pharmacokinetics over the dosing period. Following administration of SK&F 104864 at the recommended dosage of 1.5 mg/m^2 given as a 30 minute infusion, a peak plasma level of 40 ng/mL is typically obtained with a corresponding AUC of 60 ng*hr/mL. The steady-state volume of distribution ranged from L/m^2. *In vitro* studies demonstrated that 20 - 35 % of topotecan is bound to plasma proteins, depending on the experimental conditions. The oral bioavailability of the intravenous solution was 30 - 37 %.

Combined data from the phase I trials indicate that the overall mean SK&F 104864 clearance in male patients was approximately 24 % higher than in female patients. The mean volume of distribution was 237 L and 212 L in males and females, respectively. However, as SK&F 104864 is administered on the basis of body surface area, males are likely to receive a higher dose. Administration on a body surface area basis appears justified. Age did not appear to have significant influence on the clearance of SK&F 104864.

Population pharmacokinetic analysis (NONMEM) allowed inter-patient variability in **total** topotecan clearance and distribution volume to be determined. None of the covariates studied including age, weight, body surface area, creatinine clearance, ascites, medication use, and cycle influenced **total** topotecan disposition. The analysis indicated that **total** topotecan clearance was 35 % higher in patients with ECOG performance status of 0 or 1 compared to patients with an ECOG performance status of 2.

Acceptable studies have been performed in patients with renal or hepatic impairment. The recommended dose in patients with moderate renal impairment (Clcr 20 - 40 mL/min) is 0.75 mg/m^2/day.

Several attempts were made to investigate topotecan pharmacokinetic and pharmacodynamic relationships. The dose of SK&F 104864 administered, exposure to SK&F 104864 and exposure to SK&F 104864 plus SK&F 105992 were moderately correlated with hematologic toxicity (phase I studies and population analyses). No correlation was observed between **total** topotecan exposure and response (population analysis).

The major route of SK&F 104864 inactivation is through a pH-dependent reversible hydrolysis of the E-ring lactone, yielding an inactive dihydroxy carboxylic acid (SK&F 105992). Mass balance studies performed in dog and rat identified minor metabolites including a N-desmethyl derivative of SK&F 104864 and SK&F 105992. The rate of formation of N-desmethyl topotecan when incubated with microsomes prepared from rat, dog and human liver was low. Published data indicate that 20 - 60 % of the topotecan dose is excreted as SK&F 104864 and SK&F 105992 in humans. High concentrations of topotecan have been found in biliary secretions in one cancer patient (published report).

Formal drug interaction studies were **not** performed. However, *in vitro* studies using marker substrates for human P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A or CYP4A or dihydropyridine dehydrogenase indicate that these enzymes are not inhibited by topotecan.

RECOMMENDATION:

The submission has adequately addressed the Office of Clinical Pharmacology and Biopharmaceutics' requirements or guidelines. The general and labeling comments need to be sent to the sponsor.

FT

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cc: Orig. NDA
HFD-150/Division File, Catterson, Hirschfeld, Justice
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HFD-870/Chen
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TABLE OF CONTENTS **PAGE**

Synopsis 1
Recommendation 2
Abbreviations 4
Background 5
Summary of Bicavailability/Pharmacokinetics/Pharmacodynamics 6
General Comments 16
Labelling Comments 18

APPENDIX I:

Investigational Formulations 25
Analytical Methodology and Validation 26
Protein Binding and Blood:Plasma Ratio 31
Topotecan Metabolism
Preliminary Study - Rat 40
Quantitative Study - Rat 42
Preliminary Study - Dog 45
Quantitative Study - Dog 47
In Vitro Metabolism - Rat, Dog and Human Hepatic Microsomes 51
In Vitro Inhibitory Potential - Hepatic Cytochrome P450 54
In Vitro Inhibitory Potential - Dihydropyrimidine and Xanthine Oxidase 61

Clinical Pharmacokinetic/Pharmacodynamic Studies

Study 004: Phase I Study of Topotecan Administered as a 24-hour Continuous Infusion 65

Study 005: Phase I Study to Determine the Safety of SK&F 104864-A in Patients with a Solid Tumor on a Daily Basis Time Five Schedule Every 3 Weeks 75

Study 047: Single-Dose Oral Bioavailability and Pharmacokinetics of Topotecan 85

Study 097: Phase I Study of Topotecan in cancer Patients with Hepatic or Renal Dysfunction 93

Study 039: Population Pharmacokinetics and Pharmacodynamic Relationship for Topotecan in Women with Advanced Epithelial Ovarian Cancer 108

APPENDIX II

Contains the following information relating to clinical studies listed in APPENDIX I:
* patient demographic data, dose proportionality data, NONMEM output
* raw concentration versus time data (including graphs)

ABBREVIATIONS

AUC	area under the plasma concentration versus time profile
cls	clearance
Cmax	maximum plasma concentration
Clcr	creatinine clearance
dL	deciliter
hr	hour
iv	intravenous
mL	milliliters
min	minute
MTD	maximum tolerated dose
NONMEM	nonlinear mixed effects modeling
SD	standard deviation
SK&F 104864	topotecan lactone (ring-closed form)
SK&F 105992	topotecan hydroxy-acid (ring-opened form)
SS	steady-state
SA	(body) surface area
TDL	toxic dose lethal
tmax	time when Cmax observed
Vd	volume of distribution
WBC	white blood cell

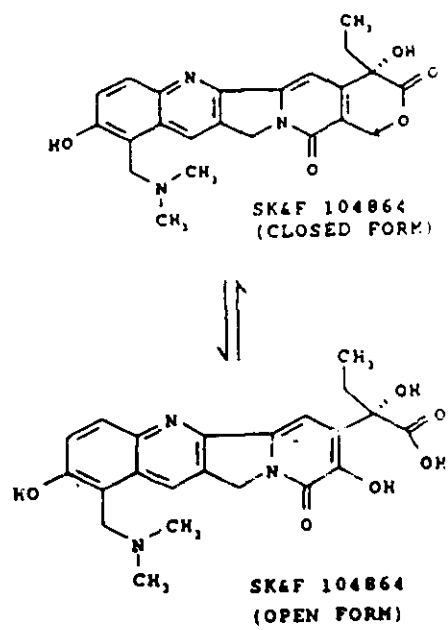
BACKGROUND

Chemistry:

Topotecan {(S)-9-[(dimethylamino)methyl]-10-hydroxycamptothecin hydrochloride}, SK&F 104864, is a novel semisynthetic derivative of camptothecin, an anticancer agent derived from stemwood of the Asian tree *Camptotheca acuminata*. It incorporates a stable basic side-chain at the 9-position of the A-ring of 10-hydroxycamptothecin which provides water solubility at acid pH. Topotecan stabilizes the DNA-topoisomerase I cleavable complex, which can result in lethal DNA damage during DNA replication.

Topotecan undergoes a pH dependent reversible hydrolysis of the E-ring lactone, yielding an inactive dihydroxy carboxylic acid (SK&F 105992). This reaction is pH dependent: at pH $\geq$10, the lactone is quantitatively opened while at pH $\leq$ 4 the lactone is exclusively present. Approximately 11 % of drug is present as the lactone form when topotecan is incubated in plasma at 37°C (equilibrium is reached within 5-6 hours).

Figure 1. Stucture of SK&F 104864 (topotecan) and its metabolite (SK&F 105992)



Rationale for Selection of Starting Dose and Treatment Regimen:

Experimentation with pre-clinical tumor models indicates that the effects of topotecan are dependent on the schedule of administration. This is consistent with topotecan's S phase-specific cytotoxicity and short half-life. With a rapidly dividing high growth fraction tumor, efficacy can

be maximized by a divided dose regimen. In more slowly proliferating models. efficacy of topotecan can be enhanced by administering the drug on a protracted daily regimen. These results are supportive of the daily X 5 every 3 week regimen that was selected for the pivotal clinical trials. The calculated LD_{10} for five consecutive daily treatments in mice was 13.8 mg/m^2. In dogs, a dose of 1.38 mg/m^2 was lethal in only 1 of 5 animals. A dose of 0.5 mg/m^2 (approximately 1/30th the mouse LD_{10} or 1/3rd the dog TDL) administered on this schedule was regarded as a safe starting dose for study in man.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETIC/PHARMACODYNAMICS:

I. BIOAVAILABILITY

Two pivotal clinical studies evaluated the safety and efficacy of topotecan. These studies used formulations AA & AC (study 034) and AC & AF (study 039). A list of the quantitative and qualitative aspects of formulations used throughout development of topotecan are provided in Appendix I. Since the drug is to be administered intravenously, bioavailability bioequivalence issues were not of concern.

The bioavailability of oral topotecan was evaluated in a cross-over, non-randomized Phase I trial (study 047). An intravenous (iv) formulation was administered orally and intravenously to 13 patients. Most patients received formulation AA. After oral administration, parent compound (SK&F 104864) was rapidly absorbed with median Tmax of 0.78 hours. The mean absolute bioavailability was 30 - 37 % depending on the method of analysis. Inter-patient variability was approximately 30 %.

II. PHARMACOKINETICS

Topotecan (SK&F 104864)

When administered according to the recommended dosage (i.e., 1.5 mg/m^2 as a 0.5 hr infusion) SK&F 104864 follows bi- or tri-exponential pharmacokinetics The terminal phase becomes apparent by 1 - 2 hours after dosing and has a half-life of 2 - 3 hours. Typical clearance values for SK&F 104864 were in the range of mL/min (Studies 004, 005 and 047). In one study (097) the average SK&F 104864 clearance was 2750 mL/min in patients with normal renal/hepatic function. Volume of distribution at steady-state was quite variable and generally in the range of L (Study 005).

SK&F 104864 pharmacokinetics appear to be independent of the dose administered. There was a general trend toward increased Cmax and AUC with an increase in dose over the range of mg/m^2 when SK&F 104864 was administered as a min infusion. However, a small sample size and moderate variability precluded evaluation dose-proportionality. No evidence of non-

linear pharmacokinetics were evident in the calculated half-life. Comparison of Cmax, AUC(0-inf) and terminal half-life values on days 1 and 4 following daily administration suggests that there were no consistent alterations in the disposition of SK&F 104864 with repeat dosing.

Clinical study 004 evaluated SK&F 104864 administered as a 24-hr infusion. Doses ranged from mg/m^2. SK&F 104864 exhibited mono- or biexponential disposition. The pharmacokinetics of SK&F 104864 were similar to those calculated following a 0.5 hr infusion. Across the dose range studied, Cmax and AUC(0-inf) values increased in a linear manner (r^2 > 0.90).

Hydroxy-acid metabolite (SK&F 105992)

When topotecan is administered as a 30-min iv infusion, SK&F 105992 is detectable at the earliest observations (study 047). By one hour after the start of a 0.5 hr infusion, concentrations of SK&F 105992 were in excess of SK&F 104864 concentrations, and overall AUCinf for SK&F 105992 was 1.9-fold greater than AUCinf of SK&F 105992. The mean terminal half-life and apparent clearance of the metabolite were 3.35 hr and 474 mL/min, respectively.

Within 6 hr after the start of a 24-hour infusion of topotecan (study 004), more than 50 % of **total** plasma levels of the drug was in the ring-opened species. On average, AUCinf for SK&F 105992 was 1.88-fold greater than that of the parent. Concentrations of SK&F 105992 peaked at the end of the infusion and declined in a mono- or bi-exponential manner. The terminal half-life and apparent clearance of the metabolite ranged from hr and mL/min, respectively.

Total topotecan (SK&F 104864 + SK&F 105992)

The pharmacokinetics of **total** topotecan was analyzed using population methods (NONMEM). Plasma concentration versus time data were obtained from clinical study 039 on day 1 of courses 1, 2 and 3. In most cases, patients were on 1.5 mg/m^2 dose. **Total** topotecan pharmacokinetics were described by a 2-compartment model. The average half-life of the terminal phase was 3.5 hr. The volume of distribution at steady-state was 69 L. The influence of demographic and patho-physiologic covariates on the clearance of **total** topotecan were studied in the population model. Clearance was related to body surface area and course. The final population model was:

CL = (q1 * SA) for course 1 and 2
CL = (q2 * SA) for course 3 and greater

The difference in **total** topotecan clearance calculated for those patients who received drug during courses 1 and 2 versus those who received 3 or more courses is probably not of clinical relevance (10.6 and 12.8 L/hr/m^2, respectively). The final model indicted that the unexplained between-patient variability in clearance was 39 %. The residual (or within- patient) variability was 47 %. Performance status was not evaluated as a covariate; however, mean clearance was 35 % higher

in patients with performance status of 0 or 1 compared to patients with a performance status of 2.

Total topotecan pharmacokinetics were also evaluated using nonparameteric methods in study 097. Mean values in patients with normal renal/hepatic function for clearance, Vdss, and terminal half-life were 18.8 L/hr/m^2, 156 L, and 3.8 hr, respectively.

Protein Binding

In vitro binding of [^{14}C]topotecan to plasma proteins of rat, dog, and man was determined by ultrafiltration. The compound was incubated in plasma at various concentrations for only 1 minute at which time the topotecan would be present predominantly as the lactone. The binding was low (32%, 33% and 35% in rat, dog and man, respectively) and essentially independent of the concentration used (Table 1).

Table 1. The in vitro binding of [^{14}C]topotecan to plasma proteins of rat, dog, and man (as determined by ultrafiltration)

Species	Concentration range (ng/mL)	Plasma protein binding (%)
Rat		31.8 ± 2.6
Dog		32.6 ± 4.2
Man		35.0 ± 3.0

Each value is the mean ± S.D. of 12 determinations.

The binding of [^{14}C]topotecan to plasma proteins was also determined by equilibrium dialysis following incubation of the drug in plasma for 30 min. The dialysis was carried over a period of 5 - 6 hours at which point the compound would predominantly be present as SK&F 105992 due to interconversion. Values obtained for the percent binding to plasma proteins in this study were lower than those obtained by ultrafiltration (Table 2) suggesting that SK&F 105992 has less affinity for binding to plasma proteins than SK&F 104864. However, differences attributable to the method of analysis cannot be ruled out.

Table 2. The *in vitro* binding of [^{14}C]topotecan to plasma proteins of rat, dog, and man (as determined by equilibrium dialysis)

Species	Concentration range (ng/mL)	Plasma protein binding (%)
Rat		13.6 ± 1.9
Dog		11.7 ± 0.6
Man		21.3 ± 1.6

Each value is the mean ± S.D. of 3 - 5 determinations.

III. METABOLISM AND EXCRETION

Identification of drug-related components was carried out by Data for radiometabolite patterns have been presented as the sum of ring-open and ring-closed forms. *In vivo* biotransformation was studied in laboratory animals. *In vitro* biotransformation was investigated in microsomes derived from liver tissue.

Rat

Topotecan accounted for virtually all of the plasma radioactivity in rats at 30 minutes after a single iv administration. A majority of the dose was excreted unchanged in the urine and feces (44% and 42 %, respectively). There were some minor metabolites present in excreta. One significant metabolite, an N-desmethyl derivative of topotecan, accounted for 4 % of the dose. Biliary excretion was found to play an important role in the elimination of drug.

Dog

In dogs, SK&F 104864 accounted for majority of the circulating radioactivity in plasma at 1 hr after an intravenous dose. An N-desmethyl derivative of SK&F 104864 accounted for 5 % of plasma radioactivity. As found in the rat, unchanged drug accounted for the majority of the dose in urine (25 %) and feces (22 %). The N-desmethyl metabolite accounted for 4 % and 17 % of the dose in the urine and feces, respectively.

Human

In vitro drug metabolism studies have **not** been performed in humans. However, observations made in one patient provide evidence for biliary secretion of topotecan. Concentrations of SK&F 104864 in bile exceeded those in plasma (Wall *et al.* Anti-Cancer Drugs, 1992).

In Vitro Biotransformation

The *in vitro* metabolism of topotecan by microsomes prepared from rat, dog and human liver tissue was evaluated. Metabolism was slow in all three species and N-desmethyl topotecan was the only metabolite identified in the incubates. Its rate of formation was comparable in preparations from the three species.

Inhibition of human cytochrome P450 by topotecan was also evaluated. Probe substrates were incubated at an appropriate concentration with microsomes in the presence of topotecan and in the presence of a mixture containing the ring-open and ring-closed forms of drug. No significant inhibition of CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A or CYP4A activity could be demonstrated.

Topotecan caused no significant inhibition of cytosolic dihydropyrimidine dehydrogenase activity. A similar observation was made for another cytosolic enzyme, xanthine oxidase; however, the

small sample size (n = 1) makes it difficult to reach firm conclusions regarding this latter enzyme.

Renal Elimination

Information in regards to the renal elimination of **total** topotecan (SK&F 104864 & SK&F 105992) was provided in three publications:

Results	Analytical Methods	Reference
25.8 % (range %) of total dose was excreted in urine over 24 hr (n = 19)	Developed by Beijnen *et al.* (see Appendix I)	Verwiji *et al.* Anals of Oncology, 1993
30 % (range %) of total dose was excreted in urine over 24 hr (n = 12)	Developed by Grochow *et al.* (see Appendix I)	Grochow *et al.* Drug Metab & Dispos, 1992
40 % (range %) of total dose was excreted in urine over 48 hr (n = 17)	Not reviewed	Wall *et al.* Anti-Cancer Drugs, 1992

The phase I studies demonstrated that SK&F 104864 clearance is dependent, in part, on renal function. SK&F 104864 clearance correlated with creatinine clearance (Clcr) (r^2 = 0.63, study 004; r^2 = 0.41, study 005; r^2 = 0.48, study 097). Moderate correlation between Clcr and SK&F 105992 clearance was also observed (r^2 = 0.57, study 004). In contrast, Clcr was not predictive of **total** topotecan clearance (r^2 =0.26, study 097). Results of the population analysis (study 039, NONMEM) indicate that creatinine clearance was **not** an important covariate in explaining inter-patient variability in **total** topotecan clearance.

IV. SPECIAL POPULATIONS

Renal Disease

Alterations in renal function have significant effects on the disposition of SK&F 104864. Patients with mild (Clcr 41 - 60 mL/min) and moderate (Clcr 20 - 40 mL/min) renal impairment exhibited a 34 % and 66 % decrease, respectively, in clearance. Dose-adjusted Cmax increased by 61 % and 128 %, respectively. Half-life was increased by 14 % and 160 % in these groups, respectively. A similar trend was observed for the disposition of **total** topotecan (SK&F 104864 & SK&F 105992).

The trend towards increased exposure in patients with mild renal failure did not have any apparent clinical consequences. In contrast, the suggested dose in patients with moderate renal impairment

is 0.75 mg/m^2/day as dose-limiting hematologic toxicity was evident at higher levels.

Hepatic Disease

The disposition of SK&F 104864 in patients with liver disease (bilirubin 1.7 - 15 mg/dL) was evaluated in 14 patients. Plasma clearance decreased by about 34 % and dose-adjusted Cmax increased by 33 % compared to control patients. Half-life was also increased approximately 27 %.

A 33 % increase in dose-adjusted Cmax for **total** topotecan (SK&F 104864 & SK&F 105992) was observed. Liver disease did not appear to influence **total** topotecan clearance or half-life.

These apparent alterations in topotecan disposition did not have clinical consequences since hepatically impaired patients did not require toxicity-related dose adjustments.

Gender

Mean pharmacokinetic parameters by gender for each study are given in Table 3. Considering studies 004, 005, 047 and 010, the overall mean SK&F 104864 plasma clearance in male patients was approximately 24 % higher than in female patients. However, as topotecan is administered on the basis of body surface area, males are likely to receive a higher dose. Dosing topotecan on the basis of body surface area appears justified.

Results from Study 097 showed much higher SK&F 104864 plasma clearance as compared to other phase I studies. Further, a greater gender difference in SK&F 104864 clearance was evident. An explanation for these findings was not provided.

The mean volume of distribution was 237 L and 212 L in males and females, respectively (results from studies 004, 005).

Table 3. SK&F 104864 Pharmacokinetics by Gender

Study No.	Regimen	N males/females	Plasma Clearance (mL/min)		Volume of Distribution (L)	
			Males	Females	Males	Females
CPMS 004	24 hr infusion	11/6	1061	1062	283	291
CPMS 005*	30 min infusion	12/5	1129	904	159	87
CPMS 047	30 min infusion	7/5	870	690	-	-
CPMS 097**	30 min infusion	5/4	4132	1409	322	249
CPMS 010***	30 min infusion	-/-	954	597	164	113

* pharmacokinetic data analyzed from first dose was use in calculation

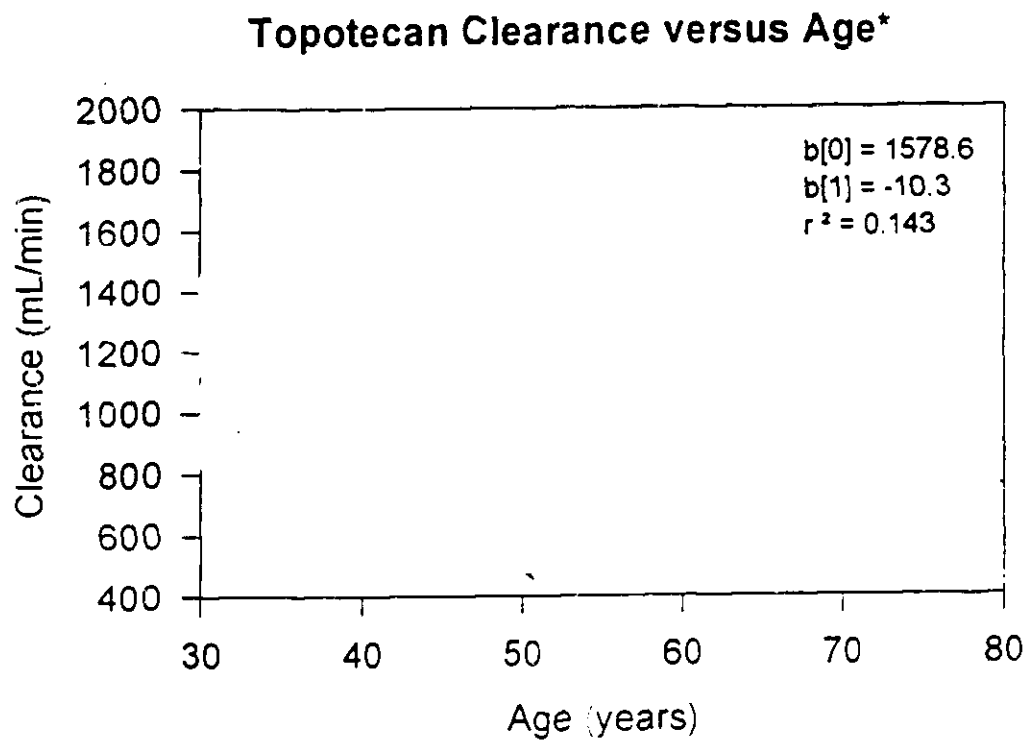
** pharmacokinetic data from group 5 (normal hepatic and renal function)

*** 17 patients total; raw data not provided for review; see Wall et al., Anti-Cancer Drugs, 1996

Elderly

Below, the correlation between SK&F 104864 clearance and age is evaluated. Data from three phase I trials were combined and included a wide range of doses administered either as a 30 minute or 24 hour infusion. A trend towards decreased clearance with age is evident; however, the clinical relevance of this is questionable.

Figure 2.



* Data obtained from studies 004 (first dose only), 005 and 047

The sponsor evaluated topotecan pharmacokinetics as a function of age using population methods (NONMEM, Study 039). In this analysis, clearance and volume of distribution of **total** topotecan (SK&F 104864 & SK&F 105992) was determined. Age was apparently not a useful covariate in explaining the variability in **total** topotecan disposition.

Race

The sponsor did not address the effect of race on the disposition of topotecan.

V. DRUG INTERACTIONS

Pharmacokinetic studies evaluating the potential for drug interactions between topotecan and concomitantly administered medications have not been formally investigated.

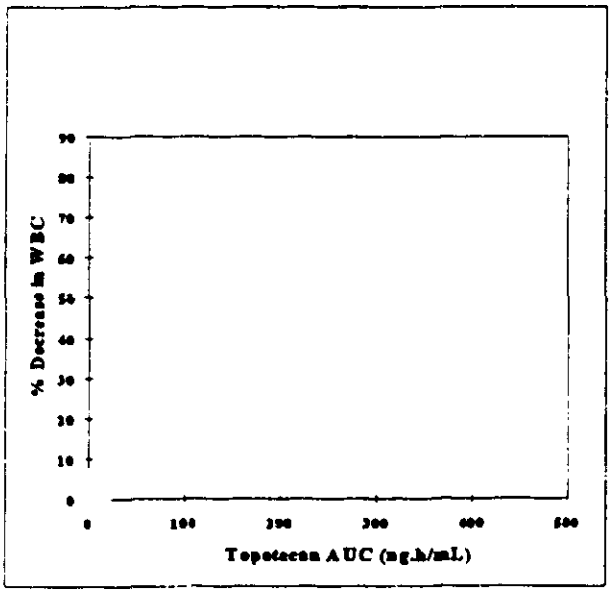
V . PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

Toxicity

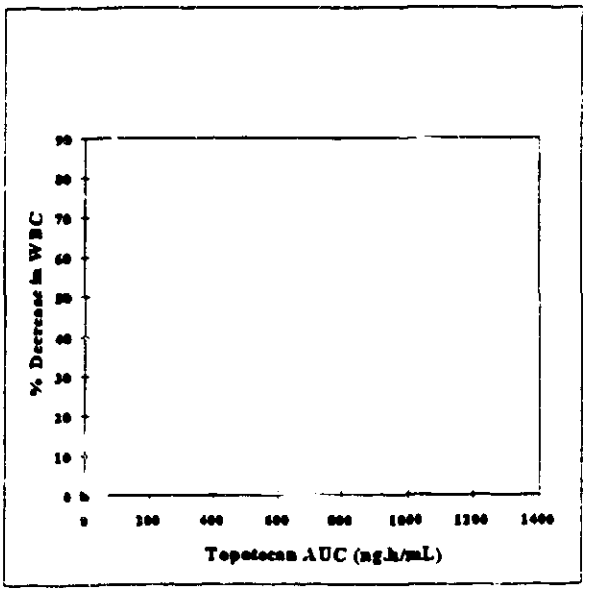
The principal measure of toxicity in patients was the percent decrease in white blood cell (WBC) count. Exposure to SK&F 104864 and SK&F 104864 plus SK&F 105992 were moderately correlated with hematologic toxicity.

Figure 3. PD relationship between a) AUCinf of SK&F 104864 or b) AUCinf of **total** topotecan and the percent decrease in WBC described by the sigmoid Emax model*

A)



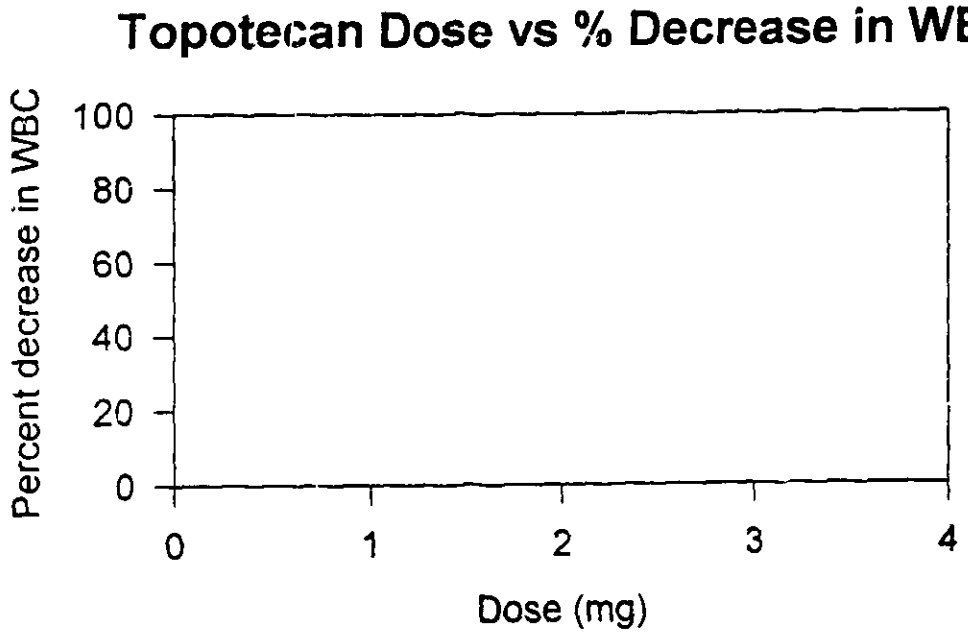
B)



* Data obtained from Study 004; topotecan was administered as a 24 hour infusion.

Data from Study 005, where topotecan was given at the recommended dosage (1.5 mg/m^2/day, 30 minute infusion), indicate that patients typically exhibit an 80 % decrease in WBC count after the first course of therapy (Figure 4).

Figure 4.

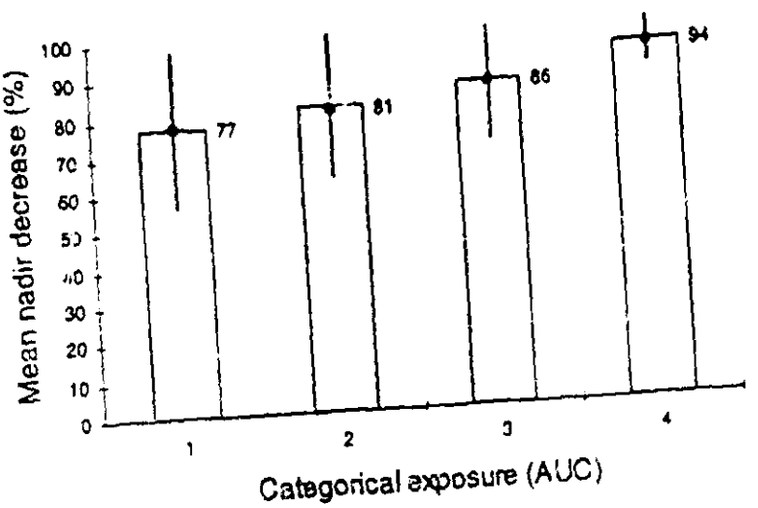


* Percent change in WBC = 100*(baseline - nadir)/baseline
AUC data from first dose and WBC data after first cycle of therapy was used

In the population analysis (Study 039), the average decrease in WBC count was 86 % and 76 % after the first and third course of therapy, respectively. Mean WBC nadir was similar in patients with **total** topotecan (SK&F 104864 & SK&F 105992) clearance values greater than the population mean (16.8 L/hr; 78.5 %) compared to the nadir in those patients with clearance values below the population mean (84.1 %). However, further sub-dividing the population by AUC did show a trend toward increased toxicity with exposure. Notably, this data is confounded by the fact that some individuals (23 % of topotecan courses) received G-CSF.

Figure 5. Data obtained from Study 39.

Total topotecan exposure after first dose versus WBC nadir after first cycle



Category	Exposure (AUC - ug.h/L)
1	70 - 130
2	130 - 190
3	190 - 300
4	> 300

Response

The relationship between **total** topotecan exposure (SK&F 104864 & SK&F 105992 AUC) and response was evaluated in the NONMEM population analysis (Study 039). Fifteen out of 100 patients were categorized as responders. Most (12/15) responders received at least three courses of therapy. No correlation was observed as **total** topotecan exposure was similar in responders and non-responders. Evaluating AUC after the first dose of course 1 of therapy (n = 100) or averaging the AUC after the first dose of courses 1, 2 and 3 (n = 48) yielded similar conclusions.

VII. ASSAY VALIDATION

GENERAL COMMENTS

1. Study 097 provided evidence that patients with hepatic impairment, defined as serum bilirubin between 1.7 - 14.9 mg/dL, exhibit greater topotecan exposure (i.e., increase in dose-adjusted C_{max}, half-life, and decrease in clearance) when compared to patients with normal liver function. Apparently, these alterations in topotecan disposition had no clinical consequences as hepatically impaired patients were able to tolerate daily doses of 1.5 mg/m^2. However, the group of liver diseased patients studied may not be fully representative of hepatically impaired patients that could receive topotecan once the drug is approved. For example, only two (unidentified) patients out of 14 patients with liver disease had biliary obstruction. This is notable since preclinical data suggest that biliary secretion plays an important role in the elimination of topotecan. Topotecan was found in high concentration in the bile of one cancer patient.

   The sponsor should continue to evaluate the influence of hepatic impairment on topotecan disposition. Those types of patients studied should be inclusive of the various forms/stages of liver disease physicians are likely to encounter.

   In order to fully characterize topotecan elimination, the sponsor should consider performing a mass balance study in cancer patients. This would also provide some insight as to whether hepatic impairment would be expected to influence topotecan elimination.

2. Co-administration of drugs with the potential to impair renal function may reduce topotecan clearance. The MTD of topotecan given on a daily times 5 dosing schedule every 21 days with a single infusion of cisplatin (75 mg/m^2) on day 1 of each course was 0.75 mg/m^2. This reduction in MTD may be due to additive toxic effects associated with concomitant therapy, a temporary reduction in renal function due to cisplatin or some other pharmacokinetic/pharmacodynamic interaction. The sponsor should address this issue. The potential for interaction with other compounds likely to be used with topotecan which may influence renal function should also be evaluated (e.g., probenecid)

3. The sponsor has performed studies evaluating the potential for topotecan to inhibit various cytochrome P450 enzymes. The Division encourages the use of such *in vitro* experiments to assess the potential for metabolic drug interactions. To fully assess such experiments, the Division requests information regarding methods validation for the various assays, as well as the assay conditions, particularly with respect to microsomal protein, substrate concentrations and incubation periods used. The general reports referenced in the Pharmacology/Toxicology Informational Amendment apparently contain much of this information and should be included in the submission.

4. The lack of correlation between total topotecan (SK&F 104864 and SK&F 105992) exposure and response may not be reflective of the association between exposure to the active species (parent compound) and response. The sponsor should continue to evaluate pharmacokinetic/pharmacodynamic relationships utilizing an assay specific for the active compound. This is particularly true if various dosing regimens are to be evaluated which may provide increased efficacy.

5. The sponsor should provide, for review, a detailed pharmacokinetic report describing the disposition of topotecan in pediatric population. This is particularly necessary if this information is to be included in the labeling.

6. The sponsor has included in the proposed labeling that topotecan did not inhibit xanthine oxidase. However, the production of uric acid was quantified in only one cytosolic fraction prepared from human liver. In future studies, enzyme activities from multiple livers, either individually or as a pooled preparation, should be utilized.

7. In the analysis of *in vitro* topotecan metabolism in human microsomal samples, a portion of the radioactivity eluted at the end of the gradient where a large UV absorbance peak was observed. Further, some radioactivity was associated with the solvent front which was present in all samples and was unidentified. It would be of interest to know:

- the percent of radioactivity accounted for relative to total radioactivity
- the possibility that topotecan metabolites were in these peaks
- were control incubations lacking the NADPH-regenerating system evaluated ? If so, did these incubations reveal similar findings ?

LABELING COMMENTS

Proposed Sponsor

Pharmacokinetics

Proposed Revisions

The pharmacokinetics of topotecan has been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30 minute infusion daily for 5 days. Topotecan exhibited multiexponential pharmacokinetics. The terminal half-life was 2 to 3 hours. Mean topotecan clearance ranged from 500 to 1800 mL/min. Area under the curve increased approximately in proportion to the increase in dose. Following the administration of topotecan as a 1.5 mg/m^2 dose given as a 30 minute infusion, a peak plasma level of 35 ng/mL is typically obtained with a corresponding AUC of 60 ng*hr/mL.

Distribution: Topotecan steady-state volume of distribution ranges from 25 to 120 L/m^2. Binding of topotecan to plasma proteins is 35 %.

Metabolism:

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.

Metabolism: Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety. At pH $\leq$ 4 the lactone is exclusively present whereas the ring-opened hydroxy-acid form predominates at physiologic pH. This reaction constitutes a major route by which topotecan is inactivated.

In vitro studies in rat, dog, and human liver microsomes indicate that metabolism of topotecan to a N-demethylated metabolite represents a minor metabolic pathway.

Excretion:

Excretion: In humans, 20 - 60 % of the dose is excreted in the urine. Therefore, renal clearance is likely to be an important determinant of topotecan elimination. Biliary excretion has been observed in one patient. Studies suggest that rats may eliminate as much as 18% of an intravenous topotecan dose by intestinal excretion.

Special Populations

Gender:

Gender: The overall mean topotecan plasma clearance in male patients was approximately

24 % higher than in female patients.

Geriatrics: Topotecan pharmacokinetics have not been specifically investigated in elderly patients. However, a population pharmacokinetic analysis in female patients did not identify age as a significant factor.

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

Renal Impairment:

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 control patients. Changes in half-life were not significant.

In patients with moderate renal impairment (Cl_{cr} 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34 % of the value in control patients. Mean half-life estimated in three renally impaired patients was 5.0 hours. Dosage adjustment is recommended in this subgroup of patients. (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment:

Hepatic Impairment: Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 - 15.0 mg/dL) decreased to about 67 % of the value in control patients. Topotecan half-life increased from 2.0 hours to 2.5 hours. However, these hepatically impaired patients were able to tolerate 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 dihydropyridine dehydrogenase suggested that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo* and cannot be ruled out.

Pharmacodynamics: The dose-limiting toxicity for topotecan is leukopenia. Correlations between decreased white blood cell count and either topotecan dose or topotecan AUC have been demonstrated. When topotecan is administered at a dose of 1.5 mg/m^2/day for 5 days, an 80 - 90 %

INDICATIONS AND USAGE

Hycamtin is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent therapy.

PRECAUTIONS

Drug Interactions: In phase I studies, myelosupression was more severe when *Hycamtin* was given after cisplatin.

When used concomitantly with platinum compounds, the dose of *Hycamtin* must be reduced due to the observed greater incidence of myelosupression (see DOSAGE AND ADMINISTRATION), and myelosuppression may require delay of subsequent courses (see Warnings).

Nursing Mothers: It is not known whether the drug is excreted in human milk.

Breast feeding should be discontinued when women are receiving *Hycamtin* (see CONTRAINDICATIONS).

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

DOSAGE AND ADMINISTRATION

The recommended dose of Hycamtin (topotecan hydrochloride) 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.

A minimum of four courses is recommended because median time to response in three clinical trials was 9 to 12 weeks.

decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

In the event of severe neutropenia, the dose should be reduced by 0.25 mg/m^2 for subsequent courses.

As an alternative, G-CSF may be administered before reducing the dose, starting from Day 6 of the course (the day after completion of topotecan administration).

Routine pre-medication for non-hematological adverse events is not required with *Hycamtin*.

Patients who require concurrent cisplatin (for directions for the administration of cisplatin, refer to the cisplatin prescribing information) and *Hycamtin* may be treated as follows: 75 mg/m^2 of cisplatin administered on day one of each course of therapy, owed by 0.75 mg/m^2 of *Hycamtin* by intravenous infusion over 30 minutes for 5 consecutive days, according to the recommended regimen described above.

A reported study recommended topotecan 1.0 mg/m^2/d for 5 consecutive days in combination with cisplatin 50 mg/m^2 on day 1 without G-CSF or cisplatin 75 mg/m^2 on day 1 with G-CSF support.[2]

No dosage adjustment is required for treating hepatically impaired patients (plasma bilirubin >1.5 to < 10 mg/dL).

No dosage adjustment is required for patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min).

Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20 to 39 mL/min). Insufficient data are available on patients

with severe renal impairment to provide a dosage recommendation.

Insufficient data are available in pediatric patients to provide a dosage recommendation.

FEB 13 1996

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

Topotecan hydrochloride (*Hycamtin*) Submission Date: Dec. 22, 1995
Injection
NDA 20-671
SmithKline Beecham Pharmaceuticals
King of Prussia, PA

Reviewer: Peter N. Zannikos

Type of Submission: New Drug Application (original)/ **45-day filing meeting**

Topotecan (SK&F 104864), a semi-synthetic water-soluble analog of camptothecin, is a potent inhibitor of topoisomerase I. Topotecan apparently stabilizes the covalent complex between topoisomerase I and DNA. This results in DNA cleavage and single-strand breaks.

The proposed indication of Topotecan is the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent therapy. The recommended treatment regimen of Topotecan is 1.5 mg/m^2 to be given as a 30-minute infusion every day for 5 days and repeated every 3 weeks.

In vivo, Topotecan undergoes spontaneous hydrolysis from the closed-ring lactone (active species) to an open-ring hydroxy acid (less active). It is not stable at physiologic pH and equilibrium processes favor hydrolysis of the lactone.

The sponsor has submitted the following studies which describe the pharmacokinetics of Topotecan following intravenous administration:

Study	Species measured in plasma	Comments
Phase I		
004	Topotecan and metabolite	24 hour infusion
005	Topotecan	
047	Topotecan and metabolite	Bioavailability of oral solution also determined
097	Topotecan and total (i.e., parent plus metabolite)	Patients with hepatic or renal impairment included
Phase III		
039	Total (parent plus metabolite)	Population analysis

The studies appear to provide descriptive pharmacokinetics of topotecan, dose proportionality, drug disposition in special populations and pharmacodynamic assessment. Drug metabolism studies have been performed in laboratory animals and with human microsomal preparations. The potential for drug-drug interactions have not been investigated to any appreciable extent.

The Biopharmaceutics section of the NDA is indexed and paginated in a well organized manner. Submission of the NDA as a CANDA, in addition to hard copy, should facilitate the review process.

Recommendation:

The NDA 20-671 (topotecan hydrochloride) is acceptable for filing pending submission of the requested assay validation data.

FT _____ 2/5/96 _____ 2/5/96

Atiqur Rahman, Ph.D., Team Leader
Div of Pharmaceutical Evaluation I

Peter N. Zannikos, Ph.D.
Div of Pharmaceutical Evaluation I

cc: ORIGINAL NDA 20-671
HFD-150: Catterson, HFD-150/DIV FILE
HFD-150: Division File
HFD-860: Malinowski, Mehta, Rahman, Zannikos
HFD-850: Chron, Drug and Reviewer's File

Pharm/Tox

Division of Oncology Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
NDA for Ovarian Cancer, Review

NDA 20-671 Reviewer: W. David McGuinn, Ph. D.

Submission: Received by CDER December 22, 1995
Received by reviewer January 2, 1996

Sponsor: **SmithKline Beecham Pharmaceuticals**
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

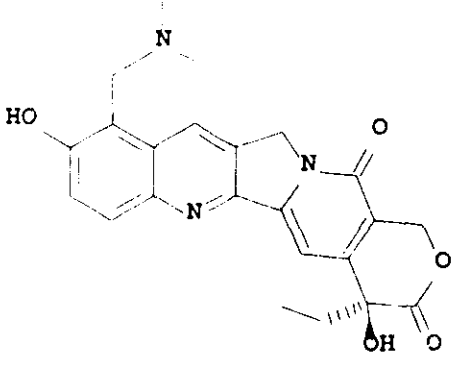
Information to be conveyed to the sponsor: NO

Drug Name: Hycamtin™, topotecan HCl for injection
or SK&F S-104864-A (hydrochloride salt)

Chemical Name: (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1 H - pyrano[3',4':6,7] indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride.

CAS-119413-54-6 CAS-123948-87-8 (free base)
Molecular Formula: $C_{23}H_{23}N_3O_5 \bullet HCl$
Molecular Weight: 457.91 (hydrochloride salt)

Structure



Indications: Ovarian Cancer

Drug Type: Topoisomerase I inhibitor, antineoplastic.

Related INDs IND
IND
IND
IND

Studies Reviewed

The following studies were reviewed by Dr. A. Taylor, February 28, 1989, under IND

	NDA volume	Page
In Vivo Studies		
PP 001 CM: Activity of Single or Multiple iv Injections of SK&F 104864-A Against Advanced ScHT-29 Human Colon Carcinoma in Female CD-1 Nu/Nu Mice	1.11	000039
PP 002 CM: Chemotherapeutic Activity of SK&F 104864-A and SK&F 104864-E Against B16 and B16F10 Melanoma in Female B6D2 F1 Mice	1.11	000061
PP 003 CM: Chemotherapeutic Effect of SK&F 104864-E in B6D2 F1 Female Mice Bearing M5076 Reticulum Cell Carcinoma	1.11	000084
PP 004 CM: Chemotherapeutic Effect of SK&F 104864-E Against Lewis Lung Carcinoma in Female B6D2F1 Mice	1.11	000099
PP 005 CM: Chemotherapeutic Effect of SK&F 104864-A and SK&F 104864-E in BALB/c and CD2F1 Mice Bearing sc Madison Lung Carcinoma	1.11	000121
PP 006 CM: Chemotherapeutic Effect of SK&F 104864-E Against sc Mammary Adenocarcinoma 16/c in Female C3H/He Mice	1.11	000135
PP 007 CM: Chemotherapeutic Effectiveness of SK&F 104864-E in BALB/c Mice Bearing sc ADJ-PC6 Plasmacytoma	1.11	000147
PP 008 CM: Chemotherapeutic Effectiveness of SK&F 104864-A and SK&F 104864-E Against Murine Colon Carcinomas in Mice	1.11	000158
PP 009 CM: Chemotherapeutic Effectiveness of SK&F 104864-A or -E in Female B6D2F1 Mice bearing ip or iv P388 Lymphocytic Leukaemia	1.11	000178
PP 010 CM: Chemotherapeutic Effectiveness of SK&F 104864-A or SK&F 104864-E Against Multidrug-Resistant Sublines of P388 Leukaemia in B6D2F1 Mice	1.11	000196
PP 011 CM: Chemotherapeutic Effectiveness of SK&F 104864-A or -E Against L1210 Leukaemia in Female B6D2F1 Mice	1.11	000221
PP 012 CM: Formulated and Bulk SK&F 104864-A: Comparison in Nontumored Female B6D2F1 Mice and in Mice Bearing Systemic (iv implanted) L1210 Leukaemia	1.11	000247
Single Dose		
Mouse, iv		
TP 002 CM: Single Dose and Five Daily Dose Acute Toxicity of SK&F 104864 in the Mouse	1.13	000002
Rat, iv		
TP 001 CM: Single Dose Dose-Range Study of SK&F 104864 in Male Rats	1.13	000072
TP 006 CM: Single Dose Toxicity of SK&F 104864 in the Rat	1.13	000239
Dog, iv		
TP 003 CM: Single Dose, Dose-Range Toxicity Study of		

SK&F 104864 in the Male Beagle Dog	1.14	000029
TP 008 CM: Single Dose Toxicity of SK&F 104864 in the Dog	1.14	000068
Multiple Dose		
Rat, iv		
TP 004 CM: The Toxicity of SK&F 104864 in the Rat After Five Daily Doses (Dose-Range Study)	1.15	000100
TP 005 CM: Five-Daily Dose Toxicity Study of SK&F 104864 in the Rat 1.16 000002		
Dog, iv		
TP 007 CM: Five Daily Dose, Dose-Range Toxicity Study of SK&F 104864 in the Male Beagle Dog	1.22	000002
TP 009 CM: Five Daily-Dose Toxicity of SK&F 104864 in the Dog	1.20	000210
Pharmacokinetics		
BP 004 CM: Plasma Concentration Characteristics of Intravenous SK&F 104864 in Rats and Mice	1.26	000003
BP 005 C: Determination of 14C-SK&F 104864-A Binding to Protein in Human, Dog and Rat Plasma and the Blood to Plasma Ratio in Dog Blood	1.26	000202
BP 002 CM: Balance/Excretion of Radioactivity in Male and Female Sprague Dawley Rats Following Intravenous Administration of 14C-SK&F-104864	1.27	000231
Analytical Methods		
BP 001 CM: A High Performance Liquid Chromatographic Method for Determination of [S]-9-Dimethylaminomethyl-10-Hydroxycamptothecin (SK&F 104864) in Dog, Rat and Mouse Plasma	1.27	000273
BP 003 CM: A High Performance Liquid Chromatographic Method for Determination of [S]-9-Dimethylaminomethyl-10-Hydroxycamptothecin (SK&F 104864) in Rat Urine	1.27	000299

The following studies were reviewed by Dr. Lee Ham, July 25, 1995, under IND

Pharmacology		
PP-1002: Direct comparison of oral administration of SK&F 104864 with parenteral treatment against systemic and localised murine tumours	1.11	000294
Pharmacokinetics		
BP-1004: Relative Bioavailability of SK&F-104864 in male Beagle dogs following administration of 5 mg of SK&F 104864-A as four different oral formulations	1.26	000181
Toxicology		
Rat, oral		
TP-1019: SK&F 104864: Single-dose oral toxicity study in rats	1.14	000002
Dog, oral		
TP-1014: Single dose oral toxicity study of SK&F 104864 in dogs	1.15	000033
TP-1021: SK&F 104864-A: 5 day oral toxicity study in dogs	1.23	000002

TP-1020: SK&F 104864-A: Dose range oral toxicity study in dogs 1.22 000043

Studies reviewed in this document

Pharmacology

In Vitro Studies	Volume #	Page
PP 013 CM: Biochemical and Cellular Pharmacological Studies of SK&F 104864, a Specific Inhibitor of Eukaryotic Topoisomerase-I.	1.11	000003
In Vivo Studies		
Addendum to SK&F Report No. PPOO1CM (October 1995)	1.11	000055
Addendum to SK&F Report No. PPOO4CM (October 1995)	1.11	000114
PP-1001/2: Combination therapy utilising SKF 104864 in female mice bearing L1210 lymphocytic leukaemia, Lewis lung carcinoma, mammary adenocarcinoma 16/c or b/6 melanoma	1.11	000260
PP-1002: Direct comparison of oral administration of SK&F 104864 with parenteral treatment against systemic and localised murine tumours	1.11	000294
Central Nervous System		
TP-1001: SK&F 104864-A: Assessment of the Effects on Locomotor Activity in the Mouse	1.12	000003
TP-1004: SK&F 104864-A: Assessment of Effects on Hexobarbital-Induced Sleeping Time in the Mouse	1.12	000019
TP-1006: SK&F 104864-A: Assessment of the Effects in the Mouse using the Irwin Dose-Range Test	1.12	000036
TP-1007: Assessment of Effects on Body Temperature in the Mouse	1.12	000063
TP-1009: SK&F 104864-A: Assessment of Anticonvulsant Activity Using the Supramaximal Electroshock Test	1.12	000084
TP-1011: SK&F 104864-A: Assessment of Analgesic Activity-Tail Pinch Test in the Mouse	1.12	000101
TP-1012: SK&F 104864-A: Assessment of Effects in the Minimal Metrazol Test in the Mouse	1.12	000118
Cardiovascular/Renal		
TP-1013: SK&F 104864-A: Effects on Cardiovascular and Respiratory Parameters in the Anaesthetized Rat	1.12	000135
TP-0012: SK&F-104864-A: Evaluation of the Effects on Cardiovascular and Respiratory Parameters in the Anaesthetized Beagle Dog	1.12	000167
Gastrointestinal		
TP-1002: SK&F 104864-A: Assessment of the Effects on Intestinal Motility Using the Charcoal Propulsion Test in the Mouse	1.12	000264
TP-1005: SK&F 104864-A: Assessment of the Effects on the Responses of the Isolated Guinea-Pig Ileum to Acetylcholine,		

Histamine and Barium Chloride	1.12	000280
TP-1008: SK&F 104864-A: Assessment of the Effects on the Isolated Guinea-Pig Ileum	1.12	000301
Urinary		
TP-1003: SK&F 104864-A: Assessment of the Effects on Urine Volume and Electrolyte Excretion in the Rat	1.12	000316
Single dose Toxicology		
TP 1023: Intravenous and Perivenous Irritation study of a Tartaric Acid Formulation in Dogs	1.15	000002
Repeat Dose Toxicology		
Rat, iv		
TP 010 CM: Five-Daily Dose Repeat Schedule Toxicity of SK&F 104864 in the Rat	1.16	000279
TP-1017: 28 day intravenous toxicity study of SK&F 104864 in rats	1.17	000002
TP-1037: SK&F 104864-A: Impurity Evaluation in a 14-Day Intravenous Toxicity Study in Rats	1.20	000002
Rat, oral		
TP-1036: SK&F 104864-A: 6-Month Oral Toxicity Study in Rats	1.19	000002
Rabbit, iv		
TP-1025: SK&F 104864-A: Maximum tolerated intravenous dose study in non-mated female rabbits	1.20	000195
Dog, iv		
TP-1034: SK&F 104864-A: One Month Intravenous Toxicity Study in Dogs	1.21	000002
Mutagenicity Studies		
In vitro Studies		
TP-0013: SK&F 104864-A: Bacterial Mutation Assay	1.25	000132
TF-1002: SK&F 104864-A: Report of mutation tests with L5178Y mouse lymphoma cells at the TK locus	1.25	000163
TP-1016: SK&F 104864-A: Chromosomal aberrations assay with human lymphocytes in vitro	1.25	000199
In vivo Studies		
TF-1001: SK&F 104864-A: Report of a micronucleus test in the mouse by the intravenous route (single-dose study)	1.25	000253
TF-1003: SK&F 104864-A: Report of a single dose micronucleus test in the mouse by the iv route to determine the no-effect dose	1.25	000298
Carcinogenicity Studies		
none submitted		

Reproductive Studies

Rat

TP-1031: SK&F 104864-A: Intravenous Study of Female Fertility and Early Embryonic Development to Implantation in Rats	1.22	000230
TP-1022/1: SK&F 104864-A: Intravenous Male Fertility Study in Rats (Segment I/A Reproduction Study)	1.24	000002
TP-1035: SK&F 104864-A: Investigative Study for		

Teratology

Rat

TP-1032: SK&F 104864-A: Intravenous Study for Effects on Embryo-Fetal Development in Rats	1.24	000183

Rabbit

TP-1029: SK&F 104864-A: Dose Range Intravenous Developmental Toxicity Study in Pregnant Rabbits	1.25	000002
TP-1030/2: SK&F 104864-A: Intravenous Study for Effects on Embryo-Fetal Development in Rabbits	1.25	000030

Special Toxicology Studies

TF-0001: To Assess the "In Vitro" Ability of SK&F 104864 to Promote the Adsorption of Plasma Proteins onto Human Red Blood Cells	1.22	000104
TP-1024/2: SK&F 104864: In vitro hemolysis testing in human blood 1.22 000116		
TP-1028/2: SK&F 104864: Intravenous hematoxicity in rats	1.22	000130
TP-1018: SK&F 104864-A: Assessment of antigenicity after subcutaneous and intravenous administration to the guinea-pig	1.22	000191
TP-1015: The Measurement of the Extent of the Covalent Binding of 14C-SK&F 104864 to Human Serum Albumin In Vitro	1.27	000485

Absorption, Distribution Metabolism, Excretion Studies

Pharmacokinetics

Single Dose Pharmacokinetics

Mouse

BP 007 CM: Determination of the Pharmacokinetic Parameters of SK&F 104864 and total drug (SK&F 104864 plus SK&F 105992) in Female Mice Following a 25 mg/kg (75 mg/m2) I.V. Dose	1.26	000025

Rat

BP/008 CM: SK&F 104864 Pharmacokinetics in Male Sprague Dawley Rats Following a Single IV Bolus Dose of SK&F 104864 (5.55 or 68.6 mg/m^2)	1.26	000039
BP-1002: Determination of the Pharmacokinetic Parameters and Bioavailability of SK&F 104864 and Total Drug in Male Beagle Dogs Following a Single Intravenous Infusion (30 min.) or 0.5 mg/kg (10 mg/m2) and Following Single Oral Administration of 1.5 mg/kg		

(30 mg/m2) of SK&F 104864-A as an Acidic Solution Formulation	1.26	000106
BF-1004: Excretion and plasma concentrations of drug related material following single intravenous administration of [14C]SK&F 104864A to male and female rats and dogs at target levels of 1 mg pure free base/kg and 0.5 mg pure free base/kg, respectively	1.26	000065
BP-1008: Pharmacokinetics of topotecan and SK&F 105992 in beagle dogs following intravenous administration of both topotecan and SK&F 105992 and following oral administration of topotecan.	1.26	000139
TP-1020: SK&F 104864: Dose range oral toxicity study of SK&F 104864 in dogs.	1.22	000043
TP-1014: SK&F 104864: Single dose oral toxicity study of SK&F 104864 in dogs.	1.15	000033
BP-1004: Relative Bioavailability of SK&F-104864 in male Beagle dogs following administration of 5 mg of SK&F 104864-A as four different oral formulations Multiple Dose Pharmacokinetics	1.26	000181
Rat		
TP-1036: SK&F 104864-A: 6-Month Oral Toxicity Study in Rats	1.19	000002
Dog		
TP-1034: SK&F 104864-A: 1 month intravenous toxicity study in dogs	1.21	000002
TP-1021: 5 day oral toxicity study in dog	1.23	000002
Protein Binding		
BP 005 C: Determination of 14C-SK&F 104864-A Binding to Protein in Human, Dog and Rat Plasma and the Blood to Plasma Ratio in Dog Blood	1.26	000202
BF-1007: [14C]SK&F 104864A: Studies of Plasma Protein Binding and Blood Cell Binding in vitro (Rat, Dog and Man)	1.26	000216
Distribution Studies		
Mouse		
BP-1003: Tissue Distribution of Radioactivity following a Single Intravenous Dose of 14C-SK&F 104864 (Target Dose: 20 mg/kg) to Male and Female Tumor Bearing B6D2F1 Mice Rat	1.26	000251
BP/009: Tissue Distribution of Radioactivity in Male Sprague Dawley Rats Following Intravenous (2 mg/kg) Administration of 14C-SK&F 104864-A2: A Qualitative Study by Whole Body Autoradiography	1.26	000282
BF-1003: Quantitative tissue distribution following a single		

intravenous administration of 14C SK&F 104864-A to rats at a target dose level of 1 mg pure free base/kg 1.26 000301

Enzyme Induction

BF-1005: The effect of SK&F 104864-A on hepatic levels of cytochrome P450 and related parameters in male and female Sprague Dawley rats after oral dosing at 0, 0.0023, 0.023 and 0.23 mg free base/kg/day 1.26 000358

BP-1010: An in vitro investigation of the inhibitory potential of topotecan (SKF 104864) on the human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2D6, CYP2E, CYP3A and CYP4A. 1.27 000003

BF-1011: An in vitro investigation of the inhibitory potential of Topotecan (SK&F 104864) on the human liver cytosolic enzymes, dihydropyrimidine dehydrogenase and xanthine oxidase 1.27 000032

Metabolism Studies

Rat

BF-1009: Quantitative biotransformation of [^{14}C]SK&F 104864 in male and female rats following intravenous dosing at 1 mg pfb/kg. 1.27 000055

BP-1009: Preliminary biotransformation of [^{14}C]SK&F 104864 in the male Sprague-Dawley rat following single intravenous administration (1 mg/kg). Vol 1.27, page 97 (IND submission #268).

BF-1008: Metabolite patterns in urine, faeces and plasma following a single intravenous administration of [^{14}C] SK&F 104864A to the rat and dog at target dose levels of 1 and 0.5 mg free base/kg respectively 1.27 000090

Dog

BF-1008: Metabolite patterns in urine, faeces and plasma following a single intravenous administration of [^{14}C] SK&F 104864A to the rat and dog at target dose levels of 1 and 0.5 mg free base/kg respectively 1.27 000090

BF-1010: Quantitative biotransformation of [^{14}C] SK&F 104864 in male and female dogs following intravenous administration at 0.37 mg pfb/kg 1.27 000139

BP-1012: Preliminary biotransformation of [^{14}C]SK&F 104864 in the male beagle dog following single intravenous administration (0.5 mg pfb/kg). 1.27 000176

BF-1012: The metabolism of [^{14}C]SK&F 104864 in rat, dog and human hepatic microsomes. 1.27 000201

Balance/Excretion Studies

Rat

BP-1006: Preliminary biliary excretion of ^{14}C-SK&F 104864 in male Sprague Dawley rats following single intravenous

administration (nominal dose 1 mg/kg)	1.27	000246
BF-1004: Excretion and plasma concentrations of drug related material following single intravenous administration of [^{14}C] SK&F 104864A to male and female rats and dogs at target levels of 1 mg pure free base/kg and 0.5 mg pure free base/kg, respectively	1.26	000065
Dog		
BP-1005/2: Preliminary balance/excretion of ^{14}C-SK&F 104864-A in male Beagle dogs following single intravenous (0.5 mg/kg) administration	1.27	000260
BF-1004: Excretion and plasma concentrations of drug related material following single intravenous administration of [^{14}C]SK&F 104864A to male and female rats and dogs at target levels of 1 mg pure free base/kg and 0.5 mg pure free base/kg, respectively	1.26	000065
Analytical Methods		
BP 006 CM: HPLC Methods for the Specific Determination of SK&F 104864 and for Determination of Total Drug (SK&F 104864 plus SK&F 105992) in Mouse, Human and Rat Plasma	1.27	000316
BP-1001: Validation of a sensitive assay for determination of SKF 104864 and total drug (SKF 104864 and SKF 105992) and drug stability verification in extracts of dog plasma	1.27	000347
BF-1006: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in human plasma using HPLC with fluorescence detection.	1.27	000384
BF-1001: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in rat plasma using HPLC with fluorescence detection	1.27	000427
BF-1002: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in dog plasma using HPLC with fluorescence detection	1.27	000453

Studies submitted but not reviewed.

CP-1019: Summary Report, Preparation of Radiolabeled SK&F 104864-A	1.27	000479

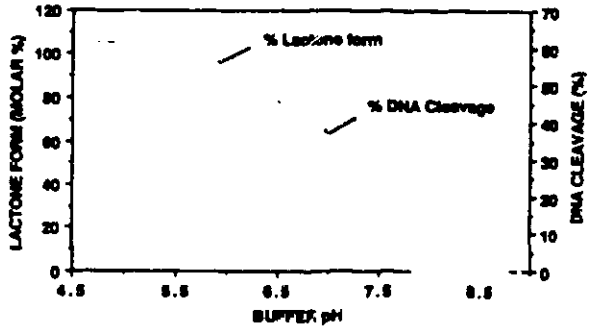
Pharmacology

In Vitro Studies

PP 013 CM: Biochemical and Cellular Pharmacological Studies of SK&F 104864, a Specific Inhibitor of Eukaryotic Topoisomerase-I. Vol 1.11, p 3

In this series of experiments, M. J. Caranfa *et al.* of SmithKline & French (SK&F) characterized the inhibition of topoisomerase I by topotecan. The following schema shows the hydrolysis of topotecan (a lactone) to form the hydroxycarboxyl open ring.

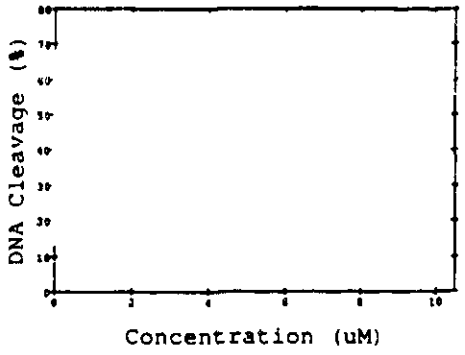
The investigators measured the concentration of each form at varying pH after equilibration. They determined concentrations of topotecan and hydroxycarbolylate by the HPLC method described below. They also measured the %DNA cleavage, that is, inhibition of topoisomerase I, by topotecan after equilibration in the various pH solutions. This assay relies on the assumption that the hydrolysis or dehydration of the two topotecan forms is a slow equilibrium. Thus, over the course of the DNA Cleavage reaction, which was done for only 30 seconds at physiological pH (7.4 in these assays), the concentration of the two forms does not change appreciably. This is a reasonable assumption. The following graph shows that the %DNA cleavage decreases directly with the percentage of the lactone form. Thus, the hydroxycarboxylate form does not inhibit topoisomerase I. The graph suggests that at physiological pH, about 20% of the topotecan is in the lactone form.



I tried to use the data points from this graph to calculate an equilibrium constant. The calculated value varied systematically over a factor of two. This suggests that the reaction is more complex than a simple hydrolysis in the buffer solution used in these experiments. W. J. M. Underberg *et al.* (*J. Pharmaceut. & Biomed. Analysis*, 1990, 8(8-12) 681-683) attempted to establish an equilibrium constant for this reaction. Unfortunately, the equation they assumed for

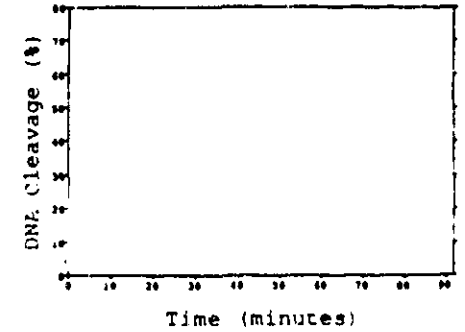
the hydrolysis reaction was incorrect and the experimental method they used was unnecessarily complex. This reaction remains to be thoroughly characterized.

The investigators in the current studies then demonstrated that topotecan causes cleavage of supercoiled pDPT2789 DNA at concentrations comparable to camptothecin. Samples of the plasmid DNA were incubated with purified topoisomerase I (17 ng) and various concentrations of camptothecin or topotecan for 30 min. After this time the reaction was stopped and the DNA was separated by agarose electrophoresis. The degree of topoisomerase inhibition is measured by the %DNA Cleavage. The following graph shows the results of this experiment. The graph suggests that half maximal inhibition (k_i) is on the order of 2 μM. I have not found a better estimate of this constant. A more rigorous analysis of this inhibition could provide useful mechanistic information, but the assay for this inhibition is difficult and time consuming. The circles show the reaction in the presence of camptothecin, the squares show the reaction in the presence of topotecan. The % DNA cleaved increases with increasing topotecan.



The binding of topoisomerase I to DNA is reversible and sequence specific. In the next experiments, Caranfa *et al.* demonstrated that the binding of topotecan to the topoisomerase I - DNA complex is also reversible. They added topotecan to topoisomerase I - DNA complex in solution. At 5, 15 or 60 minutes they added excess calf thymus linear DNA to compete out the topoisomerase-topotecan binding. The following graph shows the results of this experiment.

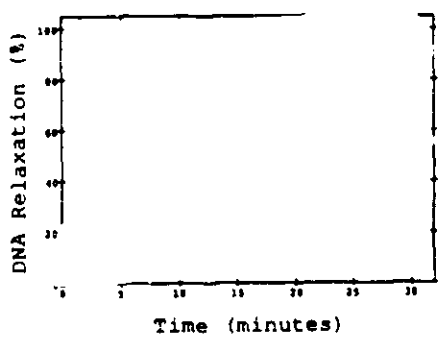
Figure 4. Reversal of the topoisomerase I-mediated cleavage of plasmid DNA by the addition of calf thymus DNA. Supercoiled DNA was treated with 34 ng topoisomerase I in the presence of 5 uM SK&F 104864. After 5, 15, or 60 min, 100-fold excess calf thymus linear DNA (nucleotide ratio to the plasmid DNA) was added, and the reactions were terminated with SDS/proteinase K at the indicated times. Closed symbols represent plasmid DNA cleavage in the absence of excess DNA; open symbols represent reversal of plasmid cleavage after the addition of excess DNA.



Topotecan did not inhibit the growth of mutant yeast strains as much as camptothecin or 10-hydroxy-camptothecin did. Of six mutant strains tested, the concentration of topotecan required to inhibit yeast growth within 12 mm of a well of the compound (IC_{12}) was greater than 800 µg/ml for all but rad52 TOP1 nys^{r}. This strain was deficient in repair mechanisms, resistant to nystatin, and deficient in cell membrane ergosterol. This last mutation increases the permeability of the yeast cell membrane. For this most sensitive mutant, the IC_{12} for camptothecin was 0.65 ± 0.05 µg/ml, for 10-hydroxy-camptothecin 9.5 ± 2.0 µg/ml and for topotecan 140 ±60 µg/ml.

The following graph shows that time course of the DNA relaxation reaction is slow as is the topotecan inhibition.

Figure 5. Time course of the conversion of supercoiled pBR322 DNA to relaxed covalently closed circular DNA by 0.5 units topoisomerase I in the presence of 5 uM camptothecin (circles), 5 uM SKF 104864 (squares), or in the absence of drug (triangles). The initial rates for topoisomerase I catalysis were linear: camptothecin, r^2 = 0.998; SKF 104864, r^2 = 0.995; no drug, r^2 = 0.998.



In Vivo Studies

Addendum to SK&F Report No. PPOO1CM (October 1995). Vol. 1.11. p 55.
Addendum to SK&F Report No. PPOO4CM (October 1995). Vol. 1.11, p 114.

These addenda provide summary tables and charts demonstrating the efficacy of topotecan. Dr. Taylor discussed these studies in his review of the original submission to IND

In PP001CM, athymic female mice tolerated a dose of 9 mg/kg s.c. of topotecan twice a week for five and one half weeks. These animals bore HT-29 human colon adenocarcinoma implants. This dose caused 3 CRs and 2 PRs in 5 treated mice. Treatment delayed tumor regrowth (T-C) by > 68 days.

In PP004CM, female B6D2F1 mice bearing s.c. implanted Lewis lung carcinoma tolerated a single dose schedule of 25 mg/kg topotecan i.p. or a multi-dose schedule of 3.75 mg/kg i.p. q3hX4. In both schedules, injections were given on days 9, 13 and 17. Both schedules delayed tumor regrowth by approximately 16 days and increased life-span approximately 80 days.

PP-1001/2: Combination therapy utilizing SKF 104864 in female mice bearing L1210 lymphocytic leukaemia, Lewis lung carcinoma, mammary adenocarcinoma 16/c or b/6 melanoma. Vol. 1.11, p 260

In this series of experiments McCabe *et al.* implanted L1210 lymphocytic leukemia, advanced systemic Lewis lung carcinoma, advanced mammary adenocarcinoma or advanced B16 melanoma in female mice. After these tumors were well established, they treated the mice with topotecan alone or in combination with cisplatin or etoposide. The follow table summarizes the major results of these experiments.

Table 1

Combination Chemotherapy with SKAF 104864-A plus Either Cisplatin or Etoposide in Female B6D2F1 Mice Bearing Advanced Systemic Lewis Lung Carcinoma

Drug/Route/ Schedule	Dose mg/kg	Weight Change Day 14 (gm)	Weight Change Day 22 (gm)	Toxic Deaths	MST[a] Days	ILS[b] %	LTS[c]
Untreated Controls	0	-6.4	-	-	15	-	-
	0	-1.1	-	-	16 (15.5	-	-
	0	-3.8	-	-	16	-	-
SKAF 104864-A (Topo) ip, Days 7 & 14	41.7	-0.3	+1.7	2/7	toxic	-	-
	25	+0.7	+0.7	0/7	31	106	-
	15	0	-1.8	0/7	20	81	-
	9	-0.4	-1.7	0/7	23	42	-
	5.4	-3.1	-	0/7	21	36	-
Etoposide (Etop) ip, Days 7 & 14	75	+0.6	-0.6	0/7	toxic	-	-
	45	-0.1	-1.6	0/7	26	68	-
	27	-0.4	-	0/7	22	42	-
	16.2	-2.1	-	0/7	20	29	-
	9.72	-3.4	-	0/7	18	16	-
Cisplatin (DDP) ip, Days 7 & 14	10	-6.0	-	3/7	toxic	-	-
	6	-3.4	-	0/7	21	36	-
	3.6	-2.7	-	0/7	20	29	-
	2.16	-3.0	-	0/7	18	16	-
	1.3	-2.4	-	0/7	17	19	-
Topo/Etop ip, Days 7 & 14	25/45	+1.3	+0.3	0/7	33	113	1/7
	25/27	+1.8	+2.1	0/7	31	106	-
	25/16.2	+1.4	+1.7	0/7	32	106	-
	25/9.72	+1.4	-1.0	0/7	29	87	-
	15/45	+0.6	+0.6	0/7	32	106	-
	15/27	+1.0	+0.4	0/7	30	94	-
	15/16.2	+0.6	-0.1	0/7	27	74	-
	15/9.72	-0.7	-4.8	0/7	24	55	-
	9/45	+0.6	-1.7	0/7	26	68	-
	9/27	+0.7	+0.3	0/7	30	94	-
	9/16.2	-0.6	-4.5	0/7	25	68	-
	9/9.72	-0.7	-3.5	0/7	24	55	-
	5.4/45	+1.3	+0.3	0/7	28	81	-
	5.4/27	+0.4	-2.6	0/7	26	68	-
	5.4/16.2	-0.6	-4.8	0/7	23	48	-
	5.4/9.72	-1.3	-4.4	0/7	23	48	-
Topo/DDP ip, Days 7 & 14	25/6	-5.7	-	6/7	toxic	-	-
	25/3.6	-2.6	-1.1	0/7	34	119	1/7
	25/2.16	-2.7	-0.3	0/7	37	139	1/7
	25/1.3	-0.9	+1.6	0/7	34	119	1/7

Table 1 (continued)

Combination Chemotherapy with SKAF 104864-A plus Either Cisplatin or Etoposide in Female B6D2F1 Mice Bearing Advanced Systemic Lewis Lung Carcinoma

Drug/Route/ Schedule	Dose mg/kg	Weight Change Day 14 (gm)	Weight Change Day 22 (gm)	Toxic Deaths	MST[a] Days	ILS[b] %	LTS[c]
	15/6	-6.4	-	6/7	toxic	-	-
	15/3.6	-0.1	-0.1	0/7	35	87	-
	15/2.16	-0.3	+0.9	0/7	31	106	-
	15/1.3	+0.3	-1.1	0/7	35	81	-
	9/6	-5.3	-	6/7	toxic	-	-
	9/3.6	-0.1	-0.1	0/7	30	88	-
	9/2.16	-0.1	-2.6	0/7	35	81	-
	9/1.3	+0.1	-0.7	0/7	23	48	-
	5.4/6	-4.6	-	6/7	toxic	-	-
	5.4/3.6	-2.6	-0.6	0/7	30	94	-
	5.4/2.16	-1.1	-1.4	0/7	30	55	-
	5.4/1.3	0	-1.0	0/7	23	48	-

a) MST = median survival time
b) ILS = increase in lifespan
c) LTS = long-term tumor-free survivors at Day 60

* Toxic deaths in untreated mice treated in parallel

Female B6D2F1 mice were implanted ip with 0.2 cc of a 1:25 homogenate (w/v) of Lewis lung carcinoma. The animals were randomly assigned to treatment groups of 7 mice. SKAF 104864-A, etoposide, and cisplatin were administered ip as a single bolus injection either alone or in combination with SKAF 104864-A on Days 7 and 14 post-implantation. The mice were weighed at treatment groups on Days 7, 14, and 22 and were checked daily for mortality for 60 days.

PP-1002: Direct comparison of oral administration of SK&F 104864 with parenteral treatment against systemic and localized murine tumours. Vol. 1.11, p. 294.

McCabe *et al.* did these experiments to establish the relative efficacy of topotecan given by different routes, *i.e.*, intravenously, intraperitoneally or orally. They used $B6D2F_1$ female mice. They implanted one of the following tumors into groups of five or six mice: a) advanced systemic L1210 Lymphocytic leukemia, b) advanced systemic Lewis lung carcinoma, c) early Lewis lung carcinoma, or d) M5076 reticulum cell sarcoma. Topotecan (lot not specified) was dissolved in sterile water and given to the mice at different schedules dependent on the time each tumor needed to establish. The following table summarizes the results of these experiments.

		Oral Topotecan			Intraperitoneal Topotecan			Subcutaneous Topotecan		
	implant	schedule	MTD mg/kg	Lifespan prolongation at MTD, %	schedule	MTD mg/kg	Lifespan prolongation at MTD, %	schedule	MTD mg/kg	Lifespan prolongation at MTD, %
L1210 Lymphocytic leukemia	i.v.	day 2 & 6	25	216	days 2 & 6	15	183			
Lewis lung carcinoma	i.v.	day 7 & 14	36	110				day 7 & 14	80	>186
Lewis lung carcinoma	s.c.	day 1, 5 & 9	16.2	90a						
B16 melanoma	i.v.	day 1,8 & 15 q3hX4	3.6	56	days 1, 8 & 15 q3hX4	3.6	49			
M5076 reticulum cell sarcoma	i.p.	day 1, 5 & 9	10	20	day 1, 5 & 9	10	75	day 1, 5 & 9	10	14
M5076 reticulum cell sarcoma	i.p.	day 1, 5 & 9 q3hX4	1.25	7	day 1, 5 & 9 q3hX4	1.25	75	day 1, 5 & 9 q3hX4	2.5	98

a = Tumor Growth Inhibition in %

These experiments establish that topotecan retains its efficacy against tumor implants when given intravenously, orally or subcutaneously.

Central Nervous System

TP-1001: SK&F 104864-A: Assessment of the Effects on Locomotor Activity in the Mouse. Vol. 1.12, p 3

TP-1004: SK&F 104864-A: Assessment of Effects on Hexobarbital-Induced Sleeping Time in the Mouse. Vol. 1.12, p 19.

TP-1006: SK&F 104864-A: Assessment of the Effects in the Mouse using the Irwin Dose-Range Test. Vol. 1.12, p 36.

TP-1007: Assessment of Effects on Body Temperature in the Mouse. Vol 1.12, p 63.

TP-1009: SK&F 104864-A: Assessment of Anticonvulsant Activity Using the Supramaximal electroshock Test. Vol. 1.12, p 84

TP-1011: SK&F 104864-A: Assessment of Analgesic Activity-Tail Pinch Test in the Mouse. Vol. 1.12, p 101

TP-1012: SK&F 104864-A: Assessment of Effects in the Minimal Metrazol Test in the Mouse. Vol. 1.12, p 118.

These are all standard tests to determine whether topotecan causes any pharmacological response other than the toxicity caused by it primary mode of action. All were done under GLP regulations. All these tests were done using male CD-1 mice and topotecan lot JW-15827-73-2. The doses given were saline control, 0.25, 0.5 and 2.5 mg/kg except for the determination of the

effect on body temperature. In this test the high dose was 3.0 mg/kg. All doses were determined as pure free base. The summary table below shows that all these tests were negative, that is, these tests found no unknown CNS pharmacological effects. Nevertheless, these doses were relatively low, well below those that cause toxicity.

Test	Study Number	positive control	result	Comment
Locomotor activity	TP-1001	Chlorpromazine HCl	No increase or decrease in locomotor activity	The standard deviations of the numerical values were as large as the values themselves. This test was not sensitive.
Hexobarbital Induced Sleeping Time	TP-1004	Chlorpromazine HCl	No increase or decrease in hexobarbital sleeping time.	
Irwin Dose-Range Test	TP-1006	None	No abnormal behavior associated with topotecan	Subjective evaluations
Effect on Body Temperature	TP-1007	Aminopyrine	No increase or decrease in rectal temperature between 5 and 120 min after dosing	
Anticonvulsant Activity by electroshock	TP-1009	Phenobarbitone Na	No increase or decrease in tonic extensor reflex	Shock was lethal to 3/10 control mice and between 2/10 and 4/10 treated mice
Analgesic Activity by tail pinch	TP-1011	Pethidine HCl	No increase or decrease in tail pinch pain response between 3 and 120 min after dosing	
Minimal Metrazol Test	TP-1012	Phenobarbitone Na	No statistically significant differences in time to first metrazol induced convulsion, or in the number of animals suffering convulsions.	Metrazol seizures were lethal to 1/10 control mice and between 1/10 and 2/10 mice in the topotecan treated groups

Cardiovascular/Renal

TP-1013: SK&F 104864-A: Effects on Cardiovascular and Respiratory Parameters in the Anaesthetized Rat. Vol. 1.12, p 135.

TP-0012: SK&F-104864-A: Evaluation of the Effects on Cardiovascular and Respiratory Parameters in the Anaesthetized Beagle Dog. Vol. 1.12, p 167.

Again these are standard tests to determine whether topotecan causes any pharmacological response other than the toxicity caused by it primary mode of action. All were done under GLP regulations. All these tests were done using topotecan lot JW-15827-73-2. Investigators measured blood pressure, heart rate, respiration rate and depth, and ECG in both species from dosing to 150 min in rats and to 270 min in dogs. The animals were anaesthetised throughout the test. The doses given to the rats and dogs were 0, 0.75, 1.5 and 15 mg/m^2 i.v. pure free base. The vehicle was isotonic saline.

This treatment caused no dose related biologically significant changes in respiration rate or depth, blood pressure, or heart rate in rats. ECG recordings were normal throughout the experiment.

In dogs, changes in heart rate, blood pressure, left ventricular pressure and left ventricular dp/dt were temporally associated with dosing. The magnitudes of these changes were less than 10 %; none of them were consistent in all the dogs and none were dose related.

Gastrointestinal

TP-1002: SK&F 104864-A: Assessment of the Effects on Intestinal Motility Using the Charcoal Propulsion Test in the Mouse. Vol. 1.12, p 264.
TP-1005: SK&F 104864-A: Assessment of the Effects on the Responses of the Isolated Guinea-Pig Ileum to Acetylcholine, Histamine and Barium Chloride. Vol. 1.12, p 280.
TP-1008: SK&F 104864-A: Assessment of the Effects on the Isolated Guinea-Pig Ileum. Vol. 1.12, p 301.

Again these are standard tests to determine whether topotecan causes any pharmacological response other than the toxicity caused by it primary mode of action. All were done under GLP regulations. All these tests were done using topotecan lot JW-15827-73-2.

Topotecan was given to male CD-1 mice at doses of 0.25, 0.5 and 2.5 mg/kg. A standard dose of charcoal was give by gavage. Topotecan cause no increase or decrease in the distance this charcoal bolus moved distal from the pyloric sphincter compared to vehicle control. Atropine sulfate, a positive control, caused a significant decrease in gut motility.

Investigators exposed isolated guinea-pig ileum to acetylcholine, histamine or barium chloride to establish base line contraction intensities. They then re-exposed these isolated ileae to the agonists in the presence of final bath concentrations of 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} g/ml of topotecan. Concentration of 10^{-8}, 10^{-7}, 10^{-6} and 10^{-5} g/ml caused no notable changes in the amplitude of contractions, but 10^{-4} g/ml of topotecan caused a weak and statistically insignificant inhibition of the acetylcholine contractions. Thus, there was no obvious dose related effect. Likewise topotecan caused no dose related changes in the resting tone of isolated guinea-pig ileum.

Urinary

TP-1003: SK&F 104864-A: Assessment of the Effects on Urine Volume and Electrolyte Excretion in the Rat. Vol. 1.12, p 316.

Algate *et al.* did this study to determine whether topotecan causes change in urinary output or electrolyte excretion. They followed GLP regulations. All these tests were done with topotecan lot JW-15827-73-2.

These investigators gave topotecan to fasted male Sprague-Dawley rats at doses of 0.127, 0.254, 2.54 mg/kg, 8 rats/dose group. The negative control was the vehicle, 0.9% w/v saline; the positive control was frusemide, 5 mg/ml. After dosing, the investigators gave the rats 25 ml/kg water p.o. gavage. The tables below show that the highest dose of topotecan caused a significant increase in urine volume (22 to 34%) between 2 and 5 hours after dosing. This dose also caused significant increases in urinary Na^+, K^+, Cl^- and protein at 5 hours post dosing. This highest dose is 10 times the clinical dose on a mg/m^2 basis, but the change in urine volume is 40% of that caused by the positive control. Nevertheless, this increase is probably not clinically significant.

Group	Treatment	Dose (mg/kg p.f.b.) i.v.	Group mean cumulative urine output (ml ± SD) at time (h) post-dose					
			1	2	3	4	5	24
1	Vehicle (0.9% w/v saline)	-	2.29 ±0.94	3.90 ±0.77	4.38 ±0.81	5.01 ±0.77	5.36 ±0.76	11.64 ±1.26
2	SKAF 104864-A	0.127	2.68 ±0.95	4.24 ±0.87	4.70 ±0.55	5.38 ±0.72	6.10 ±0.97	12.69 ±2.67
3	SKAF 104864-A	0.254	2.44 ±0.63	4.38 ±0.99	4.65 ±0.74	5.00 ±0.95	5.46 ±1.24	12.65 ±3.94
4	SKAF 104864-A	2.54	2.94 ±0.86	4.74 ±0.63	5.88*** ±1.15	9.46** ±1.01	6.81** ±1.21	14.25 ±2.92
5	Frusemide	5.0 mg/kg	7.93*** ±1.35	8.76*** ±1.66	8.76*** ±1.60	9.13*** ±1.81	9.34*** ±1.65	15.13*** ±1.77

SD Standard deviation
Significance of difference from vehicle-treated group
** P<0.01
*** P<0.001

Pharmacology Summary

Wall M.E. *et al.* (*J. Amer. Chem. Soc.* **88**: 3888-3890, 1966) isolated camptothecin from Camptotheca *acuminata* in 1966 based on activity against murine leukemia cells *in vitro* and *in vivo*. The US National Cancer Institute tested this compound in phase I and phase II trials, but abandoned it because of its toxicity; primarily hemorrhagic cystitis and unpredictable myelosuppression, emesis and diarrhea. During these early studies, investigators did not realize that the lactone was the active form of the drug, nor did they know that camptothecin bound tightly to human serum albumin. The formation of the active lactone in acidic urine probably caused the dose limiting hemorrhagic cystitis associated with camptothecin. Efficacy was probably diminished by the drug's formulation. The sponsor developed topotecan as derivative of camptothecin that is water soluble in the lactone form and binds less strongly to plasma proteins (Kingsbury W.D., *et al., J.Med. Chem.* **34**: 98-107, 1991). They anticipated that these changes would improve efficacy and decrease toxicity.

Topoisomerase I opens a single strand break in DNA at the phosphodiester bond. These single strand breaks allow the DNA to rotate and thus relieve torsional strain in supercoils caused by the moving replication fork. Topoisomerase I may also relieve torsional strain during transcription. Once the torsional strain is relieved and replication process is complete, topoisomerase I religates the phosphodiester bond.

Topotecan and related compounds inhibit DNA topoisomerase I by preventing the preventing this religation reaction. This potent cytotoxin forms a ternary complex with the topoisomerase I and DNA. Nevertheless, the binding of topotecan to topoisomerase I is reversible. This ternary complex can be isolated and characterized by electrophoresis. Camptothecins do not bind to DNA or topoisomerase I alone, but only to the DNA-topoisomerase I complex.

Topotecan stabilizes the single strand break opened in the DNA by topoisomerase I. The interaction between this stabilized complex with the advancing replication fork of the DNA replication process has not been adequately described. Nevertheless, this interaction causes double strand breaks in the DNA. Eukaryotic cells cannot efficiently repair these double strand breaks and the cells die, possibly after initiating apoptosis. Inhibition of DNA replication with an inhibitor of DNA polymerase a such as aphidicolin blocks the ability of camptothecin and

related compounds to produce double strand breaks and cytotoxicity without interfering with their effect on topoisomerase I. Thus, topoisomerase I inhibitors are S-phase specific.

Topotecan is cytotoxic to human and murine tumor cells in culture. In the human tumor stem cell assay, 1 µg/ml of topotecan inhibited a significant proportion of primary tumor explants. Consistent with the S phase-specific mechanism of the drug, longer exposures caused greater inhibition. The sponsor and other investigators have tested topotecan against a variety of *in vitro* and *in vivo* tumor models. Topotecan is active against many of these tumors and as expected efficacy increases with dose and length of exposure.

In tests performed by the sponsor and others, topotecan showed no major pharmacological activity other than the anticipated topoisomerase I inhibition. It caused no unexpected effects on locomotor activity, hexobabrital sleeping time, behavior, body temperature, electroshock response, pain response, or response to seizure producing drugs. Topotecan dosing caused only minor (<10%) and inconsistent changes in cardiac parameters (heart rate, blood pressure, left ventricular pressure) in dogs. Topotecan did not affect intestinal motility or contractility. Doses of 2.54 mg/kg in rats caused significant (22 to 34%) increases in urine volume 2 to 5 hours after dosing. This increase was accompanied by changes in urinary Na^+, K^+ and Cl^-. These minor changes may result from nephrotoxicity.

Toxicology

Single dose Toxicology

TP 1023: Intravenous and Perivenous Irritation study of a Tartaric Acid Formulation in Dogs.
Vol. 1.15, p 2.

Animals	Four female beagle dogs
Drug	SK&F 104864-A, Lot # JW-19056-68-2
Dose	1:10 and 1:100 dilution of clinical formula with tartic acid buffer. (0.25 mg base/ml and 0.025 mg base/ml) 1 ml injection volume,
Vehicle	68 mM tartaric acid, 3% mannitol, pH 3.0
route	intravenous and perivenous, left and right cephalic and saphenous veins.
Observations	
Clinical signs	daily
body weight	day -1 and day 1
gross signs	injection sites only, dogs killed 48 hours after dosing
microscopic	injection sites
GLP included and signed	

This dose of topotecan caused no deaths in this study. The dogs suffered no significant clinical symptoms during the short period after dosing. The drug formulation, vehicle, and saline control caused similar reddening at the intravenous and perivenous injection sites. Microscopic changes observed at saline, vehicle and drug injection sites were similar. They included hemorrhage, inflammation, and edema consistent with minor trauma.

Repeat Dose Toxicology

Rat, i.v.

TP 010 CM: Five-Daily Dose Repeat Schedule Toxicity of SK&F 104864 in the Rat.
Vol. 1.16, p 279.

Animals	male and female Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # JW-14479-101-3, 87.3% pure free base.
Dose	0, 0.023, 0.068, or 0.230 mg/kg/day X5 days (0, 0.136, 0.401, 1.36 mg/m^2/day) calculated as free base six rats/sex/dose, given on days 1 through 5 and again on days 22 through 26
Vehicle	0.9% saline, pH 2.60 to 2.65 with 0.1 N HCl. 1 ml/kg
route	i.v. tail vein
Observations	
physical exam	d-21, 3, 9, 17, 23, 29, 38, 43
clinical signs	daily

body weight	d-6, 1, 8, 15, 22, 29, 36, 43
food cons	d-3, 5, 12, 19, 26, 33, 40
ophthalmology	d-18, 30, 44
hematology	d-14 or -13, 8, 15, 29, 43
clinical chemistry	d-14 or -13, 8, 15, 29, 43
urinalysis	d-12, 9, 16, 30, 44
termination	3 rats/sex day 30, 3 rats/sex day 44
necropsy	gross signs
histopathology	

Mortality	all rats survived to scheduled necropsy
Clinical signs	mild hair thinning between days 9 and 43
Body weight	no dose related changes
Food Cons	no dose related changes
Ophthalmology	no dose related changes
Hematology	On d8 dose related decrease in Hbg in females, Hbg and RBC remained low in these females on d15 and continued to decrease after the second course. Nevertheless, these values returned to normal by day 44. This decrease was less than 7% of pretreatment values. WBC decreased as much as 50% from pre-treatment values in the high dose group and as much as 20% in the mid dose group. All white cell types were affected with a nadir observation on d29. Cell counts were returning to normal by day 43 but had not completely recovered.
Clinical chemistry	These results were ambiguous. Alkaline phosphatase decreased in some rats and the decrease was most pronounced in the high dose group, but a clear dose response was not established. ALT and AST increased in some rats to as much as 3 fold greater than the upper normal limit, but again a clear dose response was not established.
Urinalysis	no dose related changes
Gross Pathology	Day 30, dose related incidence of thymic atrophy Day 44, no drug induced lesions
Histopathology	Day 30, round aggregates of small lymphocytes in thymic medulla of 5 dosed rats the incidence did not increase with dose but was not seen in controls. Day 44, hyperkeratosis and follicular atrophy in three rats probably related to topotecan.
Bone Marrow	Topotecan caused treatment related increase in marrow fat, hypoplasia of the granulocytic and megakaryocytic progenitors, and erythroid hyperplasia in high dose rats. These changes were reversible.

Animals	male and female albino Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # MM-19007-184, 81.9% pure free base.
Dose	0, 0.0023, 0.0230, or 0.23 mg/kg/day for 28 days (0, 0.0136, 1.36, or 1.36 mg/m^2/day) calculated as free base 15 rats/sex/dose, 10 rats/sex/dose were killed after 28 days dosing, 5 rats/sex/dose were killed on day 57 after recovery.
Vehicle	3% mannitol$_{(aq)}$, pH 3, 1 ml/kg
route	i.v. site not specified, I presume tail vein.
Observations	
physical exam	pre-study
clinical signs	daily
body weight	daily
food cons	weekly or every 5 days
ophthalmology	d-9 and d23, d55 recovery group
hematology	d-15, d14 or 15, d27 or 28, d42, day 56
clinical chemistry	d-15, d14 or 15, d27 or 28, d42, day 56
urinalysis	d-13, d16, d29 or 30, d43, and day 57
necropsy	gross signs 10 rats/sex/dose were killed after 28 days dosing, 5 rats/sex/dose were killed on day 57 to demonstrate recovery.
histopathology	see table for group I and IV, target tissues were examined for all groups.

GLP included and signed, study by SKB

None of the rats died before scheduled necropsy. Male and female high dose rats lost approximately 8% body weight by day 16, but slowly recovered this weight before the end of dosing. Food consumption followed a similar pattern. RBC, Hbg, and Hct decreased by approximately 50% in the high dose males and females. This toxicity appears to result from decreased erythropoesis rather than hemolysis. These parameters recovered to near control values 14 days after dosing ceased.

Platelet counts decreased approximately 45% by day 14 in high dose males and females, but counts rebounded to approximately 2 times controls by day 27, that is as dosing continued. Counts returned toward normal by the 28th post-treatment day.

The high dose of topotecan caused a nearly 90% decrease in neutrophils by day 14 in male and female rats. This decrease persisted on day 27. Fourteen days after treatment stopped the rats compensated with mild over-production of neutrophils. Counts were normal 28 days after treatment ended. Monocyte, eosinophil and basophil counts followed a similar pattern. Changes in these counts in female rats in the mid dose group suggest that this group also suffered some topotecan related myelotoxicity.

Total serum protein decreased in high dose male and female rats about 7% by day 14 and remained low on day 27. ALT activity decreased as much as 22% in these rats during this period. Urine specific gravity decreased from approximately 1.030 to 1.015 in these rats on d16 and remained low on day 29. These toxicities were reversible.

Consistent with the six month toxicity study below, the most obvious gross toxicity on necropsy was ~ two thirds decrease in thymus weight in high dose rats. The pathologists noted that in 6 of 10 males and 8 of 10 females all major organs were pale. This is consistent with the anemia noted above.

The bone marrow of high dose rats was hypocellular, again consistent with the six month study. The thymus, spleen and mandibular lymph nodes were depleted consistent with expected myelotoxicity. Single-cell necrosis within the matrix of hair follicles, observed in seven of ten males and four of ten females, predicts the alopecia seen clinically with topotecan. All these changes were reversible.

All these toxicities are expected and consistent with the mechanism of topotecan. The lack of organ toxicity, particularly in the liver and gastrointestinal tract, suggests myelotoxicity is truly dose limiting. A dose high enough to cause toxicity in these organs would probably have caused unnecessary mortality. Nevertheless, the dose response curve for topotecan does not span the two orders of magnitude that separates the doses in this study, so it is not surprising that the two lower dose groups provide little useful information.

TP-1037: SK&F 104864-A: Impurity Evaluation in a 14-Day Intravenous Toxicity Study in Rats. Vol. 1.20, p 2.

Animals	male and female Sprague-Dawley rats
Drug	SK&F 104864-A containing the impurity 9-propoxymethyltopotecan, Lot # 9418-TPTC-1, the sponsor did not specify the amount of the impurity. The total purity was 85.9% topotecan as free base. pure SK&F 104864-A, Lot # MM-19117-249 containing no impurity, 0.23 mg/ml, Reference standard. The total purity was 80.2% topotecan as free base.
Dose	0, 0.0023, 0.023, 0.230 mg/kg/day X14 days (0, 0.0136, 0.136, 1.36 mg/m^2/day) ten rats/sex/dose, 0.23 mg/kg topotecan control (1.36 mg/m^2) Reference
Vehicle	3% aqueous mannitol, pH ~ 3
route	i.v. tail vein
Observations	
physical exam	pre-study, before termination
clinical signs	daily
body weight	predose, daily
food cons	predose, weekly
ophthalmology	predose, and d15
hematology	d14
clinical chemistry	d14
urinalysis	d15 or d16
termination	d15 or 16
necropsy	gross signs, organ weights
Histopathology	

Mortality	all rats survived to scheduled necropsy.
Clinical signs	no drug related clinical signs.
Body weight	2 to 7 % decrease in male and female high dose animals starting d5.

Food Consumption	no drug related changes.
Ophthalmology	no drug related changes.
Hematology	in high dose males and females Mean Hbg decreased ~20% Mean absolute reticulocyte count decreased >95% Mean Platelet count decreased 30 to 40% WBC decreased 40 to 54%
Clinical Chemistry	13 to 39% decrease in alkaline phosphatase in high dose males and females
Urinalysis	no drug related changes
Organ Weight	mean absolute and relative weight of thymus decrease for high dose male (~60%) and females (~80%) rats, decrease in mean absolute thymus weight in mid dose females (~18). Dose related.
Gross Findings	small thymus in most high dose males and females
Histopathology	in high dose males and females lymphoid depletion of the thymic cortex bone marrow hypocellularity of erythroid and myeloid precursors, degeneration of megakaryocytes single cell necrosis within hair follicles in 11 of 20 high dose rats

The sponsor did not specify the percentage of the impurity in the sample. Samples of the 0.23 mg/ml solution prepared for comparison between lots 9418-TPTC-1 and MM-19117-249 on days 1 and 14 were lower than expected (88 and 91% on day 1, respectively and 83 and 86% on day 14, respectively). The solutions for the two lower doses also contained less topotecan than intended. Thus the animals were underdosed by approximately 15 to 20%, but since the solutions of both lots were made at similar low concentrations toxicological comparisons are still valid. The sponsor did not test to determine whether the impurity bound topoisomerase I. The preparations containing the impurity caused the same spectrum of toxicities as topotecan without the impurity. The histopathology data suggest that the high dose with the impurity may be slightly less toxic than the high dose of the compound without the impurity.

The sponsor has specified an maximum % impurity of $\leq$ 1.0% for 9-propoxymethyltopotecan according to Dr. Hsieh's review. This amount is less than usual threshold of concern. The substitution of the propoxymethyl group for the (dimethylamino)methyl group is remote from the lactone ring, that is the site that interacts with topoisomerase I. This impurity probably interacts with topoisomerase much the same as topotecan. According to Dr. Hsieh's review, 9-propoxymethyltopotecan is probably slowly hydrolyzed to 9-hydroxymethyl-10-hydroxycamptothecin in the drug product. The sponsor has set a shelf life specification of not more than 1.5% for the sum of both these contaminants. Dr. Hsieh did not list 9-propoxymethyltopotecan as a quantifiable impurity in the 19 drug substance lots used in toxicology studies and clinical trials. I must assume it is among the total unknown impurities. The content of total unknown impurities in these lots ranges from 0.1 to 1.5%.

Rat, oral

TP-1036: SK&F 104864-A: 6-Month Oral Toxicity Study in Rats. Vol. 1.19, p 2.

Animals	60 male and 60 female Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # MM-19163-58, 87.3% pure free base.

Dose	0, 0.0023, 0.0230, or 0.23 mg/kg/day for six months (0, 0.0136, 1.36, or 1.36 mg/m^2/day) calculated as free base 12 rats/sex/dose, 3 rats/sex/dose for pharmacokinetic evaluation, reviewed in that section
Vehicle	3% mannitol$_{(aq)}$, pH 3, 10 ml/kg
route	oral gavage
Observations	
physical exam	pre-study
clinical signs	daily
body weight	d-6, 1, 8, 15, 22, 29, 36, 43
food cons	daily
ophthalmology	d-16 and d175
hematology	d15, 28, 89, 133 (only control and high dose) and 180 (all)
clinical chemistry	d15, 28, 89, 133 (only control and high dose) and 180 (all)
urinalysis	d16, 29, 91 and just before termination
necropsy	gross signs
histopathology	see table

GLP included and signed, study by SKB

On day 121 none of the rats showed any signs of toxicity in any of the dose groups. The investigators decided to increase the high dose four fold to 5.44 mg/m^2/d. After seven days of dosing at this level, male rats showed significant toxicity that evidently threatened the study. The investigators decreased the dose back to the original 1.36 mg/m^2/d for the remainder of the study.

Mortality	One high dose male was moribund on day 134 after seven days of dosing at 5.44 mg/m^2/d. On necropsy this rat had erosions in the stomach and duodenum, necrosis of the crypt epithelium in the jejunum and ileum and regenerative glandular hyperplasia in the colon and cecum. Microscopically, there was bilateral testicular degeneration and necrosis and lymphoid depletion of the thymus.
Clinical signs	None except for the except those associated with the 5.44 mg/m^2/d regimen.
Body weight	High dose male rats lost a significant but small amount of weight (2%) during the 5.44 mg/m^2/d regimen. This weight loss was reversible when the dose was lowered to the original 1.36 mg/m^2/d.
Food Cons	Anorexia associated with the weight loss during the 5.44 mg/m^2/d regimen. The male that died ate little to nothing after this regimen. This anorexia was probably associated with the severe damage to the GI tract.
Ophthalmology	no dose related changes
Hematology	Mean Hbg, RBC, Hct decreased ~6% in females after the 5.44 mg/m^2/d regimen (measured d133). After this dosing regimen the WBC in these females increased more than 50% and the absolute neutrophil count increased 3 fold. These paradoxical increases could be secondary to the GI toxicity or rebound from transient myelosuppression.
Clinical	On day 180, glucose was increased ~15% in all male rats. The serum cholesterol was decreased 13 to 26%, and triglycerides were decreased 10 to 42% in males in all dose groups throughout the study. These changes indicate some derangement of metabolism that is probably drug related.
Urinalysis	No dose related changes
Organ Weight	No toxicologically significant changes
Gross Pathology	No drug related gross changes

Histopathology No drug related microscopic changes

Rabbit, iv

TP-1025: SK&F 104864-A: Maximum tolerated intravenous dose study in non-mated female rabbits. Vol. 1.20, p 195.

Animals	four female New Zealand white rabbits
Drug	SK&F 104864-A, Lot # MM-19007-282, 82.4% purity
Dose	Group 1, 0.32 mg/kg/d (4.0 $mg/m^2/d$) X13, 2 rabbits
	Group 2, 0.80 mg/kg/d (10 $mg/m^2/d$) X13, 2 rabbits
Vehicle	3% $mannitol_{(aq)}$, pH 3, 1 ml/kg
route	marginal ear vein
Observations	
physical exam	pre-study
clinical signs	daily
body weight	daily
food consumption	daily
No GLP statement included	

One Group 2 rabbit was found dead on d12. By day 11 this rabbit had lost ~8% body weight, with anorexia and decreased fecal mass. The other Group 2 rabbit suffered weight loss, anorexia, and decreased fecal mass. One Group 1 rabbit had transient anorexia days 7 through 12. Thus, 10 $mg/m^2/d$ X13 exceeds the MTD in rabbits. The purity of the drug batch was low; this experiment possibly underestimates the toxicity of topotecan.

Dog, iv

TP-1034: SK&F 104864-A: One Month Intravenous Toxicity Study in Dogs. Vol. 1.21, p 2.

Animals	Forty four purebred beagle dogs
Drug	SK&F 104864-A, Lot # MM-19163-58, 87.3% pure free base.
Dose	0, 0.02, 0.1, 0.4 mg/m^2/day one months four dogs/sex
	groups 1 to 4 respectively
	0, 0.4 mg/m^2 three dogs/sex/group dosed and held for 8 week recovery
	groups 5 and 6 respectively
Toxicokinetics	d1 and d28, serial blood samples pre-dose, 0.25, 0.5, 1, 2, 4, and 6 hr.
	See review in Pharmacokinetics
Vehicle	3% $mannitol_{(aq)}$, pH 3
route	i.v., 1 ml/kg cephalic vein
Observations	
physical exam	pre-study
clinical signs	daily

body weight	weekly
food cons	weekly
ECG	pre-study and day 23
ophthalmology	pre-study and day 26
hematology	pre-study, d9, d27, d42, d56, d70, d84
clinical chemistry	pre-study, d9, d27, d42, d56, d70, d84
urinalysis	pre-study and d27
necropsy	day 29 or 30 for Groups 1 through 4, on day 89 for groups 5 and 6.
histopathology	see table

Samples of liver were reserved to determine Cytochrome P450 Analysis.
GLP included and signed, study by SKB

Mortality	one female high dose dog was killed on day 23, this dog suffered several days of anorexia and weight loss.
Clinical signs	no consistent dose related symptoms of toxicity
Body weight	no statistically significant changes
Food Consumption	variable decreases to 65% in high dose dogs
Ophthalmology	no effects
ECG	no effects
Hematology	Hct, RBC & Hbg in high dose males decreased 9 and 15% respectively WBC in high dose females decreased ~50% Recovery group, Hct, RBC & Hbg recovered by d28(males) and d42(females) post treatment. WBC recovered by day 42 (d14 post treatment)
Homeostasis	no effects
Clinical Chem	inconsistent decreases in serum cholesterol, probably not important.
Urinalysis	no toxicology significant effects.
Organ Weight	dose related decrease in mean absolute and relative thymus weight in females, this decrease was not completely reversed after eight weeks.
Gross Pathology	decreased thymus size in 5 of 8 high dose dogs, this decrease remained in 4 of 6 recovery dogs after eight weeks.
Histopathology	Thymus: atrophy consistent with decreased thymus weight, remained in 1 of 6 recovery dogs. Lymph nodes: All high dose dogs had minimal to mild follicular atrophy, reversible. Bone Marrow: Mild to severe atrophy, hypocellularity in one high dose male and in the female killed on day 23. Colon: Minimal atrophy of the mucosa in 7 of 8 high dose dogs. Testes: incidence of multinucleated spermatogonial giant cells suggest possible dose related toxicity, but the data is equivocal. Symptom remained in 1 of 3 recovery high dose dogs.

Toxicology Summary

The sponsor conducted an impressive array of preclinical studies in the mouse, rat , rabbit and dog, thus they have well characterized the toxicities associated with topotecan. In early studies, the sponsor calculated the single dose LD_{10} to be 74 mg/m^2. The following table summarizes the lethality of doses of topotecan across different species.

study	TP 002	TP 006	TP001C M	TP 1019	TP003C M	TP 008	TP-1014
species	mouse	rat	rat	rat	dog	dog	dog
strain	BDF1	SD	SD	SD	beagle	beagle	beagle
dosing duration days	1	1	1	1	1	1	1
route	i.v.	i.v.	i.v.	oral	i.v.	i.v	oral
min lethal dose mg/m^2	56.6	147.5	236	200	180	74	
max non lethal dose mg/m^2	40 35	74.9	137	100	120	7.4	170
earliest death, day	3	5	5	2		5	

In the rat the estimated LD50 for five daily i.v. dose is doses, 13.8 mg/m^2. The dose response curve appears to be unusually shallow. Rats survive 28 daily doses approximately equivalent to the clinical dose on a mg/m^2 basis. Dogs do not tolerate one third the clinical dose given for 28 days. The following table shows the lethality of topotecan across different species after multiple doses. This table shows that the dog best predicts the toxicity of the compound in humans. The MTD in the dog is 1.36 mg/m^2/d X5. This is comparable to the clinical dose in human patients, 1.5 mg/m^2/d X5.

study	TP 002	TP004C M	TP005C M	TP010C M	TP1017	TP1036	TTP1025	TP009C M	TP1034
species	mouse	rat	rat	rat	rat	rat	rabbit	dog	dog
strain	BDF1	SD	SD	SD	SD	SD	NZ	Beagle	Beagle
dosing duration days	5	5	5	5	28	180	13	5	28
route	i.v.	i.v.	i.v.	i.v.	i.v.	oral	i.v.	i.v.	i.v.
min lethal dose, mg/m^2	13.8	29.5	13.81			5.44	10	4	0.4
max non lethal dose mg/m^2	8.04	5.9	4.72	1.36	1.36	1.36	4	1.38	0.1
earliest death, day	6		7			7	12	11	23
Estimated MTD, for 5 daily doses, mg/m^2	8		4.7					1.38	

The dose limiting toxicities in all these species are myelosuppression and anemia. The onset of myelo-suppression is rapid; the degree of myelosuppression is duration and dose dependent. High repeat doses can cause profound decreases in WBC and platelet count within eight days of the start of treatment. All white cell types are affected. These changes are usually reversible when treatment is stopped. Sometimes the platelet count and the neutrophil count will rebound to higher than normal, but this increase usually returns to normal within two weeks. RBC, Hgb, and Hct also decreased with dose and duration of treatment. These toxicities appears to result from decreased erythropoesis rather than hemolysis. These parameters usually recover to near control values within weeks after dosing stops.

Repeated dosing with topotecan caused increases in ALT and AST suggesting liver damage. Histology did not confirm this toxicity, probably because myelosuppression is dose limiting. Thus, the

doses were not high enough to demonstrate clear dose related damage. Similarly, repeated dosing sometimes caused transient changes in the urinalysis parameters, suggesting mild kidney damage; but again the doses were not high enough to demonstrate clear dose dependent toxicity.

Topotecan caused the microscopic damage usually associated with myelo-suppression; bone marrow hypocellularity, cellular depletion of the spleen, thymus, and lymph nodes. Damage to the GI was remarkably rare and usually seen only in long term studies of oral dosing. Some dogs given 0.4 $mg/m^2/d$ for one month developed multinucleated spermatogonial giant cells in the testes. In rats, a dose of 0.23 mg/kg/d given for 14 days before mating through gestation day six caused a 75% increase in the number of corpora lutea. The mechanism causing this super-ovulation was not determined. Weight loss is dose dependent and associated with anorexia. Alopecia is dose dependent, but does not occur in all animals. Microscopically the hair follicles were atrophic.

Special Toxicology Studies

TF-0001: To Assess the "In Vitro" Ability of SK&F 104864 to Promote the Adsorption of Plasma Proteins onto Human Red Blood Cells. Vol. 1.22, p 104.

G. Collins of SKB incubated human RBCs with concentrations of Topotecan to 0.023 M. After this incubation, these cells were washed, then mixed with anti-human globulin serum, anti-human IgG serum, or anti-human albunin serum. Topotecan did not promote the adsorption of these plasma proteins to the washed RBCs.

TP-1024/2: SK&F 104864: In vitro hemolysis testing in human blood. Vol. 1.22, p 116.

D. T. Thudlum of SKB added the tartic acid/mannitol formulation of topotecan (lot JW-19056-68-2) to anti-coagulated human blood. Topotecan concentrations to 0.25 mg/ml did not cause hemolysis *in vitro*.

TP-1028/2: SK&F 104864: Intravenous hematoxicity in rats. Vol. 1.22, p 130.

Animal	male Sprague Dawley Rat, 18 rats/group
Drug	SK&F 104864, Lot No. MM-19007-184
Dose	0, 0.068, 0.231 or 0.8 mg/kg/d X5 , (0, 0.4, 1.36 or 4.72 $mg/m^2/d$
vehicle	3% mannitol, pH 3
route	i.v.
Observations	
body weight	
hematology	
spleen weight	
bone marrow smears	
mitogen stimulated spleen cell proliferation	
spleen cell candidacidal activity.	

Six animals per group were killed on days 6, 14 and 21.

This study determined the time course of hematologic changes and to monitor immune function after daily intravenous doses of topotecan for 5 days. Mean body weight decreased with dose up to 7% during the first 7 days. Mean body weight approached control values by day 21. A dose of 4.72 mg/m^2 of topotecan decreased mean Hbg (up to 11%) with parallel changes in RBC counts and Hct values. This dose also caused a decreased in mean platelet counts (up to 59%) and decreased bone marrow cellularity. By day 21 these parameters were recovering toward control values. Mean MCV values increased by up to 4 fL (7%) for this high dose group on days 14 and 21. Topotecan caused dose-dependent decreases in WBC counts (up to 50%) and neutrophil counts (up to 88%) by day 6 for all treated groups. Again these changes were reversible. Mean spleen weights for the 4.72 mg/m^2 group decreased (32%) by day 6, increased (38%) on day 14 and returned to control values by day 21. The high dose reduced candidacidal activity in isolated spleen cells by 38% by day 6. Following concanavalin A, phytohemagglutinin, or pokeweed mitogen stimulation, mitogen stimulated spleen cell proliferation decreased by as much as 70% by day 6 in the 1.36 and 4.72 mg/m^2 groups. Candidacidal activity increased by day 14 while mitogen response remained slightly suppressed

up to day 21 in spleen cells from rats in the 4.72 mg/m^2 group. Candidacidal activity and mitogen response in the 0.4 mg/m^2 group were indistinguishable from controls.

TP-1018: SK&F 104864-A: Assessment of antigenicity after subcutaneous and intravenous administration to the guinea-pig. Vol. 1.22, p 191.

Investigators at acute systemic anaphylaxis (ASA) and pacive cutaneous anaphylaxis. Topotecan was weekly antigenic following subcutaneous or intravenous injection. Nevertheless, it did not cause acute systemic anaphylaxis.

TP-1015: The Measurement of the Extent of the Covalent Binding of ^{14}C-SK&F 104864 to Human Serum Albumin *In Vitro*. Vol. 1.27, p 485.

Drug	^{14}C-SK&F 104864, Lot SWL-20331-250, 72 μCi/mg, >97% by TLC
	SK&F 104864, Lot JW-15880-118-2
Human Serum Albumin (HSA)	(fraction V, A1653) in PBS (pH 7.4) 4.5% w/v

L.F. Chasseaud *et al.* of incubated topotecan with HSA for 6 or 24 hr at concentrations of 20, 60, and 150 ng/ml. The total radioactivity of each duplicate sample was determined by liquid scintillation. Each 14 ml sample was then dialyzed against 200 volumes PBS for 24 hr with two buffer changes. At the end of this dialysis the amount of topotecan bound was greater than 10% of the original amount added. This was evidently higher than the investigators expected because they decided to dialyze the samples for a further 48 hours with two more buffer changes.

The experiment showed that significant amounts of topotecan remain associated with HSA after thorough dialysis. This suggests, but does not establish, that a covalent reaction occurs between HSA and topotecan (or the hydroxycarboxylate). The increase in binding with increased incubation time implies that this reaction is slow. The experiment cannot distinguish between topotecan and the open ring hydroxycarbolylate. The carboxyl oxygen of the open ring hydroxycarboxylate is strongly electronegative. Covalent binding may result from the attack of this oxygen at the carbonyl carbon of a peptide bond. If such a reaction can occur, it could cause unexpected toxicities, especially in patients receiving topotecan over long courses by continuous infusion. The following table shows the results of this experiment.

Initial Concentration ng/ml	Incubation time hr	% initial sample in precipitated protein %	% in sample after 24 hr dialysis %	% in sample after 72 hr dialysis %
		2.8	5.3	4.6
		3.9	5.9	5.4
		4.3	6.9	5.9
		10.7	21.7	19.2
		14	22.3	20.3
		17.6	26.2	24.1

A graph of percentage initial sample in precipitated protein vs initial concentration suggests that binding may not be linear with concentration, implying more than one type of binding (not shown). This experiment underestimates of the amount of topotecan bound to serum *in vivo* because of the severity of the dialysis. The investigators assume that binding of compound remaining after dialysis is irreversible (covalent). Nevertheless, not all the bound activity was recovered in precipitated HSA after the dialysis. This suggests that a significant amount of topotecan, as much as 9%, is not dialyzable, but neither is it covalently bound. A thorough mass balance would have improved this experiment.

A more useful experiment would have been to establish equilibrium constants with a Scatchard analysis. A Scatchard analysis would probably show multiple types of binding. A simple kinetic analysis might have suggested the mechanism of the reaction between topotecan and HSA.

Mutagenicity Studies

In vitro Studies

TP-0013: SK&F 104864-A: Bacterial Mutation Assay. Vol. 1.25, p 132

Drug	SK&F 104864, Batch JW-15827-73-2, tested purity 92.6 % w/w.
Concentrations	µg/plate, range finding study 312.5, 625, 1250, 2500, to 5000 µg/plate, main study
Test Organisms	S. typhimurium TA1535, TA1537, TA1538, TA98 and TA100 All strains were defective in DNA repair (*uvrB*) and have a defective lipopolysaccharide barrier on the cell wall (*rfa*) E. coli, tryptophan-dependent auxotrophic mutant
Solvent	DMSO
Negative Control	DMSO
Positive Controls	9-aminoacridine, N-ethyl-N-nitro-N-nitrosoguanidine, 2-nitrofluorene, with S-9 2-Aminoanthracene
S9	phenobarbital and β-naphthaflavone in Sprague Dawley rats.
GLP	included and signed, Huntingdon Research Centre Ltd.

Topotecan was not toxic to any of the strains to doses of 5000 µg/plate. Positive controls all gave positive results. Concentrations of topotecan to 5000 µg/plate did not cause increases in the number of revertants in any of the strains. S-9 activation did not increase the number of revertants. The investigators did not establish whether topotecan passed the cell membrane of these strains.

TF-1002: SK&F 104864-A: Report of mutation tests with L5178Y mouse lymphoma cells at the TK locus, Vol. 1.25, p 163

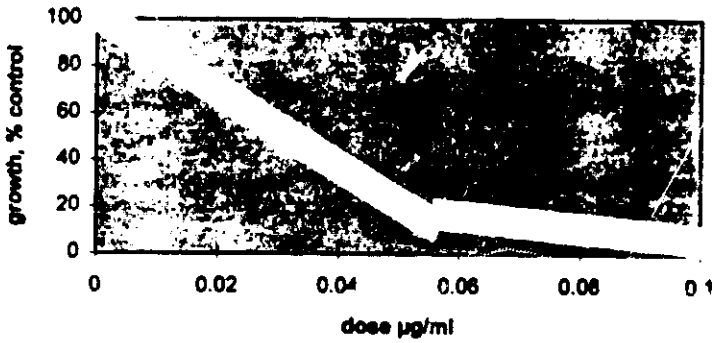
Cells	Mouse L5178Y 3.7.2.C, heterozygous at the thymidine kinase gene locus (TK +/-)
Drug	SK&F 104864, batch MM-19007-84, 91.5% pure
Concentrations	µg/ml toxicity

	µg/ml with S9 µg/ml without S9
Vehicle	DMSO
Positive control	ethyl methansulphonate (EMS) without S9 benzo(a)pyrene (Bap) with S9 assay 1 3-methylcholanthrene (3MC) with S9 assay 2
Negative control	DMSO
S9	Arochor 1254 in Sprague Dawley rats.
GLP	included and signed, SKB, The Frythe, UK These test were done twice

Cells were exposed to topotecan for four hours. They were then allowed to recover and express mutations for two days. Mutants (TK-/-) were selected in agar containing trifluorothymidine and survival was measured in non-selective agar. Colonies were counted on selective agar for TK-/- mutation and on non-selective agar for survival.

Cells grew at an acceptable rate only at concentrations below 0.16 ug/mL in the absence of S9 and below 80 ug/mL in the presence of S9. Mutation frequencies for positive and negative controls were within expected laboratory norms. Inhibition of growth was dose dependant.

Decrease in cell growth with dose without S9



In the first mutation assay, topotecan caused an significant dose related increase in mutation frequency above controls with and without S9. With S9 this increase was 4.9 fold above controls at 80 µg/ml and 1.9 fold at the lowest dose, 0.08 µg/ml. The following tables show the results for both assays with and without S9. The results in the second assay were similar. Clearly topotecan causes mutations in mammalian cells at clinically relavant concentrations.

FIRST MUTATION ASSAY - TREATMENT MEANS[a]

METABOLIC ACTIVATION: YES

TREATMENT µg/ml	% RELATIVE TOTAL GROWTH (b)	MUTATION FREQUENCY PER 10^5 cfu (b)	FOLD INCREASE IN MF OVER CONTROLS
DMSO 10 µl/ml	100.0	5.3	-
SK&F 104864-A 80.0	5.1	25.9*	4.9
SK&F 104864-A 0.4	11.5	10.5*	2.0 (1.98)
SK&F 104864-A 0.2	13.6	9.1*	1.7
SK&F 104864-A 0.08	19.3	10.3*	1.9
B(a)P 1.25	50.4	12.8*	2.4

METABOLIC ACTIVATION: NO

TREATMENT µg/ml	% RELATIVE TOTAL GROWTH (b)	MUTATION FREQUENCY PER 10^5 cfu (b)	FOLD INCREASE IN MF OVER CONTROLS
DMSO 10 µl/ml	100.0	14.2	-
SK&F 104864-A 0.1	5.7	56.2*	4.0
SK&F 104864-A 0.085	8.4	39.4*	2.8
SK&F 104864-A 0.075	9.7	38.5*	2.7
SK&F 104864-A 0.050	20.8	26.2*	1.8
EMS 600	33.3	74.2*	5.2

* Significantly different from controls p <0.005
[a] Derived from Appendix Tables C4, C5, C8 and C9
[b] See Methodology Section for calculation formulae

TP-1016: SK&F 104864-A: Chromosomal aberrations assay with human lymphocytes *in vitro*. Vol. 1.25, p 199

Cells	cultured human lymphocytes in RPMI 1640 (Dutch Modification) medium supplemented with fetal bovine serum, glutamine and antibiotics.
Drug	SK&F 104864, batch JW-15827-73-2
Concentrations	µg/ml toxicity in the presence of S9 µg/ml toxicity without S9 µg/ml assay without S9 µg/ml assay with S9
Vehicle	DMSO
Positive control	cyclophosphamide with S9 mitomycin C without S9
Negative control	DMSO
S9	Arochor 1254 in Sprague Dawley rats.
analysis	mitotic index and chromosome aberrations assessed microscopically
GLP	included and signed, Inveresk Research International These test were done twice

Topotecan was very toxic to human lymphocytes *in vitro*. It prevented cells from entering metaphase at all concentrations greater than 0.5 µg/ml with and without S9. In cultures without S9, concentrations of 0.13 and 0.25 µg/ml reduced the mitotic index. Concentrations of 0.25 µg/ml caused visible damage to cells.

In these assays the mitomycin C positive control was not clastogenic. This was because the experimenter inadvertantly applied 0.05 instead of 0.5 µg/ml. Nevertheless, topotecan was

strongly clastogenic in this test, so a positive control is unnecessary. Cyclophosphamide was strongly clastogenic.

In test 1, cells were treated for 4 hours with and without S9 and harvested at 24 hours and 48 hours. Under these conditions, topotecan caused significant structural chromosomal aberrations at 0.5 µg/ml. Cells allowed to recover for 48 hours were more damaged than those allowed to recover for 24 hours. This was probably because the cells could express the damage due to topotecan after they had resumed division. The following tables summerizes these results.

TABLE 5

SKF 104864-A: Summary of Results of First Assay With S9 Mix

Post Treatment Harvest	Agent	Conc. (µg.ml⁻¹)	Accessory Data (%)		% Cells with Structural Damage to Chromosomes				% Cells with Changes in Chromosome Number
			Cells with Gaps	Hypodiploid Cells	Breaks	Rearrangements	Others	Total	Hyperdiploid
24 h	Negative Control Dimethylsulphoxide		1.00	11.50	1.00	0.00	-	1.00	0.00
	SKF 104864-A		1.50	19.00	10.50	0.00	-	10.50	0.00
	Positive Control Cyclophosphamide*		8.00	16.67	28.00	2.00	-	28.67	0.00
48 h	Negative Control Dimethylsulphoxide		1.50	18.50	1.00	0.00	-	1.00	0.00
	SKF 104864-A*		7.60	26.00	37.00	11.00		42.00	0.00
	Positive Control Cyclophosphamide		2.50	18.00	18.50	4.00		21.50	0.00

* Reduced number of cells (150 with CPH and 100 with SKF 104864-A) scored because of high frequency of aberrations

TABLE 6

SKF 104864-A: Summary of Results of First Assay Without S9 Mix

Post Treatment Harvest	Agent	Conc. (µg.ml⁻¹)	Accessory Data (%)		% Cells with Structural Damage to Chromosomes				% Cells with Changes in Chromosome Number
			Cells with Gaps	Hypodiploid Cells	Breaks	Rearrangements	Others	Total	Hyperdiploid
24 h	Negative Control Dimethylsulphoxide		0.50	23.50	1.50	0.50	-	2.00	0.00
	SKF 104864-A		1.00	9.00	6.00	1.00	-	7.00	0.00
	Positive Control Mitomycin C		1.00	25.00	2.50	0.00	-	2.50	0.00
48 h	Negative Control Dimethylsulphoxide		1.50	25.00	2.00	0.00	-	2.00	0.00
	SKF 104864-A*		1.92	38.46	22.12	7.69	-	27.88	0.00
	Positive Control Mitomycin C		2.00	20.50	1.50	4.00	-	1.50	0.00

* Reduced number of cells (104) scored because of high frequency of aberrations and toxicity

In test 2, cells were treated for 4 hours with and without S9, but were harvested only at 48 hours. Under these conditions, topotecan caused significant damage to chromosomes at 0.25 µg/ml. Microsomal activation inceased this incidence of this damage in both test 1 and test 2.

TABLE 7

SKBF 104864-A: Summary of Results of Second Assay

With S9 Mix, 48 h Post Treatment Harvest

Agent	Conc. (µg.ml⁻¹)	Accessory Data (%)		% Cells with Structural Damage to Chromosomes				% Cells with Changes in Chromosome Number
		Cells with Gaps	Hypodiploid Cells	Breaks	Rearrange-ments	Others	Total	Hyperdiploid
Negative Control Dimethylsulphoxide		0.75	9.75	2.00	0.00	-	2.00	0.00
SKBF 104864-A		1.00	13.00	2.00	0.50	-	2.00	0.00
		1.50	6.50	2.50	0.00	-	2.50	0.00
		0.50	6.50	4.00	0.00	-	4.00	0.00
		0.50	12.50	5.00	2.50	-	7.50	0.00
Positive Control Cyclophosphamide*		2.21	12.50	13.97	2.94	-	16.18	0.00

* = Reduced number of cells (136) scored because of toxicity

In vivo Studies

TF-1001: SK&F 104864-A: Report of a micronucleus test in the mouse by the intravenous route (single-dose study). Vol. 1.25, p 253.

TF-1003: SK&F 104864-A: Report of a single dose micronucleus test in the mouse by the iv route to determine the no-effect dose, Vol 1.25, p 298.

These two studies of the induction of micronuclei and chromosomal aberrations in mouse erythrocytes are very similar so I will review them together. The sponsor conducted both tests under GLP guidelines and in both used SKF-104864A batch MM-19007-184, 91.5% purity. In both the sponsor dosed groups of 4 or 5 mice with a single i.v. dose or topotecan. After 24 or 48 hours the mice were killed and marrow from femora was removed, fixed on slides with methanol and stained with Giemsa. The slides were scored for the proportion of polychromatic cells, mature cells and the number of micronuclei in each group.

In the first experiment, topotecan killed some mice at doses of 50 mg/kg or above. Thus the dose range studied is appropriately high. The following table shows that topotecan caused a significant increase in the percent of erythrocytes with micronuclei at all non-lethal doses. The percent of cells with micronuclei is higher at lower doses. This inverted dose response is probably due to toxicity. High doses of topotecan probably prevented the cells from entering S-phase. Thus, micronuclei could not form in increasing numbers. Recovery to 48 hours did not increase the percent of cells with micronuclei and the results for both sexes were similar.

TABLE B1: SUMMARY OF MOUSE TEST RESULTS (APPENDIX, TABLES C2.1-C2.8) a

Treatment	Dosage (mg/kg)	Sex	No. of Animals	Mean Terminal Bodyweight (g)	POLYCHROMATIC CELL DATA			MATURE CELL DATA			Polychromatic Cells (% of Total Cells Scored) b
					Cells Scored	With Micronuclei	% With Micronuclei	Cells Scored	With Micronuclei	% With Micronuclei	
Negative control (pH-adjusted saline)	0	M	10	31.46	5000	5	0.1	8336	2	0.02	37.49
SK&F 104864A	0.25	M	5	30.24	2500	67	2.68	8600	1	0.02	27.79
	0.5	M	5	30.44	2500	68	2.72	5073	4	0.07	29.84
	1.0	M	5	30.60	2500	18	0.72	6475	7	0.11	27.86
	2.0	M	5	31.50	2500	32	1.28	7310	6	0.08	25.48
	4.0	M	5	31.16	2500	26	1.04	6726	11	0.16	27.10
	8.0	M	5	30.56	2500	33	1.32	6136	5	0.08	23.54
	16.0	M	5	30.52	2500	22	0.88	21009	8	0.07	17.25

a Accessory data only

b Figures may differ from those given in (Appendix Tables C2.1-C2.8) due to rounding errors and other differences in calculating values

Because the response decreased with dose in the first experiment, the sponsor could not determine a dose of topotecan that did not cause micronucleus aberration in mouse erythrocytes. Thus, they conducted the second study at much lower doses. At 0.04 mg/kg and below, the response is indistinguishable from control. A dose of 0.08 mg/kg causes a large increase in the percent of cells with micronuclei. Twice this dose causes the maximum response. The response then decreases with higher doses, consistent with the finding in the first experiment. The degree of response is similar to that of the first experiment, i.e. the results is reproducible.

TABLE B1: SUMMARY OF MICRONUCLEUS TEST RESULTS (APPENDIX, TABLES C2.1-C2.8) a

Treatment	Dosage (mg/kg)	Sex	No. of Animals	Mean Terminal Bodyweight (g)	POLYCHROMATIC CELL DATA			NORMAL CELL DATA*			Polychromatic Cells (% of Total Cells Scored)*
					Cells Scored	With Micronuclei	% With Micronuclei	Cells Scored	With Micronuclei	% With Micronuclei	
Negative control (sterile saline)	0	M	4	30.68	8000	8	0.10	15897	6	0.04	34.14
SKF 104864A	0.0025	M	4	31.20	8000	3	0.13	6425	4	0.06	31.13
	0.005	M	4	30.78	8000	3	0.13	3030	2	0.06	33.73
	0.01	M	4	30.78	8000	7	0.09	14530	11	0.08	35.50
	0.02	M	4	31.73	8000	14	0.18	12000	7	0.06	39.20
	0.04	M	4	31.78	8000	6	0.15	17005	9	0.05	31.39
	0.08	M	4	32.09	8000	22	0.44	7599	5	0.07	39.69
	0.16	M	4	30.78	8000	69	2.45	2044	3	0.11	41.29
	0.32	M	4	30.48	8000	35	1.75	2650	1	0.03	35.35

* Accessory data only

a Figures may differ from those given in (Appendix Tables C2.1-C2.8) due to rounding errors and minor differences in calculating values

As expected, topotecan causes a significant increase in chromosome aberrations in rapidly dividing cells. This increase is as much as 34 fold at 0.16 mg/kg (0.48 mg/m^2) in mice. Half this dose caused a four fold increase, thus the dose response curve for this toxicity is very steep.

Carcinogenicity Studies

None submitted.

Mutagenicity Summary

The sponsor did not do carcinogenicity tests with topotecan in laboratory animals. Nevertheless, topotecan is genotoxic to mammalian cells *in vivo* and *in vitro*. In mouse L5178Y lymphoma cells, 0.1 µg/ml of topotecan caused a four fold increase in mutations over controls. This dose was cytotoxic and increases in mutations occurred in the presence of S9. In human lymphocytes *in vitro*, 0.5 µg/ml of topotecan caused an eleven fold increase in the percentage of cells with chromosome breaks. In some cases, DNA damage caused by topotecan was greater than that caused by the positive controls. In mice, *in vivo*, 0.16 mg/kg of topotecan caused a 34 fold increase in the percentage of cells with micronuclei. Topotecan did not cause mutations in bacterial cells.

Reproductive Studies

Fertility

Rat

TP-1031: SK&F 104864-A: Intravenous Study of Female Fertility and Early Embryonic Devel-opment to Implantation in Rats. Vol 1.22, p 000230 (IND submission 232, vol 43 p 2).

Animals	100 female and 107 male Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # MM-19117-30
Dose	0, 0.0023, 0.023 and 0.23 mg/kg/d free base
	0, 0.0136, 0.136, 1.36 mg/m^2/d, dose volume 1 ml/kg
	males were not dosed
Vehicle	3% mannitol w/v in sterile water, pH 3.0
route	i.v. tail vein
Observations on F0	
Physical examination	day one of dosing, day one of cohabitation, gestation days 0 and 21
Clinical signs	daily during dosing
body weight	weekly pretreatment, daily during dosing, gestation day 7, 10, 14, 17, 21
Food consumption	weekly prior to mating, gestation day 0 to 7, 7 to 14, 14 to 21
estrous	daily 14 days prior to treatment, daily during 14 days of treatment
mating	vaginal levage daily to show presence of sperm
gross signs	termination
Delivery	Cesarean section on day 21

Observation on F1 included corpora lutea count, uterus weight, implantation sites, resorptions, live and dead fetuses, relative position and gross examination.
GLP included and signed

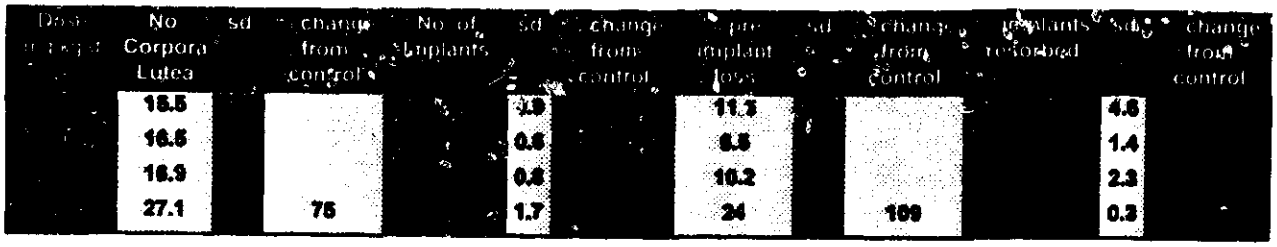
Design

Females were dosed 14 consecutive days preceding mating, during the mating trial (1 to 14 days that is until mating was confirmed) and on gestation days 0 to 6.

Mortality	No rats died prior to scheduled necropsy
Clinical signs	2/25 high dose females had pale mucous membranes and extremities on gestation d6
Body weight	high dose group 6% decrease during pre mating period
	26% decrease during gestation due to almost complete fetal resorption
	90 g smaller mean gravid uterus
	Weight gain was slower than controls. For three days immediately following dosing , these high dose rats gained weight more quickly than controls.
	The low and medium doses did not affect body weight gain.
food cons.	significantly decreased in the high dose group, 11% prior to mating, 25% during the first week of gestation, and 15% during the last week of gestation. This last decrease is probably due to the loss of almost all embryos in this group.
	The low and medium doses did not affect food consumption.
Estrous Cycle	no effect
Mating	no effect
fertility incidence	no effect

Deliveries

Intravenous Study of Female fertility and Early Embryonic Development to Implantation in Rats
Female (F0) Cesarean Section Deliveries Group Means.



Dose	No Corpora Lutea	sd	change from control	No of Implants	sd	change from control	pre-implant loss	sd	change from control	implants resorbed	sd	change from control
	16.5				0.9		11.3				4.6	
	16.6				0.6		6.6				1.4	
	16.9				0.8		10.2				2.3	
	27.1		75		1.7		24		109		0.3	

Topotecan at 0.0023 and 0.023 mg/kg/d did not significantly affect fetal weight. These two doses were to low too cause any significant fetal malformations. Only two fetuses survived a dose of 0.23 mg/kg/d, far to few to demonstrate teratogenicity. Nevertheless, one of the two surviving fetuses suffered microphthalmia.

This study showed that topotecan caused superovulation in rats. These results were confirmed in a follow-up study of the effect on ovarian function (see TP-1035 below). The highest dose in this study was lethal to > 99% of the embryos after only one week of dosing. The next lowest dose caused no change from control. The doses for this study were to widely spread and the study is not very useful.

TP-1022/1: SK&F 104864-A: Intravenous Male Fertility Study in Rats (Segment I/A Reproduction Study). Vol. 1.24, page 2

Animals	male and female Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # MM-19007-184
Dose	0.0023, 0.023 or 0.115 mg/kg/day (0.0136, 0.136 or 0.68 mg/m^2/day)
	calculated as free base for 106 or 107 days
mating	days 70 to 84, females were not dosed
Vehicle	3% mannitol in sterile water, pH 3.0, 1 ml/kg
route	i.v. tail vein
Observations on F0	
Clinical signs	daily
body weight	daily
food cons	daily
mating	fertility, mating
necropsy	gross signs, male reproductive organ weight, spermatogenesis termination (days 107 or 108)
Observations on F1	
corpora lutea, implantations, resorptions, live and dead fetuses (F1), fetal (F1) weight and morphology	

Results for F0

Mortality no drug-related deaths

clinical signs	Hyperactivity and urine-stained fur observed only in the 0.115 mg/kg/day group.
Body weight	weight gain relative to controls reduced 6% for the 0.023 mg/kg/day group
	16% for the 0.115 mg/kg/day group.
	0.0023 mg/kg/day unaffected.
Food cons.	not affected by drug treatment.
Mating	not affected
Fertility	not affected
Organ Weights	no significant effects on male reproductive organ weights
Spermatogenesis	no significant effects on numbers of testicular spermatids per testis or sperm cells per cauda epididymis.
Necropsy	Small thymus in 10 of 25 rats in the 0.115 mg/kg/day group
Results in F1	no significant effects on uterine implantation parameters, fetal weight or morphology (external, visceral and skeletal).

TP-1035: SK&F 104864-A: Investigative Study for Effects on Ovarian Function in Rats.
Vol 1.24, p 156 (IND submission 232, p 221)

Animals	154 female and 85 male Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # MM-19117-30(1)#2
Dose	0.23 mg/kg/d free base
	males were not dosed
Vehicle	3% mannitol in sterile water, pH 3.0
route	i.v. tail vein
Observations on F0	
Clinical signs	daily
body weight	daily
Estrous cycle	daily from 14 days prior to dose assignment
mating	daily by microscopic examination of vaginal lavage
gross signs	termination

Design

Dose mg/kg/d	# of females	Dose schedule	Mating schedule (1:1)
0		for 19 days prior to mating and during mating for up to 7 d	
0.23		for 19 days prior to mating and during mating for up to 7 d	
0		Daily for 1 estrous cycle starting a day of estrus and ending on proestrus	
0.23		Daily for 1 estrous cycle starting a day of estrus and ending on proestrus	
0		one day of proestrus	
0.23		one day of proestrus	

Mortality	no unscheduled deaths
Clinical signs	no drug related clinical signs (weights not reported)
Estrous	Groups 1 and 2 normal (4.3 and 4.5 cycles in 19d)
	Groups 3 and 4 slightly decreased to 4 days
	Groups 5 and 6 not measured
Mating	Group 1 and 2 no effect
	Group 3 through 6, % females mated and % which became pregnant was not affected.

Deliveries

Group	Corpora lutea dam	% increase over control	implants	increase over control	live fetuses litter	increase over control	pre implantation loss	resorptions
	17.7 ± 0.7		15.5 ± 0.7		14.3 ± 0.8		12.5%	
	26.6 ± 1.9		19.7 ± 1.4		18.3 ± 1.4		24.8%	
	16.6 ± 0.5		15.6 ± 0.4		14.9 ±0.4		5.3%	
	27.8 ± 0.9		23.3 ± 0.7		21.2 ± 0.7		14.8%	
	16.6 ± 0.4		15.8 ± 0.3		14.8 ± 0.5			
	17.1 ± 0.5		16.0 ± 0.4		14.4 ± 0.7			

The number of resorptions in Group 4 was statistically greater than Group 3 (control) but was similar to Groups 1 and 5 (controls).

Topotecan causes superovulation in the rat as does CPT-11. The mechanism of this phenomenon has not been determined. Superovulation was comparable in Group 2 (treated 19d prior to mating) and group 4 (treated 4 days prior to mating). The sponsor states "This result is more consistent with inhibition of follicular atresia than extra recruitment of follicles, which would have been supported by a greater effect in Group 2. Superovulation did not occur in females treated only on the day of proestrus before mating which suggest a lack of 'rescue' of follicles already undergoing atresia." These conclusions are reasonable, and the experiments were designed to answer just these questions.

Topotecan caused an increase in pre-implantation loss. That pre-implantation loss was greater with longer drug treatment suggests that the drug is toxic to developing oocytes. Nevertheless, the number of live fetuses per liter and the number of implants increased despite

this increase in pre-implantation loss. The super-ovulation effect more than compensates for the toxicity of topotecan.

Topotecan did not increase resorptions in this study were rats were not dosed during pregnancy. In a similar study (TP-1031) where rats were dosed through gestation day 6 with the same dose (0.23 mg/kg/d) 99.6% of implantations were resorbed. These results suggest that resorption is due to direct toxicity to the developing embryo.

Teratology

Rat

TP-1032: SK&F 104864-A: Intravenous Study for Effects on Embryo-Fetal Development in Rats. Vol 1.24, p 183 This study was done with two replicates, Study G94009 and Study G94050.

Animals	184 female and 148 male Sprague-Dawley rats
Drug	SK&F 104864-A, Lot # MM-19117-30
Dose	0, 0.001, 0.01, 0.1 mg/kg/d on days 6 to 17 of gestation (0, 0.0059, 0.059, 0.59 mg/m^2/d) Study G94009, 23 mated female rats/dose group Study G94050, 23 mated female rats/dose group males were not dosed
Vehicle	3% mannitol in sterile water, pH 3.0
route	i.v. tail vein
Observations for F0	
Clinical Signs	daily
Body Weight	gestation days 0 and 6 through 21
Food Consumption	intervals gestation days 0 to 6, 6 to 10, 10 to 14, 14 to 18, 18 to 21.
Gross signs	termination
Observations for F1	
Body weight	postpartum
number/litter/sex	postpartum
Necropsy	postpartum
GLP present and signed	

Design

Researchers allowed female (F0) rats to mate with males one to one. After mating a vaginal lavage was examined microscopically for the presence of sperm to confirm insemination. F1 offspring were delivered by Cesarean Section on d21.

F0

Mortality	no rats died before the end of the study
Clinical signs	no rats showed drug related in-life signs of toxicity
Body Weight	Rats dosed with 0.1 mg/kg/d weighed 5 to 9% less than controls on gestation days 10 to 21. This decrease was statistically significant. Weight gain decreased by 18 to 73% during 3 day intervals during dosing. The 0.01 and 0.001 mg/kg/d doses did not cause a decrease in weight.

Food Cons.	Rats in the high dose group ate 13 to 15% less than controls during dosing. These rats ate normally after dosing stopped (days 18 through 21).
Deliveries	in the 0.10 mg/kg/d group pre-implantation loss increased 1.6 fold (4.2% vs. 2.7%) Post implantation embryolethality increased by 2.5 fold (13.4% vs 5.3% implants absorbed). In this dose group litter size decreased 10% (13.8 vs 15.3 live fetuses per liter) and gravid uterus weight at term decreased 17%. Lower doses caused no changes relative to controls.

F1

Body weight	decreased in the 0.1 mg/kg/d group 10% for males and 11% for females.
malformations	increased 3.8 fold in the 0.10 mg/kg/d group (7.2% for dosed animals vs 1.9% for controls). Total malformations were higher in the 0.01 mg/kg/d dose group than in controls but the difference did not reach statistical significance. The following malformations were statistically associated with the 0.1 mg/kg/d dose by ANOVA:

	Overall malformation incidence in high dose group as mean percent per litter
External skull - domed shaped head	1.00%
External eye - no apparent eye bulge	0.87%
Brain - dilated lateral cerebral ventricles	11.6%
Brain - dilated third ventricle	7.42%
Eye - microphthalmia (anophthalmia, rosette formation of retina) (colobroma of the retina, ectopic orbit)	11.8%
Skull - frontal dome shaped	1.28%
Skull - incompletely ossified parietal	1.28%
Skull - incompletely ossified frontal	1.28%
Cervical vertebrae- one or more arch fused	2.60%
Thoracic Vertebrae - one or more centra split	2.91%

Topotecan caused clinically detectable maternal toxicity (decreased weight gain) at a dose of 0.10 mg/kg/d (0.59 mg/m^2/d through gestation. Maternal body weight decreased up to 9%. This decrease was associated with anorexia and reversed when dosing stopped. This dose caused an increase in pre-implantation loss (1.6 fold) and post-implantation embryolethality (2.5 fold). Fetal malformations increased by 3.8 fold and fetal weight decreased by 11%. Malformations were statistically increased in the brain, the eyes, the skull, and the vertebrae. Increases in malformations in the other dose groups were not statistically significant.

Rabbit

TP-1029: SK&F 104864-A: Dose Range Intravenous Developmental Toxicity Study in Pregnant Rabbits Vol. 1.25, p 00002 (IND submission 232, vol 43, p 149).

Animals	25 female and 35 male New Zealand White Rabbits
Drug	SK&F 104864-A, Lot # MM-19117-30
Dose	0, 0.01, 0.1, 0.32, 0.56 mg/kg/d, 5 females/dose group
	0, 0.125, 1.25, 4.0, 7.0 mg/m^2/d (Based on 12.5 kg/m^2)
Schedule	single dose on days 6 through 20 of gestation.
	males were not dosed
Vehicle	3% mannitol w/v in sterile water, pH 3.0
route	i.v. marginal ear vein, 1 ml/kg
Observations for F0	
physical exam	gestation days 6, 20, and 29
Clinical Signs	daily days 0 to 29 of gestation
Body Weight	gestation days 0, 6 through 20, 29
Food Consumption	intervals gestation days 0 through 29
Necropsy	termination
Uterus	weight, implantation, resorptions, live and dead fetuses
Observations for F1	
Body weight	postpartum
number/litter/sex	postpartum
gross signs	postpartum

GLP present and signed

Four of five females in the 0.56 mg/kg/d group and one of five females in the 0.32 mg/kg/d group died during dosing. Topotecan caused dose related maternal toxicity (reduced feces and urine volume, red fluid in the service pans) at doses of 0.56, 0.32, and 0.1 mg/kg. Doses of 0.56 and 0.32 caused significant decreases in body weight and 100% fetal resorption. These animals were anorexic. Topotecan did not affect fetal body weight or fetal morphology. The no observed effect dose was 0.01 mg/kg/d.

TP-1030/2: SK&F 104864-A: Intravenous Study for Effects on Embryo-Fetal Development in Rabbits Vol. 1.25, page 30

Animals	110 female and 40 male New Zealand White Rabbits
Drug	SK&F 104864-A, Lot # MM-19117-30
Dose	0, 0.001, 0.01, 0.1, mg/kg/d, 23 females/dose group
	0, 0.0125, 0.125, 1.25 mg/m^2/d (Based on 12.5 kg/m^2)
Schedule	single dose on days 6 through 20 of gestation.
	males were not dosed, each female was mated twice to same male
Vehicle	3% mannitol w/v in sterile water, pH 3.0
route	i.v. marginal ear vein, 1 ml/kg

Observations for F0		
	physical exam	gestation days 6 and 29
	Clinical Signs	daily days 0 to 29 of gestation
	Body Weight	gestation days 0, 6 through 20, 29
	Food Consumption	gestation days 0 through 29
	Necropsy	termination gestation day
	Uterus	weight, implantation, resorptions, live and dead fetuses
Observations for F1		
	Body weight	postpartum
	number/litter/sex	postpartum
	gross signs	postpartum
GLP present and signed		
Results in F0		
	Mortality	None
	Clinical Signs	No drug related signs
	Body Weight	41% decrease in weight gain relative to controls in high dose group
	Food cons.	no changes
	Cesarean Deliveries	4.4 fold increase in implantation resorptions in high dose group (35% resorbed vs 8%)
		24% decrease in litter size for the high dose group
Results in F1		
	fetal body weight	7.5% decreased in males (statistically significant) high dose group
		5% decrease in females (not significant) high dose group
	malformations	no significant differences from controls.

Reproductive Toxicity Summary

Topotecan caused embryonic and fetal death in rabbits and rats. In rabbits, a dose of 0.32 mg/kg/d on days six through 20 of gestation causes fetal resorption. This dose caused significant maternal toxicity. In rats, a dose of 0.23 mg/kg/d given for 14 days before mating through gestation day six caused 99.6% fetal resorption, 24% pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/d (0.4 times the clinical dose on a mg/m^2 basis) given to rats on days six through 17 of gestation caused a 2.5 fold increase in post-implantation mortality. This dose also caused a 3.8 fold 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), scull and vertebrae.

Pharmacokinetics

Single Dose Pharmacokinetics

Mouse

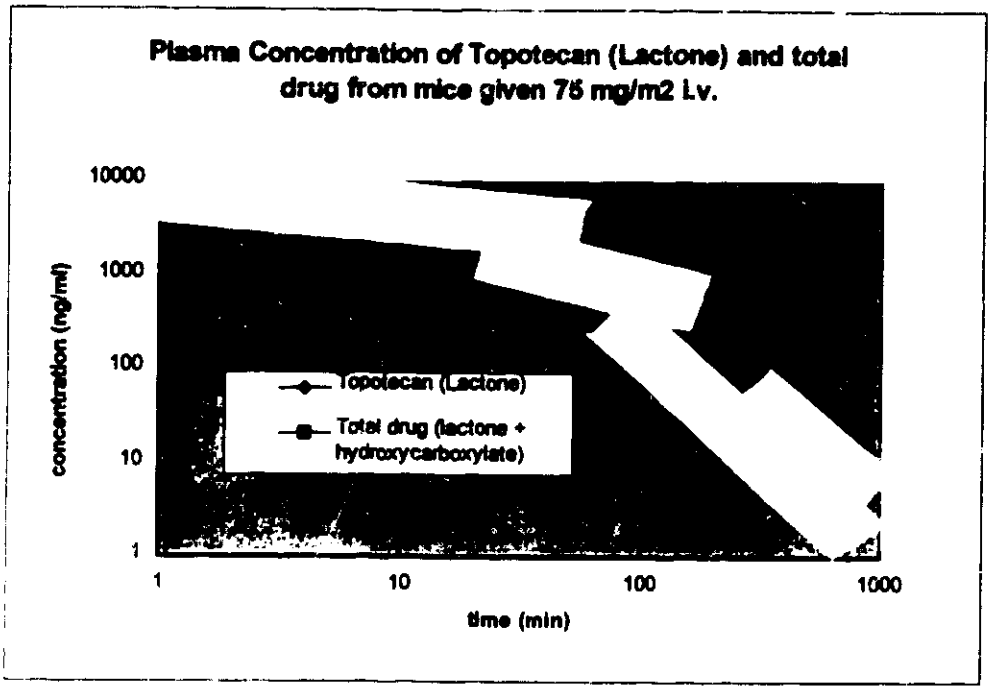
BP 007 CM: Determination of the Pharmacokinetic Parameters of SK&F 104864 and total drug (SK&F 104864 plus SK&F 105992) in Female Mice Following a 25 mg/kg (75 mg/m^2) I.V. Dose. Vol 1.26, p 25.

Animal	Female B6D2F1 (C57 X DBA2) mice, three mice per time point
Drug	SK&F 104864-A, Lot JB 14324-164B
Dose	25 mg/kg (75 mg/m^2), 10 ml/kg
route	i.v. tail vein
vehicle	sterile isotonic saline
time points	0 to 1440 minutes

In this pharmacokinetic study, total drug, lactone and hydroxycarbolylate, and topotecan were determined by the HPLC method described below under analytical methods. The dose is the single dose mouse LD_{10}; nevertheless only 3 of 54 mice were unavailable for sampling at the end of the study. The investigators did not report clinical symptoms or mortality. The following table shows the pharmaco-kinetic parameters calculated from the data. The $t_{1/2}$ values are estimations of the elimination half-life using the time points from 120 to 720 minutes.

		Topotecan (lactone)	Total Drug
$t_{1/2}$	min	115	125
$AUC_{0\text{-}infinity}$	min*mg/ml	169	267
Cl_p	ml/min/m^2	444	280
Vd_{ss}	l/m^2	19.8	15.2
Mrt	min	44.8	54.1

The investigators chose arbitrary times to define the elimination half-life. The graph of the data below shows that the elimination and distribution of the drug are complex. The kinetic behavior before 240 min does not appear to fit a simple two-exponential model. After 240 min the plasma concentration increases, suggesting enterohepatic recirculation. The numbers in the table above do not reflect these complexities. At physiological pH, most of the drug should exist as the hydroxycarboxylate. Nevertheless, even though the concentration of lactone is consistently less than that of the hydroxycarboxylate, the difference between the lactone and total drug is small. This implies that most of the drug exists as lactone and that some factor in plasma is stabilizing this form. Note also that the vehicle the investigators chose was isotonic saline. The pH of this solution was not determined, so the ratio of lactone to hydroxycarbolyl compound cannot be estimated. Since the equilibrium between these two compounds is slow, the hydration reaction at physiological pH will affect the kinetics in the first hour of the experiment.



Rat

BP/008 CM: SK&F 104864 Pharmacokinetics in Male Sprague Dawley Rats Following a Single IV Bolus Dose of SK&F 104864 (5.55 or 68.6 mg/m^2). Vol. 1.26, p 39.

Animal	male Sprague-Dawley rats
Drug	SK&F 104864-A, Lot JB 14324-164B
Dose	5.55 or 68.6 mg/m^2, four rats per dose
Vehicle	not given, pH not defined
Surgical Preparation	Cannulae in both exterior juglar veins.
route	i.v. bolus through one cannula
sampling	opposite cannula, pre-dose ,2, 5, 10, 15 and 30 min, 1, 1.5, 2, 4, 6, 8, 10, and 24 hours.
Analysis	HPLC with fluorescence detection

	5.55 mg/m^2 dose				68.6 mg/m^2 dose			
parameters	SK&F	S.D.	total drug	S.D.	SK&F	S.D.	total drug	S.D.
MRT min	54	4			123	37		
$T_{1/2}$ λ1 min	9	2	3	2	23	7	37	11
$T_{1/2}$ λ2 min	54	12	54	2	100	66	57	10
$T_{1/2}$ λ3 min	n.d.c		n.d.		339	72	276	67
V_{ss}, L/m^2	26.3	1.6			46.1	13		
L/kg	4.3	0.3			7.6	2.2		
AUC µg-min/ml	11.7	1.2	26.9	2.8	184	30	404	69
%extrap. 0-t1	7	1	4	0	6	3	4	2
%extrap. t-infinity	6	6	9	8	1	1	0.3	1
CL_{pl} ml/min/m^2	475	55			380	59		

Dog

BP-1002: Determination of the Pharmacokinetic Parameters and Bioavailability of SK&F 104864 and Total Drug in Male Beagle Dogs Following a Single Intravenous Infusion (30 min) or 0.5 mg/kg (10 mg/m^2) and Following Single Oral Administration of 1.5 mg/kg (30 mg/m^2) of SK&F 104864-A as an Acidic Solution Formulation. Vol. 1.26, p 106.

Animal	male beagle dogs
Drug	SK&F 104864-A, Lot JB 14324-164B
Dose	1.5 mg/kg (30 mg/m^2 oral)
	0.5 mg/kg (10 mg/m^2) three dogs in a two way cross over
Vehicle	Oral dose prepared in water (0.3 mg/ml) pH 3.0 to 3.5 with HCl
	i.v. dose prepared in isotonic saline (0.5 mg/ml), pH 3.0 to 3.5 with HCl.
route	Oral dose by gastric intubation
	i.v. dose 30 min infusion into the right saphenous vein over 30 min.
sampling	indwelling catheter, left cephalic vein. Times, 15 min to 24 hours.
Analysis	HPLC with fluorescence detection

		i.v. dose 0.5 mg/kg				oral dose 1.5 mg/kg			
parameters		Topecan sd lactone		Total Drug sd		Topecan sd lactone		Total Drug sd	
C_{max}	ng/ml	219	38	337	34	122	46	234	45
T_{max}	hr	end of infusion		end of infusion		0.44	0.13	1.01	0.01
$T_{1/2}\lambda 1$	min	100	27	113	24	202	68	160	79
AUC	µg-min/ml	266	37	854	83	277	114	880	368
% extrapolated		2.4	0.4	1.0	0.2	5.4	2.1	1.2	0.3
CL	ml/min/m^2	32	5						
V_{ss}	L/kg	2.6	0.4						
Bioavailabitily %						35	16		

BP-1008: Pharmacokinetics of topotecan and SK&F 105992 in beagle dogs following intravenous administration of both topotecan and SK&F 105992 and following oral administration of topotecan. Vol 1.26, p. 139. (IND

The following table shows model independent pharmacokinetic parameters for topotecan and SK&F 105992 in female dogs following single intravenous infusions or an oral dose of either topotecan hydrochloride or SK&F 105992 (hydroxy carbolylate).

dosed/route/(dose)	C_{max} (ng/mL)		AUC_{0-inf} (ng.h/mL)	
	Topotecan	SK&F 105992	Topotecan	SK&F 105992
	137		173	
	30.3		74.1	
	611		883	

Data are mean values (n = 4) Topotecan doses were of the hydrochloride salt. After the intravenous doses, the plasma clearance (CL)) of topotecan and SK&F 105992 were 17.6 and 6.00 L/h, respectively and the corresponding values for the steady state volume of distribution were 17.4 and 2.27 L. Bioavailability (F) of topotecan after oral administration was 50%.

TP-1014: SK&F 104864: Single dose oral toxicity study of SK&F 104864 in dogs. Vol. 1.15, p 33.

Investigators gave female dogs topotecan doses of 1, 10, 30 and 60 mg fb/m^2. They drew blood at serial times and assayed plasma samples on day 1. T_{max} occured within 1 h; C_{max} and $AUC_{0\text{-}inf}$ values increased approximately proportional with dose. The following table shows model independent pharmacokinetic parameters for topotecan on Day 1 of this oral toxicity study with topotecan hydrochloride in female dogs at 1, 10, 30 and 60 mg fb/m^2.

Dose (mg/m^2)	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng h/mL)
1	4.19	5.70*
10	52.1	90.4
30	180	335
60	244	506

Data are mean values (n = 2). * - $AUC_{0\text{-}2}$

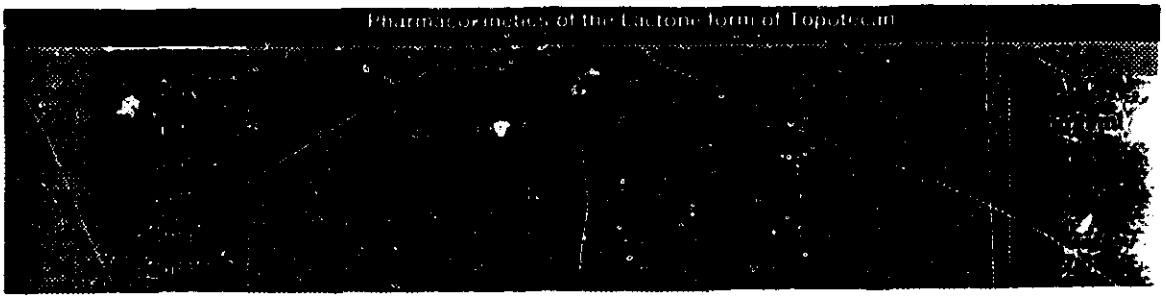
Multiple Dose Pharmacokinetics

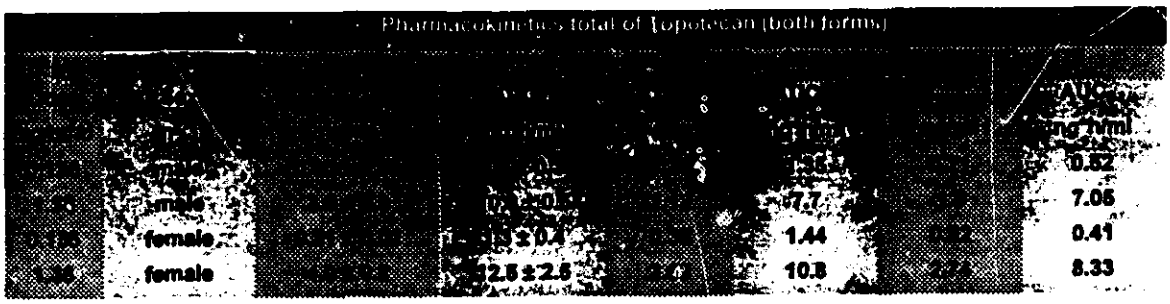
Rat

TP-1036: SK&F 104864-A: 6-Month Oral Toxicity Study in Rats. Vol. 1.19, p 2.

I have reviewed the experimental details of this study above. The rats used for pharmacokinetic studies on day 1 were a satellite group dosed with the main group. On day 1 of dosing, investigators drew blood (0.25 ml) before dosing and at 0.25, 0.5, 1, 1.5, 2, 4, and 6 hr from this group. On days 36, 121 and 176 they drew blood from rats in the main dosing study, before dosing, and at 0.5, 1, 2, 4 and 6 hours. Two rats/sex/dose group were used for each time point to generate composite pharmacokinetic profiles. Plasma topotecan was determined by the HPLC method described below.

Topotecan concentration was below the limit of quantitation in all samples from controls and the 0.0136 mg/m^2/d dose groups. T_{max} varied between 0.25 and 4 hours. C_{max} and AUC increased proportionately with dose. The first table below shows that topotecan (lactone) C_{max} and AUC remained relatively constant with time. However, the second table shows that total topotecan (both forms) C_{max} and AUC decreased on day 176. The decrease in AUC was as much as 70%. Parameters for male and female rats were similar. The male rats in the high dose group had increased serum glucose and decreased cholesterol and triglycerides as the study progressed. These changes might be related to the changes in C_{max} and AUC in the males, but the problem remains for the females. There is insufficient information to explain these changes.





Dog

TP-1034: SK&F 104864-A: 1 month intravenous toxicity study in dogs. Vol. 1.21, p 2. (IND submission 244, 6/16/95).

Model-independent pharmacokinetic parameters for total drug in dogs following repeated intravenous administration of topotecan hydrochloride for 28 days.

Parameter (units)	Day of study	Parameter value (mean ± S.D., n = 4-7)	
		0.4	0.4
	1	9.59 ± 4.44	9.12 ± 1.03
	28	11.7 ± 2.05	11.8 ± 1.55
	1	17.9 ± 4.4	20.2 ± 4.8
	28	27.1 ± 8.6	29.7 ± 7.4

Total drug = topotecan plus SK&F 105992. Doses were administered as bolus injections.

TP-1021: 5 day oral toxicity study in dog. Vol. 1.23, p 2.

Model independent pharmacokinetic parameters for topotecan following repeat oral administration of topotecan hydrochloride at 1.36 and 4 mg fb/m^2 to male and female dogs.

		C$_{max}$ (ng/mL)	AUC$_{0-24}$ (ng h/mL)
		Female	Female
	Day 1	5.37 ± 0.7	5.17 ± 1.92
	Day 5	4.86 ± 0.6	6.66 ± 1.89
	Day 1	13.2 ± 2.1	20.9 ± 6.89
	Day 5	11*	23.4*

Data are mean values ± SD of 3 animals except for * which are means of 2 animals.

Protein Binding

BP 005 C: Determination of ^{14}C-SK&F 104864-A Binding to Protein in Human, Dog and Rat Plasma and the Blood to Plasma Ratio in Dog Blood. Vol. 1.26, p 202.

BF-1007: [^{14}C]SK&F 104864A: Studies of Plasma Protein Binding and Blood Cell Binding in vitro (Rat, Dog and Man). Vol. 1.26, p. 216.

The first of these two studies reports lower values for protein binding than the second. This was due to differences in the experimental method. The latter study is more recent and used a more sophisticated ultrafiltration technique. The sponsors conclusion accurately sums up the results of this experiment.

"The percentage binding of ^{14}CSK&F 104864 to plasma protein was similar in all three species and ranged between 25.3 to 39.7%. There were no major concentration effects on the extent of plasma protein binding."

Distribution Studies

Mouse

BP-1003: Tissue Distribution of Radioactivity following a Single Intravenous Dose of ^{14}C-SK&F 104864 (Target Dose: 20 mg/kg) to Male and Female Tumor Bearing B6D2F1 Mice. Vol. 1.26, p. 251.

Investigators determined the distribution of radioactive material in male and female tumor bearing B6D2F1 mice following a single intravenous dose of ^{14}C-topotecan hydrochloride (60 mg/m^2). Radioactivity rapidly distributed into all tissues (including tumors) and peak concentrations occurred within 0.5 h after dosing. The tissue half-life was longer in female mice (12-60 h) in males (4-14 h). The elimination half life from ovary was longer than that from most other tissues (55 h). At 24 hours, concentrations in all tissues except the GI tract were less than 0.9% of the administered dose. Relatively high concentrations of radioactivity in the GI tract wall and its contents suggest that some of the dose was eliminated by biliary/intestinal secretion.

Rat

BP/009: Tissue Distribution of Radioactivity in Male Sprague Dawley Rats Following Intravenous (2 mg/kg) Administration of 14C-SK&F 104864-A2: A Qualitative Study by Whole Body Autoradiography, Vol. 1.26, p. 282.

BF-1003: Quantitative tissue distribution following a single intravenous administration of ^{14}C-SK&F-104864-A to rats at a target dose level of 1 mg pure free base/kg. Vol. 1.25, p 301 (IND submission 232, vol. 43, p 171).

Animal	21 male and 21 female Sprague Dawley Rats, 3/sex/time point
Drug	^{14}C SK&F-104864-A, batch KTG 19152-23, specific activity 2.057 GBq/mmol pure free base (4.881 MBq/mg pure free base, chemical purity > 97%. non radioactive reference batch number MM-19117-155 chemical purity > 97%
Dose	1 mg/kg, dose volume 1 ml/kg administered over 5 min.
Vehicle	3% mannitol$_{(aq)}$, pH 3.0,
time points	0, 025, 1, 6, 24, 72 and 120 hours
GLP included and signed	

After the researchers administered the dose of 1 ml/kg, they killed the rats by CO_2 asphyxiation 3/sex at each time point. Tissues were collected and processed in triplicate by combustion. The samples were then counted for radioactivity. The counting efficiency was 97% so the results were reported directly and not corrected for efficiency. The following table shows the distribution of radioactivity with time in selected tissues.

Main tissue concentration of total radioactivity after a single i.v. injection of 14C-topotecan to male rats. The dose was 1 mg pure free base/kg

time	plasma	liver	brain	kidney	testes	muscle	heart	skin
	0.604		0.045		0.078		1.937	
	0.275		0.022		0.105		0.595	
	0.189		0.016		0.153		0.239	
	0.02		0.002		0.049		0.011	
	0.024		0.001		0.008		0.007	
	0.005		0.001		0.004		0.005	
	0.004		0.001		0.003		0.005	

Topotecan distributed similarly in male and female rats. The concentration of the drug was highest just after the end of infusion in all but five tissues, liver and testes in males and exorbital lachrymal gland, pituitary and skin in females. The highest concentrations at time 0 occurred in kidney, adrenals, liver, pituitary, pancreas, thyroid, submaxillary gland, spleen, and bone marrow respectively. At the end of the infusion the tissues containing the largest proportion of the dose were liver (16.1%), muscle (15.8), kidney (6.4%), white fat (2.4%) and skin (3.5%). At this time all other samples contained less than 1% of the dose. Topotecan cleared rapidly from most tissues. At one hour after dosing relatively high concentration of the drug remained only in liver, muscle, and skin. After six hours no tissue contained more than 1% of the dose.

Enzyme Induction

BF-1005: The effect of SK&F 104864-A on hepatic levels of cytochrome P450 and related parameters in male and female Sprague Dawley rats after oral dosing at 0, 0.0023, 0.023 and 0.23 mg free base/kg/day. Vol. 1.26, p. 358

Daily doses for fourteen days did not induce 7–ethoxyresorufin O–deethylase (CYP1A), testosterone 6β or 16β–hydroxylase (CYP3A and CYP2B respectively), chlorzoxazone 6–hydroxylase (CYP2E) or lauric acid 12–hydroxylase (CYP4A) activity in the rat.

BP-1010: An *in vitro* investigation of the inhibitory potential of topotecan (SKF 104864) on the human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2D6, CYP2E, CYP3A and CYP4A. Vol 1.27, page 3 (IND 32,693 submission #268)

Cytochrome P-450 is probably the enzyme responsible for the formation of the N-demethylated metabolite SK&F 105992. This catabolite is the only topotecan derivative excreted by humans and animals. Conjugation products are not found. Both the lactone form of topotecan and the hydroxycarboxylate form are N-demethylated. The sponsor studied the rates of specific P-450 reactions in human liver microsomes in the presence and absence of topotecan. Topotecan did not inhibit any of these P-450 reactions significantly. The following table shows the substrates tested and the P-450 isoform predominately associated with the catabolism of these substrates. The results are averages from microsomes isolated from the livers of three human donors, three assays for each donor liver. To determine the reaction inhibition by

topotecan, the researchers dissolved the drug in cold menthol. To determine the inhibition caused by equilibrium mixture of topotecan and its hydroxycarboxylate derivative the researchers incubated topotecan in phosphate buffer for 4 hr at 37C.

Mean % of control activity
Substrate incubated with microsomes and topotecan for
15 minutes before the reaction was initiated by the addition of regenerating system.

Cytochrome P-450	Reaction	Topotecan		Equilibrium Mixture	
		% control	SD	% control	SD
1A2	caffeine N-demethylase	106.8	23.4	106.6	17.7
2A6	coumarin 7-hydroxylase	98.9	11.5	98.6	3.4
2C8 and 2C9	tolbutamide hydroxylase	98.8	7.5	99.9	6.0
2C19	S-mephenytoin 4-hydroxylase	96.3	4.8	100.8	9.4
2D6	bufuralol 1'-hydroxylase	117.8	13.9	109.6	26.6
2E1	lauric acid ω-1-hydroxylase	97.2	5.8	92.8	13.0
3A4	cyclosporin oxidase	107.9	4.4	98.7	8.5
4A	lauric acid ω-hydroxylase	92.7	25.2	101.8	6.0

BF-1011: An in vitro investigation of the inhibitory potential of Topotecan (SK&F 104864) on the human liver cytosolic enzymes, dihydropyrimidine dehydrogenase and xanthine oxidase. Vol. 1.27, p. 32.

Topotecan, 10μM, did not inhibit the normal *in vitro* catalysis of the human cytosolic enzymes, xanthine oxidase and dihydropyrimidine dehydrogenase.

Metabolism Studies

Rat

BF-1009: Quantitative bio-transformation of [^{14}C]SK&F 104864 in male and female rats following intravenous dosing at 1 mg pfb/kg. Vol. 1.27, p 55 (IND 32,963, serial 268).

Animal	7 male and 7 female Sprague Dawley Rats 3/sex for urine and feces collection 4/sex for blood collection
Compound	[^{14}C]SK&F 104864 Lot KTG-19152-23, Specific activity 110 μCi./mg, 83% pfb in 3% aqueous mannitol pH 3 to 1 mg pfb/ml (nominally 132 μCi/ml).
Assay	isocratic HPLC with UV and radio-label detection.
Administration	Single i.v. dose

GLP statement included and signed.

Results

The following table shows the total cumulative amount of topotecan or metabolites in urine and feces at 24 hr as a percentage of the initial radioactive dose. The table also shows the relative amount of each compound in plasma at 30 min and 4 hours.

	Urine (as % of dose)		feces (as % of dose)		plasma 30 min (% of plasma radioactivity)		plasma 4 hr (% of plasma radioactivity)	
	male	female	male	female	male	female	male	female
Topotecan	46	41	41	42	81	83	42	33
desmethyl metabolite	0.7	0.6	2.8	2.7	0	0	<3%	<3%
Polar metabolites	<3% of dose		<2% of dose					

The investigators identified the single major metabolite as the N-demethylated compound by Mass Spectroscopy. The radioactivity that could not be identified in plasma (> 45 % at both collection times) eluted late off the HPLC column. Late elution from this reverse phase column implies hydrophobicity greater than topotecan. This activity was probably parent compound and metabolite bound to proteins. Protein was precipitated from the plasma drawn after 30 minutes. In these experiments, the investigators accounted for 91 and 86% of the total dose in male and female rats respectively.

BP-1009: Preliminary biotransformation of [^{14}C]SK&F 104864 in the male Sprague-Dawley rat following single intravenous administration (1 mg/kg). Vol 1.27, page 97 (IND 32,963, serial 268)

The sponsor determined that rats excreted topotecan predominantly as the parent compound. Male rats converted less than 4% of the administered dose to the N-desmethyl derivative. Researchers found four minor metabolites, but did no experiments to identify them. These metabolites were less than 1% of the administered dose. Plasma contained only the parent compound. This is a preliminary study. I have done a more comprehensive review of the final study above, BF-1009.

BF-1008: Metabolite patterns in urine, faeces and plasma following a single intravenous administration of [^{14}C]SK&F 104864A to the rat and dog at target dose levels of 1 and 0.5 mg free base/kg respectively. Vol. 1.27, page 90

The sponsor submitted a termination report of these studies in submission #268, September 18, 1995. This report was only a summary. In the NDA submission the sponsor says that the studies were terminated because the HPLC method could not efficiently separate the parent compound from the metabolites.

Dog

BF-1010: Quantitative biotransformation of [^{14}C]SK&F 104864 in male and female dogs following intravenous administration at 0.37 mg pfb/kg, Vol 1.27, page 139 (IND

Animal	3 male and 3 female beagle dogs
Compound	[^{14}C]SK&F 104864 Lot KTG-19152-23, Specific activity 110 µCi./mg, 83% pfb
	in 3% aqueous mannitol pH 3 to 0.37 mg pfb/ml (nominally 11.1 µCi/ml).
Assay	isocratic HPLC with UV and radio-label detection.
Administration	Single i.v. dose
Analysis	urine (~48 hr) feces (~72 hr), blood (at 1 and 6 hours)

Results

	Urine (as % of dose)		feces (as % of dose)		plasma 1 hr (% of plasma radioactivity)		plasma 6 hr (% of plasma radioactivity)	
	male	female	male	female	male	female	male	female
Total Topotecan	25	25	30	14	66	65	53	60
desmethyl metabolite	2.9	4.1	12	13	4	6	<5	<5
Polar metabolites	<4.5		<3					
Remainder	unrecovered		unrecovered		unrecovered		unrecovered	

The numbers in the table above are averages for three dogs. The samples were not collected over the same time periods for all the dogs, but the averages reflect the approximate distribution of the different compounds. The investigators identified the single major metabolite as the N-demethylated compound by Mass Spectroscopy. The radioactivity that could not be identified in plasma (> 30 % at both collection times) eluted late off the HPLC column or was unrecoverable. As in the rat study, late elution from this reverse phase column implies hydrophobicity greater than topotecan. This activity was probably parent compound and metabolite bound to proteins. Protein was precipitated from the plasma drawn after 1 hour. In these experiments, the investigators accounted for 70 and 56% of the total dose in male and female dogs respectively.

BP-1012: Preliminary biotransformation of [^{14}C]SK&F 104864 in the male beagle dog following single intravenous administration (0.5 mg pfb/kg). Vol 1.27, page 176 (IND

Researchers found 33% of the topotecan dose in the urine of dosed dogs (90% of recovered radioactivity). Ten % of the radioactivity (3% of the dose) was the N-desmethyl metabolite. The concentration of the parent compound in the feces was four times higher than

that of the N-desmethyl metabolite and accounted for approximately 40 % of the dose. This is a preliminary study. I have done a more comprehensive review of the final study above, BF-1010.

BF-1012: The metabolism of [^{14}C]SK&F 104864 in rat, dog and human hepatic microsomes. Vol 1.27, Page 201 (IND . GLP signed.

[^{14}C]SK&F 104864 lot KTG-19152-23, 110 μCi/mg.

Smith-Kline Beecham studied the *in vitro* metabolism of topotecan with rat, dog and human microsomes. Researchers incubated microsomes with topotecan, 5 and 50 μM, and NADPH regenerating system for 30 minutes. These concentrations of topotecan are significantly higher than the concentrations expected *in vivo*, where C_{max} after a single i.v. dose is approximately 0.1 μM. Topotecan is oxidized slowly to a single desmethyl catabolite. The open ring form of topotecan, SK&F 105992, exists pH dependant equilibrium with topotecan. This open ring form predominates at the reaction pH, 7.4. This form is also demethylated by cytochrome P-450. The following table shows the reaction rates, the rate for patient H115 was not included in this table. The sponsor did not explain this omission.

microsomes	Topotecan pmol/min/mg protein	mean ± SD	CYP1A2 (caffeine N3-demethylase) pmol/min/mg	
rat	1.2			
Dog	2.8			
Human				
H32	1.4		168	
H105	1.4		23.8	
H114	2.1	1.6±0.4	68.5	
H115			22.7	70±68

The rate of topotecan oxidation to the desmethyl catabolite is much slower than the demethylation of caffeine, a reaction catalyzed predominately by CYP1A2. This is consistent with the observation that hepatic metabolism clears little topotecan *in vivo*. Dogs and rats oxidize topotecan at similar rates.

Balance/Excretion Studies

Rat

BP-1006: Preliminary biliary excretion of ^{14}C-SK&F 104864 in male Sprague Dawley rats following single intravenous administration (nominal dose 1 mg/kg). Vol. 1.27, p 000246 (IND

Animal	male Sprague-Dawley rats with bile duct cannulae
Drug	^{14}C-SK&F 104864-.2HCl, Code SWL-203310-250, >98%, 35.6 mCi/mmol
Dose	1.213 ± 0.015 mg/kg or 7.157 mg/m^2
Route	single dose i.v.
Vehicle	Sterile 3% mannitol, pH 3.0 with HCl
Final dosing solution	87.57 µCi/1.22 mg/g solution, actual dose 1.21 mg/kg, 87.367 µCi/kg
Analysis	quantitative combustion followed by scintillation counting
Samples	bile, excreta and blood

Collection period	Bile	Urine	Feces	GI Tract	Carcass	Cage Rinse	Total
	19.1 ± 1.5						19.1 ± 1.5
	3.8 ± 0.7						3.8 ± 0.7
	1.3 ± 0.5						1.3 ± 0.5
							32 ± 16
	1.0 ± 0.2						19.6
	25.3 ± 2.5		18 ± 2		1.7 ± .6		98.3 ± 0.8

Note that rats eliminated 18% of the administered dose in the feces even though they were cannulated. This implies that some topotecan may be excreted by the intestine.

BF-1004: Excretion and plasma concentrations of drug related material following single intravenous administration of [^{14}C]-SK&F 104864A to male and female rats and dogs at target levels of 1 mg pure free base/kg and 0.5 mg pure free base/kg, respectively. Vol 1.26, p. 65.

Animal	8 male and 8 female Sprague Dawley rats 3 male and 3 female beagle dogs
Drug	^{14}C-SK&F 104864-A, lot KTG 19152-23, 2.057 GBq/mmol, >97% pure SK&F 104864-A, Lot MM-19117-155, > 97% pure
Dose	0.5 mg/kg for dogs, 5 ml/kg 1 mg/kg for rats, 1 ml/kg
Route	single dose i.v.

Vehicle	Sterile 3% aqueous mannitol, pH 3.0 with HCl
Analysis	quantitative combustion followed by scintillation counting
Samples	excreta, cage wash, carcase, GI, GI contents and blood

GLP included and signed

In both species the radioactivity was cleared quickly. In the rat, ~40% of the total dose was eliminated in the urine in the first 8 hours after dosing; over ~30% was eliminated in the feces in the first 24 hours. In the dog, ~25 % was eliminated in the urine after 8 hours, and ~45% in the feces after 24 hours. Little of the dose given to rats was found in the carcass, the GI tract or the cage wash.

	% administered dose at 120 hrs			
	male rat	female rat	male dog	female dog
	50.6	50.8	37.5	46.3
	39.9	40.2	50.4	42.6
	3	5.2	1.6	1.7
	0	0		
	0	0		
	1.1	0.7		
	94.5	96.8	89.5	90.6

Dog

BP-1005/2: Preliminary balance/excretion of ^{14}C-SK&F 104864-A in male Beagle dogs following single intravenous (0.5 mg/kg) administration. Vol 1.27, p 260.

In IND . the sponsor submitted a correction to the original IND . Researchers used only three dogs and not four in this experiment as originally reported. They excluded dog 3 because he was to aggressive to handle. Thus the results are given for dogs 1, 2, and 4.

In IND the sponsor submitted a revised report for this study. This report included only results and discussion.

Animal	three non-naive SB colony male Beagles, see note above
Drug	^{14}C-SK&F 104864-A, Code SWL-22123-158, 99.4%, 35.6 mCi/mmol SK&F 104864-A, Lot MM-19117-30(1)2
Dose	0.5 mg/kg or 10 mg/m^2
Route	single dose i.v., infusion 0.5 mg(base)/ml/kg over 30 min.
Vehicle	Sterile saline, pH 3.5 with HCl
Final dosing solution	0.53 mg/4.1159 µCi/g solution
Analysis	quantitative combustion followed by scintillation counting
Samples	excreta and blood

Mean (± S.D.) Percent Recovery[1] of Radioactivity in Urine, Feces, and Cage Rinse Following Single Intravenous Infusion (0.5 mg/kg) of ^{14}C-SKF 104864-A to Male Beagles

Collection Period (h)	Urine	Feces	Cage Rinse	Total Recovery
0-24	36.4 ± 3.2	42.0 ± 3.0	1.6 ± 0.7	80.0 ± 5.0
24-48	2.1 ± 1.6	3.4 ± 3.9	0.2 ± 0.1	5.7 ± 5.4
48-72	1.0 ± 0.8	1.8 ± 1.4	0.4 ± 0.2	3.2 ± 1.7
72-96	0.3 ± 0.1	0.5 ± 0.3	1.9 ±0.2	2.7 ± 0.3
0-96	39.8 ± 1.4	47.7 ± 1.5	4.1 ± 0.6	91.6 ± 0.8

[1] Data are expressed as mean percent of dose administered ± S.D. (n=3).

Topotecan is eliminated almost equally in the urine and feces of dogs. Most of the elimination is complete by 24 hours.

Pharmacokinetics summary

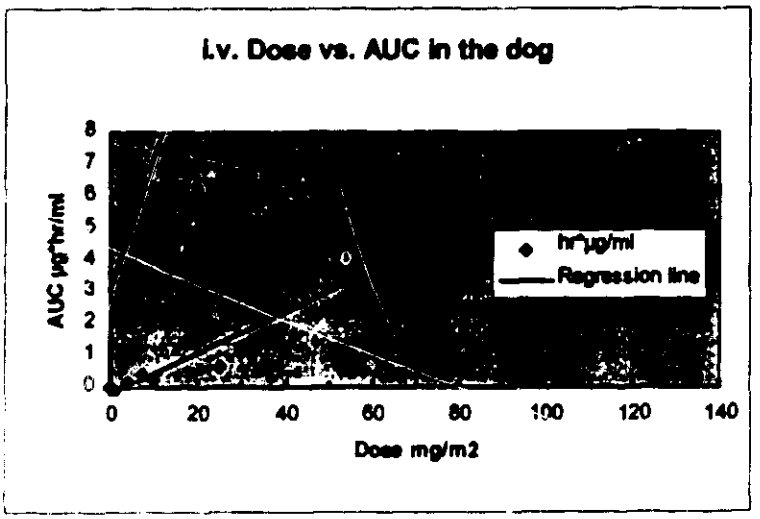
Summary table of excretion data:

study	BF-1004				BP 002CM		BP-1005
time	% administered dose to 120 hrs				% dose to 96 hrs		% dose to 96 hrs
dose	5.9 mg/m^2		10 mg/m^2		5.9 mg/m^2		10 mg/m^2
	male rat	female rat	male dog	female dog	male rat	female rat	male dog
urine	50.5	50.5	37.5	46.3	45.8	40	39.8
feces	39.9	40.2	50.4	42.6	46.5	52.9	47.7
respired air					0.4	0.3	
cage wash	3	5.2	1.6	1.7	2.3	1.7	4.1
GI tract	0	0					
GI tract contents	0	0					
Carcass	1.1	0.7			0.5	0.5	
Total	94.5	96.6	89.5	90.6	95.5	95.4	91.6

Summary table of single dose pharmacokinetics

Species		mouse	Rat		Dog (male)			
Study		BP 007CM	BP 0005CM		TP-10034			BP-1002
Dose	mg/m^2	75.00	5.55	68.60	0.02	0.1	0.4	10
$t_{1/2b}$	hr	1.92	0.90	1.67				1.7
$AUC_{0-infinity}$	hr*µg/ml	2.82	0.196	3.07	0.00085	0.00618	0.0179	0.266
Cl_p	L/hr/m^2	26.64	28.50	22.80				38.4
Vd_{ss}	l/m^2	19.80	25.30	46.10				56
Mrt	min	0.75	0.90	2.05				

The following figure demonstratese that AUC is approximately linear with dose over a wide dose range in the dog. The correlation coefficient for the regression line is 0.98.



Intravenous doses of topotecan are distributed through the body in less than ten minutes. The elimination half-life, $t_{1/2}\beta$ in dogs is about 100 minutes. The rat eliminates topotecan faster than the dog; $t_{1/2}\beta$ is about 50 minutes. The studies in the rat suggest a second elimination phase, $t_{1/2}\gamma$ ~349 minutes. Studies in the mouse suggest significant diurnal enterohepatic recirculation. In all these species, AUC and C_{max} increases proportional to dose and repeat dose studies suggest some accumulation only at the highest doses.

The volume of distribution at steady state is greater than total body water, 2.8 l/kg in the dog, suggesting depot sequestration. Topotecan should accumulate in fat or in hypoxic, i.e., acidotic, tissues. One hour after an intravenous dose in rats, the highest concentrations of radiolabeled topotecan are in the liver, muscle and skin. Little of the dose remained anywhere in the animal after 120 hours. A small amount of topotecan may enter the brain. Because of the hydrolysis reaction, the time verses concentration curves for topotecan and that of total administered dose should diverge. They do, but not to the extent the equilibrium constant would suggest, as mentioned above. Some factor in the plasma stabilizes the topotecan. In all species tested protein binding is between 25.3 and 39.7%. This is much less than the original topoisomerase I inhibitor, camptothecin.

Oral bioavailability of topotecan in the dog is about 35%. Rats with bile duct cannulae still secrete about 18% of an intravenous dose of topotecan in the feces. This suggests significant intestinal secretion. After 24 hours rats excrete approximately 43% of a topotecan dose in the urine and about 41% in the feces as the parent compound. Less than 1% of the dose appears in the urine as the N-demethylated metabolite, about 3% of the dose appears in the feces as this metabolite. The N-demethylated compound is the only major metabolite formed by any species. Hepatic microsomes from rat, dog and human form the N-demethyl metabolite from the parent compound at about the same rate, 1 to 3 pmol/min/mg. Cytochrome P450 CYP1A2 is possibly responsible for most of this reaction. Less than 3% of the dose appears as unidentified polar metabolites. At 24 hours dogs eliminate less of a topotecan dose in both the urine and the feces, but the proportion in each is about the same. Again the N-demethyl compound is the only

major identified metabolite. Topotecan does not induce any major hepatic cytochrome P450 isozymes nor does it inhibit any major cytochrome P450 activities *in vitro*.

The following table shows C_{max} in the dog after a single i.v. dose. If the inhibitory constant for topotecan is approximately μM these doses provide only just high enough concentrations of topotecan. Nevertheless, numbers are deceiving. The actual k_i at the enzyme active site is not known and the presance of the hydroxy carboxylate may influence concentrations of topotecan at the active site even if it is not active.

Dose mg/m^2	C_{max} ng/ml	C_{max} μM
4	137	0.33
10	219	0.52
25	611	1.45

Analytical Methods

BP 006 CM: HPLC Methods for the Specific Determination of SK&F 104864 and for Determination of Total Drug (SK&F 104864 plus SK&F 105992) in Mouse, Human and Rat Plasma, Vol. 1.27, page 316

BP-1001: Validation of a sensitive assay for determination of SKF 104864 and total drug (SKF 104864 and SKF 105992) and drug stability verification in extracts of dog plasma. Vol 1.27, page 347.

BF-1006: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in human plasma using HPLC with fluorescence detection. Vol 1.27, p 384 (IND

BF-1001: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in rat plasma using HPLC with fluorescence detection, Vol. 1.27, page 427

BF-1002: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in dog plasma using HPLC with fluorescence detection. Vol. 1.27, page 453

These studies are validations of an HPLC method for determining topotecan in plasma. They are similar to the analysis described in study BF-1006 and this last study probably supersedes the earlier ones. The sponsor developed these separations because earlier methods (studies BP-001 and 003, reviewed by Dr. Taylor) could not distinguish topotecan from the hydrolysis product, SK&F 105992. These improvements were accomplished by acidifying part of the sample to convert all the topotecan to the lactone. Study BF-1001 and BF-1002 were done at approximately the same time in the Netherlands. The two validations are essentially identical, one done for rat plasma and one for the dog plasma. The assay described in BF-1006 is more sensitive and better documented than the other assays. It was also done with human plasma and so is the most relevant. I have provided a comprehensive review of this study below. Differences between this study and the others are minor.

BF-1006: Analysis of topotecan and topotecan as the total of the lactone plus carboxylate form in human plasma using HPLC with fluorescence detection. Vol 1.27, p 384 (IND

Drug		Topotecan, batch MM-15906-194, 89.2% analytical purity
Plasma		Human Control
HPLC		
	pumps	Spectra System P1000
	column	Zorbax SB-C18, 3.5 µm, 4.6X75 mm,
	guard	Chrompack, Reversed Phase, 3X10 mm
	detector	FP920 Intelligent Fluorescence Detector
	λ	excitation 361 nm, emission 527 nm,
	flow	1.0 ml/min
	injection	50 µl loop

Temp ambient

Eluent $TEMED_{aq}$ 0.01 M pH 6:methanol:Hexane-1-sulfonic acid sodium $salt_{MeOH}$ 0.1 M

65:25:10 v/v/v

This study validates the HPLC method for determining topotecan concentration in human plasma. The lactone form of topotecan is fluorescent; the open ring hydroxycarboxylate form is not. The two forms exist in pH dependent equilibrium, acidic conditions favoring the lactone form. The concentration of topotecan in plasma was determined by quantitative HPLC with fluorescence detection. The concentration of total topotecan forms (lactone plus hydroxycarboxylate) was determined by adding 7% perchloric acid to the plasma sample before HPLC separation. This addition of acid converts all the topotecan to the lactone form. The concentration of open ring hydroxycarboxylate in the original plasma sample is then the difference between the topotecan concentration and the total concentration.

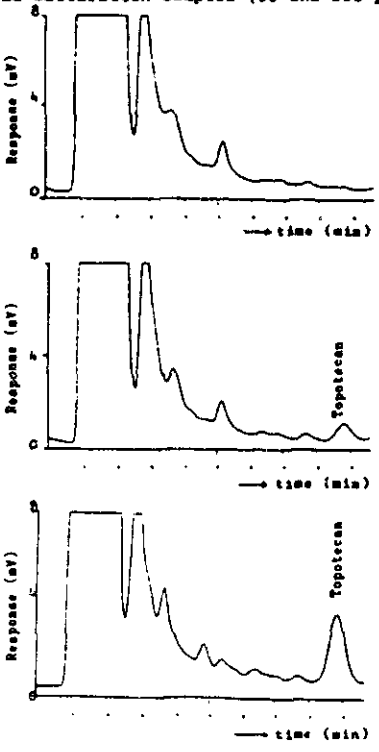
The assay was well controlled and standardized. The researchers determined that the assay was linear between 50 and 10,000 pg/ml (0.119 and 23.7 fM) with a correlation coefficient of 0 996. The average accuracies were within 85 and 115%. The average within-run and between-run precisions were less than 15%. The recovery of topotecan was 71.9% ± 5% at 250 pg/ml and 86.1% ± 3.4% at 10,000 pg/ml. Topotecan lactone was not stable in plasma at -30C or -70C after 7 or more weeks. The HPLC analysis must be done as soon after sample collection as possible. The HPLC assay is acceptable for quantifying topotecan in human plasma.

Appendix 4.1.
Assay performance data for the determination of topotecan.

Nominal Concentration (pg/ml)		Run1	Run2	Run3	Average Within-Run Precision	Between-Run Precision	Average Accuracy
50	Mean	53.8	50.0	54.0	9.0	4.3	105.2
	S.D.	5.6	4.2	4.5			
	C.V.	10.4	8.4	8.3			
	Acc.	107.6	100.0	108.0			
	n	6	6	6			
100	Mean	97.2	111.2	101.7	7.9	12.1	100.0
	S.D.	6.7	5.4	11.3			
	C.V.	7.7	4.9	11.1			
	Acc.	87.2	111.2	101.7			
	n	6	6	6			
250	Mean	226.8	214.3	215.7	5.6	3.1	87.6
	S.D.	16.0	10.6	10.3			
	C.V.	7.1	4.9	4.8			
	Acc.	90.7	85.7	86.4			
	n	6	6	6			
5000	Mean	5294.2	5230.0	5147.8	3.8	1.4	104.5
	S.D.	154.5	253.1	184.7			
	C.V.	2.9	4.8	3.6			
	Acc.	105.9	104.6	103.0			
	n	6	6	6			
10000	Mean	10509.7	10919.5	10539.8	3.0	2.1	106.6
	S.D.	475.5	237.8	252.6			
	C.V.	4.5	2.2	2.4			
	Acc.	105.1	109.2	105.4			
	n	6	6	6			

S.D. : Standard Deviation
C.V. : Coefficient of Variation (%)
Acc. : Accuracy (%)
n : Number of determinations

Appendix 1.2.
Chromatograms typical for the analysis of topotecan as total of lactone and carboxylate: human control plasma and two spiked plasma calibration samples (50 and 250 pg/ml).



NDA Summary

Hycamtin or topotecan is a semi-synthetic derivative of camptothecin. Camptothecin is a natural product extracted from the bark of the tree Camptotheca *acuminata*. The chemical name for this compound is (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1 H - pyrano[3',4':6,7] indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride. Topoisomerase I is a nuclear enzyme that relieves torsional strain in DNA by opening single strand breaks. Once topoisomerase I creates a single strand break, the DNA can rotate in front of the advancing replication fork. Topotecan binds reversibly to the Topoisomerase I - DNA complex and prevents religation of these single strand breaks. Current research suggests that double strand DNA damage occurs during DNA synthesis when progressing replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I and DNA. Mammalian cells cannot efficiently repair these double strand breaks. This damage probably initiates apoptosis.

In basic solution, hydroxyl ions hydrolyze topotecan to the hydroxy carboxylate open ring form. At physiological pH the open ring form predominates. Topotecan, the closed ring lactone form, is stabilized by acid, that is when pH is less than 4. The open ring form does not bind to Topoisomerase I and does not cause DNA damage. The equilibration between the open ring form and topotecan is relatively slow. When topotecan is prepared in acidic mannitol (the clinical formulation) and then added to buffer at physiological pH, the active lactone equilibrates with the inactive hydroxy carboxylate in about an hour. Thus, an hour after injection into a patient the concentrations of topotecan should be much smaller than the total concentration of both lactone and hydroxy carboxylate. AUC values from single dose kinetics in the mouse, rat and dog suggest that the concentration of topotecan in plasma remains within a factor of three of the concentration of total drugs, not different by several orders of magnitude as predicted by the equilibrium reaction. Plasma proteins possibly stabilize topotecan in the lactone form. The available studies did not explain this discrepancy between *in vivo* and *in vitro* behavior. Nevertheless, using the total drug concentrations in cell culture assays, I estimated the inhibitory binding constant of topotecan at the DNA site to be approximately μM. Because of the hydrolysis reaction, the actual binding constant is probably much lower. Topotecan is a very potent inhibitor of DNA replication.

The sponsor conducted an impressive array of preclinical studies in the mouse, rat , rabbit and dog, thus they have well characterized the toxicities associated with topotecan. In early studies, the sponsor calculated the single dose LD_{10} to be 74 mg/m^2 and for five daily doses, 13.8 mg/m^2, in the rat. The dose response curve appears to be unusually shallow. Rats survive 28 daily doses approximately equivalent to the clinical dose on a mg/m^2 basis. Dogs do not tolerate one third the clinical dose given for 28 days. Dogs appear to best predict the toxicities of topotecan.

The dose limiting toxicities in all these species are myelosuppression and anemia. The onset of myelo-suppression is rapid; the degree of myelosuppression is duration and dose dependent. High repeat doses can cause profound decreases in WBC and platelet count within eight days of the start of treatment. All white cell types are affected. These changes are usually reversible when treatment is stopped. Sometimes the platelet count and the neutrophil count will rebound to higher than normal, but this increase usually returns to normal within two weeks. RBC, Hgb, and Hct also decreased with dose and duration of treatment. These toxicities appears to result from decreased erythropoesis rather than hemolysis. These parameters usually recover to near control values within weeks after dosing stops.

Repeated dosing with topotecan caused increases in ALT and AST suggesting liver damage. Histology did not confirm this toxicity, probably because myelosuppression is dose limiting. Thus, the doses were not high enough to demonstrate clear dose related damage. Similarly, repeated dosing sometimes caused transient changes in the urinalysis parameters, suggesting mild kidney damage; but

again the doses were not high enough to demonstrate clear dose dependent toxicity.

Topotecan caused the microscopic damage usually associated with myelo-suppression: bone marrow hypocellularity, cellular depletion of the spleen, thymus, and lymph nodes. Damage to the GI was remarkably rare and usually seen only in long term studies of oral dosing. Some dogs given 0.4 mg/m²/d for one month developed multinucleated spermatogonial giant cells in the testes. In rats, a dose of 0.23 mg/kg/d given for 14 days before mating through gestation day six caused a 75% increase in the number of corpora lutea. The mechanism causing this super-ovulation was not determined. Weight loss is dose dependent and associated with anorexia. Alopecia is dose dependent, but does not occur in all animals. Microscopically the hair follicles were atrophic.

The sponsor did not do carcinogenicity tests with topotecan in laboratory animals. Nevertheless, topotecan is genotoxic to mammalian cells *in vivo* and *in vitro*. In mouse L5178Y lymphoma cells, 0.1 µg/ml of topotecan caused a four fold increase in mutations over controls. This dose was cytotoxic and increases in mutations occurred in the presence of S9. In human lymphocytes *in vitro*, 0.5 µg/ml of topotecan caused an eleven fold increase in the percentage of cells with chromosome breaks. In some cases, DNA damage caused by topotecan was greater than that caused by the positive controls. In mice, *in vivo*, 0.16 mg/kg of topotecan caused a 34 fold increase in the percentage of cells with micronuclei. Topotecan did not cause mutations in bacterial cells.

Topotecan caused embryonic and fetal death in rabbits and rats. In rabbits, a dose of 0.32 mg/kg/d on days six through 20 of gestation causes fetal resorption. This dose caused significant maternal toxicity. In rats, a dose of 0.23 mg/kg/d given for 14 days before mating through gestation day six caused 99.6% fetal resorption, 24% pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/d (0.4 times the clinical dose on a mg/m² basis) given to rats on days six through 17 of gestation caused a 2.5 fold increase in post-implantation mortality. This dose also caused a 3.8 fold 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), scull and vertebrae.

Intravenous doses of topotecan are distributed through the body in less than ten minutes. The elimination half-life, $t_{1/2}\beta$ in dogs is about 100 minutes. The rat eliminates topotecan faster than the dog; $t_{1/2}\beta$ is about 50 minutes. The studies in the rat suggest a second elimination phase, $t_{1/2}\gamma$ ~349 minutes. Studies in the mouse suggest significant diurnal enterohepatic recirculation. In all these species, AUC and C_{max} increases proportional to dose and repeat dose studies suggest some accumulation only at the highest doses.

The volume of distribution at steady state is greater than total body water, 2.8 l/kg in the dog, suggesting depot sequestration. Topotecan should accumulate in fat or in hypoxic, i.e., acidotic, tissues. One hour after an intravenous dose in rats, the highest concentrations of radiolabeled topotecan are in the liver, muscle and skin. Little of the dose remained anywhere in the animal after 120 hours. A small amount of topotecan may enter the brain. Because of the hydrolysis reaction, the time verses concentration curves for topotecan and that of total administered dose should diverge. They do, but not to the extent the equilibrium constant would suggest, as mentioned above. Some factor in the plasma stabilizes the topotecan. In all species tested protein binding is between 25.3 and 39.7%. This is much less than the original topoisomerase I inhibitor, camptothecin.

Oral bioavailability of topotecan in the dog is about 35%. Rats with bile duct cannulae still secrete about 18% of an intravenous dose of topotecan in the feces. This suggests significant intestinal secretion. After 24 hours rats excrete approximately 43% of a topotecan dose in the urine and about 41% in the feces as the parent compound. Less than 1% of the dose appears in the urine as the N-demethylated metabolite, about 3% of the dose appears in the feces as this metabolite. The N-demethylated compound is the only major metabolite formed by any species. Hepatic microsomes from rat, dog and human form the N-demethyl metabolite from the parent compound at about the same rate, 1 to 3 pmol/min/mg. Cytochrome P450 CYP1A2 is possibly responsible for most of this reaction. Less

than 3% of the dose appears as unidentified polar metabolites. At 24 hours dogs eliminate less of a topotecan dose in both the urine and the feces, but the proportion in each is about the same. Again the N-demethyl compound is the only major identified metabolite. Topotecan does not induce any major hepatic cytochrome P450 isozymes nor does it inhibit any major cytochrome P450 activities *in vitro*.

Topotecan is one of the first topoisomerase I inhibitor available as a cancer chemotherapeutic drug. Its limiting toxicities are well characterized in mice, rats, rabbits and dogs, and these toxicities are those usually associated with a potent cytotoxin. Nevertheless, much of the biochemistry of this unusual compound remains unknown.

W. David McGuinn, Jr. Ph. D.
May 24, 1996 5/24/96

5/24/96
Joseph J. DeGeorge, Ph. D.

cc: /HFD-150
/J. DeGeorge
/S. Hirschfeld
/D.Catterson
/D. McGuinn

Division of Oncology Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
NDA for Ovarian Cancer, Review

NDA 20-671 **Reviewer: W. David McGuinn, Ph. D.**

Submission: 000 Received by CDER December 22, 1995
Received by reviewer January 2, 1996

Sponsor: ***SmithKline Beecham Pharmaceuticals***
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

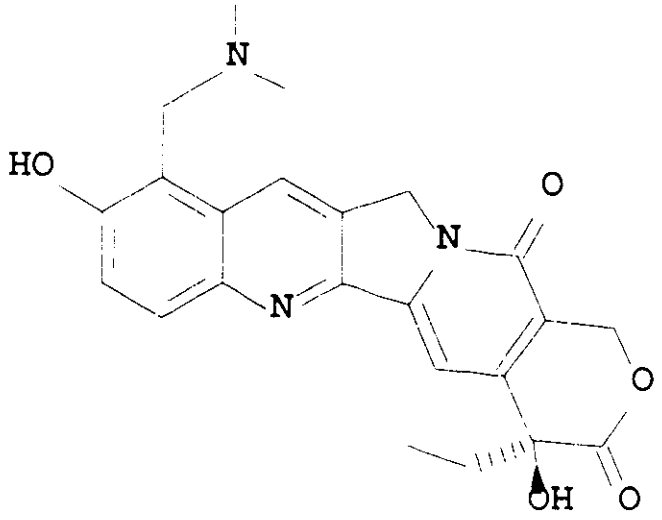
Information to be conveyed to the sponsor: YES

Drug Name: ***Hycamtin™, topotecan HCl for injection***
or SK&F S-104864-A (hydrochloride salt)

Chemical Name: (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1 H -pyrano[3',4':6,7] indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride.

CAS-119413-54-6 CAS-123948-87-8 (free base)
Molecular Formula: $C_{23}H_{23}N_3O_5 \bullet HCl$
Molecular Weight: 457.91 (hydrochloride salt)

Structure



Indications: Ovarian Cancer
Drug Type: Topoisomerase I inhibitor, antineoplastic

Labeling

1) In the section CLINICAL PHARMACOLOGY the first paragraph should be changed to read:

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. Current research suggests that the cytotoxicity of topotecan is 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.

2) The following sentence in the section on ***metabolism*** should be changed from:

to:

Other possible minor metabolites of topotecan have been detected but not identified.

3) The following sentence in the section on ***excretion*** should be changed from:

to:

Much of the intravenous topotecan dose is hydrolyzed to the open-ring hydroxy-acid. This open ring hydrolysis product does not inhibit topoisomerase I.

4) The following sentence should be added as the last sentence in the paragraph on ***excretion***.

Studies suggest that rats may eliminate as much as 18% of an intravenous topotecan dose by intestinal excretion.

5) The last paragraph in the **WARNINGS** section should read:

Pregnancy. Hycamtin can cause fetal harm when given to a pregnant woman. The effects of topotecan on pregnant women have not been studied. If topotecan is used during a patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming pregnant. Topotecan caused embryonic and fetal death in rabbits and rats. In rabbits, a dose of 0.32 mg/kg/d (about twice the clinical dose on a mg/m^2 basis) on days six through 20 of gestation cause fetal resorption. This dose caused significant maternal toxicity. In the rat, a dose of 0.23 mg/kg/d (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day six caused fetal resorption, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/d (about half the clinical dose on a mg/m^2 basis) given to rats on days six 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), scull and vertebrae.

5) The section **Carcinogenesis, Mutagenesis, Impairment of Fertility** should be changed from:

to:

Carcinogenicity tests with topotecan have not been done in laboratory animals. Nevertheless, topotecan is genotoxic to mammalian cells *in vivo* and *in vitro*. Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation *in vitro*. It was clastogenic to mouse bone marrow *in vivo*. Topotecan did not cause mutations in bacterial cells. Some dogs given 0.4 mg/m^2/d for one month developed multinucleated spermatogonial giant cells in the testes. In rats, a dose of 0.23 mg/kg/d (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day six caused a 75% increase in the number of corpora lutea. The mechanism causing this super-ovulation has not been determined.

6) The section **Pregnancy** should be changed from:

to:

Pregnancy: Pregnancy Category D. (See WARNINGS section).

Suggested changes:

1) Throughout the document should be replaced with "cytochrome P450 isozymes".

2) The following sentence in the section on ***Drug Interactions*** should be should be changed from:

to:

Intravenous doses of Hycamtin up to 1.36 mg/m^2 given to rats for 14 days did not induce the activity of hepatic cytochrome P450 isozymes CYP1A, CYP3A, CYP2B, CYP2E, or CYP4A.

W. David McGuinn, Jr. Ph. D.

cc: /HFD-150
/J. DeGeorge
/S. Hirschfeld
/D.Catterson
/D. McGuinn

stat

STATISTICAL REVIEW AND EVALUATION

MAY 20 1996

N.D.A.:	#20-671
APPLICANT:	SmithKline Beecham Pharmaceuticals
NAME OF DRUG:	Hycamtin (Topotecan hydrochloride)
INDICATION:	Metastatic Carcinoma of the Ovary after Failure of Initial or Subsequent Therapy
REVIEWING CHEMIST:	Yung-Ao Hsieh, Ph.D.
LOT NUMBERS:	1814H00, 1824H00, 1834H00, 2825H01, 2835H01, 2845H01
TOPIC:	Stability testing statistical analysis
DOCUMENTS REVIEWED:	NDA #20-671, two stability submissions (dated 12/22/95 and 3/29/96, respectively)

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1. BACKGROUND

The objective was to determine the stability of topotecan based on the time when an appropriate confidence band crosses its associated specification limit. The parameters under study were topotecan content, total degradation products, and the individual degradation products SB-211307 and SKF-S-107564. Thus there were four parameters to consider. Three batches each of 4 mg vials and 5 mg vials were analyzed. The first intersection of a confidence band and its associated specification limit is the expiry. The specification limits are 92.5% for topotecan content (compared to a one-sided 95% lower confidence band), 3% for total degradation products (compared to a one-sided 95% upper confidence band), 1% for SB-211307 degradation (compared to a one-sided 95% upper confidence band), and 1.5% for SKF-S-107564 degradation (compared to a one-sided 95% upper confidence band). The assays were performed under two sets of conditions. The first was 25 degrees Celsius and 60% relative humidity. The second was 30 degrees Celsius and 75% relative humidity. Batch numbers appear in Sponsor's Table 17. It appears as though the degradation product SB-211307 was not assayed with the 4 mg vial.

2. SPONSOR'S RESULTS

In addition to providing batch numbers, Sponsor's Table 17 also provides expiry dates. Based on the time at which the confidence interval intersected with the specification limit, each expiry given is at least 24 months. Thus 24 months is the proposed expiration date, when stored between 15 degrees and 30 degrees Celsius, with the provision that the vial contain the statement "protect from light". It is mentioned that those assays which were performed at what was nominally called 12 months were actually performed at 11.5 months. Details for the analyses leading to the expiries in Sponsor's Table 17 appear in Sponsor's Tables 18-57 and Sponsor's Figures 1-40. Of these, Sponsor's Tables 18-39 (first submission) go as far as 12 months (11.5 months), while Sponsor's Tables 40-57 (first submission) go only as far as six months. These tables are for the 4 mg batches. In the subsequent submission there is data up to 12 months for Tables 18-40 and Tables 43, 46, 49, 52, and 55 while Tables 41, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, and 57 go only as far as nine months.

3. REVIEWER'S RESULTS

Poolability seems not to be an issue, as batch-to-batch variation is consistently minimal. While the confidence bands for drug content are often two-sided, instead of one-sided, after consultation with our Chemistry Reviewer, this reviewer feels it is appropriate, in this case, for a one-sided confidence band to be used for topotecan content as well as for degradation products. Thus the methodology presented is appropriate.

Sponsor's Figure 1 and Table 18 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 2 and Table 19 present a proper analysis which shows no crossing of the specification limit within 39 months. The running minimum is now 39 months.

Sponsor's Figure 3 and Table 20 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 4 and Table 21 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 5 and Table 22 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 6 and Table 23 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 7 and Table 24 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 8 and Table 25 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 9 and Table 26 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 10 and Table 27 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 11 and Table 28 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 12 and Table 29 present a proper analysis which shows no crossing of the specification limit within 27 months. The running minimum is now 27 months.

Sponsor's Figure 13 and Table 30 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 14 and Table 31 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 15 and Table 32 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 16 and Table 33 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 17 and Table 34 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 18 and Table 35 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 19 and Table 36 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 20 and Table 37 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 21 and Table 38 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 22 and Table 39 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 23 and Table 40 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 24 and Table 41 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 25 and Table 42 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 26 and Table 43 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 27 and Table 44 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 28 and Table 45 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 29 and Table 46 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 30 and Table 47 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 31 and Table 48 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 32 and Table 49 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 33 and Table 50 present a proper analysis which shows no crossing of the specification

limit within 48 months. Sponsor's Figure 34 and Table 51 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 35 and Table 52 present a proper analysis which shows no crossing of the specification limit within 48 months.

Sponsor's Figure 36 and Table 53 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 37 and Table 54 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 38 and Table 55 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 39 and Table 56 present a proper analysis which shows no crossing of the specification limit within 48 months. Sponsor's Figure 40 and Table 57 present a proper analysis which shows no crossing of the specification limit within 48 months.

The minimum time of a confidence band crossing a specification limit is 27 months. However, it is not suggested that 27 months be used as the expiry. While linearity appears reasonable over the range studied in most of the figures, there are exceptions, and extrapolation can be uncertain. Thus it seems prudent to allow extrapolation of no more than six or nine months beyond the last actual data point. After consultation with the chemist it was decided that it would be best to provide one expiry based on 25 degrees Celsius and another based on 30 degrees Celsius.

The expiry is limited by, and thus should be based upon, Sponsor's Figures 24, 25, 33, and 34. Sponsor's Figure 24 (topotecan assay, 4 mg vials, 25 degrees Celsius, Set Down #1082) goes out to nine months and has four time points. Linearity appears reasonable. Thus an expiry of 18 months, based on Sponsor's Figure 24, appears reasonable. Sponsor's Figure 25 (topotecan assay, 4 mg vials, 25 degrees Celsius, Set Down #1083) goes out to nine months and has four time points. Linearity again appears reasonable. Thus an expiry of 18 months, based on Sponsor's Figure 25, also appears reasonable. That is, for 25 degrees Celsius an expiry of 18 months is recommended.

Sponsor's Figure 33 (topotecan assay, 4 mg vials, 30 degrees Celsius, Set Down #1082) goes out to nine months and has four time points. Linearity appears questionable. A linear model was fit in which the topotecan content was regressed on both time and time-squared. The slope for the quadratic term was significant ($p=0.03$) so a linear model with only the term for time would suffer from significant lack of fit. The model fit predicts a topotecan content of 98% at 12 months and 93% at 15 months, with prediction intervals of (94%, 102%) and (86%, 101%), respectively. These prediction intervals are tighter than the Working-Hotelling bands as they do not provide simultaneous coverage probability. Thus 13 months seems to be a reasonable expiry.

Sponsor's Figure 34 (topotecan assay, 4 mg vials, 30 degrees Celsius, Set Down #1083) goes out to nine months and has four time points. Linearity appears questionable. A linear model was fit in which the topotecan content was regressed on both time and time-squared. The slope for the quadratic term was significant ($p=0.04$) so a linear model with only the term for time would suffer from significant lack of fit. The model fit predicts a topotecan content of 99% at 12 months and 94% at 15 months, with prediction intervals of (94%, 104%) and (84%, 103%), respectively.

These prediction intervals are tighter than the Working-Hotelling bands as they do not provide simultaneous coverage probability. Thus 13 months seems to be a reasonable expiry.

4. SUMMARY AND CONCLUSIONS

In light of the uncertainty present in Sponsor's Figures 33 and 34 (second submission), it seems prudent to allow an expiry of no more than 13 months for storage at 30 degrees Celsius. As expected, a lower temperature should provide a longer expiry, and an expiry of 18 months seems warranted for storage at 25 degrees Celsius. More data, not only for these two analyses, but also for the others which go only as far as nine months, might provide a firm basis for extending the expiry to 24 months or even beyond.

Vance Berger, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco C. Gnecco 5/17/96
Dr. Chi 5/24/96

CC:

Archival NDA #20-671
HFD-150 / Division File
HFD-150 / Dr. Wood
HFD-150 / Dr. Hsieh
HFD-150 / Ms. Catterson, CSO
HFD-710 / Dr. Chi
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file

VBERGER / 5-14-96 / WP6.1 - C:\TOPOTECA\CONSULT.DOC
This review consists of five pages of text and 45 pages of Sponsor's tables.

STABILITY OF THE DRUG PRODUCT

Table 1[1] : Validation Batches Tested

Storage Test Reference N°	Dose Strength	Formula Code	Drug Substance Batch number (s) and Site of Manufecture	Bulk Product Batch Number	Date and Site of Manufacture	Batch Size (Vials)	Stability Test Initiation Date	Months of Stability Data Provided	Storage Container/ Pack Type
1057	4 mg	AS	417-TPTC-1 SB, Cork, Ireland	2825H01	Mar 1995 SB, Bldg.16A	vials	Mar 1995	12 months	5 mL USP Type I flint vial, butyl stopper
1082	4 mg	AS	9416-TPTC-1 SB, Cork, Ireland	2835H01	May 1995 SB, Bldg.16A	vials	May 1995	9 months	5 mL USP Type I flint vial, butyl stopper (
1083	4 mg	AS	9418-TPTC-1 SB, Cork, Ireland	2845H01	May 1995 SB, Bldg.16A	vials	May 1995	9 months	5 mL USP Type I flint vial, butyl stopper (
1002	5 mg	AF	9417-TPTC-1 SB, Cork, Ireland	1814H00	Sept 1994 SB, Bldg.16A	vials	Dec 1994	11.5 months	5 mL USP Type I flint vial, butyl stopper
1003	5 mg	AF	9416-TPTC-1 SB, Cork, Ireland	1824H00	Nov 1994 SB, Bldg.16A	vials	Dec 1994	11.5 months	5 mL USP Type I flint vial, butyl stopper
1004	5 mg	AF	9418-TPTC-1 SB, Cork, Ireland	1834H00	Nov 1994 SB, Bldg.16A	vials	Dec 1994	11.5 months	5 mL USP Type I flint vial, butyl stopper

[1] Updated

000115

STABILITY OF THE DRUG PRODUCT

Table 2[1]: Development Batches Tested

Storage Test Reference N°	Dose Strength	Formula Code	Drug Substance Batch number (s) and Site of Manufacture	Bulk Product Batch Number	Date and Site of Manufacture	Batch Size (Vials)	Stability Test Initiation Date	Months of Stability Data Provided	Storage Container/ Pack Type
770	5 mg	AC[2]	MM-19007-282	U92119	Nov 1992	vials	Dec 1992	36 months	5 mL USP Type I flint vial, butyl stopper
794	5 mg	AC	MM-19117-30	U93056	April 1993	vials	Apr 1993	24 months	5 mL USP Type I flint vial, butyl stopper
862	5 mg	AC	MM-19117-268	U93231	Nov 1993	vials	Jan 1994	24 months	5 mL USP Type I flint vial, butyl stopper
897	5 mg	AF	MM-19163-58	U94036	Feb 1994	vials	Mar 1994	12 months	5 mL USP Type I flint vial, butyl stopper
947	5 mg	AF	MM-19163-42	U94118	June 1994 SB Bldg.16A	vials	July 1994	12 months	5 mL USP Type I flint vial, butyl stopper
1058	4 mg	AR	9417-TPTC-1 SB Cork, Ireland	X015H01	March 1995 SB Bldg. 16A	vials	March 1995	6 months	5 mL USP Type I flint vial, butyl stopper

[1] Updated
[2] Formulae AC and AF are identical

STABILITY OF THE DRUG PRODUCT

3. Stability Protocol (4 mg and 5 mg Vials; Validation batches, Stored in 5 mL USP Type I Flint Vials with Butyl Stoppers)

The batches listed in Table 1 were manufactured at SmithKline Beecham Pharmaceuticals, Building 16A, Conshohocken, PA as part of the validation of topotecan vials. The batches were tested in accordance with the validation stability protocol.

Validation batches for 4 mg vials (batches 2825H01, 2835H01 and 2845H01) and 5 mg vials (batches 1814H00, 1824H00 and 1834H00) are being tested to the stability protocol outlined in Table 3. Table 4 lists the tests and analytical methods utilized in Schedules A, B, C and D.

Table 3: Storage Conditions and Testing Points

TIME (Month)	25°C/60% RH & 30°C/60% RH	40°C/75% RH	Diffused Light 30°C (as is)	Diffused Light 30°C (vials in box)
Initial	A	---	---	---
1	---	C	D	D
3	C	C	---	---
6	C	C	---	D
9	C	---	---	---
12	B*	---	---	D
18	C	---	---	---
24	B	---	---	D
36**	B	---	---	---
48**	B	---	---	---

* LAL tests will not be performed at this time point.
Sterility will not be performed at 25°C/60% RH; it will be performed at 30°C/60% RH

** These samples will be tested on an "as needed" basis for extension of shelf-life.

STABILITY OF THE DRUG PRODUCT

Figure 1: Topotecan Assay Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1002

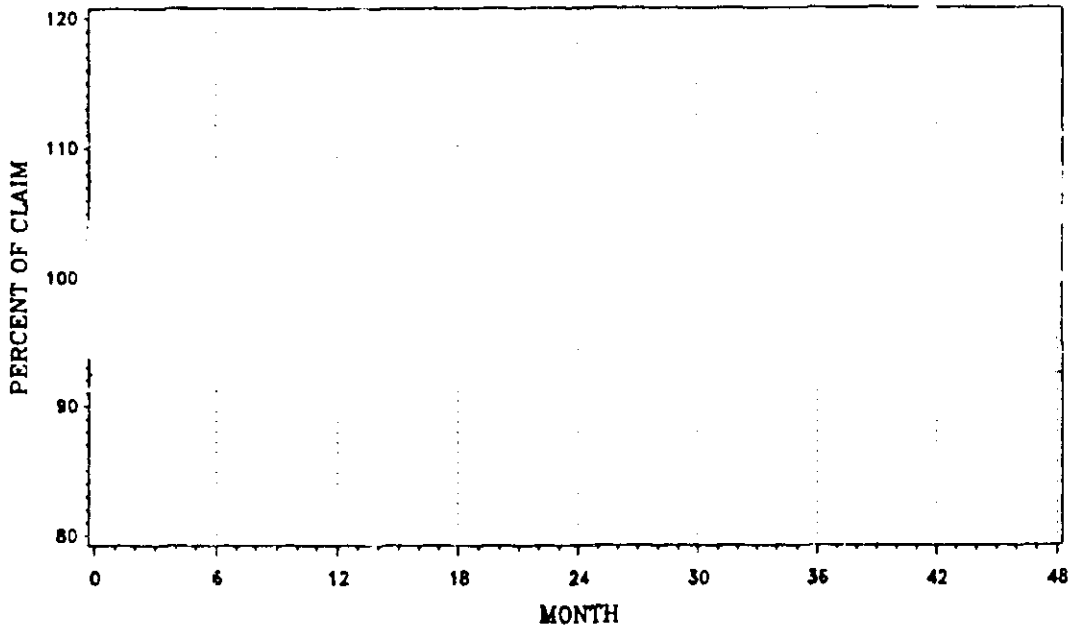


Table 18: Assay % of Label Claim Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
100.4	100.8	100.4	99.0	100.4
100.4	100.6	99.6	99.6	100.8
100.4	100.2	100.2	99.8	100.0

STABILITY OF THE DRUG PRODUCT

Figure 2: Topotecan Assay Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003

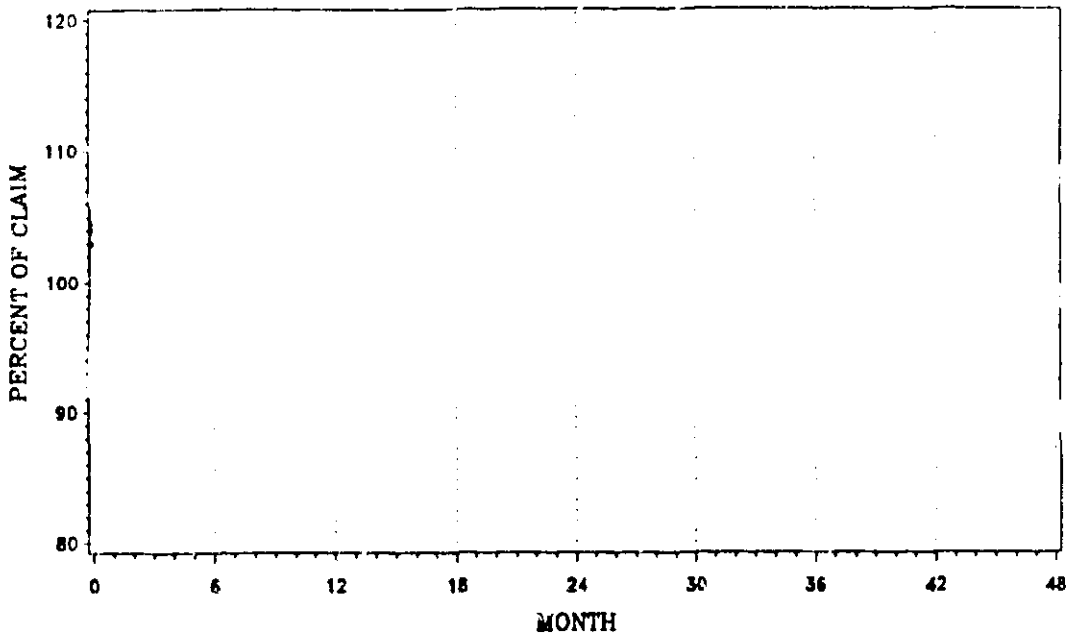


Table 19: Assay % of Label Claim Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
103.0	103.2	103.2	101.6	103.0
104.6	104.4	103.0	102.0	99.4
104.0	103.4	102.6	102.0	102.4

STABILITY OF THE DRUG PRODUCT

Figure 3: Topotecan Assay Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1004

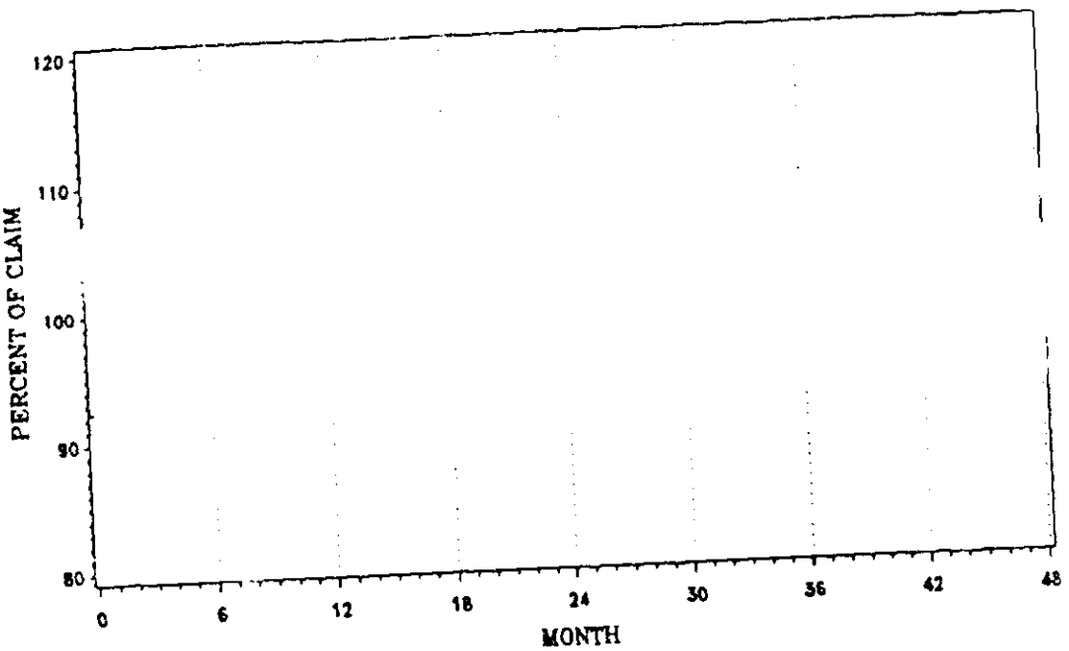


Table 20: Assay % of Label Claim Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
102.2	101.8	102.4	101.0	101.0
102.6	102.6	102.4	101.2	101.0
103.4	101.0	102.2	101.0	101.2

STABILITY OF THE DRUG PRODUCT

Figure 4: Topotecan Total Degradation Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1002

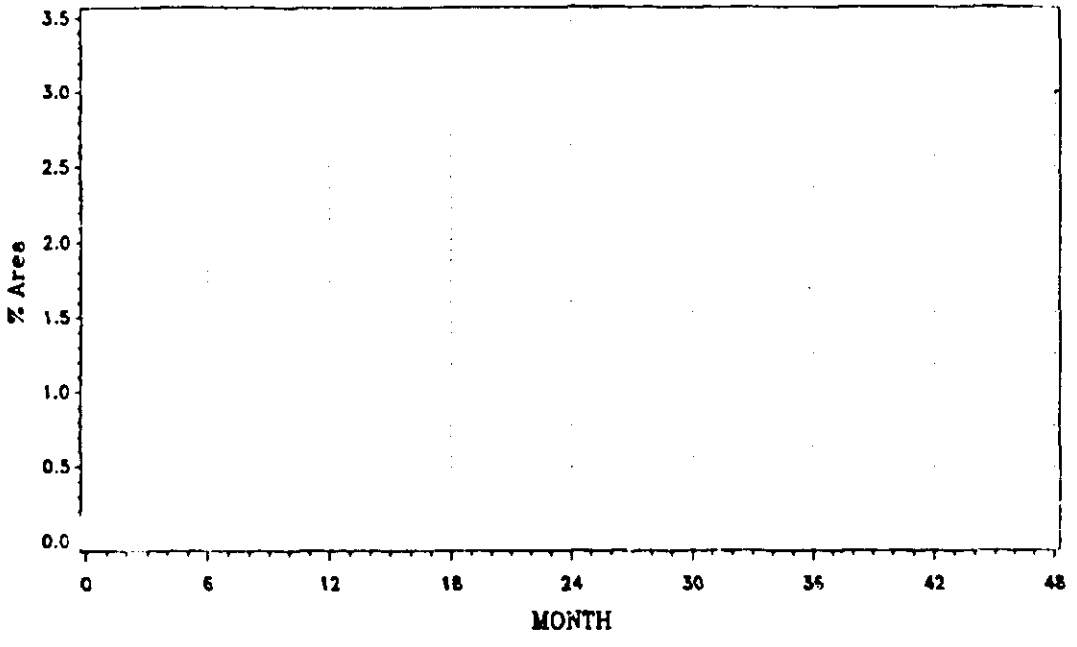


Table 21: Degradation % Area, Total Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
0.07	0.07	0.03	0.05	0.05
0.06	0.06	0.02	0.04	0.05

STABILITY OF THE DRUG PRODUCT

Figure 5: Topotecan Total Degradation Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003

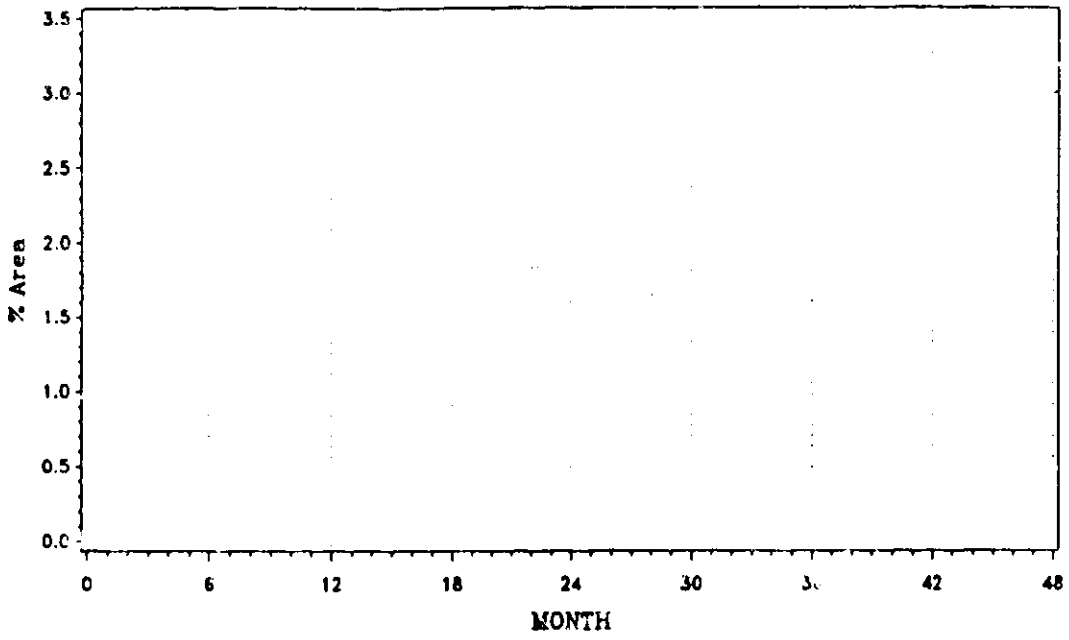


Table 22: Degradation % Area, Total Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
0.07	0.08	0.07	0.09	0.00
0.06	0.09	0.07	0.52	0.02

STABILITY OF THE DRUG PRODUCT

Figure 6: Topotecan Total Degradation Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1004

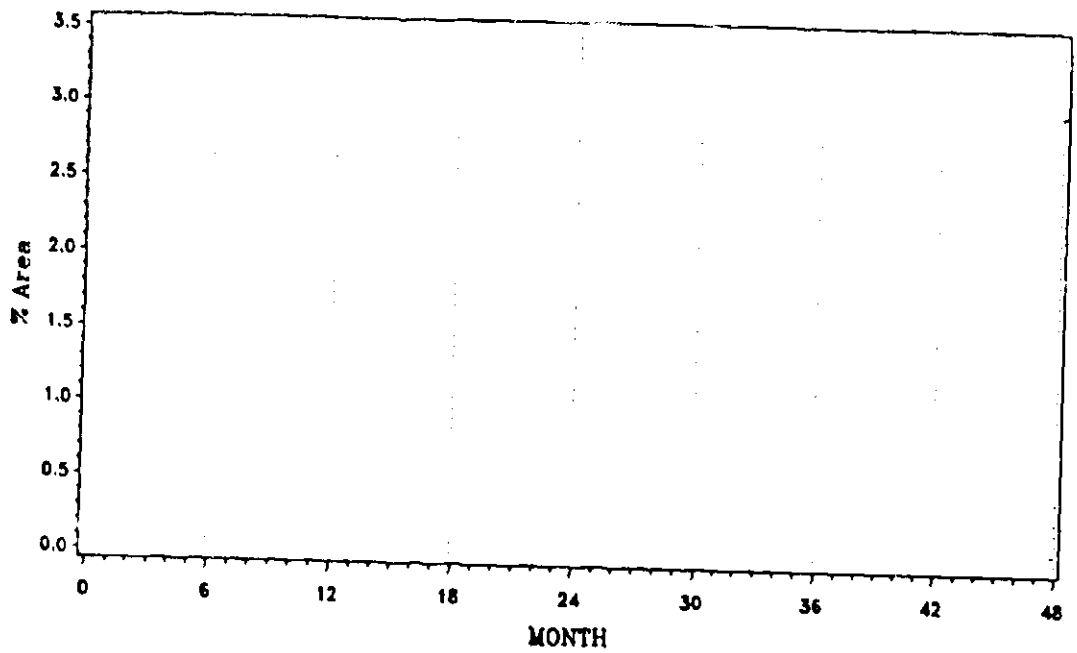


Table 23: Degradation % Area, Total Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
0.26	0.47	0.45	0.52	0.26
0.26	0.46	0.39	0.50	0.24

STABILITY OF THE DRUG PRODUCT

Figure 7: Topotecan Degradation, SB-211307 Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003 and 1004

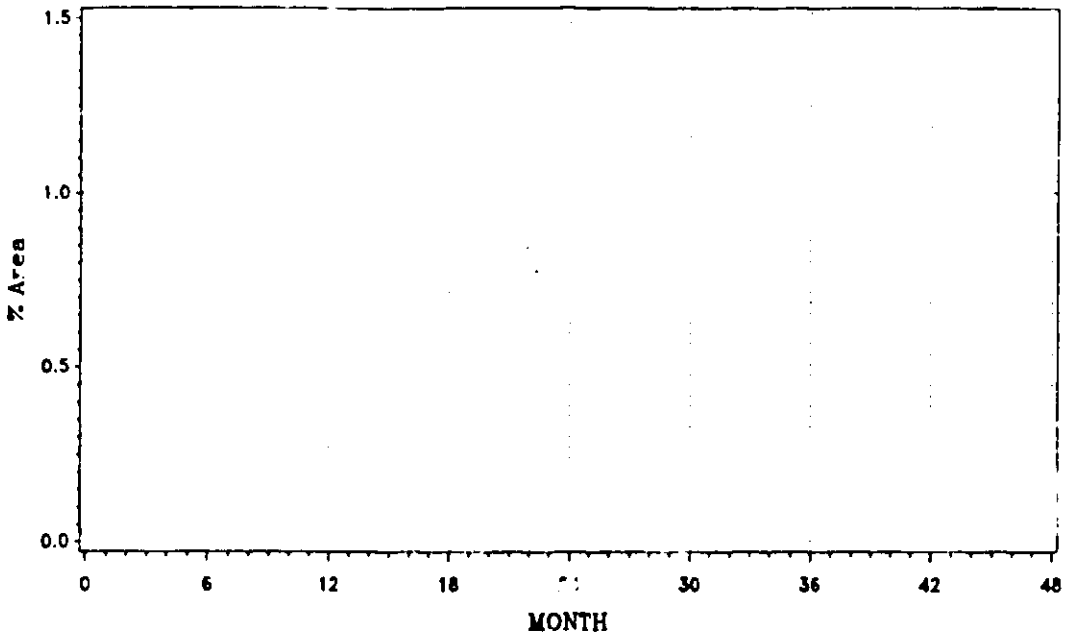


Table 24: Degradation % Area, SB-211307 Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003 and 1004

Initial	3 months	6 months	9 months	12 months
Set down 1003				
ND	0.01	0.02	0.02	ND
ND	0.02	0.02	0.14	0.02
Set down 1004				
0.03	0.04	0.05	0.06	0.06
0.03	0.04	0.05	0.06	0.06

ND = None detected

STABILITY OF THE DRUG PRODUCT

Figure 8: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1002

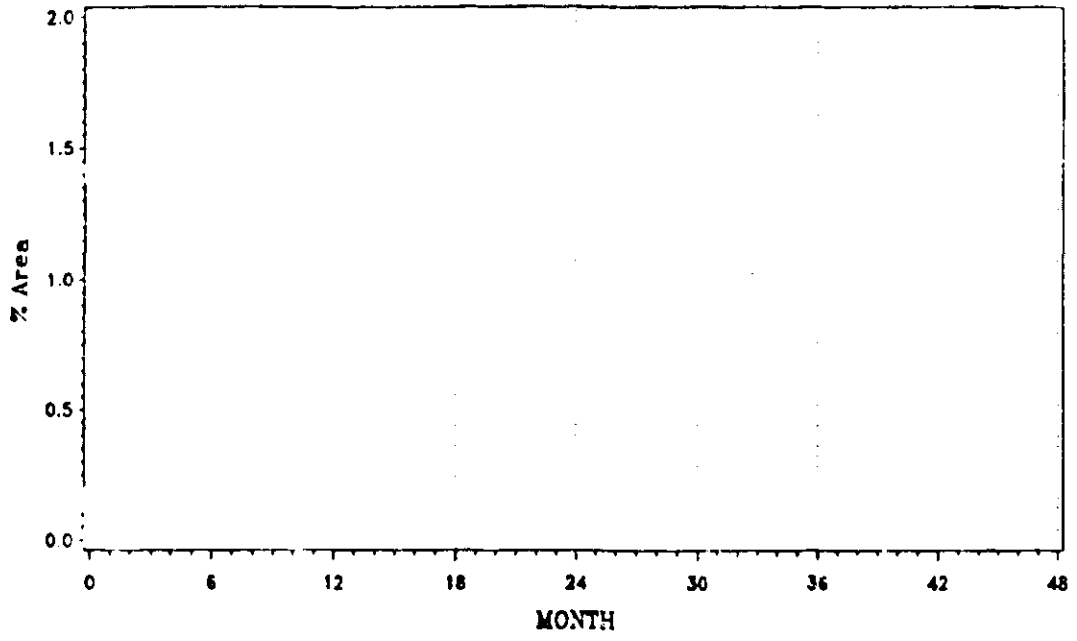


Table 25: Degradation % Area, SKF-S-107564 Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
0.07	0.07	0.03	0.05	0.05
0.06	0.06	0.02	0.04	0.05

STABILITY OF THE DRUG PRODUCT

Figure 9: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003

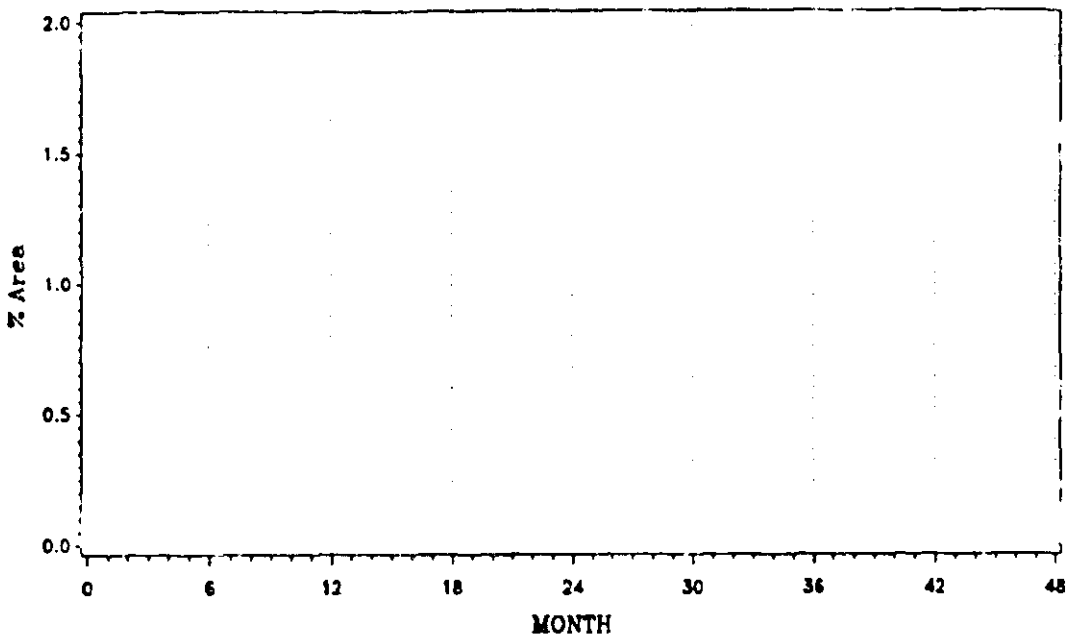


Table 26: Degradation % Area, SKF-S-107564 Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
0.07	0.07	0.05	0.06	ND
0.06	0.07	0.05	0.05	ND

ND = None detected

STABILITY OF THE DRUG PRODUCT

Figure 10: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1004

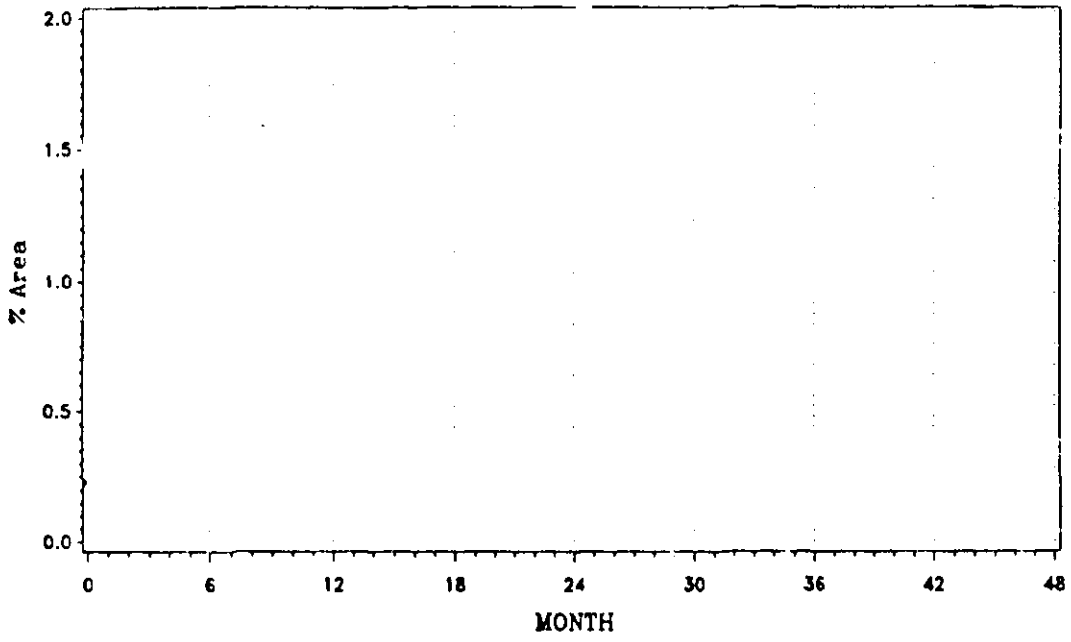


Table 27: Degradation % Area, SKF-S-107564 Topotecan 5 mg Vials
Temp 25°C/60% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
0.23	0.38	0.40	0.36	0.20
0.23	0.35	0.34	0.35	0.18

STABILITY OF THE DRUG PRODUCT

Figure 11: Topotecan Assay Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

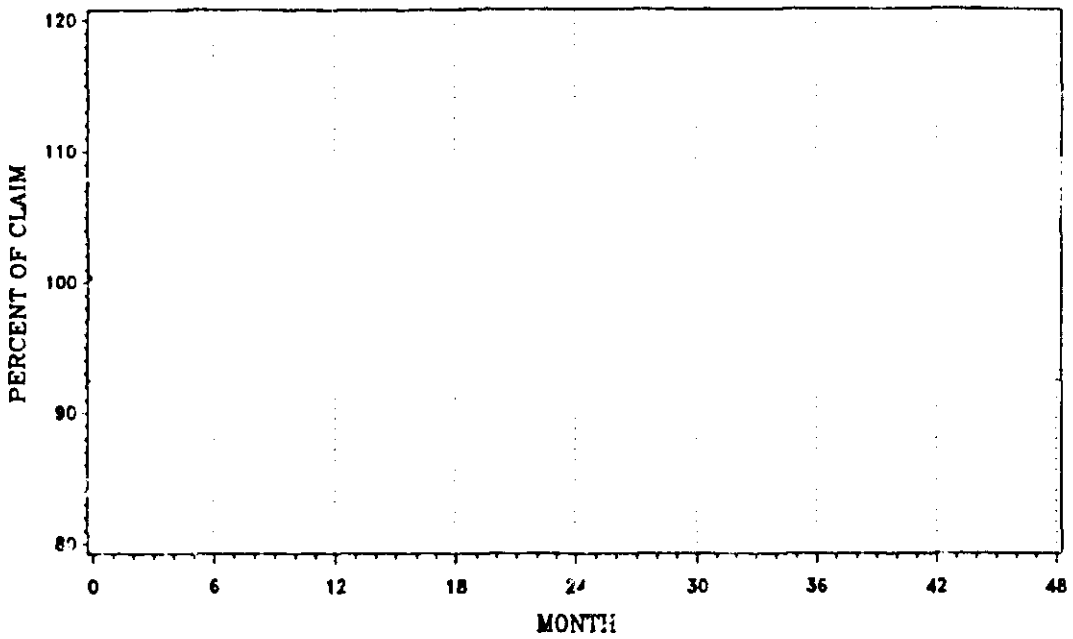


Table 28: Assay % of Label Claim Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
100.4	99.6	100.8	100.6	99.8
100.4	101.4	102.2	98.8	102.4
100.4	98.2	101.2	99.8	100.2

STABILITY OF THE DRUG PRODUCT

Figure 12: Topotecan Assay Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

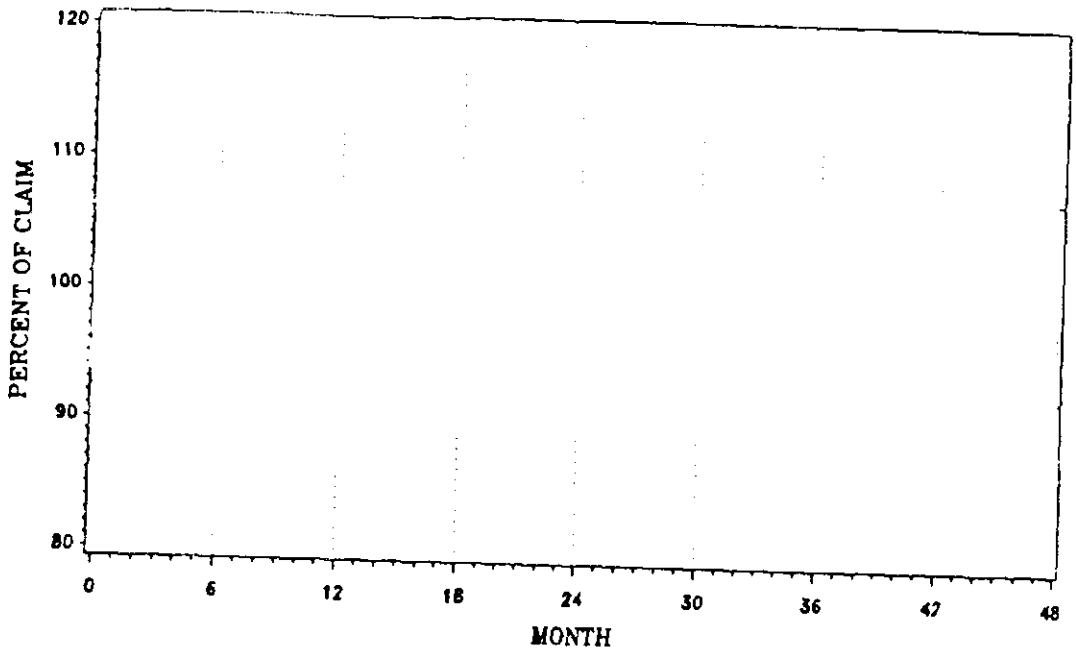


Table 29: Assay % of Label Claim Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
103.0	104.2	102.4	102.8	98.2
104.6	103.6	102.4	102.0	103.0
104.0	103.8	102.8	102.4	98.2

STABILITY OF THE DRUG PRODUCT

Figure 13: Topotecan Assay Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

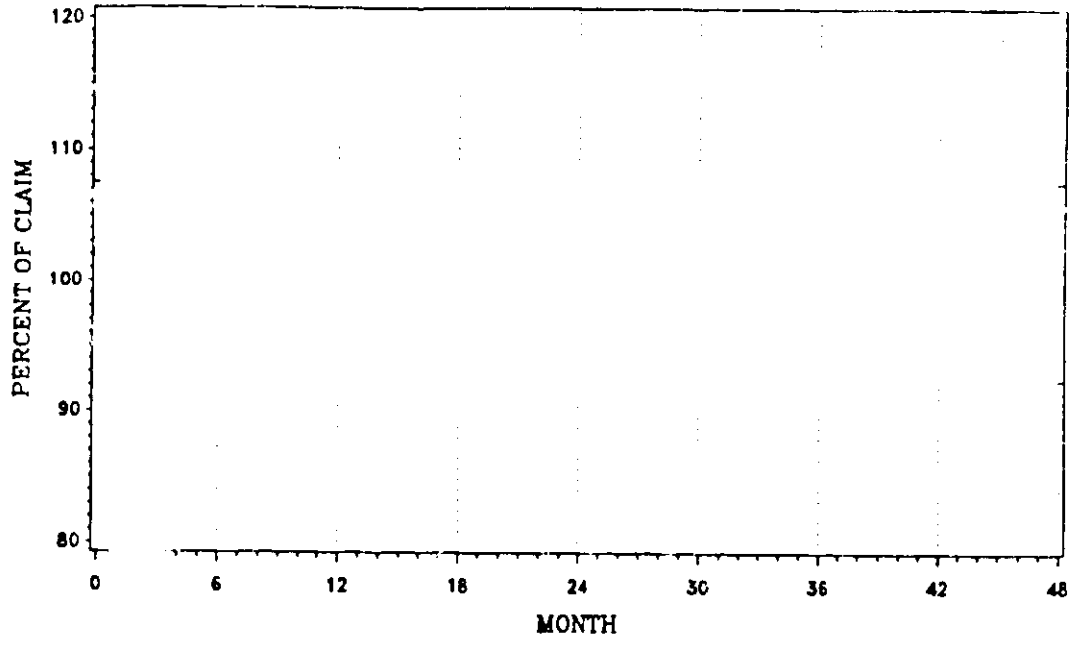


Table 30: Assay % of Label Claim Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
102.2	101.2	101.0	101.6	101.4
102.6	101.4	101.8	101.2	101.2
103.4	101.0	102.4	100.8	101.0

STABILITY OF THE DRUG PRODUCT

Figure 14: Topotecan Total Degradation Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

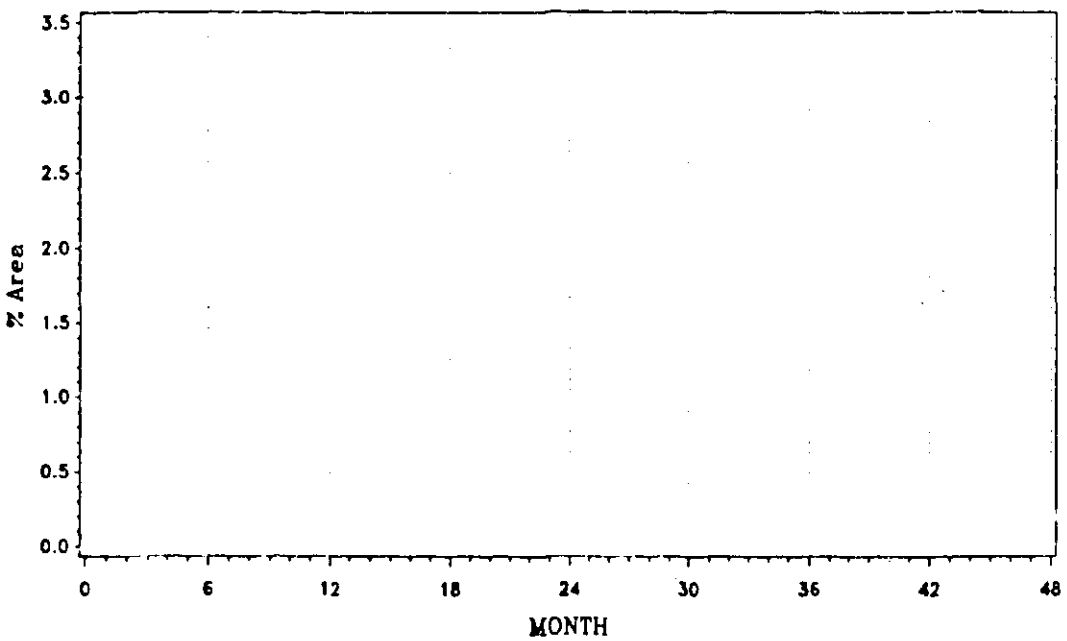


Table 31: Degradation % Area, Total Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
0.07	0.06	0.06	0.09	0.06
0.06	0.06	0.06	0.08	0.05

STABILITY OF THE DRUG PRODUCT

Figure 15: Topotecan Total Degradation Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

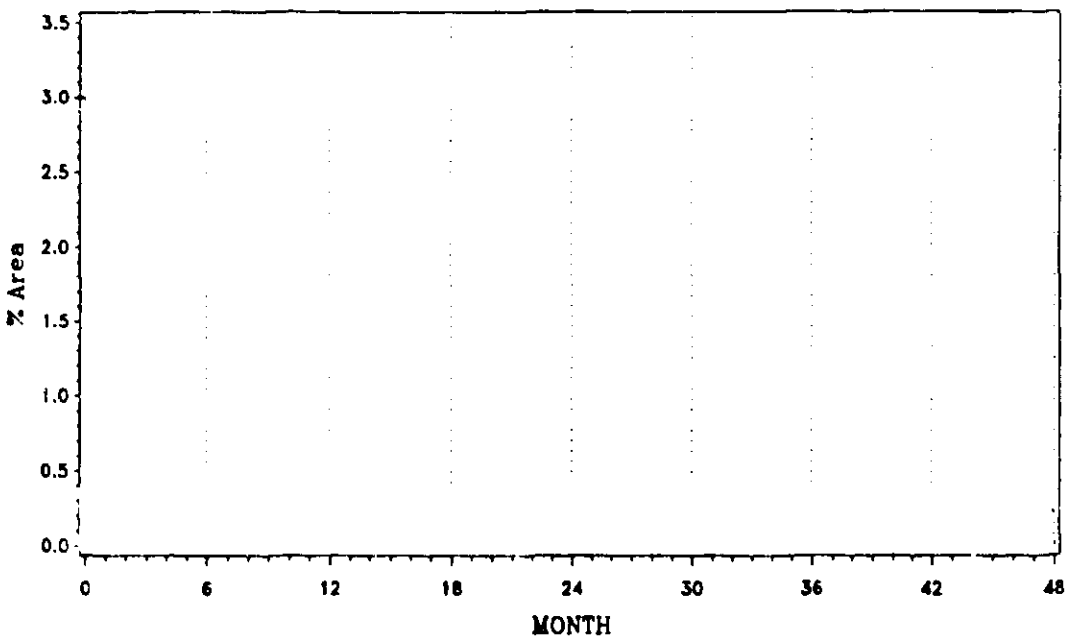


Table 32: Degradation % Area, Total Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
0.07	0.10	0.09	0.08	0.04
0.06	0.09	0.08	0.08	0.01

STABILITY OF THE DRUG PRODUCT

Figure 16: Topotecan Total Degradation Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

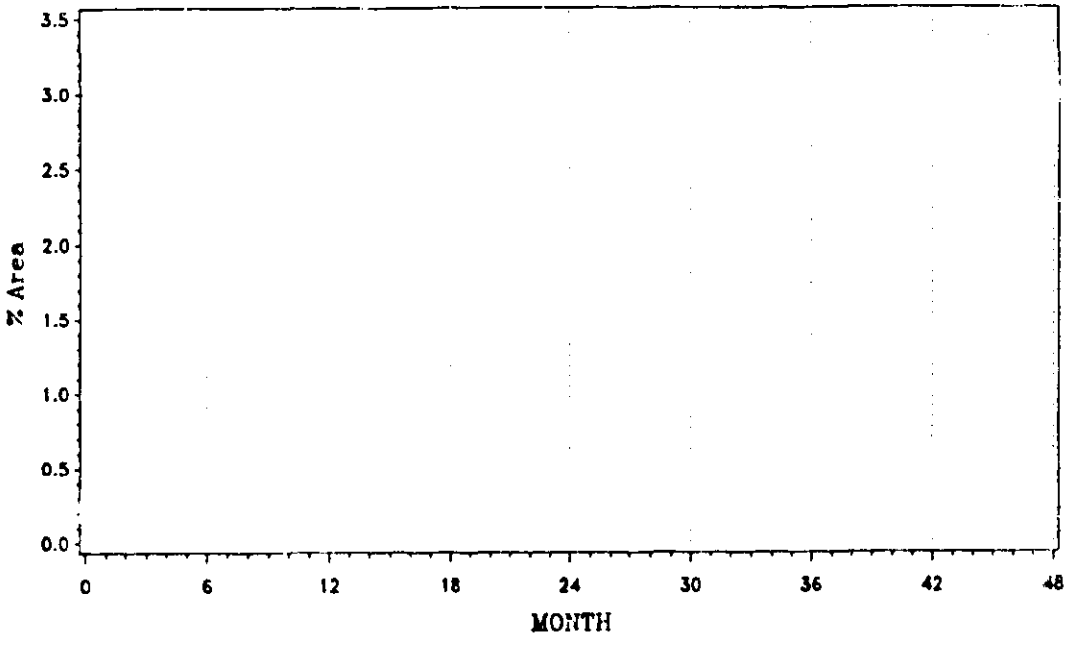


Table 33: Degradation % Area, Total Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
0.26	0.45	0.41	0.49	0.23
0.26	0.42	0.41	0.50	0.23

STABILITY OF THE DRUG PRODUCT

Figure 17: Topotecan Degradation, SB-211307 Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

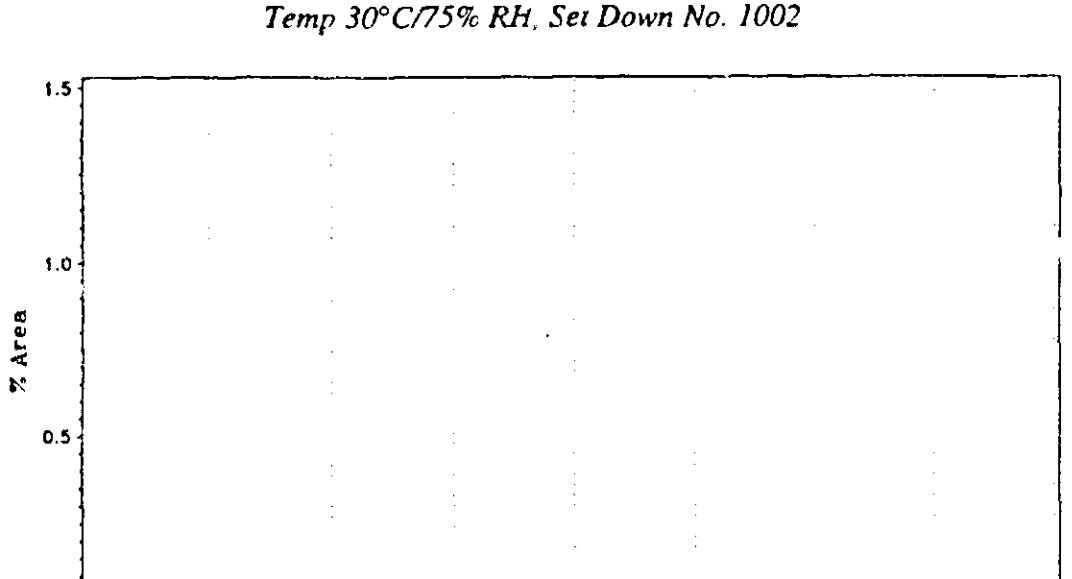


Table 34: Degradation % Area, SB-211307 Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
ND	ND	0.03	0.04	ND
ND	ND	0.04	0.02	ND

ND = None detected

STABILITY OF THE DRUG PRODUCT

Figure 18: Topotecan Degradation, SB-211307 R· ression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

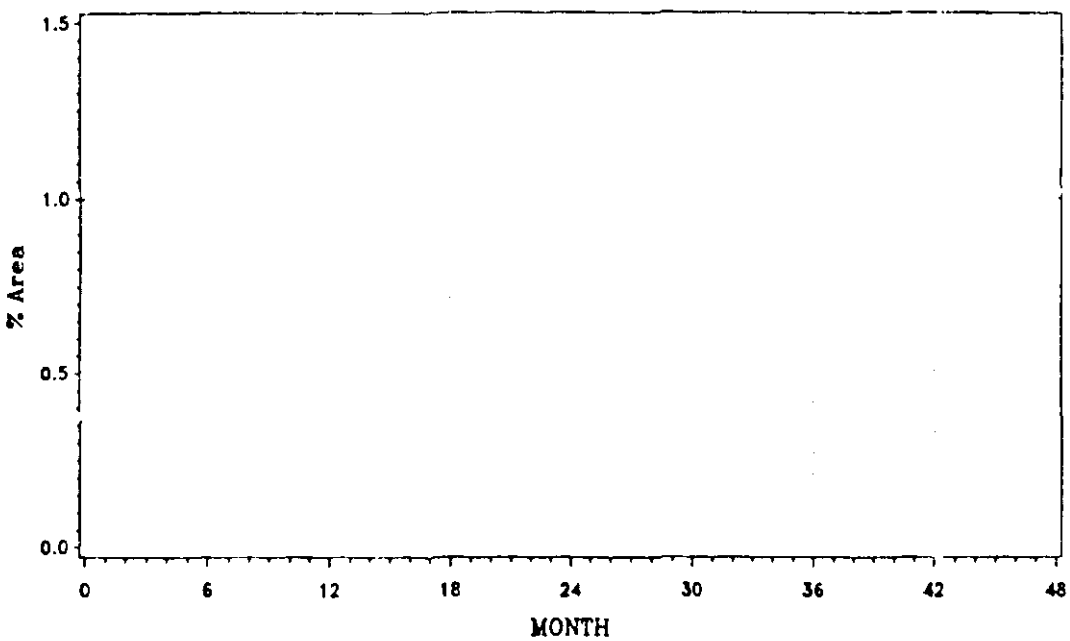


Table 35: Degradation % Area, SB-211307 Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
ND	0.02	0.03	0.03	0.04
ND	0.02	0.03	0.03	0.01

ND = None detected

STABILITY OF THE DRUG PRODUCT

Figure 19: Topotecan Degradation, SB-211307 Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

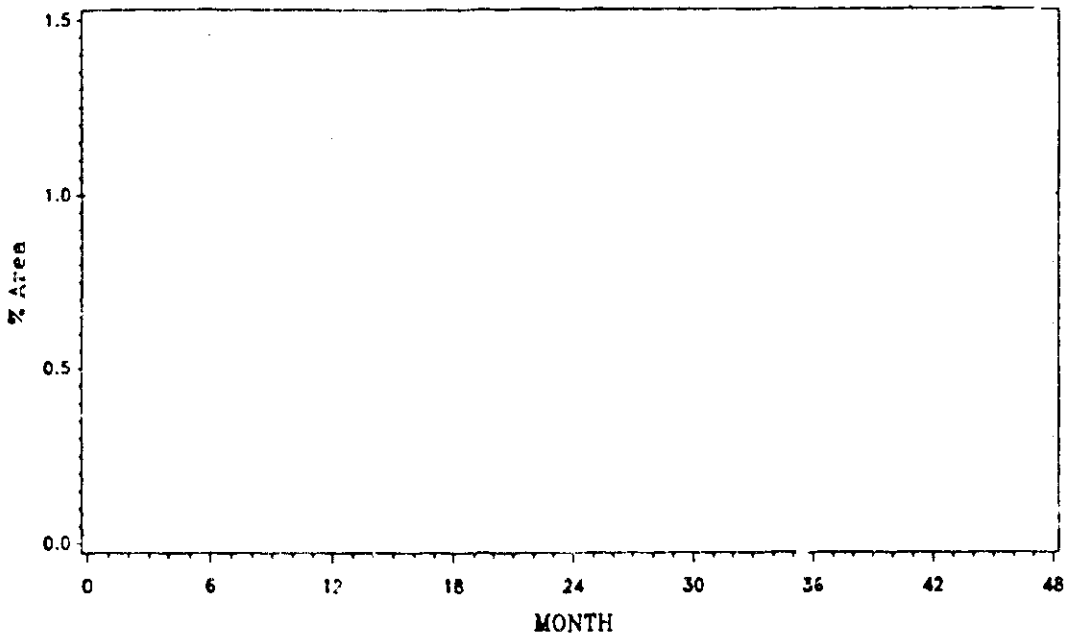


Table 36: Degradation % Area, SB-211307 Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
0.03	0.04	0.06	0.05	0.05
0.03	0.05	0.04	0.05	0.05

STABILITY OF THE DRUG PRODUCT

Figure 20: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

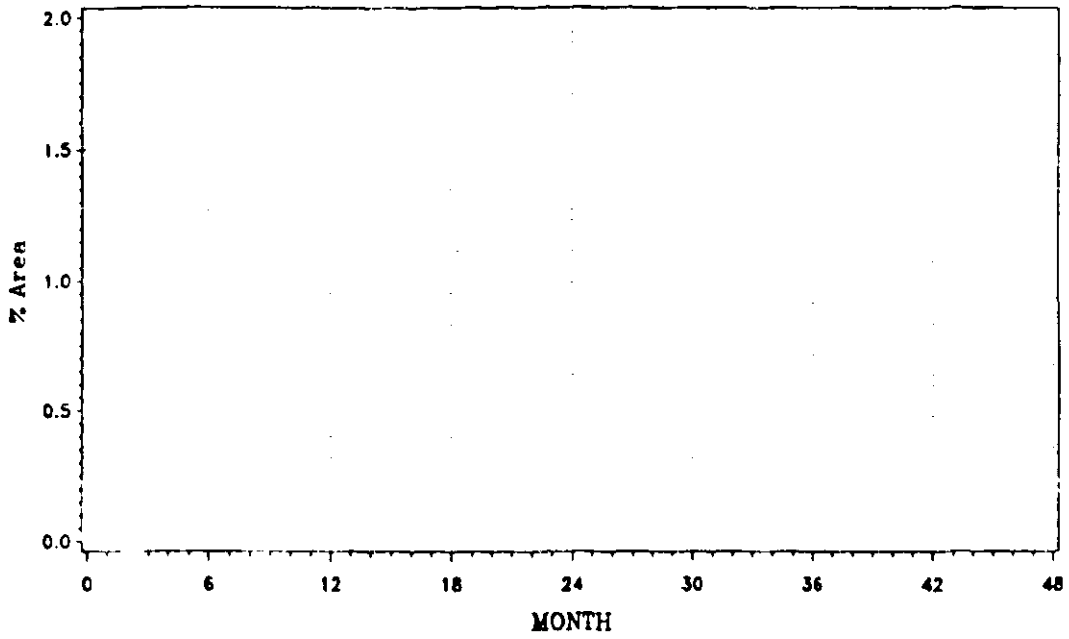


Table 37: Degradation % Area, SKF-S-107564 Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1002

Initial	3 months	6 months	9 months	12 months
0.07	0.06	0.03	0.05	0.06
0.06	0.06	0.02	0.06	0.05

STABILITY OF THE DRUG PRODUCT

Figure 21: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

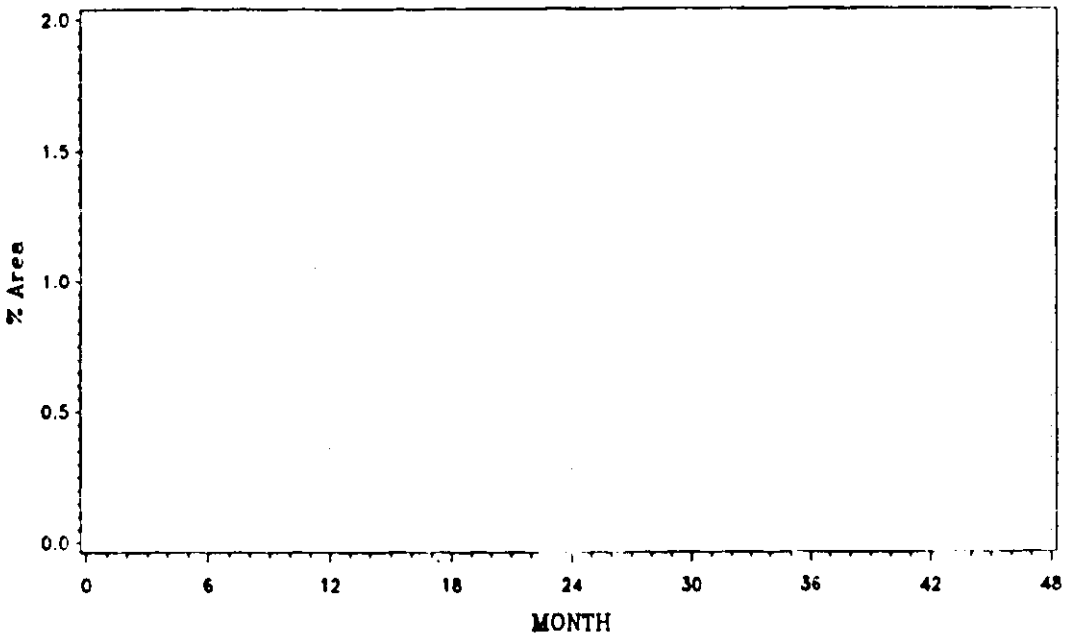


Table 38: Degradation % Area, SKF-S-107564 Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1003

Initial	3 months	6 months	9 months	12 months
0.07	0.08	0.06	0.05	ND
0.06	0.07	0.05	0.05	ND

ND = None detected

STABILITY OF THE DRUG PRODUCT

Figure 22: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

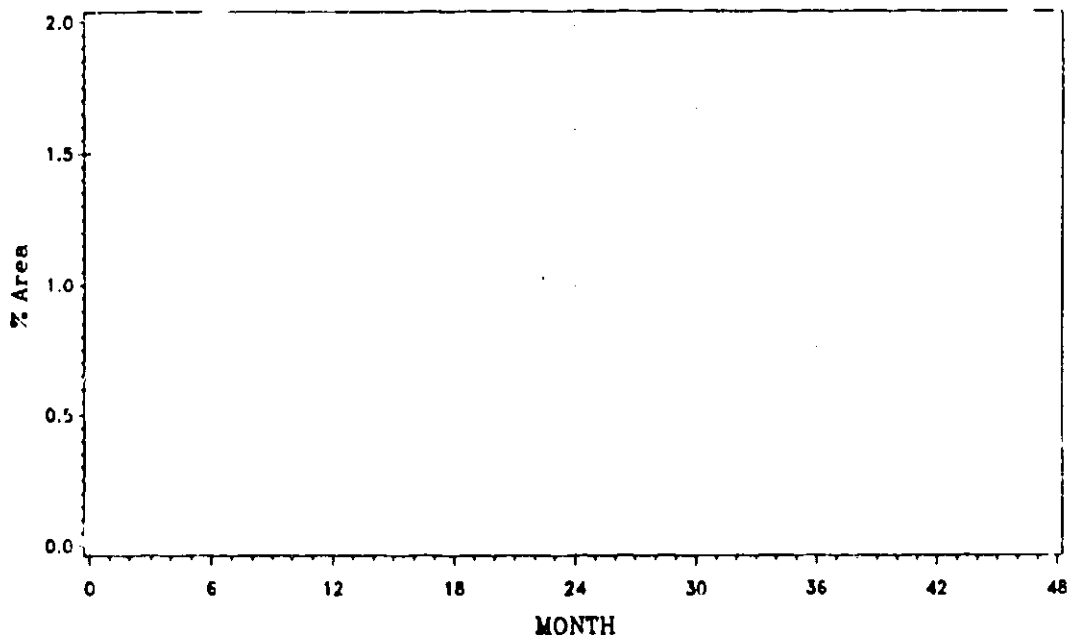


Table 39: Degradation: % Area, SKF-S-107564 Topotecan 5 mg Vials
Temp 30°C/75% RH, Set Down No. 1004

Initial	3 months	6 months	9 months	12 months
0.23	0.41	0.31	0.35	0.18
0.23	0.37	0.32	0.34	0.18

STABILITY OF THE DRUG PRODUCT

Figure 23: Topotecan Assay Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1057

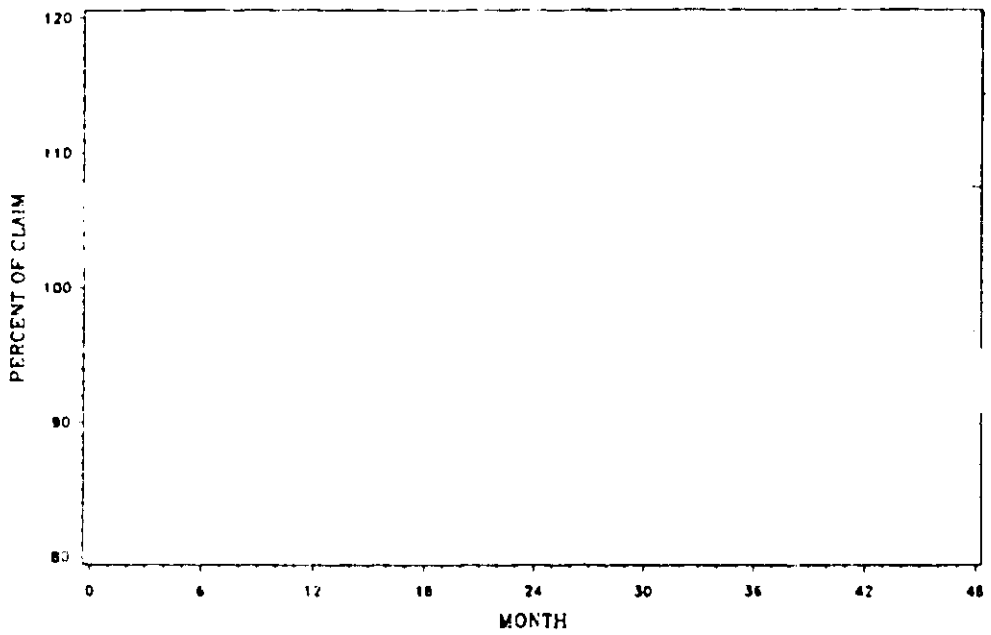


Table 40[1]: Assay % of Label Claim Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1057

Initial	3 months	6 months	9 months	12 months
103.8	106.8	103.3	102.8	104.8
103.0	105.5	103.0	102.3	104.8
103.0	106.0	102.0	102.5	104.8

STABILITY OF THE DRUG PRODUCT

Figure 24: Topotecan Assay Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1082

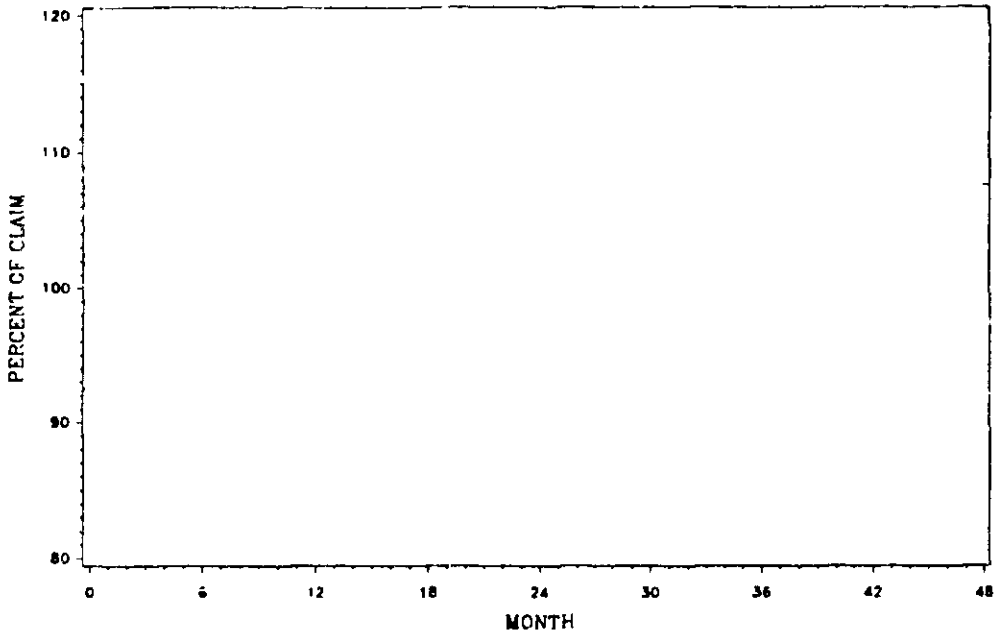


Table 41[1]: Assay % of Label Claim Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1082

Initial	3 months	6 months	9 months
102.5	102.8	101.3	102.3
101.8	103.5	101.5	101.5
102.3	102.8	101.5	100.5

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 25: Topotecan Assay Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1083

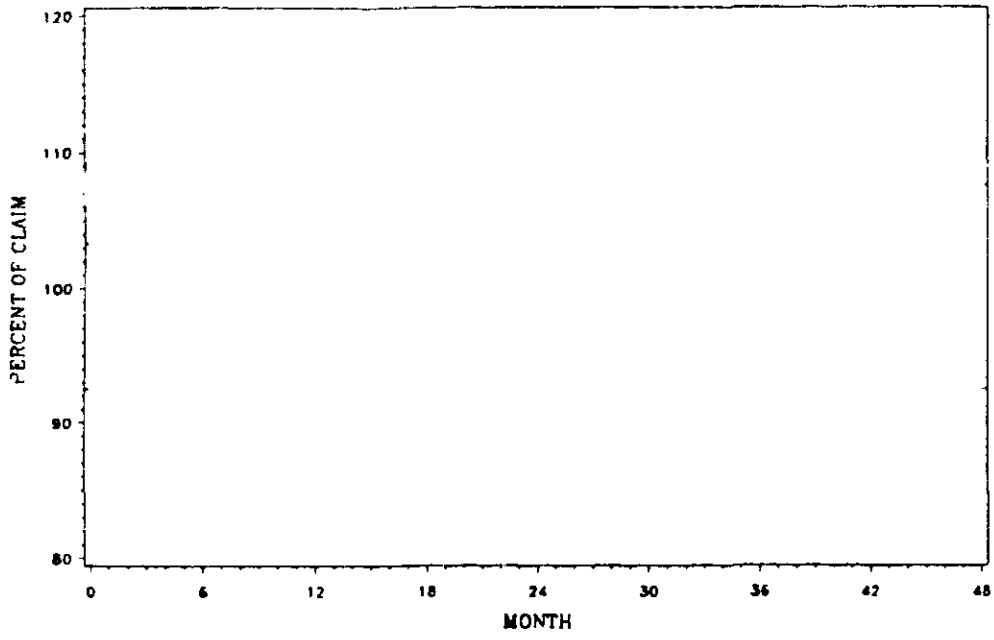


Table 42[1]: Assay % of Label Claim Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1083

Initial	3 months	6 months	9 months
102.0	105.8	103.3	102.0
103.5	105.8	102.8	103.0
103.3	106.0	102.0	103.0

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 26: Topotecan Total Degradation Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1057

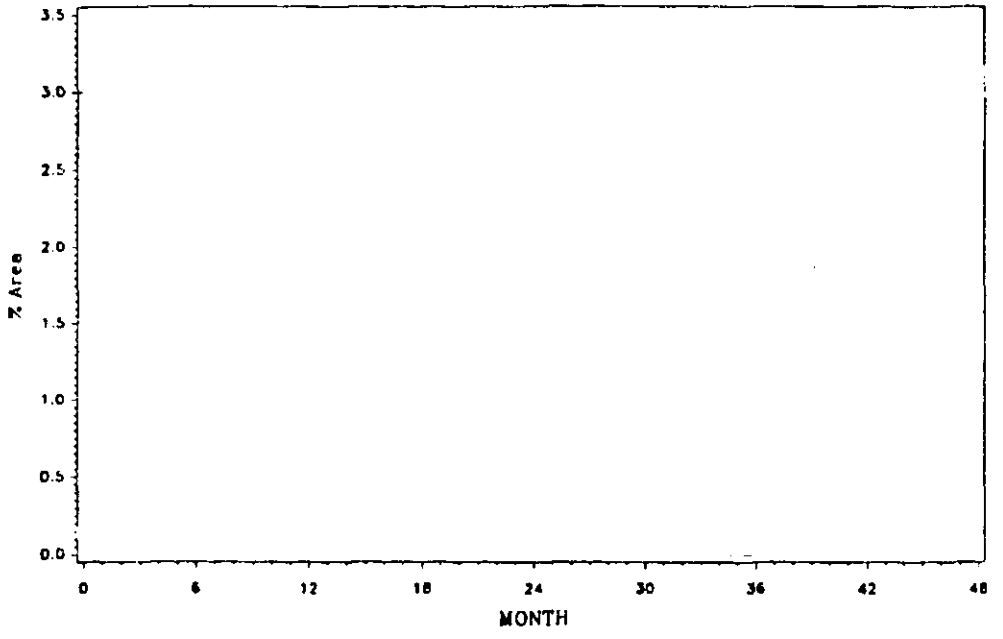


Table 43[1]: Degradation % Area, Total Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1057

Initial	3 months	6 months	9 months	12 months
0.09	0.04	0.06	0.03	0.06
0.10	0.05	0.06	0.04	0.08

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 27: Topotecan Total Degradation Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1082

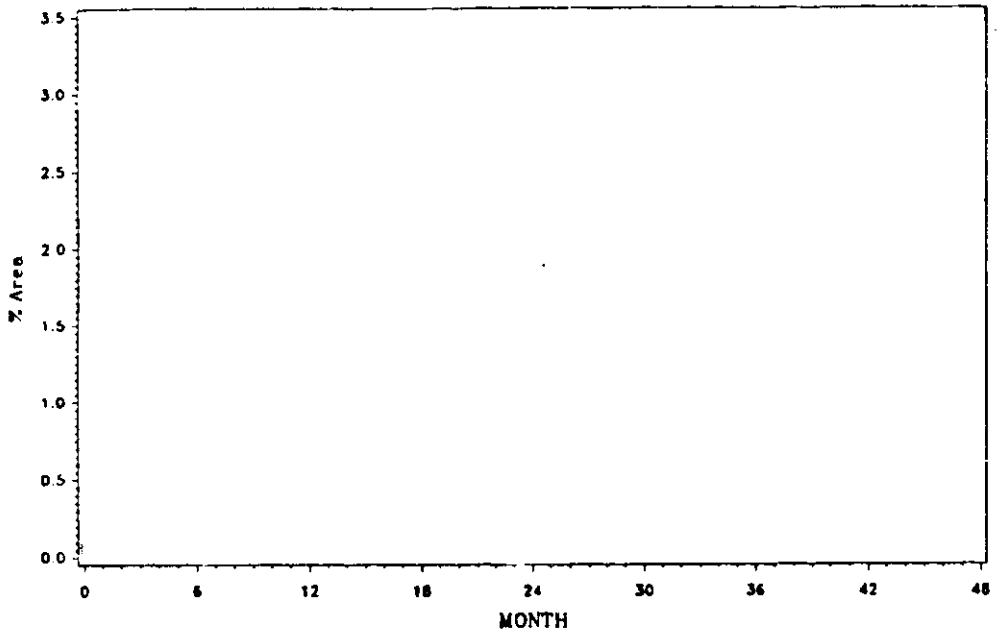


Table 44[1]: Degradation % Area, Total Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1082

Initial	3 months	6 months	9 months
0.04	0.05	0.03	0.07
0.08	0.05	0.05	0.08

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 28: Topotecan Total Degradation Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1083

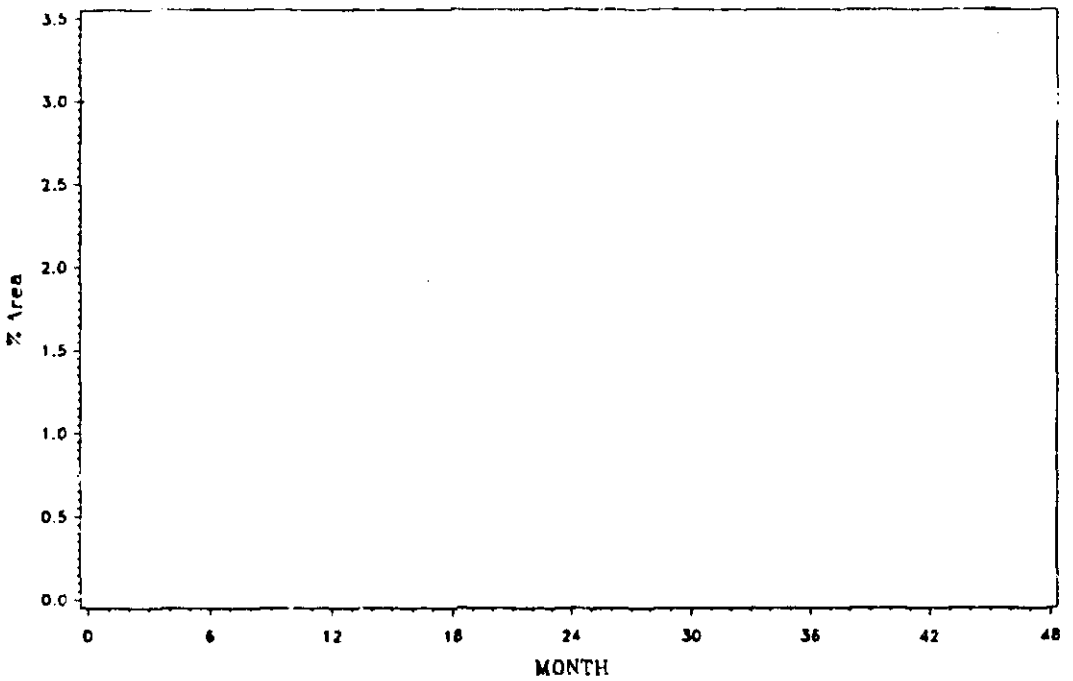


Table 45[1]: Degradation % Area, Total Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1083

Initial	3 months	6 months	9 months
0.55	0.56	0.55	0.56
0.52	0.56	0.57	0.56

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 29: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1057

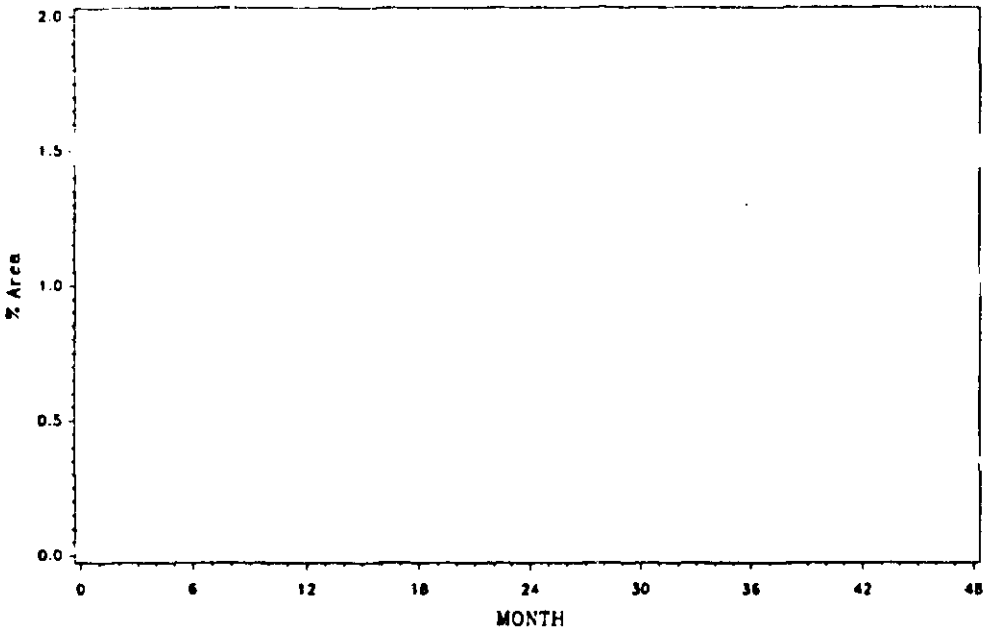


Table 46[1]: Degradation % Area, SKF-S-107564 Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1057

Initial	3 months	6 months	9 months	12 months
0.09	0.04	0.06	0.03	0.06
0.10	0.05	0.06	0.04	0 08

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 30: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1082

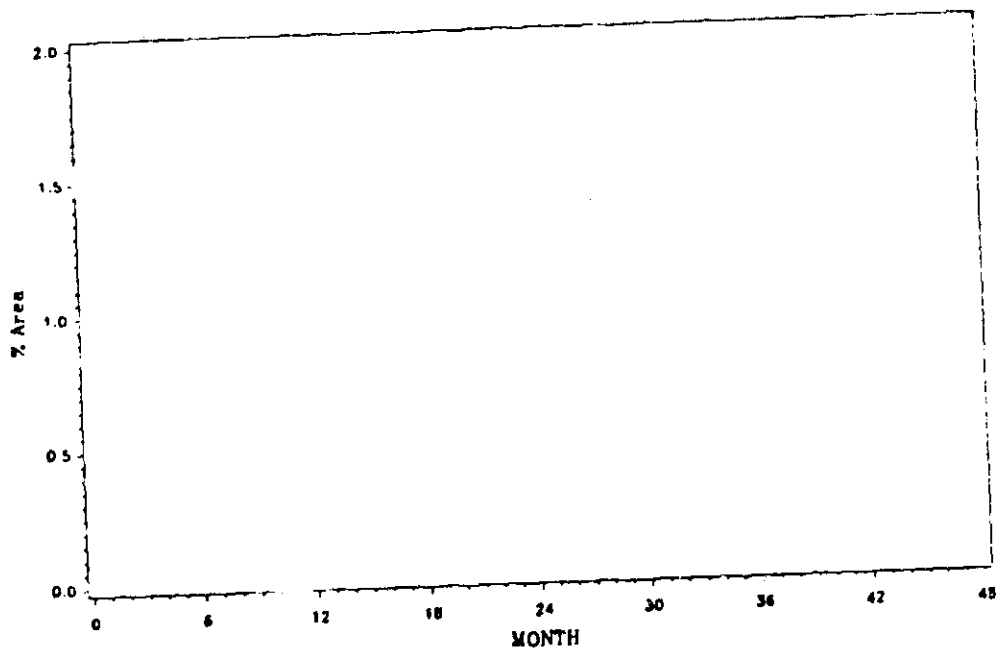


Table 47[1]: Degradation % Area, SKF-S-107564 Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1082

Initial	3 months	6 months	9 months
0.04	0.05	0.03	0.07
0.08	0.05	0.05	0.08

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 31: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1083

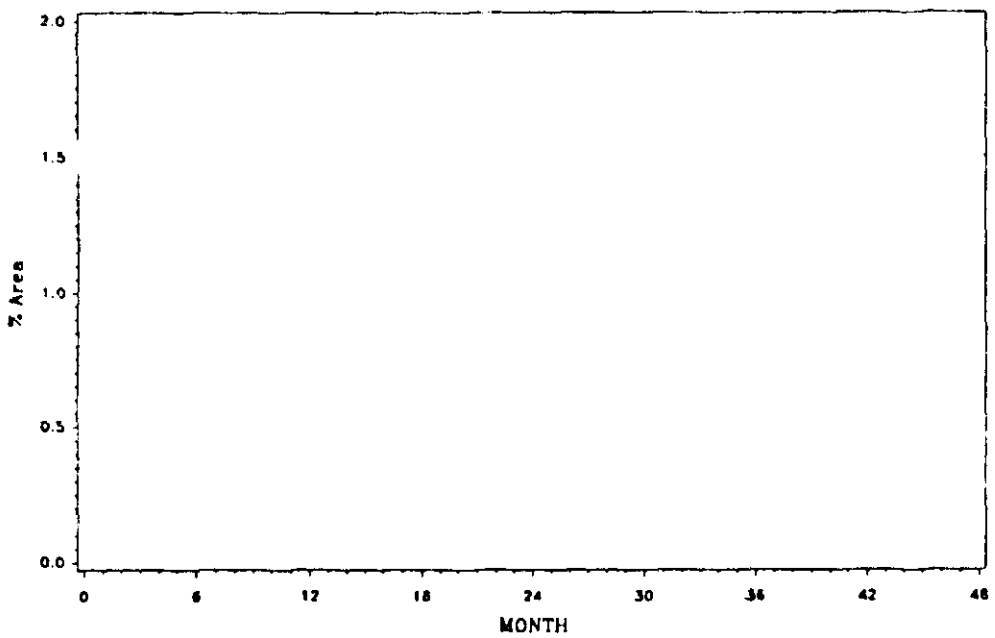


Table 48[1]: Degradation % Area, SKF-S-107564 Topotecan 4 mg Vials
Temp 25°C/60% RH, Set Down No. 1083

Initial	3 months	6 months	9 months
0.39	0.37	0.35	0.38
0.35	0.37	0.37	0.36

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 32: Topotecan Assay Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1057

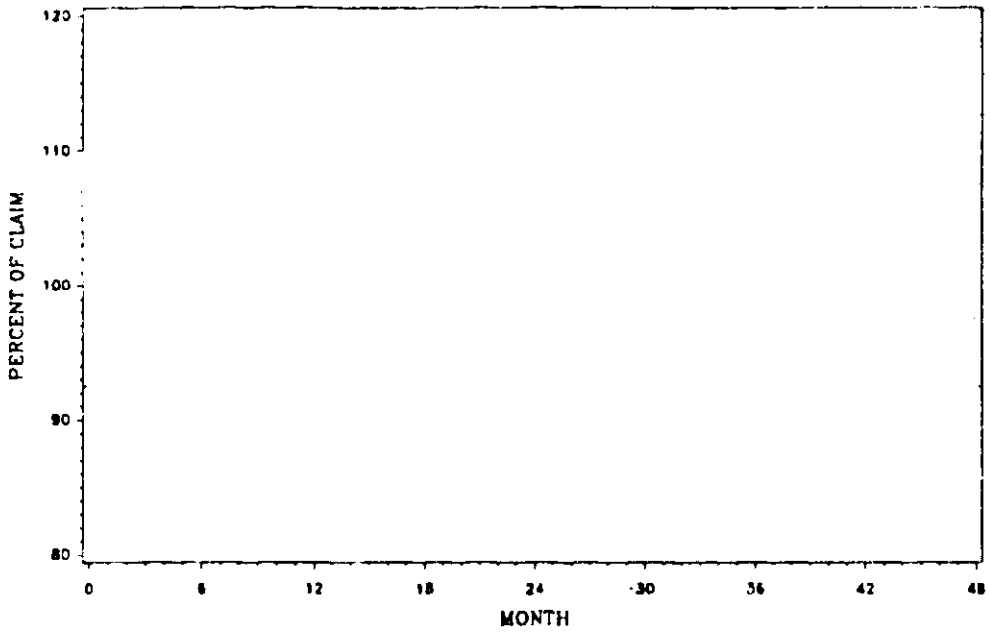


Table 49[1]: Assay % of Label Claim Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1057

Initial	3 months	6 months	9 months	12 months
103.8	106.8	102.8	103.0	105.5
103.0	105.8	102.8	. ..5	105.5
103.0	107.5	104.3	103.3	105.3

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 33: Topotecan Assay Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1082

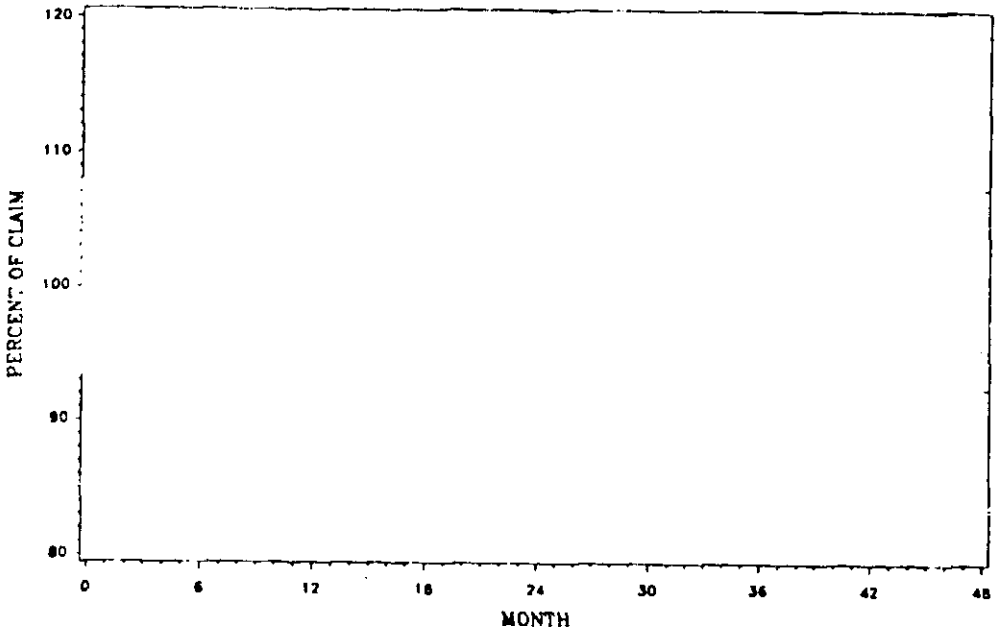


Table 50[1]: Assay % of Label Claim Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1082

Initial	3 months	6 months	9 months
102.5	104.3	101.8	100.8
101.8	103.8	102.5	101.5
102.3	105.0	101.8	102.0

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 34: Topotecan Assay Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1083

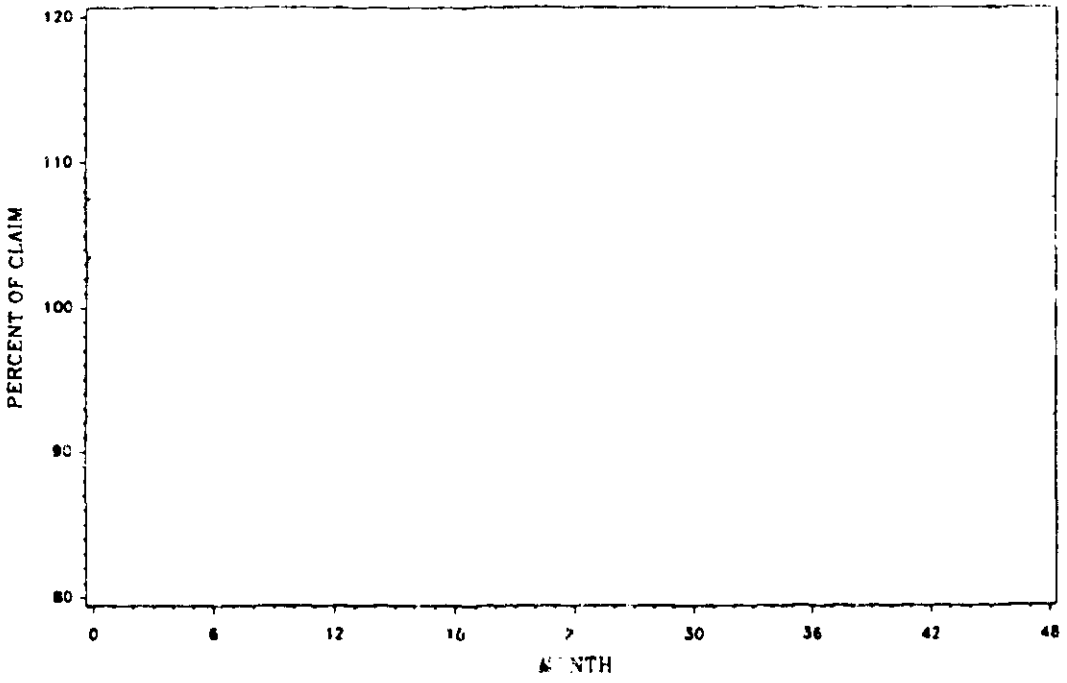


Table 51[1]: Assay % of Label Claim Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1083

Initial	3 months	6 months	9 months
102.0	105.3	103.5	102.8
103.5	106.3	103.0	103.8
103.3	105.5	103.0	101.5

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 35: Topotecan Total Degradation Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1057

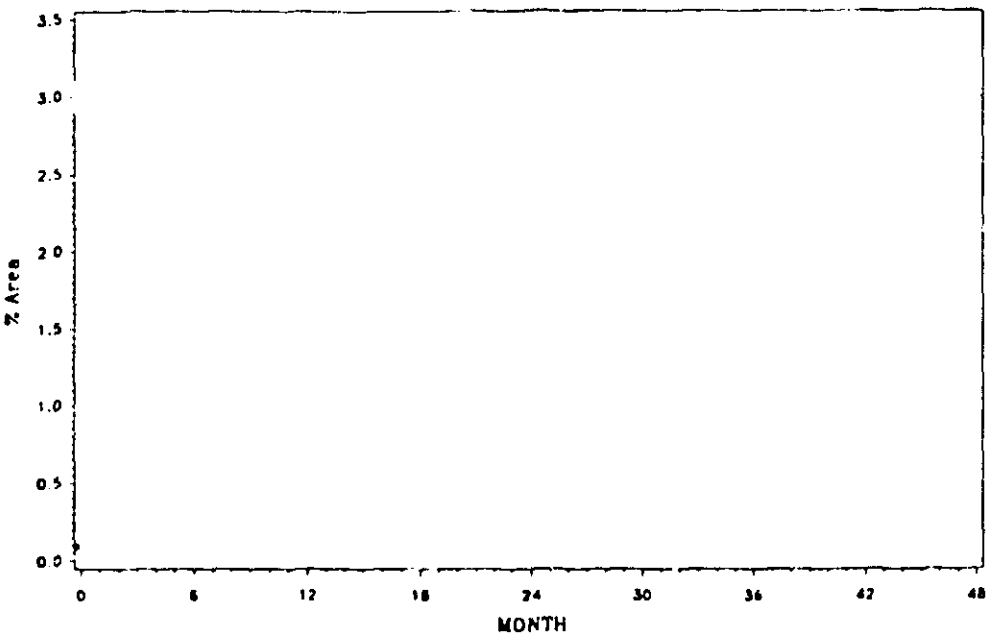


Table 52[1]: Degradation % Area, Total Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1057

Initial	3 months	6 months	9 months	12 months
0.09	0.04	0.06	0.05	0.08
0.10	0.03	0.06	0.06	0.07

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 36: Topotecan Total Degradation Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1082

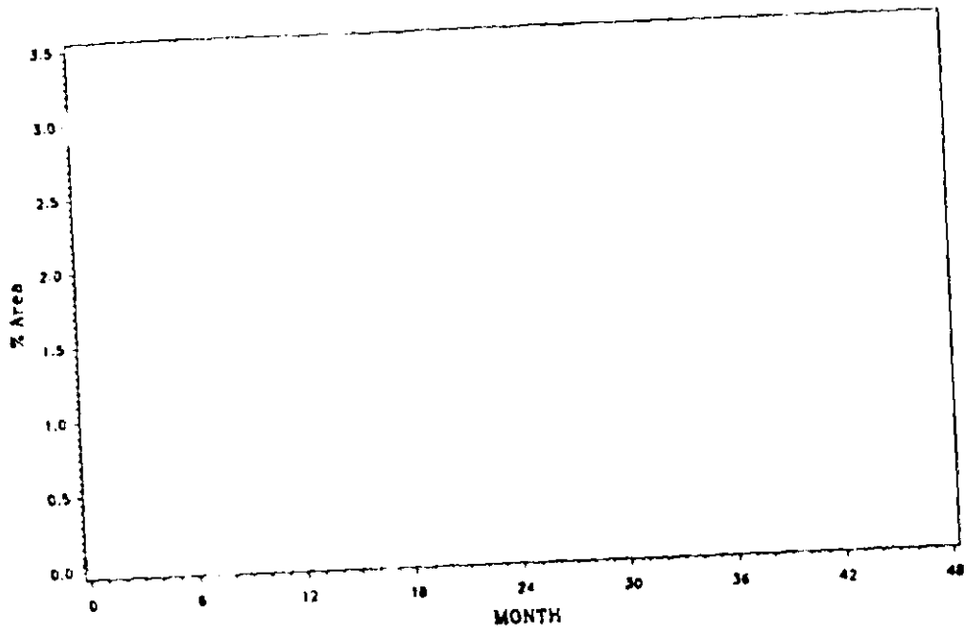


Table 53[1]: Degradation % Area, Total Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1082

Initial	3 months	6 months	9 months
0.04	0.05	0.04	0.07
0.08	0.05	0.04	0.09

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 37: Topotecan Total Degradation Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1083

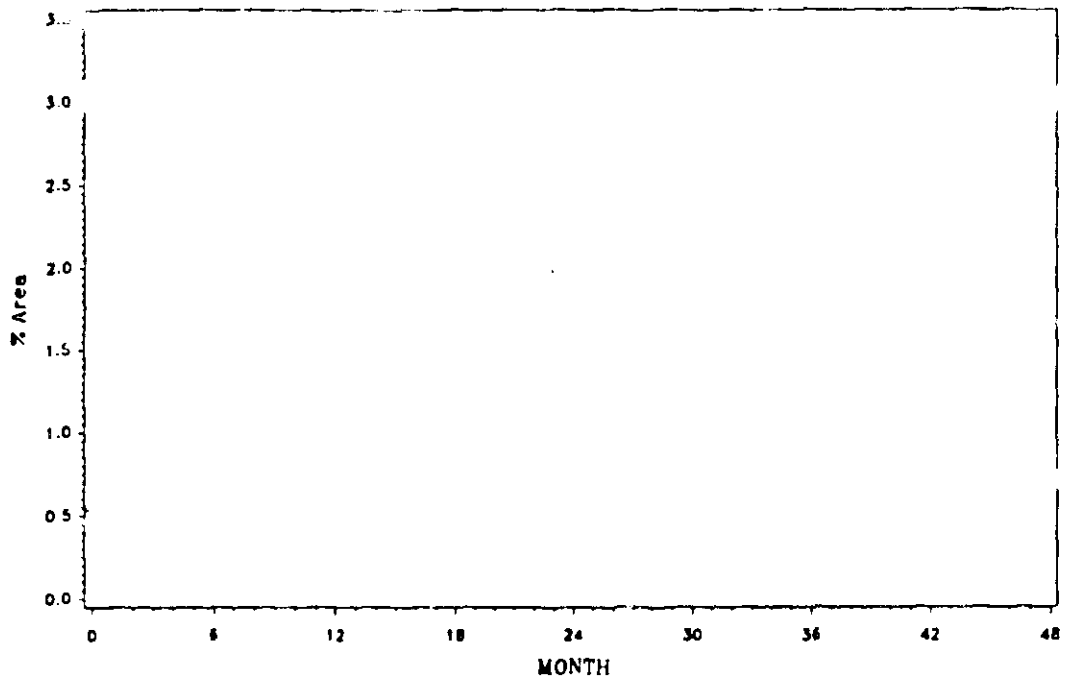


Table 54[1]: Degradation % Area, Total Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1083

Initial	3 months	6 months	9 months
0.55	0.58	0.60	0.58
0.52	0.58	0.60	0.60

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure38: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1057

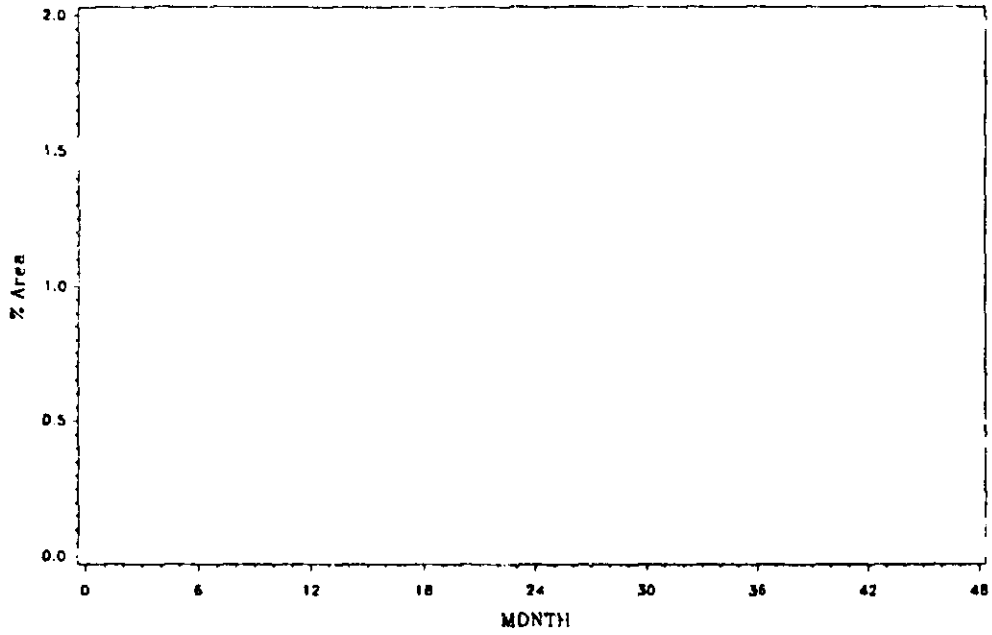


Table 55[1]: Degradation % Area, SKF-S-107564 Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1057

Initial	3 months	6 months	9 months	12 months
0.09	0.04	0.06	0.05	0.08
0.10	0.03	0.06	0.06	0.07

[1] Updated

STABILITY OF THE DRUG PRODUCT

Figure 39: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1082

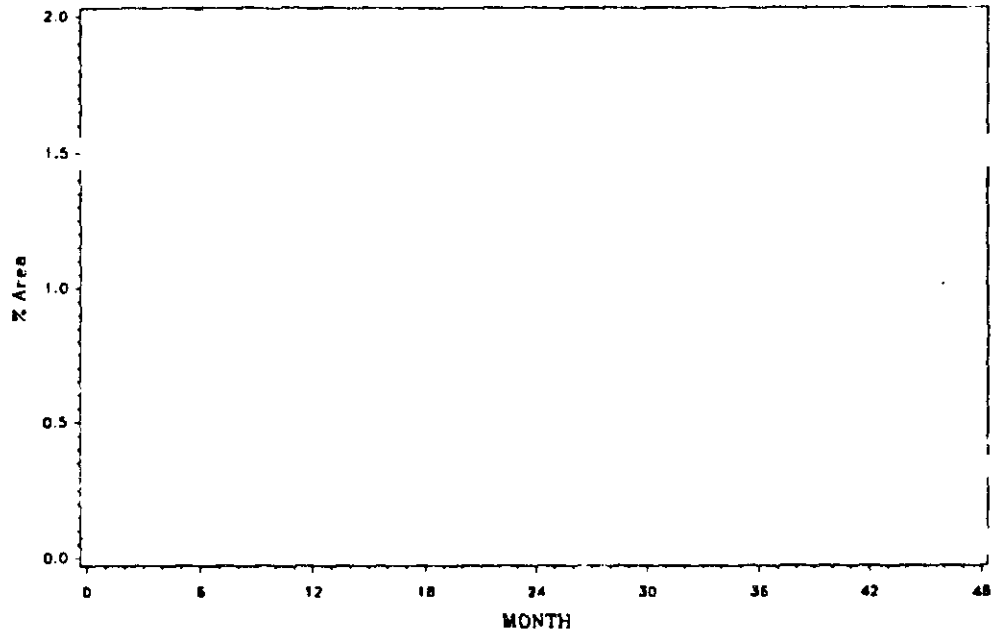


Table 56[1]: Degradation % Area, SKF-S-107564 Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1082

Initial	3 months	6 months	9 months
0.04	0.05	0.04	0.07
0.08	0.05	0.04	0.09

[1] Updated

ITEM 3.B. Drug Product
Hycamtin™ (topotecan hydrochloride) for Injection

STABILITY OF THE DRUG PRODUCT

Figure 40: Topotecan Degradation, SKF-S-107564 Regression Analysis
Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1083

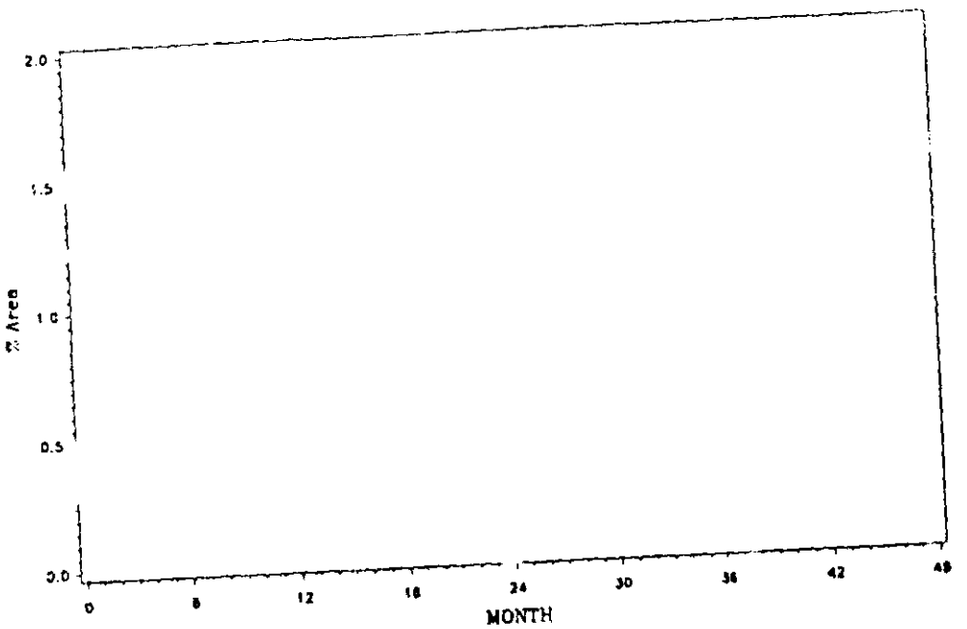


Table 57[1]: Degradation % Area, SKF-S-107564 Topotecan 4 mg Vials
Temp 30°C/75% RH, Set Down No. 1083

Initial	3 months	6 months	9 months
0.39	0.38	0.19	0.18
0.35	0.38	0.22	0.19

[1] Updated

STATISTICAL REVIEW AND EVALUATION (ADDENDUM #2)

N.D.A.: #20-671

APR 25 1996

APPLICANT: SmithKline Beecham Pharmaceuticals

NAME OF DRUG: Hycamtin (Topotecan hydrochloride)

INDICATION: Metastatic Carcinoma of the Ovary after Failure of Initial or Subsequent Therapy

DOCUMENTS REVIEWED: NDA Volumes 1, 40, 67, 73, and 85 (12/21/95)

MEDICAL OFFICER: Steven Hirschfeld, M.D.

Additional analyses were performed on the FDA medical officer's definition of duration of response. These were not presented in the reviewer's original statistical review due to time constraints. Separate analyses were performed for Study 034 and Study 039. No adjustment was made for any covariates. Consequently, the p-value for treatment effect in Study 039 would be the same for the logrank test and the Cox proportional hazards regression model. The information is contained in the following two tables.

Reviewer's Table 1: Duration of Response, Study 039				
	Sponsor's Definition		FDA Definition	
	Topotecan	Taxol	Topotecan	Taxol
n	23	15	22	14
median	32.1 weeks	19.7 weeks	22.2 weeks	12.0 weeks
95% CI	(20.6, ∞)	(18.7, 24.3)	(12.6, ∞)	(6.6, ∞)
hazard ratio (taxol : topotecan), p-value	2.38 (p=0.222) *		3.62 (p=0.065) 95% CI (0.846, 15.455)	

Reviewer's Table 2: Duration of Response, Study 034		
	Sponsor's Definition	FDA Definition
n	16	15
median	16.3 weeks	18.0 weeks
95% CI	*	(7.0, ∞)

* This reviewer was unable to locate a confidence interval for the hazard ratio provided by the sponsor. Also, the sponsor reported a hazard ratio of 0.42 for Study 039, but this hazard ratio was inverted to 2.38 for consistency with the reviewer's result.

Vance Berger, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco C. Gnecco 4/22/96
Dr. Chi 4/25/96

CC:

Archival NDA #20-671
HFD-150 / Division File
HFD-150 / Dr. Justice
HFD-150 / Dr. Hirschfeld
HFD-150 / Ms. Catterson
HFD-344 / Dr. Lisook
HFD-710 / Dr. Chi
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file

STATISTICAL REVIEW AND EVALUATION (ADDENDUM)

N.D.A.:	#20-671
	APR 18 1996
APPLICANT:	SmithKline Beecham Pharmaceuticals
NAME OF DRUG:	Hycamtin (Topotecan hydrochloride)
INDICATION:	Metastatic Carcinoma of the Ovary after Failure of Initial or Subsequent Therapy
DOCUMENTS REVIEWED:	NDA Volumes 1, 40, 67, 73, and 85 (12/21/95)
MEDICAL OFFICER:	Steven Hirschfeld, M.D.

Page 19 of the review states that a careful review of the medical records lead to a classification of 18 of the 111 patients from Study 034 as having sepsis. Page 20 states that 40 patients from Study 039 had sepsis. Actually, these patients did not necessarily have sepsis, but by virtue of their fever and neutropeni they were at higher risk for sepsis.

Vance Berger, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco 4/18/96
Dr. Chi 4/18/96

CC:

Archival NDA #20-671
HFD-150 / Division File
HFD-150 / Dr. Justice
HFD-150 / Dr. Hirschfeld
HFD-150 / Ms. Catterson
HFD-344 / Dr. Lisook
HFD-710 / Dr. Chi
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file

D. Callinson

STATISTICAL REVIEW AND EVALUATION

N.D.A.:	#20-671	APR 2 1995
APPLICANT:	SmithKline Beecham Pharmaceuticals	
NAME OF DRUG:	Hycamtin (Topotecan hydrochloride)	
INDICATION:	Metastatic Carcinoma of the Ovary after Failure of Initial or Subsequent Therapy	
DOCUMENTS REVIEWED:	NDA Volumes 1, 40, 67, 73, and 85 (12/21/95)	
MEDICAL OFFICER:	Steven Hirschfeld, M.D.	

STATISTICAL ISSUES:

1. Protocol 034, listed as one of the two pivotal studies, uses historical controls.

2. None of the key trials were blinded. Differences in drug administration routes made it difficult or impossible to blind the studies, so this is not a criticism, but it is a statistical issue to be aware of when interpreting the results of these studies.

3. Based on the plots of the log-log-survivals (SAS PROC LIFETEST) of the four time-to-event endpoints for Study 039, the hazards do not appear to be proportional. Thus the logrank test should be preferred to the Cox proportional hazards regression model.

4. Study 012 was designed to enroll 40 patients but enrolled only 30 patients. Study 034 was designed to have 100 evaluable patients but only 92 met the inclusion criteria.

5. There are discrepant data records in several places. Different datasets provided contradictory treatment assignment information, for example, for Patients (all datasets agree except for the WEIGHT1 data set). It was confirmed with the sponsor on 3/15/96 that Patient was randomized to receive Taxol, while Patient was randomized to receive Topotecan. Also, within RESPONS1 Patient has two records for best response (as do Patients), and these two do not agree. One is 4 (the code for progressive disease) and one is 8 (the code for missing).

6. Not all hematologic AEs were collected. In fact, they were only collected if there were *sequelae involved*.

7. Study 034 has different lists of secondary efficacy parameters on pages 10, 11, and 19 of Volume 73 of the NDA. On page 23 of Volume 73 it is stated that the protocol was modified on 6/28/95 to add time to progression and survival as secondary endpoints. The study closed 2/28/95, so one has to wonder what prompted this action a full four months after the close of the study.

8. There seems to be no rationale for the sample size selected for Study 033. However, this was not a pivotal study.

9. There appeared to be large variability in response rates across centers. In particular, in Study 039, Centers 071, 077, 078, 102, 112, and 113 had unusually high response rates. Most of the responses occurred in Europe, and not in the United States.

1. BACKGROUND

Topotecan is currently not marketed in any country (NDA Volume 1, page 000003). In total, 1276 patients contributed to the safety profile, of which 445 patients, with relapsed ovarian cancer, were treated with the proposed 30-minute infusion for five consecutive days every 21 days. Topotecan will be marketed, pending FDA approval, as a 4 mg vial of powder for reconstitution. There were two studies identified by the sponsor as pivotal. These were Protocols 034 and 039. Only Study 039 was randomized, so Study 039 is the focus of this review. Studies 012 and 033 were classified by the sponsor as supportive. There were also numerous smaller studies. In no studies were AEs specifically solicited.

STUDY DESCRIPTIONS

STUDY 039

Study 039 was a randomized, comparative, multicenter (61 investigators throughout North America and Europe), open-label Phase III study comparing Topotecan to Paclitaxel in women with epithelial ovarian cancer. The study ran between 2/7/94 and 6/20/95.

All patients had recurrent ovarian cancer after failing (progressing with at least two cycles of or having stable disease following at least four cycles of) initial treatment with a platinum-based regimen. In particular, the patients had a histologic diagnosis of epithelial ovarian carcinoma with bidimensionally measurable disease.

Patients were stratified according to three baseline factors. These were

1. platinum sensitivity, classified as
    a. platinum-refractory, with progressive disease or stable disease while on the initial platinum-based therapy,
    b. platinum-resistant early, with a response and then subsequently relapse within three months of the discontinuation of the initial platinum-based therapy,
    c. platinum-resistant interim, with a response and then subsequently relapse between three and six months after the discontinuation of the initial platinum-based therapy,
    d. platinum-resistant late, with a response and then subsequently relapse more than six months after the discontinuation of the initial platinum-based therapy;
2. age
    a. under 65 years,
    b. at least 65 years;

and

3. baseline ascites

   a. present,
   b. absent.

Thus there were 4x2x2 = 16 randomization lists, each with a block size of two. Patients were randomized to receive either

1. Topotecan 1.5 mg/m^2/day for five consecutive days every 21 days

or

2. Paclitaxel 175 mg/m^2/day infused over three hours for one day every 21 days.

Patients failing on the treatment arm were allowed to cross over to the control arm. When a patient experienced neutropenia caused by the chemotherapy, G-CSF was used to allow the dose intensity to be maintained.

The primary efficacy parameters were

1. response rate (the proportion of patients who attained either a complete response or a partial response),

2. response duration (measured, in weeks, from time of initial documented response to the first sign of disease progression),

3. time to progression (the time, in weeks, from first study drug administration until documented progressive disease or initiation of alternate therapy, or for patients who did not provide evidence of progression, the date of death was used as a surrogate, with censoring only if death was used as a surrogate and was not caused by the progression or if the patient was lost-to-follow-up),

and

4. toxicities.

The secondary efficacy parameters were

1. time to response (the time, in weeks, from the first dose of the randomized study medication to the time of initial documented response),

2. survival (the time, in weeks, from the first dose of the randomized study medication, until death due to any cause, or censored at the time of loss-to-follow-up).

3. quality of life (the self-administered EORTC QLQ-C30).

and

4. population pharmacokinetics (Volume 40, page 30).

Time to event endpoints were assessed using Kaplan-Meier curves and Cox regression modeling. Patients were evaluable for efficacy if they had a documented CR or PR at least four weeks apart, or had stable disease for at least eight weeks after study treatment, or had progressive disease after at least one full cycle of the study medication (page 54, Volume 40).

The target enrollment was 100 evaluable patients per arm. Of the 235 randomized, 112 actually received Topotecan during the randomized phase and 114 received Taxol during the randomized phase. The other nine patients never received study medication. The sample size was based on an assumed response rate for Taxol of 24%. If this held true, then there would be 90% power that the upper 95% confidence limit for the true difference in response rates would not exceed 20%, the equivalence range (page 54, Volume 40).

STUDY 034

Study 034 was an open, multi-center (26 centers in nine nations), Phase II study of Topotecan administered intravenously as five daily infusions every 21 days to women with advanced epithelial ovarian carcinoma. These 111 women had failed prior chemotherapy with cisplatin or carboplatin. These patients were classified as platinum refractory (progressive disease or stable disease while on platinum-based chemotherapy) or platinum resistant (patients who responded and then relapsed, further subdivided into early, or within three months of discontinuation of chemotherapy; interim, or between three and six months after such discontinuation; and late, or more than six months after such discontinuation).

The duration of this study was over a year, from 5/31/93 to 2/28/95. The primary objective was to evaluate response rate and response duration (defined as the duration between the initial documented response and the first sign of disease progression, page 44, Volume 73). The secondary objective was to evaluate time to progression (the interval from initiation of study drug until the first documented sign of disease progression or death due to progressive disease, with right-censoring for loss-to-follow-up or receiving subsequent therapy, per page 45 of Volume 73), survival, toxicities, bioavailability, and pharmacokinetics. It is listed on page 11 of Volume 73 that another secondary endpoint was time to response (defined, on page 45 of Volume 73, as the duration between initiation of the study and the first documented response). This was not listed on either page 10 or page 19 of Volume 73.

The goal was to enroll 100 evaluable patients. This would allow for a 95% confidence interval for the true response rate to have a length of 9% on either side, if the true response rate were between 20% and 30%, as stated on page 41 of Volume 73. Of the 111 enrolled, 92 met

the inclusion criteria and 90 completed the study (page 51, Volume 73). There were 18 patients who withdrew from the study (10 for adverse experiences, six for loss-to-follow-up, one for a protocol violation, and one for another (unspecified) reason, as on page 53 of Volume 73). These 18 patients, plus three patients ongoing at the time the study ended, account for the difference between the 111 patients enrolled and the 90 patients who completed the study. An interim assessment of response took place three months after the 50th patient was enrolled. The decision was to continue accruing patients if there were at least six responses or if there were fewer responses but they were durable complete responses.

STUDY 012

Study 012 was an open, single-center, Phase II study to evaluate the efficacy and toxicity of Topotecan administered intravenously as five daily infusions every 21 days to women with advanced epithelial ovarian carcinoma. These 30 women had failed prior chemotherapy (no more than two regimens) with cisplatin or carboplatin, meaning that they were refractory, defined on page 25 of Volume 67 of the NDA (or page 8 of the protocol) as progression during therapy, less than a complete response after an adequate trial of chemotherapy, or a measurable relapse within six months of attaining a complete response. Sequential or concurrent use of cisplatin, carboplatin, and cyclophosphamide was considered as one regimen. At least four weeks must have elapsed between cessation of prior chemotherapy and entry into the study, and at least 30 days must have elapsed between administration of any investigational drug and study entry (page 25 of Volume 67 of the NDA or page 8 of the protocol). The duration of this study was nearly two years, from 11/5/91 to 10/11/93, and took place at only one center, MD Anderson. The primary objective was to evaluate the overall response rate and response duration (time from initial documented response to the first sign of progressive disease). The secondary objective was to evaluate the toxicities.

On page 36 of NDA Volume 67, Section 3.11.1, appears the statistical rationale for the choice of sample size. A Gehan design was used, in which there were two stages of patient recruitment. With a significance level of 5% and an interest in detecting a response rate of 20%, 14 patients were to be recruited in the first stage. If no responders were observed in this initial stage, then the trial was to be terminated. If, on the other hand, at least one responder was observed, then an additional 26 patients were to be recruited, for a total of 40 evaluable patients. This would ensure a standard error of no greater than 8%. On page 37 of NDA Volume 67, Section 4.2.1, it is stated that data collection was slow, resulting in enrollment of only 30 patients.

STUDY 033

Study 033 was an open, multi-center, Phase II study of Topotecan administered intravenously as five daily infusions every 21 days to women with advanced epithelial ovarian carcinoma. These 139 women, from 49 centers in both the USA and Europe, had failed prior chemotherapy with both Paclitaxel and at least one of cisplatin and carboplatin. The failures were of two types. The refractory patients had progressive disease or stable disease while on the last

chemotherapy. The resistant patients responded and subsequently relapsed after discontinuation of the last prior chemotherapy. If the relapse was within three months, then the patient was an early relapse; if it was between three and six months, then the patient was an interim relapse; and if the relapse was more than six months after discontinuation of the last prior chemotherapy, then the patient was a late relapse.

The patients were stratified by the number of previous chemotherapy regimens given (one or two). The duration of this study was over a year, from 3/1/94 to 6/20/95. The primary objective was to evaluate response rate, response duration (defined as the elapsed time, in weeks, from first documented response until the first documented disease progression), and time to progression (the time, in weeks, elapsed from first study drug administration to documented progression of measurable disease). If a patient did not progress during the study, then the date of clinical progression or of death (whichever came first) was used as a surrogate for time to progression. The value was censored if it was a death not due to disease progression or a loss-to-follow-up. The secondary objective was to evaluate time to response (the time, in weeks, from the first dose of study medication to the time of initial documented response, or undefined for non-responders, per page 45 of Volume 85), survival, toxicities, and quality of life.

The study design called for 100 evaluable patients, with 50 patients per stratum (Volume 85, page 27). To be evaluable for response, the patient could not have any protocol violations which affected the ability to evaluate the efficacy of Topotecan. In addition, evaluable patients needed to be classified as one of the following:

1. PR or CR after Topotecan treatment that was documented by measurements taken at least four weeks apart;

2. Stable disease for at least eight weeks after Topotecan treatment;

or

3. Progressive disease after a full cycle of Topotecan treatment (Volume 85, page 48).

There appears to be no rationale provided for the sample size selected.

OTHER STUDIES

There were other Phase I and safety studies as listed beginning page 268 of Volume 1.

2. EFFICACY RESULTS AND REVIEWER'S COMMENTS:

The only study considered for efficacy information was Study 039, as this was the only randomized study. The primary efficacy parameters of this study were

1. response rate,

2 response duration (measured from time of documented response),

and

3. time to progression.

The secondary efficacy parameters were

1. time to response,

2. survival,

and

3. quality of life (the self-administered EORTC QLQ-C30).

RESPONSE RATE

The FDA reviewers re-created the response data set from Study 039 by applying the standards put forth in the study protocol to the raw lesion size data. The agreement with the sponsor's data was quite good. In fact, there were only six of 226 (3%) discrepancies. These discrepancies appear in Reviewer's Table 1.

Reviewer's Table 1: Discrepancies in Response Definitions, Study 039			
Patient ID	Randomized Treatment	Sponsor's Classification	FDA Classification
	Taxol	Partial Response	No Response
	Taxol	Partial Response	No Response
	Topotecan	Partial Response	Complete Response
	Topotecan	Partial Response	No Response
	Taxol	Partial Response	Complete Response
	Taxol	No Response	Partial Response

The summary data derived by the FDA reviewers appear in Reviewer's Table 2.

Reviewer's Table 2: Response, Study 039				
	No Response	Partial Response	Complete Response	Total
Taxol	100 (87.7%)	10 (8.8%)	4 (3.5%)	114
Topotecan	90 (80.4%)	16 (14.3%)	6 (5.4%)	112
Total	190	26	10	226

The sponsor used the chi-square test ($p = 0.138$) on dichotomized response super-categories (i.e., responder or non-responder) to analyze the best response data. The 95% confidence interval for the difference in rate of response was, based upon the sponsor's data, (-2.3, 17.1), on pages 11 and 74 of Volume 40. Since the upper limit is under 20%, the response rates appear to be at least comparable. In fact, Topotecan appears to produce a better response rate than Taxol. Since the chi-square test on dichotomized data is known to be inefficient under some circumstances (Yates, 1948; Cochran, 1955; Armitage, 1955; Moses, Emerson, and Hosseini, 1984; Rahlfs and Zimmermann, 1993), this reviewer also performed an additional analysis, namely the exact one-sided Smirnov test with fixed margins (Hilton, Mehta, and Patel, 1994) using StatXact software. The exact p-value from the Smirnov test based on the FDA data was 0.0918, showing marginal significance that Topotecan is, in fact, associated with a higher response rate than Taxol. When using this test on the sponsor's data (*intent-to-treat*), the p-value is 0.1792. When using this test on the sponsor's evaluable subset, the p-value is 0.0849.

Logistic regression was also used in SAS to assess the prognostic usefulness of various

covariates in predicting response. Details appear in the appendix.

DURATION OF RESPONSE

The median duration of response, measured from the time of the first documented response to the time of progression, was 32.1 weeks (with a 95% confidence interval from 20.6 weeks to infinite weeks) in patients treated with Topotecan and 19.7 weeks (with a 95% confidence interval from 18.7 weeks to 24.3 weeks) in patients treated with Taxol. The estimated risk ratio is 0.42, and did not reach statistical significance ($p=0.222$). Nevertheless, it is impressive that the entire 95% confidence interval for the Topotecan group lies above the median for the Taxol group.

TIME TO PROGRESSION

The median time to progression, measured from the time of the first study drug administration until documented progression, was 23.1 weeks (with a 95% confidence interval from 17.1 weeks to 29.6 weeks) in patients treated with Topotecan and 14.0 weeks (with a 95% confidence interval from 11.9 weeks to 18.3 weeks) in patients treated with Taxol. The estimated risk ratio is 0.58, and was statistically significant ($p=0.002$).

TIME TO RESPONSE

The median time to response, measured from the time of the first study drug administration until documented response, was 9.0 weeks (with a 95% confidence interval from 6.6 weeks to 12.1 weeks) in patients treated with Topotecan and 6.0 weeks (with a 95% confidence interval from 5.6 weeks to 9.1 weeks) in patients treated with Taxol. The estimated risk ratio is 0.48, and was statistically significant ($p=0.041$).

SURVIVAL

Survival was defined by the sponsor from the date of randomization until either death or the last known alive date (which would constitute a right-censored time). The survival data were not mature at the time of analysis. In particular, 179 of 226 (79%) patients were censored (still alive at the time of clinical cutoff) on the 039 study. The pattern of censoring appears in Reviewer's Table 3.

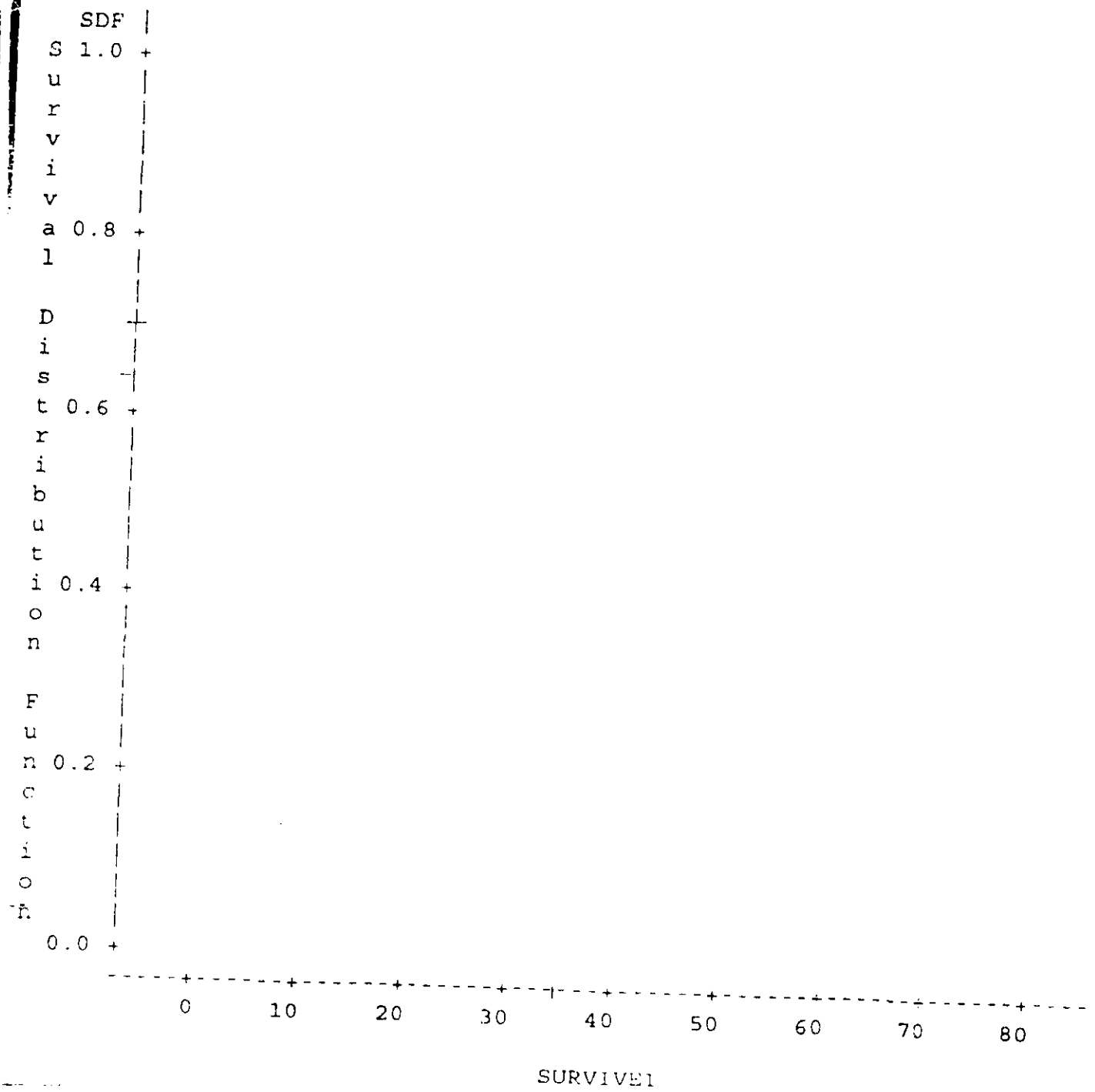
Reviewer's Table 3: Censoring Pattern for Survival Study 039			
	Events	Censored Patients	Total
Taxol	22 (19%)	92 (81%)	114
Topotecan	25 (22%)	87 (78%)	112
Total	47	179	226

As a preliminary step, the Kaplan-Meier survival plot was produced (SAS PROC LIFETEST), along with the plot of the log of the negative log of the survival. These appear as Reviewer's Plot 1 and Reviewer's Plot 2, respectively.

Reviewer's Plot 1: Kaplan-Meier Survival Plot
Study 039

The LIFETEST Procedure

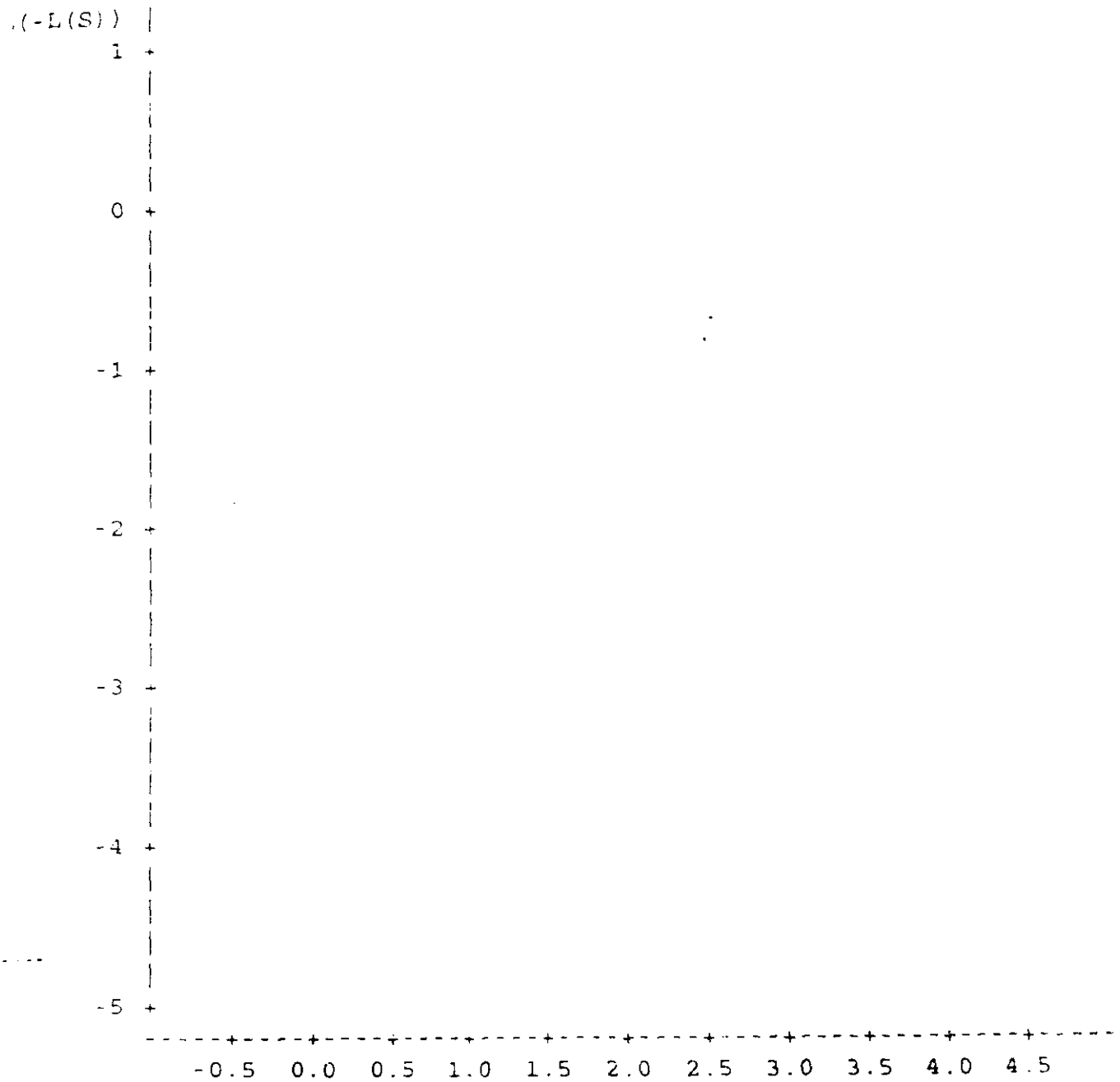
Survival Function Estimates



Reviewer's Plot 2: The Log(-Log(Survival)) Plot
Study 039

The LIFETEST Procedure

Log(-Log(Survival Function)) Estimates



This latter plot should be parallel for the proportional hazards assumption, which underlies the Cox regression model, to hold. The survival plots cross at around 35 weeks. Before 35 weeks, Taxol is associated with a higher survival rate. After 35 weeks, Topotecan is associated with a higher survival rate. This means that the log(-log(survival)) plot also has a crossing of the two curves, and thus they cannot be parallel. The proportional hazards assumption seems, therefore, quite suspect. It is worth noting that roughly 70% of the patients on the Topotecan arm survived beyond 35 weeks, while this figure is 65% percent for the Taxol arm. The significance of this finding is not the difference, but rather the large proportion of patients for which Topotecan seems to promote improved survival (those who survive beyond 35 weeks), as compared to the small proportion of patients for whom Taxol might be preferred (those who do not survive beyond 35 weeks). The estimated median survivals were 61.3 weeks (Topotecan) and 42.6 weeks (Taxol), with 95% lower limits of 60.1 weeks and 35.9 weeks, respectively. The log-rank test, which is sensitive to differences late in time, yielded a p-value of 0.5305, while the Wilcoxon test, which is sensitive to differences early in time (see Lee, Desu, and Gehan, 1965), yielded a p-value of 0.1468. The sponsor's p-value was (Volume 40, page 79) 0.515, with a risk ratio of 1.21. Among those patients who responded to therapy, only one patient from each treatment group failed to survive the duration of the study (Volume 40, page 79).

When we stratify for the variable which separates those patients predicted to respond from those not predicted to respond, the log-rank p-value becomes 0.0049 and the Wilcoxon p-value becomes 0.0038. These p-values are testing, simultaneously, the null hypothesis of **no** treatment effect and no effect for the prediction variable. Thus one cannot infer a treatment effect based on these low p-values. Those predicted to respond survive longer, on average, than those not predicted to respond.

As a descriptive, but not inferential technique, Cox regression (SAS PROC PHREG) was run to determine which variables were prognostic for survival. The model included terms for drug ($p=0.0372$), body surface area ($p=0.0101$), number of baseline lesions ($p=0.0547$), total size of the baseline lesions ($p=0.0010$), the predicted probability of responding ($p=0.1628$), and the number of days since last chemotherapy ($p=0.0003$).

Because some patients were crossed over during the course of the study, it was felt that to attribute survival information to the correct treatment the survival times should be right-censored at the time of such crossing over, or, in fact, at the time that a patient stops treatment medication in favor of a different treatment. This involved an alternative definition of survival time, and even more patients were censored. The pattern of censoring appears in Reviewer's Table 4.

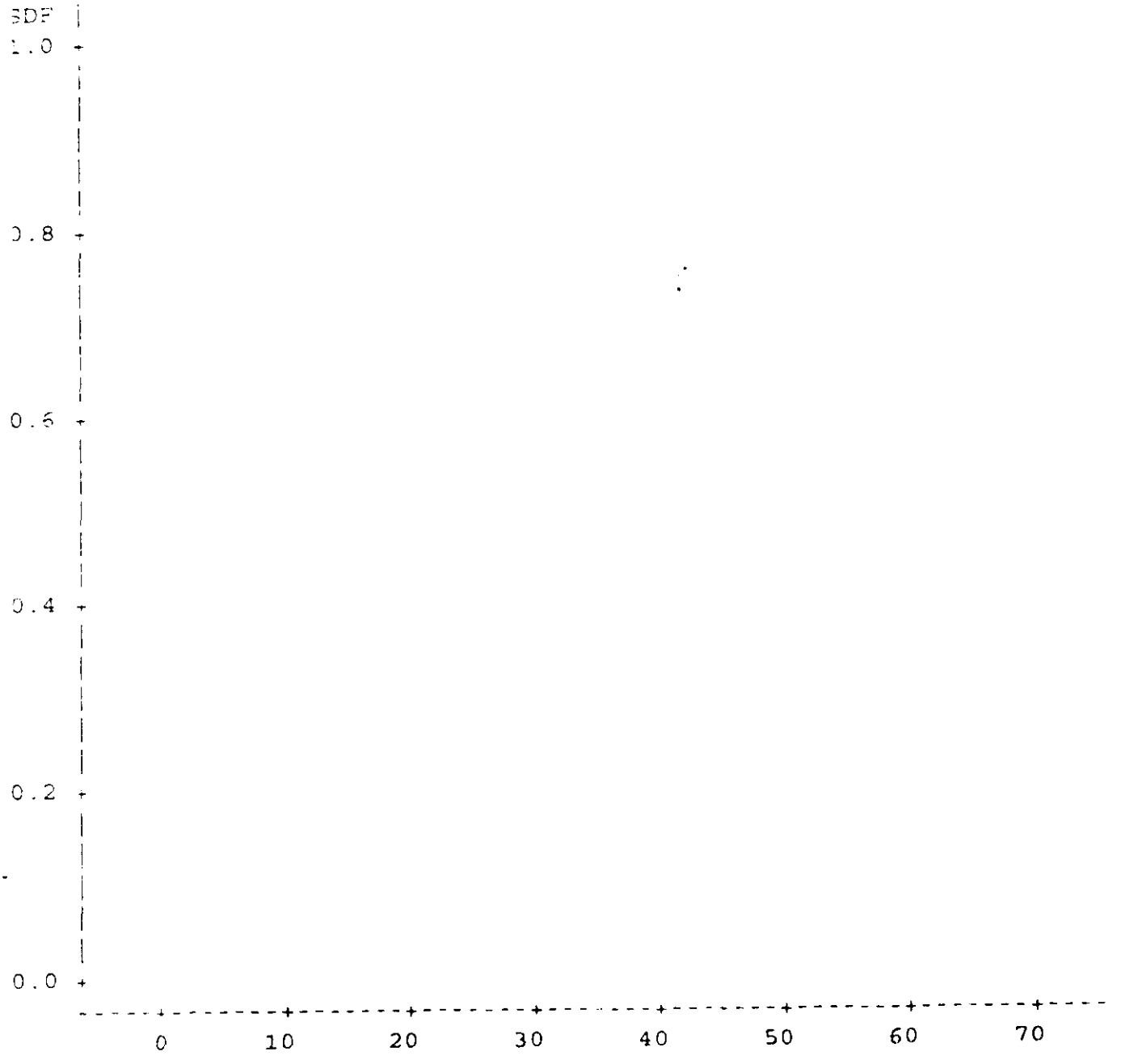
Reviewer's Table 4: Censoring Pattern for the Alternative Definition of Survival Study 039			
	Events	Censored Patients	Total
Taxol	8	106	114
Topotecan	11	101	112
Total	19	207	226

As a preliminary step, the Kaplan-Meier survival plot was produced (SAS PROC LIFETEST), along with the plot of the log of the negative log of the survival time. These appear as Reviewer's Plot 3 and Reviewer's Plot 4, respectively.

Reviewer's Plot 3: Kaplan-Meier Survival Plot
Alternative Definition of Survival
Study 039

The LIFETEST Procedure

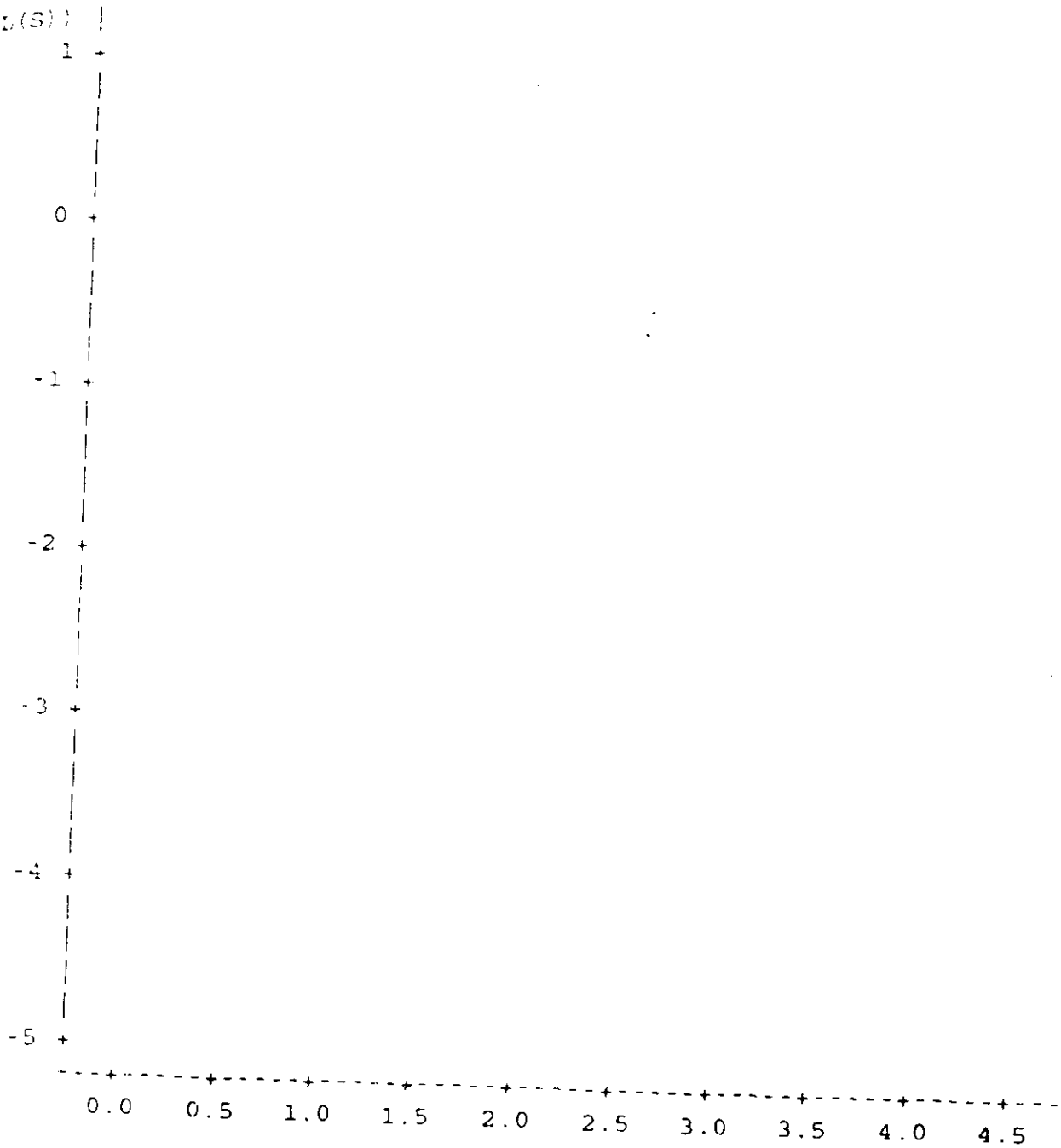
Survival Function Estimates



Reviewer's Plot 4: The Log(-Log(Survival)) Plot
Alternative Definition of Survival
Study 039

The LIFETEST Procedure

Log(-Log(Survival Function)) Estimates



This latter plot should be parallel for the proportional hazards assumption, which underlies the Cox regression model, to hold. Clearly there is no parallelism, so the proportional hazards assumption seems suspect. The estimated median survivals were 61.3 weeks (Topotecan) and 39.1 weeks (Taxol). The log-rank test had a p-value of 0.9641, while the Wilcoxon test had a p-value of 0.4377. With the low number of events, it would be difficult to attain significance.

When we stratify for the variable which separates those patients predicted to respond from those not predicted to respond, the log-rank p-value becomes 0.1000 and the Wilcoxon p-value becomes 0.1548. These p-values are testing, simultaneously, the null hypothesis of no treatment effect and no effect for the prediction variable.

As a descriptive, but not inferential technique, Cox regression (SAS PROC PHREG) was run to determine which variables were prognostic for survival. The only term which appeared to be predictive was the number of days since last chemotherapy ($p=0.0001$). The p-value for drug was 0.2228.

QUALITY OF LIFE

As mentioned on page 81 of Volume 40, the quality of life questionnaires were administered at screening, on Day 8 and Day 15 of each cycle, and immediately prior to each subsequent cycle of chemotherapy. The changes from baseline were minimal. As indicated in Sponsor's Table 23 (Volume 40, page 81), almost all median changes from baseline were zero. This was based on between 70 and 75 patients randomized to the Topotecan arm, and between 81 and 88 patients randomized to the Taxol arm, depending on the QOL parameter.

3. SAFETY:

The sponsor reported 445 patients evaluable for safety and used these in their integrated summary of safety. We did not have access to all of the data, so we only used the 111 patients from Study 034 and the 226 patients from Study 039, for a total of 337 patients. Of the 226 patients on the 039 study, 112 were randomized to Topotecan and 114 were randomized to Taxol. Of the 114 randomized to Taxol, 53 were crossed over to Topotecan. Thus $111+112+53$, or 276 patients were evaluable for the evaluation of the safety of Topotecan. This includes 552 cycles on Study 034, 555 cycles on the randomized phase of Study 039, and 176 cycles on the crossover phase of Study 039, for a total of 1283 cycles of Topotecan. By the rule of three (Hanley and Lippman-Hand, 1983), a 95% confidence interval for the probability of any adverse event not experienced is (0, 3/276) in terms of patient counts and (0, 3/1283) in terms of cycles. Numerically, these are then (0.00, 0.01) and (0.000, 0.002), respectively.

The adverse event of most concern was sepsis. Eleven patients on the 039 study were reported by the sponsor as having sepsis, of whom six died (three of sepsis). Of these 11 patients, eight had sepsis on the randomized phase, of whom five died. Of these eight, six were randomized to Topotecan, and only two were randomized to Taxol. This information appears in

Reviewer's Table 5.

Reviewer's Table 5: Sepsis Pattern by Randomized Treatment Randomized Phase Only Study 039			
	Sepsis	No Sepsis	Total
Taxol	2	112	114
Topotecan	6	106	112
Total	8	218	226

The baseline factors which were most predictive of sepsis were age, age^2, days since last treatment, and body surface area. There did not seem to be a treatment difference ($p=0.9530$) or a treatment interaction with body surface area ($p=0.9803$). A reduced logistic regression model was run with only these variables. The results appear in Reviewer's Table 6.

Reviewer's Table 6: Logistic Regression (SAS) to Predict Reported Sepsis Study 039			
Variable	Estimated Coefficient	p-value	Estimated Odds Ratio
Intercept	-28.9325	0.0036	0.000
Days Since Last Chemotherapy	0.0266	0.0371	1.027
Body Surface Area	5.8191	0.0817	336.654
Age	0.7481	0.0051	2.113
Age*Age	-0.0063	0.0069	0.994

It is interesting to note that the estimated odds ratio for days since last chemotherapy was 0.973 when predicting response, and 1.027 when predicting sepsis. As expected, the two numbers are on opposite sides of one, but they are also equally far from one.

No patients in the 034 study were reported by the sponsor as having sepsis. However, a careful review of the medical records lead to a classification of 18 of these 111 patients as having sepsis. It is notable that of these 18 patients, seven were enrolled at Center 7, including four with consecutive accession numbers. These were Patients

A similar

review of the medical records from Study 039 lead to 40 patients being classified as having sepsis (across both treatment groups and both phases of the study).

Sponsor's Table 26 (Volume 40, page 85) is reproduced here for completeness. This table lists the incidence (both by patient and by cycle) of leukopenia, neutropenia, thrombocytopenia, and anemia by grade for Study 039. The exact one-sided Smirnov test was applied to the by-patient data. For each of the four adverse events there was strong statistical significance ($p=0.0000$). That is, Topotecan was associated was larger grades (more severity) than was Taxol. The test statistic was the largest difference in empirical cumulative distribution functions, and was computed to be 0.6401 for leukopenia (85% of the patients randomized to receive Topotecan were classified as Grades 3 or 4 vs. 21% of those patients randomized to receive Taxol); 0.5606 for neutropenia (79% of the patients randomized to receive Topotecan were classified as Grade 4 vs. 23% of those patients randomized to receive Taxol); 0.7944 for thrombocytopenia (82% of the patients randomized to receive Topotecan were classified as Grade 1, 2, 3, or 4 vs. 3% of those patients randomized to receive Taxol); and 0.5084 for anemia (94% of the patients randomized to receive Topotecan were classified as Grades 2, 3, or 4 vs. 43% of those patients randomized to receive Taxol).

Table 26: Number (%) of Patients and Courses with Hematologic Toxicity by Worst CTC Grade*

Study Drug Total Patients/Courses	Topotecan n = 112	 n = 555	Paclitaxel n = 114	 n = 550
Leukopenia Grade	Patients n = 110 n (%)	Courses n = 549 n (%)	Patients n = 112 n (%)	Courses n = 546 n (%)
0	0 (0.0)	53 (9.7)	15 (13.4)	179 (32.8)
1	1 (0.9)	67 (12.2)	34 (30.4)	180 (33.0)
2	16 (14.5)	152 (27.7)	40 (35.7)	136 (24.9)
3	56 (50.9)	220 (40.1)	20 (17.9)	48 (8.8)
4	37 (33.6)	57 (10.4)	3 (2.7)	3 (0.5)
Neutropenia Grade	Patients n = 111 n (%)	Courses n = 548 n (%)	Patients n = 112 n (%)	Courses n = 545 n (%)
0	2 (1.8)	80 (14.6)	14 (12.5)	168 (30.8)
1	2 (1.8)	37 (6.8)	14 (12.5)	99 (18.2)
2	2 (1.8)	73 (13.3)	26 (23.2)	114 (20.9)
3	17 (15.3)	153 (27.9)	32 (28.6)	115 (21.1)
4	88 (79.3)	205 (37.4)	26 (23.2)	49 (9.0)
Thrombocytopenia Grade	Patients n = 111 n (%)	Courses n = 550 n (%)	Patients n = 112 n (%)	Courses n = 546 n (%)
0	3 (2.7)	87 (15.8)	92 (82.1)	510 (93.4)
1	34 (30.6)	240 (43.6)	15 (13.4)	31 (5.7)
2	19 (17.1)	86 (15.6)	2 (1.8)	2 (0.4)
3	27 (24.3)	84 (15.3)	1 (0.9)	1 (0.2)
4	28 (25.2)	53 (9.6)	2 (1.8)	2 (0.4)
Anemia Grade	Patients n = 111 n (%)	Courses n = 550 n (%)	Patients n = 112 n (%)	Courses n = 546 n (%)
0	0 (0.0)	14 (2.5)	12 (10.7)	115 (21.1)
1	7 (6.3)	131 (23.8)	52 (46.4)	314 (57.5)
2	59 (53.2)	317 (57.6)	41 (36.6)	106 (19.4)
3	41 (36.9)	82 (14.9)	4 (3.6)	8 (1.5)
4	4 (3.6)	6 (1.1)	3 (2.7)	3 (0.5)

*Toxicity is based on the patient's worst grade for the study, or for the course; percentages are based on the

Of the 112 patients randomized to Topotecan on Study 039, 55 (49%) experienced serious adverse events. Of these, 12 (11%) withdrew from the study due to their adverse events. The most common of these were hematologic toxicities with sequelae. Of the 114 patients randomized to Taxol on Study 039, 35 (31%) experienced serious adverse events. Of these, 8 (7%) withdrew from the study due to their adverse events. The most common of these were intestinal obstruction and abdominal pain.

4. SUMMARY AND CONCLUSIONS:

When considering the risk/benefit ratio, it is worth noting that most patients who respond do not go on to develop sepsis infection. Thus sepsis cannot be regarded as the price one pays for a response. Rather, there are some patients for whom Topotecan works well, and others for whom it does not. Earlier some insight was given into the characteristics of these two patient populations. Nevertheless, it seems clear, based on the data submitted, that Topotecan has a place as the therapy of choice in certain patient populations. In Study 034 the cross-tabulation of response and sepsis appears in Reviewer's Table 7.

Reviewer's Table 7: Response vs. Sepsis Study 034			
	No Response	Response	Total
Sepsis	16	2	18
No Sepsis	79	13	92
Total	95	15	110

Of those patients with sepsis, 11% responded, as compared to the 14% of the patients without sepsis who responded. In Study 039 response was broken down into complete response and partial response. The cross-tabulation appears in Reviewer's Table 8.

Reviewer's Table 8: Response vs. Sepsis Study 039				
	No Response	Partial Response	Complete Response	Total
Sepsis	7	1	0	8
No Sepsis	183	25	10	218
Total	190	26	10	226

Of those patients with sepsis, 12% responded, as compared to the 16% of the patients without sepsis who responded. When considering only the patients on the 039 study who received Topotecan, the cross-tabulation appears in Reviewer's Table 9

Reviewer's Table 9: Response vs. Sepsis Study 039 Topotecan Arm Only				
	No Response	Partial Response	Complete Response	Total
Sepsis	5	1	0	6
No Sepsis	85	15	6	106
Total	90	16	6	112

Of those patients with sepsis, 17% responded, as compared to the 20% of the patients without sepsis who responded. When considering only the patients on the 039 study who received Taxol, the cross-tabulation appears in Reviewer's Table 10.

Reviewer's Table 10: Response vs. Sepsis
Study 039
Taxol Arm Only

	No Response	Partial Response	Complete Response	Total
Sepsis	2	0	0	2
No Sepsis	98	10	4	112
Total	100	10	4	114

Of those patients with sepsis, 0% responded, as compared to the 12% of the patients without sepsis who responded.

Topotecan appears to be efficacious compared to taxol for the treatment of relapsed ovarian cancer. From Study 039 we recall the higher response rate (20% vs. 12%), with a 95% confidence interval for the difference in response rate of (-2.3% to 17.1%). Topotecan also had the larger median duration of response (32.1 weeks vs. 19.7 weeks) with 95% confidence intervals of (20.6 weeks to ∞ weeks) vs. (18.7 weeks to 24.3 weeks), larger median time to progression (23.1 weeks vs. 14.0 weeks) with 95% confidence intervals of (17.1 weeks to 29.6 weeks) vs. (11.9 weeks to 18.3 weeks), and apparently better long-term survival (but worse short-term survival). Topotecan is, however, also associated with an increased incidence of leukopenia, neutropenia, thrombocytopenia, and anemia, as illustrated in Sponsor's Table 26 above.

On the basis of the efficacy and safety findings, this reviewer recommends that Topotecan be approved for secondary treatment of ovarian cancer. Thus, while Topotecan's safety profile, in terms of adverse events, is somewhat inferior to Taxol's, these adverse events were usually not serious enough to warrant withdrawal from the study (11% vs. 7% withdrawn for Topotecan and Taxol, respectively). In this reviewer's opinion, the drug's improved efficacy profile, in terms of increased response rate and more durable responses, as well as longer times to progression, compensate to some extent for the safety concerns. Thus this reviewer finds that approval of Topotecan is warranted for the indication of second-line treatment of ovarian cancer.

Vance Berger, Ph.D.
Mathematical Statistician

Concur: Dr. Gnecco 4/2/96
Dr. Chi 4/2/96

CC:

Archival NDA #20-671
HFD-701 / Dr. Anello
HFD-150 / Division File
HFD-150 / Dr. Justice
HFD-150 / Dr. Hirschfeld
HFD-150 / Ms. Catterson
HFD-344 / Dr. Lisook
HFD-710 / Dr. Chi
HFD-710 / Mr. Ornicke
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file

C:\WPFILES\TOPOTECA\REVIEW.DOC

This review consists of 32 pages of text, including one appendix, 18 tables, and four figures.

APPENDIX: EXPLORATORY MODEL TO PREDICT TUMOR RESPONSE

Logistic regression was also used in SAS to assess the prognostic usefulness of various covariates in predicting response. Details appear in the appendix. The response was trichotomous (complete response, partial response, or no response), combining the patients with progressive disease with the patients with stable disease into the "no response" super-category. In addition to allowing for a more precise test for treatment effect by adjusting for covariates, this model also allowed us to explore the characteristics of those patients who responded, as distinct from those patients who did not respond. The idea was to develop a screen of patients with recurrent ovarian cancer such that those patients who "pass the test" comprise a new patient population with a response rate considerably higher than the entire population of unselected patients. This hypothesis was tested by applying the screen to the patients from Study 034 and predicting who would respond, then comparing this information to the observed responses.

The variables which were considered were

1. the sum of the products of the diameters of the baseline lesions;
2. the baseline body weight;
3. the age at baseline;
4. the body surface area at baseline;
5. the number of days since the last administration of the prior chemotherapy;
6. the classification with regard to prior chemotherapy (refractory, early resistant, interim resistant, late resistant);
7. the baseline CA125;
8. the baseline creatinine;
9. the baseline SGOT;
10. the baseline SGPT;

and

11. the baseline bilirubin.

The modeling approach used was to start with univariate analyses for each of the 11 variables, to see which appeared to be predictive of response. Those which were predictive were then included in a multivariate model. This model was then reduced, by removing those variables whose contributions did not seem to warrant their inclusion, to arrive at a final model. This final model was then modified by consideration of some plots, which suggested, for example, the inclusion of a quadratic term for age. This final model was then run separately for the patients within each treatment group. The coefficients for age, age squared, and body surface area differed in the two models. In a model for all patients, which included treatment, interaction terms were included for age, age squared, and body surface area.

The variables which remained in the final model were, therefore, the days since last

previous chemotherapy, body surface area (m^2), age (in years), treatment (0=Topotecan, 1=Taxol), and drug interactions with age, age squared, and body surface area. Notice that the term for age squared has been removed even though its interaction with treatment is still in the model. The estimated coefficients, p-values (for testing that the coefficient is zero), and odds ratios are given in Reviewer's Table A3. To reduce rounding error in the prediction, the estimated coefficients are given to as many places as are available in SAS.

A positive estimated coefficient is associated with an estimated odds ratio greater than one, or a tendency for a lower probability of response with higher values of the variable in question. Thus the more days since prior chemotherapy the better. Clearly more elapsed time since prior chemotherapy is indicative of better health (as evidenced by the length of time the patient can survive without chemotherapy). Thus one should interpret this finding as observational and not causal. In particular, one would not recommend withholding treatment from patients with ovarian cancer in the hopes that doing so would ultimately lead to a higher response rate. As expected, the fewer baseline lesions the better. Also, the smaller women tended to respond better than the larger women, as measured by body surface area. Other measures of body size, which were not collected (such as lean body mass), may yield a less pronounced effect. Also Topotecan appears to be highly significantly better than Taxol, but again caution is required in interpreting this main effect, because of the presence of the significant interactions. It appears as though age and body surface area are predictive of response, but the form of the dependence is different across the two treatments. Notice that the contribution made by age is quadratic, and not just linear. With more data, it might be fruitful to explore how age and body surface area predict response in each of the treatment groups. This could possibly lead to different dosing strategies depending on the age and body surface area of the patient with ovarian cancer upon presentation.

The estimated coefficients given in the above table were used to predict response for both the 112 Topotecan patients on Study 039 and the 110 (some patients had missing values of the prognostic factors required to classify them as either a predicted response or not) Topotecan patients on Study 034. When doing so, we used 30% as a cut-off for predicted probability of responding. That is, if the model predicted a probability of responding of 30% or better, then the patient in question was predicted to be a responder. This cut-off was somewhat arbitrary, and relied on some judgement. The rationale was that this was a round number which gave roughly the same number of predicted responders as observed responders (29 vs. 22).

The predicted probability of response was $\exp(X'B)/[1+\exp(X'B)]$, where X is the vector of values for the particular patient for each of the eight variables in the above table, and B is the set of estimated coefficients for these eight variables. Of the 112 Topotecan patients from Study 039, 29 were predicted responders and 83 were not. Of the 29 who were, 15 responded, for a response rate (in this selected population) of 52%. In the 83 who were not, seven responded, for a response rate of 8%. Overall, there were 22 responders out of 112, for a response rate of almost 20%. This information is summarized in Reviewer's Table A1.

Reviewer's Table A1: The Screen for Responders Based on 039 Data Applied to 039 Data			
	No Actual Response	Actual Response	Total
Not Predicted Response	76	7	83
Predicted Response	14	15	29
Total	90	22	112

While a 52% response rate certainly seems impressive, recall that this was self-validation, because the model was tested on the same data from which it was derived. A better assessment of the performance of the model comes from cross-validation by checking its ability to predict response in Study 034. Of course, all of the patients on Study 034 received Topotecan, which was coded as DRUG=0. Thus, the drug term, as well as all interactions (which are products involving the drug term), would have no effect on these predictions. This leaves only days since last chemotherapy, number of baseline lesions, and body surface area in the model.

Of the 110 patients from Study 034 who were classified as likely to respond or not, 30 were predicted responders and 80 were not. Of the 30 who were, 12 responded, for a response rate (in this selected population) of 40%. In the 80 who were not, three responded, for a response rate of under 4%. Overall, there were 15 responses out of 110, for a response rate of almost 14%. This information is summarized in Reviewer's Table A2.

Reviewer's Table A2: The Screen for Responders Based on 039 Data Applied to 034 Data			
	No Actual Response	Actual Response	Total
Not Predicted Response	77	3	80
Predicted Response	18	12	30
Total	95	15	110

Among the 15 responders in Study 034, the mean days since prior chemotherapy was 179,

while this mean was only 79 for the 95 non-responders. This striking difference should be interpreted cautiously, as mentioned above. Other means appear in Reviewer's Table A4. It is notable that the responders actually had more baseline lesions, on average, than the non-responders (2.2 vs. 1.6), even though this quantity figured into the model for predicting response probabilities in the reverse direction. That is, more baseline lesions was associated with a lower predicted probability of response. Thus it seemed prudent to re-run the original logistic regression but without the term for the number of baseline lesions. The result appears in Reviewer's Table A5.

It seems preferable to leave the number of baseline lesions in the model. However, in some cases this may be difficult to assess. In such cases the model is still useful. Instead of using the numbers in Reviewer's Table A3, with a zero for the number of lesions, one would use the numbers in Reviewer's Table A3. In fact, one could substitute a 0 or a 1 for drug (as well as the interactions) and predict success for the patient under either regimen (Topotecan or Taxol).

The estimated coefficients, p-values (for testing that the coefficient is zero), and odds ratios for predicting response by logistic regression are given in Reviewer's Table A3. The estimated coefficients are given to as many places as SAS gave, as they were used in the prediction equation and we did not want rounding error to affect the prediction.

Reviewer's Table A3: Logistic Regression (SAS) to Predict Response

Variable	Estimated Coefficient	p-value	Estimated Odds Ratio
Intercept	-1.8017	0.5746	0.165
Days Since Last Chemotherapy	-0.0310	0.0001	0.969
Number of Baseline Lesions	0.4780	0.0589	1.613
Body Surface Area (m-squared)	3.5480	0.0628	34.743
Drug (0=Topotecan, 1=Taxol)	104.9000	0.0090	999.000
Drug*Age	-2.9587	0.0180	0.052
Drug*Body Surface Area	-8.4944	0.0048	0.000
Drug*Age*Age	0.0239	0.0180	1.024

Means of prognostic factors, for both responders and non-responders, appear in Reviewer's Table A4.

Reviewer's Table A4: Means for Responders and Non-responders On Study 034		
	Non-responders (n=95)	Responders (n=15)
Age	56 years	63 years
Days Since Prior Chemotherapy	79 days	179 days
Body Surface Area	1.68	1.74
Number of Baseline Lesions	1.6	2.2
Predicted Probability of Responding	17%	49%

The original logistic regression model, but without the term for the number of baseline lesions, was tested. The result appears in Reviewer's Table A5.

Reviewer's Table A5: Logistic Regression (SAS) to Predict Response Without the Number of Baseline Lesions Study 039			
Variable	Estimated Coefficient	p-value	Estimated Odds Ratio
Intercept	0.5638	0.8503	1.757
Days Since Last Chemotherapy	-0.0278	0.0001	0.973
Body Surface Area	2.4917	0.1682	12.082
Drug	109.7000	0.0083	999.000
Drug*Age	-3.1946	0.0132	0.041
Drug*Body Surface Area	-7.3331	0.0106	0.001
Drug*Age*Age	0.0259	0.0128	1.026

The only effects which seemed to be drastically changed from the original model were the intercept and the body surface area. Using this new model to predict response, and still using the cutoff at 30%, we predict that 25 of the 112 Topotecan patients on the 039 study would respond. Of these, 13 actually did respond, for a 52% response rate. Of the 87 thought not to have a high chance for response, nine responded, for a response rate of 10%. This information appears in Reviewer's Table A6.

Reviewer's Table A6: The Screen for Responders
Based on 039 Data
Applied to 039 Data (Topotecan)
Without the Number of Baseline Lesions

	No Actual Response	Actual Response	Total
Not Predicted Response	78	9	87
Predicted Response	12	13	25
Total	90	22	112

To predict response in patients from the 034 study, we are now using only days since last prior chemotherapy and body surface area. Using this new model to predict response, and still using the cutoff at 30%, we predict that eight of the 110 patients on the 034 study would respond. Of these, 3 actually did respond, for a 38% response rate. Of the 102 thought not to have a high chance for response, 12 responded, for a response rate of 12%. This information appears in Reviewer's Table A7.

Reviewer's Table A7: The Screen for Responders
Based on 039 Data
Applied to 034 Data
Without the Number of Baseline Lesions

	No Response	Response	Total
Not Predicted Response	90	12	102
Predicted Response	5	3	8
Total	95	15	110

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micro

Letter to
APR - 3 1996

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 2 of an Amendment to NDA 20-671
April 2, 1996

A. 1. **APPLICATION NUMBER:** 20-671 BI

APPLICANT: SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

2. **PRODUCT NAMES:** Hycamtin, topotecan hydrochloride for injection.

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 4 mg and 5 mg vials of sterile lyophilized powder. The reconstituted drug is to be administered by intravenous infusion.

4. **METHOD(S) OF STERILIZATION:** The drug product is filled and lyophilized.

5. **PHARMACOLOGICAL CATEGORY:** Anti-neoplastic, for treatment of ovarian cancer after of first-line or subsequent chemotherapy.

6. **DRUG PRIORITY CLASSIFICATION:** 1P

B. 1. **DATE OF INITIAL SUBMISSION:** December 21, 1995

2. **AMENDMENT:** March 5, 1996 (Subject of this review)

3. **RELATED DOCUMENTS:** INDs:
DMFs:

4. **RECEIVED FOR REVIEW:** March 20, 1996

5. **DATE OF CONSULT REQUEST:** March 18, 1996

C. **REMARKS:**

The current amendment responds to the questions from the microbiologist with regard to the deficiencies in NDA 20-671. All the questions have been addressed and the answers are satisfactory.

D. CONCLUSIONS:

The application is recommended for approval on the basis of sterility assurance.

Brenda Uratani 4/2/96

Brenda Uratani, Ph.D.

PHC 4/3/96

cc:

NDA 20-671, Minor Microbiology Amendment
HFD-150 /Div. File
HFD-805 /Uratani
HFD-150 /CSO/D. Catterson
drafted by: Brenda Uratani, 4/2/96
R/D initialed by P.Cooney, 4/2/96

FEB 20 1996

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of NDA 20-671
February 20, 1996

A. 1. **APPLICATION NUMBER:** 20-671

APPLICANT: SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

2. **PRODUCT NAMES:** Hycamtin, topotecan hydrochloride for injection.

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 4 mg and 5 mg vials of sterile lyophilized powder; the reconstituted drug is to be administered by intravenous infusion.

4. **METHOD(S) OF STERILIZATION:** The drug product is filled and lyophilized.

5. **PHARMACOLOGICAL CATEGORY:** Anti-neoplastic, for treatment of ovarian cancer after failure of first-line or subsequent chemotherapy.

DRUG PRIORITY CLASSIFICATION: 1P

B. 1. **DATE OF INITIAL SUBMISSION:** December 21, 1995

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:** INDs:
DMFs:

4. **RECEIVED FOR REVIEW:** January 30, 1996
Date of Consult Request: January 19, 1996

C. **REMARKS:**

Topotecan hydrochloride for injection, a single use parenteral formulation, is produced as a sterile lyophilized powder and contains no preservatives. It is a derivative of camptothecin, a specific inhibitor of mammalian topoisomerase-I with demonstrated anti-tumor activity. The drug product is to be manufactured by SmithKline Beecham facility in Conshohocken, PA. Bacterial endotoxin testing is to be carried by the

and sterility testing is to be performed by

D. CONCLUSIONS:

The submission does not contain sufficient information to assure the sterility and safety of the drug product. The results provided were too abbreviated. The NDA also lacks specific validation data and methodologies. The submission is, therefore, not recommended for approval as submitted. The sponsor should be provided with a copy of the FDA's "Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products". Specific comments are provided in "Review Notes" and in the "Microbiologist's Draft Letter to Applicant".

Brenda Uratani 2/20/96

Brenda Uratani, Ph.D.

2/24/96

cc:

NDA 20-671
HFD-150/Div. File
HFD-805 /Uratani
HFD-150/CSO/Catterson
drafted by: Brenda Uratani, 2/20/96
R/D initialed by P.Cooney, 2/20/96

Chem

DIVISION OF ONCOLOGY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-671 **CHEM.REVIEW #:** 02 **REVIEW DATE:** 23-May-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	29-Mar-96	03-Apr-96	15-Apr-96
Amendment	29-Apr-96	30-Apr-96	01-May-96

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharceuticals
Four Falls Corporate Center
Rt. 23 and Woodmont Avenue
King of Prussia, PA 19406

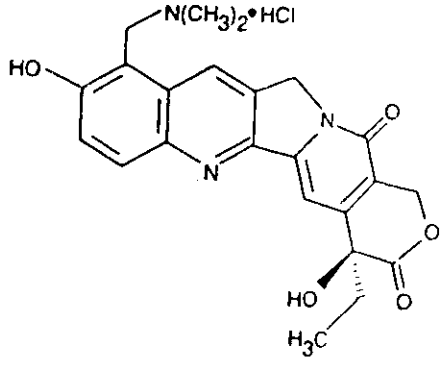
DRUG PRODUCT NAME

Proprietary:	Hycamtin™
Nonproprietary/USAN:	Topotecan Hydrochloride
Code Name/#:	SK&F-104864-A
Chem.Type/Ther.Class:	1 P/neoplastic

PHARMACOL.CATEGORY/INDICATION: - Metastatic carcinoma of the ovary

DOSAGE FORM: Sterile lyophilized powder for injection
STRENGTHS: 4 mg
ROUTE OF ADMINISTRATION: Intravenous Infusion
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



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

Indolizino[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride

Molecular Formula: $C_{23}H_{23}N_3O_5$-HCl
Molecular Weight: 457.91 (hydrochloride salt), 421.45 (free base)
CAS Number: 119413-54-6 (hydrochloride salt), 123948-87-8 (free base)

RELATED DOCUMENTS (if applicable):
DMF

CONSULTS:

Consult	Status	Comments
EER	Completed	
Methods Validation	Hold	
Microbiology	Completed	
Statistics	Completed	
Environmental Ass.	Completed	

REMARKS/COMMENTS: The amendments adressed the CMC deficiencies listed in an Information Request communicated to the applicant on April 23, 1996. Most of the deficiencies in the original NDA have been resolved. However, the applicant failed to provide adequate stability data to justify the reduced testing frequency of the proposed stability study protocol for annual stability study of future production batches of the drug substance under long-term storage conditions (See comment to question I. (5) in Review Notes). The proposed stability study protocol needs to be amended.

Deficiencies in DMF (providing for an alternate source of purified were responded in DMF amendments dated April 30, 1996 and May 10, 1996 from the DMF holder The DMF holder has as yet to submit a copy of the master production record in English. A copy of the master production record in Spanish is available and the holder has committed that an English version of the master production record will follow.

The firm has specified that the drug product is to be stored between 15° and 30°C in the labellings [See the firm's response to Question III. (1) B in Review Notes]. For storage at 30°C, the allowed shelf life of the drug product is 13 months [See Statistical Review and Evaluation (dated May 20, 1996)].

CONCLUSIONS & RECOMMENDATIONS: It is recommended that the NDA may be approved if the applicant commits to (1) amend the proposed stability study protocol for the anuual stability studies of future production batches of the drug substance and (2) assure that a copy of the master production record in English is provided by the DMF holder to the Agency in a reasonable time frame

Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

RHWood 5-26-96
Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

cc:
Orig. NDA 20-671
HFD-150/Division File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/DCatterson

APR 23 1996

DIVISION OF ONCOLOGY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-671 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 22-Mar-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	21-Dec-95	22-Dec-95	04-Jan-96

NAME & ADDRESS OF APPLICANT: SmithKline Beecham Pharceuticals
Four Falls Corporate Center
Rt. 23 and Woodmont Avenue
King of Prussia, PA 19406

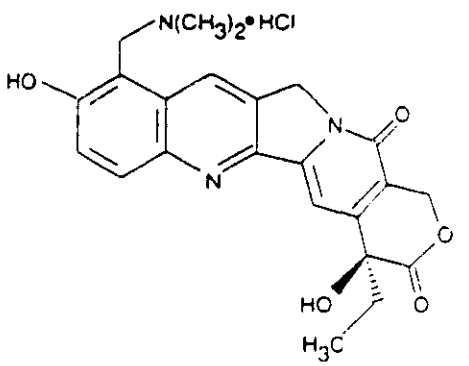
DRUG PRODUCT NAME

Proprietary:	Hycamtin™
Nonproprietary/USAN:	Topothecan Hydrochloride
Code Name/#:	SK&F-104864-A
Chem.Type/Ther.Class:	1 P/neoplastic

PHARMACOL.CATEGORY/INDICATION: - Metastatic carcinoma of the ovary

DOSAGE FORM: Sterile lyophilized powder for injection
STRENGTHS: 4 mg
ROUTE OF ADMINISTRATION: Intravenous Infusion
Rx/OTC: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



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 Weight: 457.91 (hydrochloride salt), 421.45 (free base)

CAS Number: 119413-54-6 (hydrochloride salt), 123948-87-8 (free base)

RELATED DOCUMENTS (if applicable):
DMF

CONSULTS:

Consult	Status	Comments
EER	Pending	
Methods Validation	Hold	Methods may require modification
Microbiology	Pending	
Statistics	Pending	
Environmental Ass.	Pending	

REMARKS/COMMENTS: Topotecan is a semi-synthetic drug substance. The starting material, crude is obtained from suppliers. The crude purified in the first step of the synthesis. An alternate source of purified is The material is extracted and purified in their facility in and released by analytical laboratory in A uniform specification is established for acceptance of purified camptothecin, which may be manufactured by SmithKline Beecham (SB) or purchased from

The drug substance was synthesized in

DMF for the alternate source of purified was reviewed. A Deficiency Letter was issued to the DMF holder on March 14, 1996.

The ^{1}H NMR(DMSO-d_6) of topotecan hydrochloride appears to suggest a strong intramolecular hydrogen bonding between the 10-OH and 9-(dimethylamino)methyl function. This intramolecular hydrogen bonding, through protonation of the dimethylamino nitrogen, promotes the degradation of topotecan. For example, in the presence of residual water and n-propanol (it was recrystallized from aqueous n-propanol), topotecan hydrochloride degrades to 9-propoxymethyl-10-hydroxycamptothecin (SB 223932) and 9-hydroxymethyl-10-hydroxycamptothecin (SK&F S-107564) on storage and SB 223932 was observed to convert into its hydroxy analogue, SK&F S-107564 through the protonation of the propoxy oxygen atom via the intramolecular hydrogen bonding. A second degradation pathway of topotecan hydrochloride is photooxidation. The proposed drug substance specification is validated by the batch analysis data of topotecan hydrochloride used in preclinical and clinical studies.

Most of the degradant levels in the drug product are reasonably well controlled by the proposed specification; however, we are concerned with the elevated level of the photooxidixed product, SB 211307 allowed in the drug product.

Four different formulations of topotecan hydrochloride have been used in clinical trials; although the formulation of the 4 mg commercial product has not been tested, the 5 mg vials of equivalent quantitative composition have been studied in Phase I, II and III trials. This deficiency was consulted to medical and pharmacology reviewers.

The proposed expiration date of the drug product of 24 months under recommended storage conditions, based on the regression analysis of the stability data of validation batches of 4 mg and 5 mg vials, is consulted to HFD-710 for review.

CONCLUSIONS & RECOMMENDATIONS: The deficiencies which are listed in the Draft Information Request should be communicated to the applicant. It is recommended that all the deficiencies should be fully addressed prior to approval.

Yung-Ao Hsieh 3-22-96
Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

RHWood 4-23-96
Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

cc:
Orig. NDA 20-671
HFD-150/Division File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/DCatterson

E.A. and FONSI

ORIGINAL

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

HYCAMTIN™

(Topotecan Hydrochloride)

Injection (4 and 5 mg lyophilized vials)

NDA 20-671

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Oncologic Drug Products
(HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-671

Hycamtin™

Topotecan Hydrochloride

Injection (4 and 5 mg lyophilized vials)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Hycamtin™, SmithKline Beecham Pharmaceuticals has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a), (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product.

Topotecan hydrochloride is a semisynthetic drug which is administered as an injection in the treatment of ovarian cancer. The drug substance will be manufactured at SmithKline Beecham (Manufacturing) Limited, Currabinny, Carrigaline, County Cork, Ireland. The drug product will be manufactured at SmithKline Beecham Pharmaceuticals, Building 16A, 801 River Road, Conshohocken, Pennsylvania, USA. The finished drug product will be used in hospitals and clinics.

The manufacture of semisynthetic topotecan hydrochloride starts with purified or crude Camptothecan, which is obtained from the fruit of the *Camptotheca acuminata* tree and the wood of the *Nothapodytes foetida* tree. Neither of these species are found in Appendix I-III of the "Convention on International Trade in Endangered Species of Wild Fauna and Flora" or 50 CFR Chapter I of the US Fish and Wildlife Service. The Environmental Assessment provides sufficient reports and information to support the proposition that harvesting will not have a detrimental impact.

Topotecan hydrochloride may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Chemical and physical test results indicate that Topotecan hydrochloride will most likely be predominantly in the aquatic environmental compartment and will undergo both hydrolytic and photolytic degradation.

The predicted No Environmental Effect Concentration (NOEC), based on toxicity data, is considerably higher than the estimated Maximum Expected Environmental Concentration (MEEC), suggesting no adverse impact.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/24/96
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

4/24/96
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
(Material Safety Data Sheet for drug substance included)

Copies:

HFD-150
YUNG AO HSIEH, chemist
Debra Catterson, CSO
Original NDA
Division File for NDA

HFD-205

FOI Copy

HFD-357

EA File
Docket File
C. Berninger 4/23/96, 4/23/96

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

1. **DATE:** 17 November 1995

2. **NAME OF APPLICANT:** SmithKline Beecham Pharmaceuticals
P.O. Box 7929
One Franklin Plaza
Philadelphia, PA 19102

3. **ADDRESS:** SmithKline Beecham Pharmaceuticals

4. **DESCRIPTION OF THE PROPOSED ACTION:**

4.1 Description of the Requested Approval

SmithKline Beecham Pharmaceuticals is requesting approval to manufacture, package and market Hycamtin™ (topotecan hydrochloride) for Injection for the treatment of ovarian cancer. Topotecan hydrochloride (SK&F S-104864-A) is a water soluble analog of camptothecin and a reversible inhibitor of mammalian topoisomerase I. Topotecan hydrochloride has anti-tumor activity in a variety of animal tumor models and is efficacious when administered by the intravenous route. Hycamtin™ will be prepared as 4 mg and 5 mg lyophilized vials. Topotecan hydrochloride will be administered at 1.5 mg/m^2 by IV infusion over 30 minutes daily for 5 consecutive days every three weeks.

4.2 Need for the Proposed Action

The therapeutic indication for Hycamtin™ (topotecan hydrochloride) for Injection is for the treatment of metastatic ovarian cancer in patients who have failed previous therapy. In preclinical models, topotecan hydrochloride has demonstrated activity (tumor growth inhibition, tumor growth delay, or increased lifespan) in rapidly proliferating murine leukemias, yet also has activity against transplantable solid tumors of diverse histotype and growth rate. Its broad spectrum of activity extends to sublines of chemosensitive tumors with acquired multi-drug resistance. The unique mechanism of action for topotecan hydrochloride and lack of cross resistance with other current treatment may provide therapeutic advantage over currently available anti-neoplastic agents as second-line therapy following tumor regrowth.

This Environmental Assessment reflects effluent discharges based on estimated production of drug substance and product during the 5th year of production, as well as detailed information on the waste treatment and disposal processes at SmithKline Beecham (Manufacturing) Limited in Cork (Ireland) for drug substance production, and SmithKline Beecham Pharmaceuticals, Conshohocken, PA (US) for drug product production.

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

The manufacture of topotecan hydrochloride drug substance and product will take place at SmithKline Beecham facilities that are also currently manufacturing other pharmaceutical products.

4.3 Locations where Drug Substance will be Produced

Topotecan hydrochloride, the drug substance in the product which is the subject of the proposed action, is manufactured in four process stages from crude camptothecin, or three process stages from purified camptothecin.

Purified camptothecin is expected to be purchased from SmithKline Beecham's principal supplier, produced at the facilities listed below. This purified camptothecin is entered into the topotecan hydrochloride synthetic process at the SmithKline Beecham (Manufacturing) Limited site.

The topotecan hydrochloride manufacturing facility is described below.

4.3.1. Cork, Ireland

SmithKline Beecham (Manufacturing) Limited
Currabinny, Carrigaline
County Cork, Ireland

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is located approximately twelve miles south of Cork City on the southern shores of Cork Harbor. There is a total landbank of 130 acres, but the facility occupies only 28 acres. The immediate area is rural, with some farms and dwellings within a half mile radius of the boundary fence. The site discharges an aqueous waste into Cork Harbor after on-site biological treatment.

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

4.4 Location where Drug Product will be Produced

4.4.1. Conshohocken, Pennsylvania, US

Hycamtin™ (topotecan hydrochloride) for Injection (4 mg and 5 mg vials) is manufactured and packaged at the following facility:

SmithKline Beecham Pharmaceuticals
Building 16A - Containment Facility
801 River Road
Conshohocken, PA 19428
United States

The Building 16A - Containment Facility (hereafter referred to as Building 16A) is located within a larger production building - a "building within a building" - located in an industrial/residential area of Conshohocken, PA. The facility is bordered on the east by River Road (PA Route 23) and the Lonza Inc. chemical plant; on the south and west by the SmithKline Beecham, Research and Development complex; and on the north by Swedeland Road (PA Route 320) and small commercial businesses and private residences. All aqueous discharges from Building 16A are directed to a deactivation system prior to discharge to the process waste system and SmithKline Beecham waste water treatment facility. Discharge streams are deactivated by chemical reaction, and by using an advanced oxidation process (involving ultraviolet light and hydrogen peroxide) prior to discharge from the facility.

4.5 Locations where Product will be Used

The subject of this Environmental Assessment is the use of Hycamtin™ in the United States of America. Predominant use is expected to coincide with areas of greatest population density.

4.6 Locations where Product will be Disposed of

All Hycamtin™ returned goods will be collected at the following site:

From this site, the materials will be shipped to the following licensed facilities for disposal (e.g., destruction by high temperature incineration).

SmithKline Beecham Pharmaceuticals
Bristol Industrial Park
Weaver Pike
Bristol, Tennessee 37620

Documentation for these disposal facilities is provided in Appendix I.

5. DESCRIPTION OF CHEMICAL SUBSTANCE THAT IS THE SUBJECT OF THE PROPOSED ACTION:

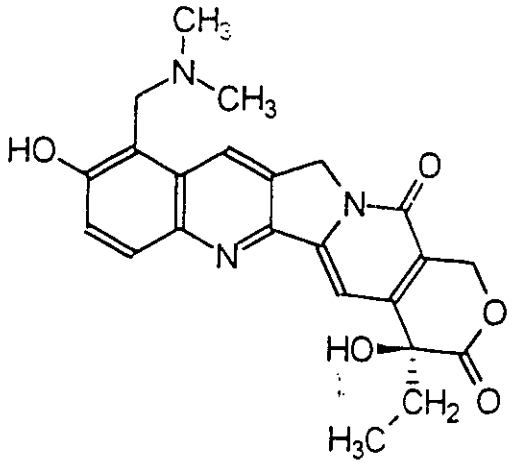
Topotecan hydrochloride drug substance is described below. The components used in the manufacture of the drug substance and their CAS registry numbers are listed in Confidential Tables 1 and 8 (for Cork). The components (and their CAS registry numbers) used in the manufacture of the drug product (at Conshohocken) are listed in Confidential Table 15. The environmental fate and effects of topotecan hydrochloride itself, which is considered to represent the "worst-case" scenario in terms of any potential for environmental impact, is described in Items 7 and 8 of this assessment.

5.1 Complete Nomenclature for Topotecan Hydrochloride:

BAN, USAN, INN:	Topotecan Hydrochloride
Chemical Name:	(*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
5.1.1 CAS Number:	119413-54-6 123948-87-8 (free base)
5.1.2 Laboratory Code:	SK&F S-104864-A (hydrochloride salt)
5.1.3 Molecular Formula:	$C_{23}H_{23}N_3O_5 \cdot HCl$

5.1.4. Molecular Weight: HCl salt: 457.91
free base: 421.45

5.1.5. Structural Formula:



5.1.6. Description: Yellow to yellow-orange solid
5.1.7. Melting Point Range: Melts with decomposition at 213-218°C
5.1.8. Additives: Not applicable
5.1.9. Impurities:

Organic impurities arising from the synthesis are determined by HPLC. Solvent content is measured by GC and the inorganic impurities (heavy metals and residue on ignition) are monitored by USP methods. Identification is included on the drug substance specification. Topotecan hydrochloride must be protected from light, and no degradants are likely to arise under normal storage conditions (<5°C, protected from light).

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

6.1 Introduction from Production of Substances

6.1.1 Introduction from Production of Purified Camptothecin (Purchased Intermediate)

Purified camptothecin is produced by For details on the preparation of camptothecin at facilities, please refer to Drug Master File for camptothecin, which was filed with the FDA on October 18, 1995. is expected to remain in compliance with applicable permits and regulations during the production of camptothecin.

6.1.2 Introduction from Purification of Camptothec... and Production of Topotecan Hydrochloride (Drug Substance) at Cork, Ireland

Production of topotecan hydrochloride (drug substance) will be carried out at SmithKline Beecham (Manufacturing) Limited, Cork, Ireland, using purified camptothecin prepared by and/or using crude camptothecin purchased from suppliers and purified at the Cork facility. All data tables for drug substance production at Cork, Ireland, are presented in Confidential Attachment 3. Environmental evaluations of the impacts from purification and drug substance production follow.

All processes will take place in a newly constructed facility, built specially for the production of topotecan hydrochloride. The facility utilizes control equipment, such as glove boxes, closed process equipment (open only to glove boxes) and HEPA air filters, to minimize exposure to personnel. The following evaluations of the anticipated environmental impact of topotecan hydrochloride production are based on estimates of maximum daily production and on existing waste treatment systems at Cork. Engineering estimates are used to predict anticipated discharge levels; however, the evaluations do not reflect any changes in treatment process operations or technology which might be implemented before actual approval of the application.

SmithKline Beecham (Manufacturing) Limited, Cork, Ireland, is expected to remain in compliance with applicable waste effluent permits throughout the production of topotecan hydrochloride drug substance. The Cork facility is regulated under an Integrated Pollution Control (IPC) license (Reference Number in Register of Licenses: 4; License issued on December 6, 1994), under authority of the Irish Environmental Protection Agency and the Environmental Protection Agency Act, 1992. This license contains permit levels and monitoring procedures for all site emissions (wastewater, air, incinerators, etc.), as well as

guidelines for the establishment of an Environment Management Programme, to assess all operations for the use of cleaner technology and the minimization of waste.

6.1.2.1. Waste Stream Summary and Disposition

The input chemicals (for overall production and per process stage) for topotecan hydrochloride production are listed in Confidential Tables 1 and 2. The types and amounts of wastes generated during topotecan hydrochloride production are given in Confidential Tables 3, 4A, 4B, 4C, and 4D. The waste streams generated at SmithKline Beecham (Manufacturing) Limited will be disposed of such that release into the environment (on-site and/or off-site disposal) will not exceed site permit levels (see Appendix II). The current disposition of all topotecan hydrochloride process waste streams along with a future disposition scenario are presented in Confidential Table 5.

6.1.2.2. Material Balance

Material balance information for the chemical inputs, process intermediates and effluents was determined, thus accounting for all materials and amounts used in or produced by the process. Waste outputs include leftover material resulting from production, and assay solutions sampled before and after filtration.

6.1.2.3. Controls Exercised on Wastes

1.2.3.1. Air and Off-Gases

The production site buildings at SmithKline Beecham (Manufacturing) Limited vent approximately 102,500 m^3 of air per hour. Air from the buildings where chemical processes are performed flows through two scrubbers. As it is discharged to the atmosphere, air is monitored by gas chromatography (and other methods) for several compounds. Fugitive emissions are monitored if there is reason to suspect a gaseous leak.

6.1.2.3.2. Incinerated Wastes

Most topotecan hydrochloride waste streams are currently sent off site for incineration. All disposal contractors are audited by SmithKline Beecham. Nonetheless, Cork's incinerators are described below, since a future disposition scenario (see Confidential Table 5) may include their use.

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

At the Cork facility, topotecan hydrochloride process wastes are planned to be detoxified prior to on-site incineration, in order to limit exposure as well as to meet incineration permit requirements of the local and regional authorities. There are three high-temperature natural-gas fired incinerators on site: two caloric down-fired units, and one hygrotherm horizontal unit. Only those wastes arising from the manufacture on-site of pharmaceutical active ingredients and intermediates shall be incinerated on-site. The manufacturing wastes could be organic solvents and residues from production operations, or aqueous wastes contaminated with solvents, salts and residues, or gas streams containing organic and inorganic gases or contaminated air.

At discharge, gases from the site's incinerators are continuously monitored for CO and total organic carbon (TOC). Individual incinerators are also monitored for sulphur dioxide (SO_2) or hydrochloric acid (HCl). The incinerators emissions are scrubbed with a caustic scrubber and the scrubber liquor is sent to the biotreatment facility. Liquid process effluents are usually stored prior to incineration.

6.1.2.3.3 Biotreatment System

None of the wastes from the topotecan hydrochloride process are treated in the on-site wastewater biotreatment facility (see Confidential Table 5 in Confidential Attachment 3). The incinerator caustic scrubber liquor is usually treated in the on-site biotreatment facility

The biotreatment facility incorporates a 6300 m^3 basin of activated sludge, which has a retention time of approximately 20 days. The waste to be biotreated (including sanitary effluents, floor washes, incinerator quench streams, scrubber liquor, and environmental spent liquors) is sent to an equalization tank prior to neutralization in a second tank. The wastes are then sent to the aeration basin. After aeration, the waste is sent to a clarifier. The clarifier is dosed with polyelectrolytes, and the clarified effluent is then sent to a dissolved air flotation (DAF) plant, and then to the disposal pipeline. Effluent wastes are then sent to the final holding tank prior to discharge. The treated liquid effluent is disposed of via pipeline into Cork Harbour. The sludge generated at the biotreatment facility is mechanically dewatered prior to off-site disposal to a landfill.

Several parameters of the effluent are monitored on a continuous or daily basis, such as inlet and outlet flows, pH, TDS and COD. The levels of several metals are also monitored, on a monthly or annual basis. Fish toxicity tests are also performed, twice per year.

6.1.2.3.4. Solid Waste

Spent solid waste from topotecan hydrochloride production is sent off-site for incineration or/and recovery (see Confidential Table 5). There are currently no limits as to the amount of solid wastes disposed of off-site. All SB disposal contractors are audited by SmithKline Beecham.

6.1.2.4. Certification of Compliance

SmithKline Beecham (Manufacturing) Limited, Cork (Ireland) is committed to environmental control and will operate within its permits during production of topotecan hydrochloride drug substance. A citation of and statement of compliance with applicable emissions requirements is provided in Appendix II.

6.1.3 Introduction from Production of Hycamtin™ in Conshohocken, PA

Hycamtin™ manufacturing will take place in the SmithKline Beecham Pharmaceuticals, Building 16A - Containment Facility in Conshohocken, Pennsylvania, US The newly constructed facility is housed within a larger, existing production facility - a "building within a building" design configuration. All tables for topotecan hydrochloride drug product manufacturing at Conshohocken, PA are located in Confidential Attachment 4. An inspection of Building 16A has been carried out by FDA inspectors from the Philadelphia District Office in December 1994.

The following Hycamtin™ manufacturing operations will be carried out in Building 16A: component preparation, aseptic manufacturing, filling, lyophilization and stoppering, packaging, capping and vial washing. Material balances were developed around these operations based on calculations that assumed a 5% loss of the components making up the filling solution to equipment cleaning. This represents a worst case scenario since the 5% value also includes the weight of product lost to process samples (which do not become part of the aqueous waste streams). The following evaluations of the anticipated environmental impacts of Hycamtin™ production are based on estimated maximum daily production and on existing waste characteristics of aqueous waste water discharged from the entire SmithKline Beecham Research and Development complex at the site, to which Building 16A's aqueous waste is discharged prior to pretreatment and discharge to the Upper Merion Township POTW.

Based on the following evaluations, Building 16A is expected to remain in compliance with its Upper Merion Township Wastewater Discharge Permit during production of Hycamtin™ for Injection

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

6.1.3.1. Waste Stream Summary and Disposition

A list of the input chemicals and quantities used in Hycamtin™ manufacturing are presented in Confidential Tables 6 and 7. Amounts presented in Table 7 are representative of a typical batch production of 4 mg Hycamtin™ vials. A summary of the types and quantities of waste generated from manufacturing operations are presented in Confidential Tables 8 and 9 The waste streams generated from drug product manufacturing operations will be disposed of using appropriate procedures, such that release into the environment (as aqueous waste, considering a loss of 5% from process sampling and equipment cleaning) should not exceed the manufacturing facility's aqueous waste permit levels. All waste disposal contractors used for Building 16A are audited by SmithKline Beecham Pharmaceuticals.

6.1.3.2. Controls Exercised on Wastes

The main control governing the disposition of aqueous waste from Hycamtin™ manufacturing operations is the Upper Merion Township Wastewater Discharge Permit.

6.1.3.2.1.Aqueous Wastes

Dilute aqueous waste from Hycamtin™ manufacturing operations is collected in a 2,000 gallon holding tank and passed through an ultraviolet light and hydrogen peroxide deactivation system to destroy any topotecan that may be present in the facility waste. Waste discharged from this deactivation system is combined with the waste effluent from the adjacent SmithKline Beecham Research and Development complex, pretreated at the on-site pretreatment facility and discharged to the Upper Merion Township sewer system for treatment at the public owned treatment works (POTW). SmithKline Beecham must comply with the monitoring requirements set forth in its Upper Merion Township Industrial Wastewater Discharge Permit.

Estimates of the Total Suspended Solids (TSS), Total Dissolved Solids (TDS), Chemical Oxygen Demand (COD) and Biological Oxygen Demand (BOD) contributions to aqueous waste discharged from the Hycamtin™ manufacturing facility are presented in Confidential Table 10. An evaluation of the potential impact of these parameters on compliance with the Upper Merion Township, Industrial Wastewater Discharge Permit has been included in Confidential Table 11.

Review of projected fifth year production requirements (Confidential Table 12), calculated aqueous waste effluent parameters and a comparison with the industrial wastewater discharge permit levels resulted in the determination that SmithKline Beecham Pharmaceuticals will continue to meet its effluent permit criteria and remain in compliance

with applicable emissions requirements during Hycamtin™ manufacturing operations at Conshohocken, PA.

6.1.3.2.2 Solid Waste

Spent solid waste from Hycamtin™ production is sent off-site for disposal. There are currently no limits as to the amount of solid wastes disposed of off-site. All SmithKline Beecham disposal contractors are audited by SmithKline Beecham.

6.1.3.3 Safety

Building 16A operates under both site and departmental emergency procedures. Plant operators are trained under an established training plan, and a personal training record is maintained for each operator.

Disposable protective coveralls, overshoes, hats and gloves together with appropriate respirators are worn by site personnel when manufacturing drug product. Care is taken to avoid creating excessive dust through the use of closed systems. Appropriate Standard Operating Procedures are followed for the use and cleaning of equipment and manufacturing areas.

A safety directive has been established for cleaning spills. In the locations where product is manufactured and handled, floor drains lead to a wastewater deactivation system which treats the spilled liquid with ultraviolet (UV) light and hydrogen peroxide. Spilled material is collected in accordance to spill control procedures. The material is disposed of using methods described in the Material Safety Data Sheet and the safety directive. Powder spills are cleaned using a Type H dedicated vacuum cleaner, and the collected material is disposed of by the same route as other solid waste materials.

6.1.3.4 Certification of Compliance

SmithKline Beecham Pharmaceuticals, Building 16A - Containment Facility, Conshohocken, PA (US) will operate within its permits during the production of Hycamtin™ for Injection. A citation of and statement of compliance is provided in Appendix III Material Safety Data Sheets for Hycamtin™ and topotecan hydrochloride, and a summary of environmental fate and effects data for topotecan hydrochloride, are given in Appendix IV.

6.2 Introduction from Use of Drug Product

After administration of a Hycamtin™ dose, the vial and any remaining drug (as well as other medical waste, i.e. syringes, gauze, etc.) will be disposed of by the hospital physician using established procedures at the site. Medical waste would be expected to be disposed of using practices acceptable for potentially hazardous hospital wastes. Disposal by high-temperature incineration or by landfilling in a secured hazardous waste landfill are the expected disposal practices.

Incineration is the most widely used method for disposal of medical waste in the U.S., and many states have established requirements and guidelines that apply specifically to medical waste incinerators. According to data presented in the EPA Guide for Infectious Waste Management (1986), five states require that medical waste be incinerated, while the majority of states require that medical waste either be incinerated or landfilled [1].

For the purposes of determining potential environmental fate and effects, it is assumed that 100% of the applied topotecan hydrochloride dosage will be excreted into the environment as topotecan. This may be taken as a "worst case" scenario, since the toxicities of any metabolites or its carboxylate form (see Item 7.1) would be expected to be equal to or less than topotecan hydrochloride itself.

Estimates of the Maximum Expected Emitted Concentrations (MEEC) and the Predicted Environmental Concentrations (PEC) of topotecan from use of Hycamtin™ is given in Confidential Attachment 7. Analyses of the fate and effects of topotecan are presented in Item 7 and Item 8, respectively, of this assessment

6.3. Introduction from Disposal of Drug Product

Hycamtin™ returned goods will be collected and disposed of as described in Item 4.6 of this assessment. Based on the controlled and highly efficient thermal destruction of unused Hycamtin™, no significant amount of material should be introduced into the environment from disposal.

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

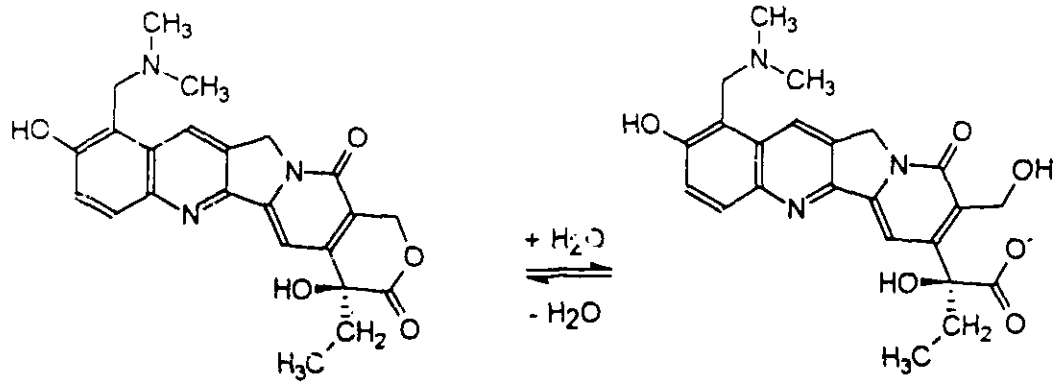
7.1 Metabolism and Hydrolysis

The only known metabolite of topotecan is the mono-N-desmethyl species, SB-209780. During *in vivo* metabolism studies with rats and dogs, this metabolite accounted for 3-4% and 16% of the dose, respectively. During recent *in vitro* studies with rat, dog, and human hepatic microsomes, the rate of metabolite production in human microsomes appeared to fall between the rates observed for rats and dogs (see reference [2], presented in Confidential Attachment 1). Thus the extent of biotransformation of topotecan hydrochloride in man is likely to be low.

SK&F S-104864-A (topotecan hydrochloride) undergoes a pH dependent, reversible hydrolysis reaction in aqueous solution (see figure below). The lactone species exhibits topoisomerase I activity while the carboxylate species does not [3]. The lactone species is favored at low pH while the carboxylate species is favored at high pH. The N-desmethyl metabolite is also known to undergo this reversible pH dependent hydrolysis [2].

Reversible Hydrolysis of Topotecan (SK&F S-104864-A).

SK&F S-104864 (lactone) SK&F S-105992 (carboxylate)



The following figure summarizes the equilibrium distribution of lactone (SK&F S-104864-A) and carboxylate (SK&F 105992) species as a function of pH; see reference [4]. A copy of this report may be found in the Chemistry, Manufacturing and Controls section (Item 3.A. Drug Substance) of this application. The equilibrium point, where the species are present in equal amounts, is at pH ~6.8. It is probable that both the parent compound and N-desmethyl metabolite are excreted at least partially in the carboxylate form.

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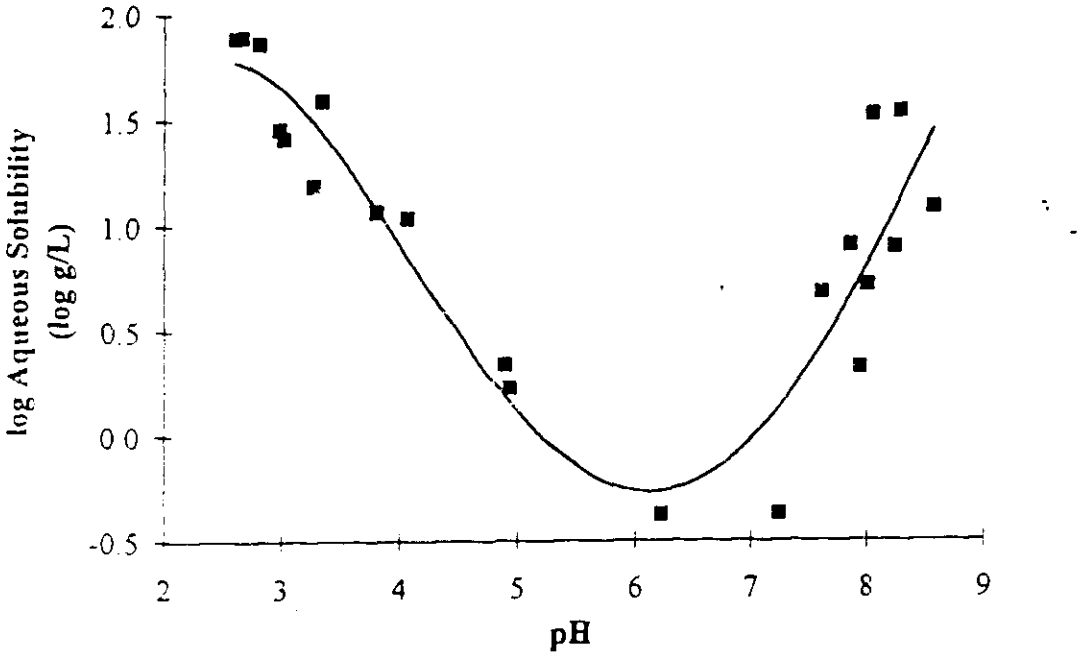
7.2.2 Aqueous Solubility

Aqueous solubility data for topotecan hydrochloride are summarized below [6], and a copy of the study report may be found in Confidential Attachment 1.



The solubility data approximate what would be predicted for a zwitterionic compound (the line in the solubility figure is an empirical fourth-order polynomial fitted curve). At the solubility minima at pH 6-7, the predominant species of topotecan is the neutral zwitterion. The solubility increases significantly towards either end of the pH range as anionic or cationic species become more predominant. Even at the solubility minima, topotecan is quite soluble (420 mg/L). The solubility data suggest that topotecan will be relatively mobile in the aquatic environment.

7.2.3. Octanol/Water Distribution Coefficients

Octanol/water distribution coefficients of topotecan hydrochloride were determined at three pH values in pH buffers of ionic strength 0.005 [4]. The experimental data are summarized below.

pH	Mean	Log Mean
5.1	0.60	-0.22
7.4	0.50	-0.30
9.3	0.26	-0.59

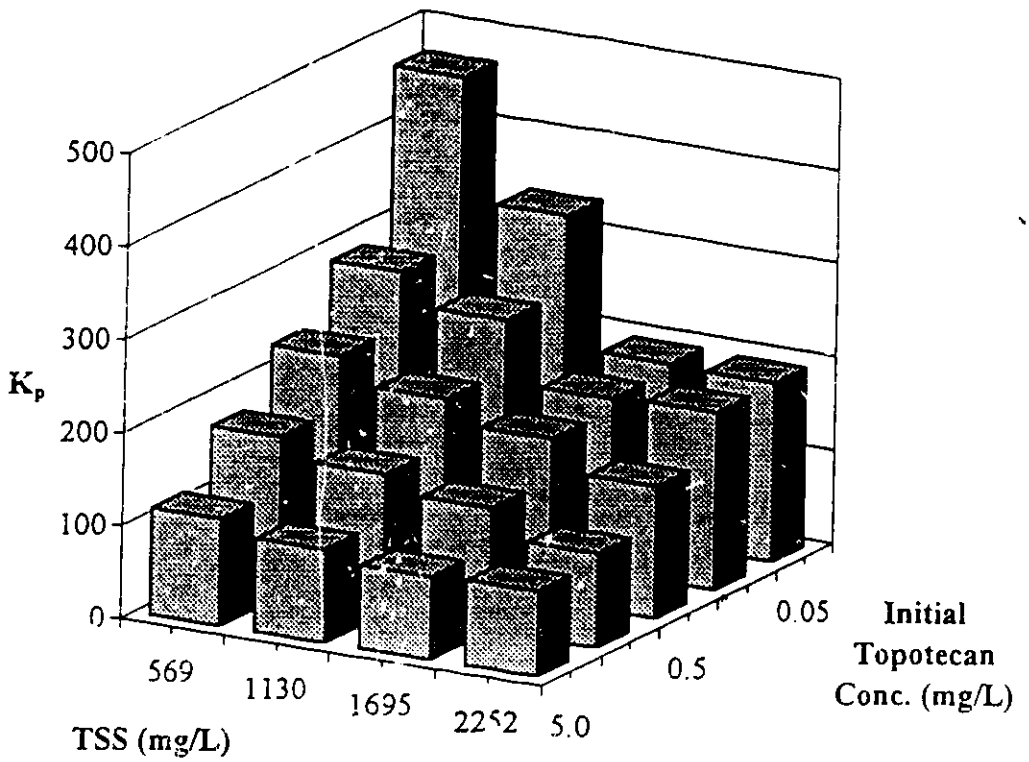
The octanol/water partition coefficient (Pow) cannot be calculated from the data since topotecan contains ionized functional groups across the entire pH range. The experimental data strongly suggest that the potential for topotecan to bioconcentrate or bioaccumulate is very low.

7.2.4. Activated Sludge Adsorption

Experiments were conducted to determine the rate and extent of adsorption of topotecan hydrochloride and ^{14}C-topotecan hydrochloride to authentic and lyophilized activated sludge solids [7]. A copy of the study report may be found in Confidential Attachment 1. During a preliminary experiment, the mean sludge/water distribution ratio (Kd) was 361 ± 14.3 mL/g (SD, N=3) after ~20 hours of contact. The sludge total suspended solids (TSS) concentration was 1800 ± 92 mg/L (SD, N=3), and the mean percent adsorbed was 38.0 ± 0.93 percent (SD, N=3). The initial topotecan concentration was 10.3 mg/L.

A two-variable isotherm experiment was conducted to determine the effects of varying the topotecan hydrochloride and sludge solids concentrations on the extent of adsorption. Lyophilized activated sludge solids were used as the adsorbent. Initial topotecan hydrochloride concentrations ranged from mg/L.

In general, Kp was inversely related to both TSS and topotecan concentration (see figure below). The Kp value obtained at the highest TSS (2252 mg/L) and the lowest topotecan concentration (0.05 mg/L) is most representative of the conditions found in a WWTP aeration basin. This Kp value was 192 (log Kp 2.28).

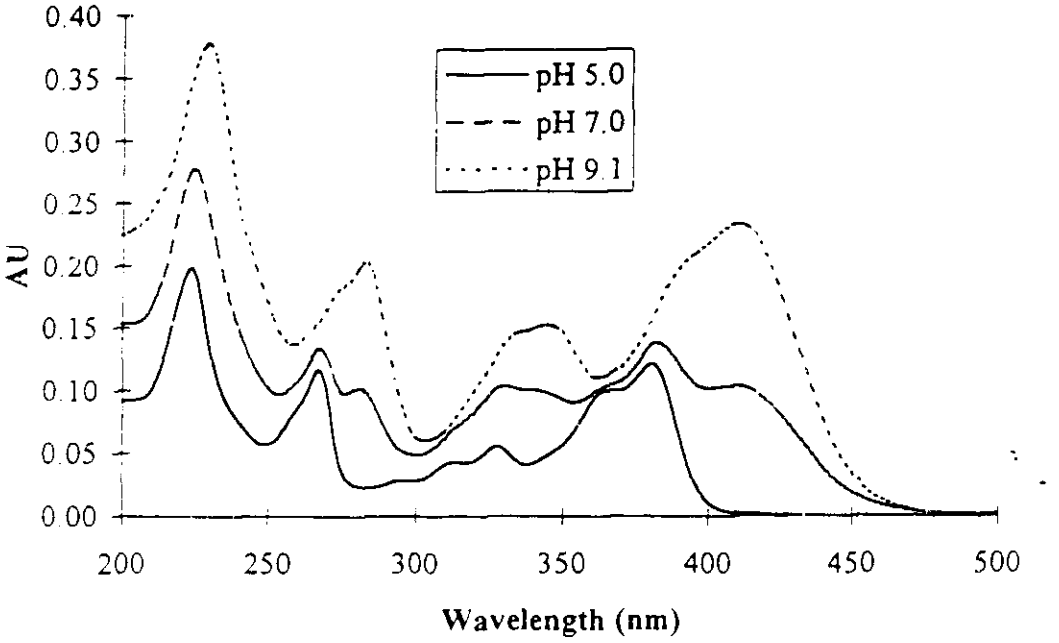


7.2.5 UV/vis Spectrum

UV/vis spectra of topotecan hydrochloride were determined in aqueous buffers at approximate pH values of 5, 7, and 9 [6]. A copy of the study report may be found in Confidential Attachment 1. The spectra shifted towards higher wavelengths as a function of solution pH. Representative spectra are shown below (note - the topotecan hydrochloride concentrations at the three pH values were not the same).

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection



Absorption maxima and corresponding extinction coefficients ($\varepsilon\lambda$) for topotecan hydrochloride are shown below.

pH	λ_{max} (nm)	log ε_λ ($M^{-1}cm^{-1}$)
5.04	224	4.73
5.04	268	4.50
5.04	328	4.18
5.04	380	4.52
7.02	224	4.63
7.02	268	4.32
7.02	328	4.20
7.02	382	4.33
9.11	230	4.56
9.11	284	4.29
9.11	346	4.17
9.11	410	4.36

The direct photolysis kinetics of topotecan hydrochloride were estimated from the UV/vis spectrum using the procedures of Leifer [8]. Using an estimated quantum yield of 0.001, the predicted photolysis rate constants (k_{dE}) and half-lives ($t_{1/2}$) under summer irradiance conditions are shown below.

pH	k_{dE} (hr^{-1})	$t_{1/2}$ (min)
5.04	1.18	35.3
7.02	1.93	21.5
9.11	2.11	19.7

The UV/vis absorption data suggest that topotecan hydrochloride is susceptible to rapid direct sunlight photolysis and that the photoreaction rate may vary with solution pH.

7.2.6 Volatility

The physical and chemical properties of topotecan hydrochloride strongly suggest that the molecule will be non-volatile in the environment. Topotecan hydrochloride is highly soluble in water, is ionized at all pH values, and has the capacity to hydrogen bond with water.

7.3 Transformation and Depletion Mechanisms

7.3.1 Direct Sunlight Photolysis

The direct aquatic photolysis kinetics of topotecan hydrochloride were experimentally determined in pH 5, 7, and 9 buffer solutions [9]. A copy of the study report may be found in Confidential Attachment 1. Aqueous solutions of topotecan hydrochloride (0.23 mg/L) were exposed to sunlight in quartz tubes on 23 May 1995 in King of Prussia, Pennsylvania, USA (~40 °N latitude) under sunny conditions.

Chemical actinometer solutions consisting of 1.00E-5 M p-nitroanisole and 1.05E-5 M pyridine were photo-exposed simultaneously so that the direct quantum yield of topotecan could be calculated [9]. First order photodegradation rate constants (k_{dE}), half-lives ($t_{1/2}$), and direct quantum yields (ϕ_d) were calculated for topotecan and the actinometer solution and are shown below.

ENVIRONMENTAL ASSESSMENT

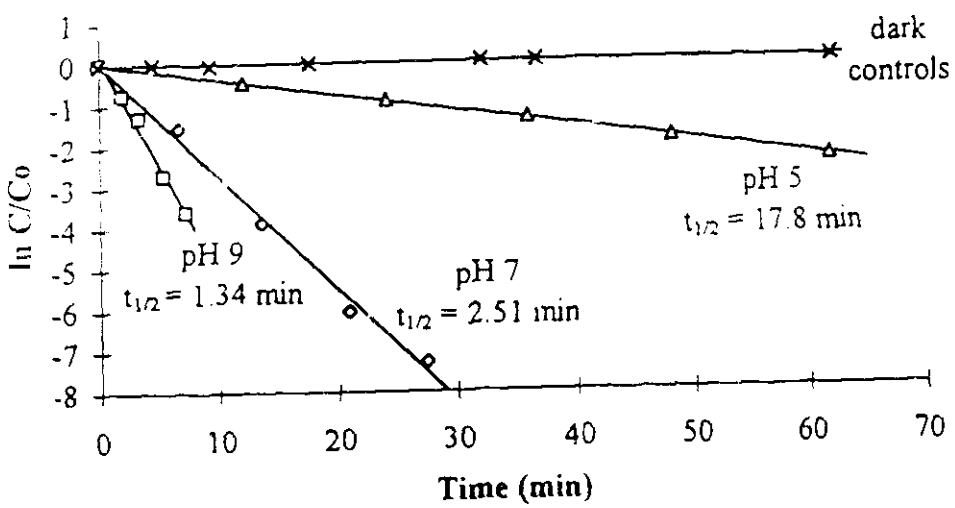
Hycamtin ™ (topotecan hydrochloride) for Injection

Topotecan Hydrochloride Photolysis Kinetics

Sample	pH	$k_{d\Sigma}$ (min^{-1})	$t_{1/2}$ (min)	ϕ_d
Topotecan	5	0.0389	17.8	3.55E-3
Topotecan	7	0.276	2.51	2.52E-2
Topotecan	9	0.518	1.34	4.72E-2
PNA-PYR (a)	nd	0.00816	85.0	4.87E-3

(a) p-nitroanisole/pyridine actinometer

The data indicate that topotecan photolyzed rapidly under conditions of direct sunlight irradiance. As predicted from the UV/vis spectra, the first-ord r photodegradation rate of topotecan was positively related to solution pH. A first-order kinetics plot of the topotecan photolysis data is shown below.



Subsequent experiments were conducted to attempt to identify and determine the persistence of topotecan photodegradants using HPLC with fluorescence, diode array, and/or mass spectrometry detection. One primary photodegradant was detected but the exact molecular structure could not be established [10]. A copy of the study report may be found in Confidential Attachment 1. Appearance of the degradant coincided with the disappearance of topotecan. The degradant also photodegraded, though at a slower rate than topotecan. In an experiment which was conducted for 7 days, the following first-order direct photolysis kinetics data were calculated (based on a 24 hour day).

Compound	k (hr^{-1})	$t_{1/2}$ (hrs)	r^2
Topotecan	1.10	0.63	0.981
Photodegradant	0.0055	126	0.983

No products derived from photolysis of the primary photodegradant were detected in the chromatograms.

7.3.2. Microbial Biodegradation

The biodegradation of topotecan hydrochloride was assessed in activated sludge matrices [11]. A copy of the study report may be found in Confidential Attachment 1. The experimental design utilized a batch activated sludge (BAS) test system that used freshly-collected activated sludge from a municipal wastewater treatment plant.

The solution concentration of topotecan did not significantly decrease over 28 days. The initial concentration of topotecan was 29 mg/L and 22 mg/L after 28 days. A 24% loss during this period was attributed to biomass sorption since the loss was observed in initial samples and no further topotecan removal was observed during the course of the study. The sorption phenomena was also observed during other investigations with other sorbants.

7.3.3 Hydrolytic Stability

The hydrolytic stability of topotecan hydrochloride was investigated at pH values of 2.5, 3.0, 3.6, and 4.1 at 50, 60, and 70°C. Stability was inversely related to temperature and pH. The pH 3.0 data, extrapolated to 25°C, indicated a half-life of ~35 years [4].

7.4 Summary - Predicted Environmental Fate of Topotecan Hydrochloride in the Environment

Experimental data suggest that topotecan will not be significantly biodegraded in wastewater treatment plants (WWTPs) or the ambient environment. Topotecan entering WWTPs is expected to adsorb to sludge solids to a limited extent. Using the Kp value of 192 and an assumed total suspended solids (TSS) concentration of 2500 mg/L, the fraction of topotecan expected to adsorb may be calculated using the following equation.

$$F_s = (K_p \cdot F_{tss})/(1+(K_p \cdot F_{tss}))$$

where:
Fs = fraction adsorbed
Kp = sludge/water distribution coefficient (192)
Ftss = weight fraction of suspended solids in WWTP aeration basin (0.0025)

For topotecan, Fs equals 0.32. Therefore, assuming no depletion, ~32 % of the topotecan entering a WWTP is expected to adsorb to activated sludge solids and ~68 % is expected to enter receiving waters via WWTP effluent.

In receiving waters at pH ~7, the carboxylate species will be slightly more abundant than the lactone species. The primary depletion mechanism for topotecan in the aquatic compartment is predicted to be photolysis. At pH 7, the photodegradation rate constant for topotecan was determined to be 0.276 min-1 [9]. This rate constant was determined in quartz tubes, so that the test solutions were irradiated from all directions. A correction factor of 2.2 $\pm$ 0.3 was experimentally determined to predict actual environmental rate constants (irradiance from one direction) from rate constants obtained in quartz tubes [8]. Applying this correction factor to the pH 7 experimental data yields a predicted environmental rate constant of (0.276 min^{-1}/2.2) 0.125 min^{-1}. The corresponding half-life is 5.5 minutes (0.693/0.125).

In summary, topotecan hydrochloride will distribute primarily to the aquatic environmental compartment and is expected to be subject to rapid photodegradation when exposed to sunlight. At a typical aquatic pH of 7, the carboxylate form of topotecan (which does not exhibit topoisomerase activity) will be the predominant species present.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Human and Mammalian Health Effects Summary

8.1.1 Acute Toxicity Studies

8.1.1.1 Oral Toxicity [12]

The acute oral toxicity of topotecan hydrochloride has been examined in the mouse and in the rat. The oral LD_{50} values were 983 mg/kg for rats and 749 mg/kg for mice. Topotecan hydrochloride exhibited moderate toxicity following a single, oral treatment.

8.1.1.2 Skin Irritation [12]

Topotecan hydrochloride was classified as a mild irritant to rabbit skin. Redness occurred up to one day following direct application in rabbits for 4 hours. Skin appeared normal two days after treatment.

8.1.1.3 Eye Irritation [12]

Topotecan hydrochloride was classified as a moderate irritant in rabbit eyes. Conjunctival redness, swelling and discharge, with iritis and corneal opacity occurred up to 3 days after direct application in rabbits. Eyes appeared normal 7 days after treatment. Water irrigation reduced irritation.

8.1.1.4 Sensitization [12]

Topotecan hydrochloride was classified as a non-sensitizer to guinea pig skin. No adverse skin reactions or irritation occurred in guinea pigs used to test for allergic reaction or sensitization (maximization test)

8.1.2 Chronic Toxicity Studies [12]

8.1.2.1 Carcinogenicity

Topotecan hydrochloride is listed as an animal carcinogen, according to SmithKline Beecham criteria (category 2) Substances classified as category 2 are positive in animal carcinogenicity studies by a mechanism not related to genetic damage and where a threshold is considered to exist It is not listed as a carcinogen by IARC, NTP or US OSHA

8.1.2.2 Reproduction Toxicology

The rat and rabbit were used to assess the potential of topotecan hydrochloride to cause embryo toxicity. These studies did not indicate any teratogenic effects in rabbits. In studies with rats, teratogenic effects occurred at dose levels significantly higher than human clinical doses. After birth, decreased pup growth also occurred, which was apparently related to impaired maternal lactation.

8.1.2.3 Mutagenicity Studies

Topotecan hydrochloride was determined to be non-mutagenic in bacteria (Ames test) and other laboratory tests (*in vivo* cytogenetics, mouse lymphoma and mouse micronucleus tests).

8.2 Acute Aquatic Toxicity Studies

Acute aquatic toxicity studies were conducted on the water flea (*Daphnia magna*), the fathead minnow (*Pimephales promelas*), and a bacterium (*Photobacterium phosphoreum*).

A full report summarizing the contract studies of the acute toxicity of topotecan hydrochloride to *Daphnia magna* and to *Pimephales promelas* is given as reference [13], which may be found in Confidential Attachment 2. Although a no-observable-effects-concentration was not explicitly described for the fish acute toxicity, one was produced by subsequent examination of the data (see table below). A memorandum summarizing the results of the bacterial toxicity study (Microbics Microtox®) with topotecan hydrochloride is given as reference [14].

The results of the studies described above are summarized below.

Toxicity Test	Topotecan concentration (as free base, mg/L)
Daphnia magna (48-hour exposure)	
EC_{50}	61.8
Pimephales promelas (96-hour exposure)	
LC_{50}	45.7
NOEC	25
Photobacterium phosphoreum (15-minute exposure)	
EC_{50}	102

8.3 Other Toxicity Studies

8.3.1 Photolytically-Degraded Topotecan Solution Acute Toxicity

Experimental evidence presented in Item 7.3.1 of this assessment indicates that topotecan rapidly degrades in aqueous solution under direct sunlight irradiance. A typical half-life at neutral pH is 2.5 minutes, with the formation of a slower-degrading primary photodegradant. In an effort to assess the relative toxicity of this photodegradant, the toxicity of a solution of photolytically-degraded topotecan to *Daphnia magna* was determined. A memorandum summarizing the relative toxicity assessment is given as reference [15]. At a nominal topotecan solution concentration of approximately 35 mg/L, 85% of daphnids were observed to have a demonstrable effect, whereas only 30% of daphnids in a similar sunlight-exposed topotecan solution (that had been exposed to the sun for 16.3 hours) were observed to be affected. This investigation demonstrated that photolytically-degraded topotecan

hydrochloride solution was less toxic to *Daphnia magna* than the corresponding undegraded topotecan hydrochloride solution.

8.4. Summary: Predicted Environmental Effects of Topotecan hydrochloride in the Environment

At concentrations predicted to be emitted into and exist in the environment (see Confidential Attachment 7), topotecan hydrochloride should exhibit no toxic effects upon organisms in the environment. Thus, the production and use of topotecan hydrochloride is not expected to result in any adverse environmental impacts.

9. USE OF RESOURCES AND ENERGY

9.1 Sourcing of Camptothecin

9.1.1 Past Sourcing of Camptothecin

Camptothecin and topotecan hydrochloride stocks currently held by SmithKline Beecham were obtained from two distinct plant sources, from several separate manufacturers who performed the extraction processes to obtain camptothecin. Camptothecin from was obtained from the "Tree of Joy" (*Camptotheca acuminata*), the three main suppliers in

These suppliers reported that they harvested only mature fruits/achenes (seeds) from *Camptotheca acuminata* trees. A summary of the life history of *Camptotheca acuminata* is presented in Appendix V (additional details may be found in the USDA document "*Camptotheca acuminata* Decaisne (Nyssaceae). Source of Camptothecin, an Antileukemic Alkaloid" [16]; a copy is given in Appendix VI), and an assessment of the impacts on the tree from harvesting may be found in Confidential Attachment 5.

Since *Camptotheca acuminata* is a relatively common tree found in in 12 provinces (see Appendix V) totaling nearly 1 million square miles, and harvesting was performed via the collection and processing of seeds, impacts upon the *Camptotheca acuminata* population are believed to have been negligible (see Confidential Attachment 5).

Camptothecin was also obtained from from *Nothapodytes foetida* (known as "Stinking Weed", which is actually a tree) from two suppliers:

These suppliers harvested and processed the wood from *Nothapodytes foetida* trees. A summary of the life

history of *Nothapodytes foetida* (excerpted from confidential documents provided by (presented in Confidential Attachment 6)) is presented in Appendix VII. An assessment of the impacts on this tree from past harvesting may also be found in Confidential Attachment 6.

The estimated total amount of *Nothapodytes foetida* plant material harvested by to produce camptothecin for SmithKline Beecham represents 44% of one year's estimate of a sustainable harvest (see Confidential Attachment 6). The harvest is not likely to have occurred in just one year, however, since camptothecin was supplied to SmithKline Beecham over the course of several years. Information provided by supports the belief that past harvests of the plant had a negligible impact on its population: regrowth characteristics of *N. foetida*, as well as the harvesting strategies that are employed because of its regrowth capacity, allow for the regrowth and sustainable harvest of the same plants every three to four years (see Confidential Attachment 6). Thus, in terms of effects upon the *N. foetida* population, impacts upon this plant are believed to have been negligible.

9.1.2 Future Sourcing of Camptothecin

Camptothecin and topotecan hydrochloride stocks currently held by SmithKline Beecham are expected to be able to support production of Hycamtin™ for Injection for use well into at least 1997. In the future, SmithKline Beecham's requirements for purified camptothecin are currently expected to be fulfilled by SmithKline Beecham's principal supplier. For details on the processing, extraction and purification of camptothecin at facility, please refer to Drug Master File for camptothecin, which was filed with the FDA on October 18, 1995.

Details on *Nothapodytes foetida* harvesting, provided by are given in Confidential Attachment 6. Based on projected drug substance requirements, will continue to extract and purify camptothecin from *Nothapodytes foetida* harvested from the wild. To supply camptothecin for the present indication (based on current projections into the year 2003), an annual harvest of approximately 8% of the estimated sustainable level of harvest would be required (see Confidential Attachment 6). SmithKline Beecham's current requirements of camptothecin for topotecan hydrochloride production are thus within the estimated natural carrying capacity of the population of *Nothapodytes foetida*, and any impacts upon this population are thus expected to be negligible. The level of sustainable plant harvest, determined by was derived in part by taking into account current harvesting methods and *Nothapodytes foetida* life history information, including the fact that biological characteristics of *N. foetida* allow for the regrowth and re-harvest of the same plants every three to four years (see Confidential Attachment 6).

The capacity for *Nothapodytes foetida* to regrow from a stump cut off at ground level (as well as other factors; see Confidential Attachment 6) has also led to initiate an evaluation of the use of plantations to produce camptothecin (see Item 10.1). Further details may also be found in Confidential Attachment 6.

9.2 Use of Resources And Energy At Cork, Ireland

The percent of total site resources expected to be utilized at the Cork facility to produce topotecan hydrochloride drug substance is estimated to be less than 1% of the site's total consumption, due to the low anticipated production volumes (see Confidential Attachment 7).

The effects on the use of resources and land for the production of topotecan hydrochloride drug substance are minimal because of the relatively low production volumes and associated wastes, and the existing controls and treatment units that will be used.

9.2.1 Effect Upon Endangered Species And Historic Places

The production of topotecan hydrochloride substance and the disposal of associated wastes should have no impact on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by topotecan hydrochloride substance production or waste disposal activities since the production will take place outside of the United States.

9.3 Use of Resources and Energy at Conshohocken, PA

Hycamtin™ manufacturing will be carried out in the SmithKline Beecham Pharmaceuticals, Building 16A - Containment Facility. Building 16A is housed within Building 16, and has completely separate Air Handling Systems than that of the larger building. Building 16A utilizes approximately 11,000 square feet of space previously used as warehouse storage. All of Building 16A's utilities are supplied via the larger facility. Since no monitoring of Building 16A's utilities is performed, accounting figures were used to calculate the resource utilization for Hycamtin™ manufacturing:

Electrical (MW/Lot)	Gas/Oil (Cu Ft/Lot)	Water (Gallons/Lot)
365	0	13,567

These estimates are high since they represent the utilities requirements for all of Building 16A during the period of a single drug product manufacturing run and do not give the fraction related solely to production operations.

9.3.1. Effect Upon Endangered Species And Historic Places

The production of Hycamtin™ and the disposal of associated wastes should have no effect on threatened or endangered species. Property listed in or eligible for listing in the National Register of Historic Places will not be impacted by Hycamtin™ production or waste disposal activities since production takes place in Building 16A, a containment facility built within Building 16 at the Conshohocken site.

10. MITIGATION MEASURES

10.1. Camptothecin Sourcing Mitigation

In the future, SmithKline Beecham's requirements for purified camptothecin are currently expected to be fulfilled by SmithKline Beecham's principal camptothecin supplier, which plans to obtain wild-sourced *Nothapodytes foetida* that is harvested at just 8% of the estimated sustainable level. Current harvesting practices allow for regrowth and reharvest of the same plants every three to four years.

undertook investigations into the geographic range, distribution and life history of *Nothapodytes foetida* (see Appendix VII), and, partly as a result, is continuing with an evaluation of the use of plantations as a source of camptothecin. Partial or total use of *Nothapodytes foetida* plantations could reduce or eliminate reliance upon wild sources. Current estimates indicate that plantations would not have to be large to fulfill projected camptothecin requirements- see Confidential Attachment 6. The fact that camptothecin is also found in more than one plant species (although in lesser concentrations [17]) and could be obtained from several suppliers would also reduce potential pressures to harvest *Nothapodytes foetida* at a rate that would have an impact upon the natural population.

10.2. Production Mitigation At Cork

Plans to minimize waste output at Cork have been considered and implemented at the outset of topotecan hydrochloride development and production. The Integrated Pollution Control (IPC) license contains guidelines for the establishment of an Environment Management Programme to assess all operations for the use of cleaner technology and the minimization of waste.

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

The production of topotecan hydrochloride will take place in a newly constructed building that was designed for handling high potency compounds, such as topotecan hydrochloride. Airstreams from the process building are filtered through HEPA filters prior to venting to the atmosphere. Glove boxes are utilized for the handling of all active process materials.

Most waste streams will be incinerated by a licensed offsite waste contractor. Some waste streams will be sent off-site for recovery of solvents; and one waste stream will be sent off-site for recovery of a catalyst.

A specialized treatment process was developed by SmithKline Beecham's Environmental Research Laboratory for the effluent streams. This process completely destroys all known topotecan hydrochloride, camptothecin and camptothecin-like compounds to below current detection limits. Effluent streams generated by the specialized treatment process would then be evaluated for biotreatment on site. Implementation of this treatment process is pending successful piloting.

10.3 Mitigation At Conshohocken, PA

Potential adverse environmental impacts associated with the proposed action are minimized at the Conshohocken facility through the use of engineering and administrative controls The production of Hycamtin™ will take place in the newly constructed building that was designed for handling high potency compounds see Item 6.1.3. Dilute aqueous waste from manufacturing operations is collected and passed through an ultraviolet light and hydrogen peroxide deactivation system to destroy any topotecan that may be present in the facility waste. Closed systems are used wherever possible to minimize creating excessive dust Facility spill prevention and control plans have been demonstrated to be effective in the prevention of spill emergencies.

11. ALTERNATIVE TO THE PROPOSED ACTION:

From purification of camptothecin and production of topotecan hydrochloride, no potential adverse environmental impacts have been identified for the proposed action. Based on current camptothecin requirement projections, impacts upon the population of *Nothapodytes foetida* are expected to be negligible. Also, the potential for sourcing camptothecin from *Nothapodytes foetida* plantations, as well as from *Camptotheca acuminata* trees from several suppliers, further mitigates any potential impacts upon wild plant populations The only alternative to the proposed action is that of no action, thus depriving patients an important therapy The approval of Hycamtin™ (topotecan hydrochloride) for Injection for the treatment of ovarian cancer will provide an important benefit to patients requiring its administration, with no known adverse environmental risk

12. LIST OF PREPARERS:

12.1. List of Contributors:

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Plant Engineering
SmithKline Beecham (Manufacturing) Limited
Cork, Ireland

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Conshohocken, PA 19428

12.2. List of Preparers:

Staff, Environmental Research Laboratory, SmithKline Beecham

Robert E. Hannah, Acting Director, Project Research
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David R. Orvos, Ph.D., Associate Senior Investigator
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(See Appendix VIII for Curricula Vitae of contributors and preparers)

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the Environmental Research Laboratory of SmithKline Beecham.

Date: Nov 17, 1995

Signature: George Wellman

Dr. George Wellman
Vice President & Director
Chemical Development
SmithKline Beecham

14. REFERENCES:

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2. Draper, M.A., F.J. Hollis, and S.E. Clarke, "The Metabolism of [^{14}C]SK&F 104864 in Rat, Dog and Human Hepatic Microsomes", SmithKline Beecham Pharmaceuticals, SB Report No. BF-1012/SKF-104864/1, DMPK Report No. DR95268, 13 October 1995.

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4. Physicochemical Properties of SK&F S-104864-A; SmithKline Beecham Analytical Sciences Report Number 3257A, SB Report No. CP-1010/SKF-104864/2, 23 October 1995.

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6 S. Ziegenfuss\R.E. Hannah, "Summary Report - Aqueous Solubility and UV/vis Spectrum of SK&F 104864 (topotecan), ERL Study #S93019P", SmithKline Beecham Environmental Research Laboratory Memorandum, 8 November 1995

7. P.S. Ziegenfuss, "SK&F 104864-A (Topotecan HCl): Adsorption to Activated Sludge", SmithKline Beecham Environmental Research Laboratory Study #S93018P, Report # ERL9516, 3 November 1995.

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10. SmithKline Beecham Environmental Research Laboratory Memorandum, J. Brum/R. Hannah, P.S. Ziegenfuss, "Topotecan Photodegradant: Analysis via LC/ESI/MS for ERL Study # S93017P", 6 October 1995.

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13 V.L. Cunningham, "SK&F 104864: Aquatic Toxicity Results for SK&F S-104962, SK&F S-104961, and SK&F 104864-A", Environmental Research, SmithKline Beckman, Report #ER89/10/1, 13 January 1989

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ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

15. APPENDICES:

15.1. Appendix I: Documentation for Disposal of Drug Product
- 15.1.1. SmithKline Beecham Pharmaceuticals, Bristol, Tennessee
- 15.1.2. Ogden Martin Systems of Lake, Inc.

15.2. Appendix II: Drug Substance Production at Cork, Ireland.
- 15.2.1. Certification of Compliance
- 15.2.2. Consent Limits

15.3. Appendix III: Drug Product Production at Conshohocken
- 15.3.1. Certification of Compliance
- 15.3.2. Consent Limits

15.4. Appendix IV: Material Safety Data Sheet/Data Summary
- 15.4.1. MSDS for Topotecan hydrochloride
- 15.4.2. Data Summary for Topotecan hydrochloride
- 15.4.3. MSDS for Hycamtin™

15.5. Appendix V: Life History of Chinese Tree, *Camptotheca acuminata.*

15.6. Appendix VI: U.S. Department of Agriculture, "*Camptotheca acuminata* Decaisne (Nyssaceae): Source of Camptothecin, an Antileukemic Alkaloid", Technical Bulletin No. 1415, April 1970, 26 pp., Washington, D.C.

15.7. Appendix VII. Life history of Indian Tree, *Nothapodytes foetida.*

15.8. Appendix VIII: Curricula Vitae of Preparers
- 15.8.1. Robert E. Hannah
- 15.8.2 Wilmer Tirado
- 15.8.3. Dave A. Christiansen Jr.
- 15.8.4. P. Scott Ziegenfuss
- 15.8.5. David R. Orvos, Ph.D.
- 15.8.6. Ajit K. Ghorpade, Ph.D.
- 15.8.7. Joseph X. Phillips
- 15.8.8. Chris Werner
- 15.8.9. Robert E. Herrmann
- 15.8.10. Leo C. Hsu, Ph.D.
- 15.8.11. Jeffrey L. Brum, Ph.D.
- 15.8.12. Ian McAuliffe (Cork, Ireland)
- 15.8.13. Vince Grillo (Conshohocken, PA)
- 15.8.14. Dr. Wulf Ohlendorf
- 15.8.15. Virginia L. Cunningham, Ph.D

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SB
SmithKline Beecham
Pharmaceuticals

COMPLIANCE STATEMENT

SmithKline Beecham(Manufacturing)Ltd. states that it is in compliance with, or on an enforceable schedule to be in compliance with,all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of TOPOTECAN at it's facilities in Currabinny,Carrigaline,Co.Cork,Ireland.

F. A. Groeger 25th October, 1995

Name : Dr.F.A.Groeger.
Title : Team Leader Quality Assurance/Regulatory Control.

25 Oct 95

Name : Mr.Finbar Lehane.
Title : Process Team Leader.

Aqueous Discharge Limits for Cork, Ireland

Parameters	Units	Permit Limits
Total Ammonia (as N)	mg/L	50
Suspended Solids	mg/L	250
Zinc	mg/L	1.0
Copper	mg/L	0.5
COD	mg/L	4,000
BOD	mg/L	500
Nitrates (as N)	mg/L	15.0
Phosphate	mg/L	24.0
pH	-	6 - 9
Number of Toxicity Units [1]	TU	10.0
Organohalogens [2]	-	-

The volume of trade effluent discharged to the controlled waters shall not exceed 600 m^3 in any period of twenty-four hours.

The flow rate of trade effluent discharged to the controlled waters shall not exceed 151.2 m^3 per hour.

[1] *The toxicity of the effluent shall be determined on an appropriate aquatic species. The number of toxic units (TU) = 100/96 hour LC50 in percentage vol/vol so that higher TU values reflect greater levels of toxicity.*

[2] *Screening for a priority pollutant list is required (such as CPL 40, US EPA volatile and/or semi-volatile).*

Source: Integrated Pollution Control (IPC) licence
Issued Oct. 94 - Environmental Protection Act, 1992
Emission limits from 1st October 1995

APPENDIX III

GENERAL COMPLIANCE STATEMENT

SmithKline Beecham states that it is in compliance with, or also on an enforceable schedule to be in compliance with, all emission and OSHA requirements set forth in permits, consent decrees and administrative orders applicable to the production of Hycamtin® (brand of Topotecan hydrochloride) Sterile Powder at its facility at 801 River Road, Conshohocken, Pennsylvania, 19428.

Gregory C. Miller
Director, Quality Assurance
Anti-Infectives
September 13, 1995

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APPENDIX IV

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:
TOPOTECAN

TRADENAMES/SYNONYMS:
(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 * SK&F 104864-A * SK&F S-104864-A * SKF 104864-A * SKF S-104864-A * 104864-A (SK&F) * 104864-A (SK&F-S) * 104864-A (SKF) * 104864-A (SKF-S)

CHEMICAL FAMILY:
Semisynthetic alkaloid.

MOLECULAR FORMULA:
C23-H23-N3-O5 . H-Cl

MOLECULAR WEIGHT:
457.9

COMPANY:
SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:
709 SWEDELAND ROAD
KING OF PRUSSIA, PA, 19406
U.S.A.

U.K. OFFICE:
NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
SOUTHDOWNVIEW WAY, WORTHING
WEST SUSSEX, BN14 8NQ, ENGLAND

PHONE NUMBERS:
++1-610-270-7600 ++44-(0)1903-822650

EMERGENCY AND AFTER HOURS CONTACT:
++1-612-221-3999, EXTENSION 221
++1-800-228-5635, EXTENSION 221 (Toll Free USA/Canada)

2.COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS	CAS REGISTRY NO	PERCENT
TOPOTECAN	119413-54-6	97

CONTAMINANTS:
No contaminants present with a greater hazard than Topotecan.

3. HAZARDS IDENTIFICATION

SKIN CONTACT:
Measures should be taken to avoid skin contact. Effects of direct contact with this material are not known.

EYE CONTACT:
Measures should be taken to avoid eye contact. Effects of direct contact with this material are not known.

INHALATION:
Measures should be taken to avoid breathing this material. Effects after over exposure are not known but symptoms might include nausea, diarrhea or vomiting.

INGESTION:
Measures should be taken to avoid ingestion. Symptoms after over exposure are not known but might include nausea, diarrhea or vomiting.

CONDITIONS AGGRAVATED BY EXPOSURE:
Exposure during pregnancy might have an adverse effect on developing offspring, based on effects of other cytotoxic materials.

4. FIRST-AID MEASURES

SKIN CONTACT:
Remove contaminated clothing and wash exposed area with soap and water then obtain medical assistance.
NOTE TO PHYSICIAN:
None.
EYE CONTACT:
Wash eyes with water for at least 15 minutes then obtain medical assistance.
NOTE TO PHYSICIAN:
None.
INHALATION:
Move exposed subject to fresh air. In case of known or possible over exposure, refer to a physician. If breathing has stopped, institute basic life support and seek immediate medical attention. Observe for chest pain, difficulty breathing, loss of consciousness or other adverse effects which may be delayed.
NOTE TO PHYSICIAN:
This is a cytotoxic agent. Manifestations of over exposure may include myelosuppression or gastrointestinal toxicity. Monitoring of complete blood counts is recommended in cases of over exposure.
INGESTION:
In the event of swallowing this material, the decision to induce vomiting must be made by appropriately trained personnel. Seek medical assistance in such cases.
NOTE TO PHYSICIAN:
This is a cytotoxic agent. Manifestations of over exposure may include myelosuppression or gastrointestinal toxicity. Monitoring of complete blood counts is recommended in cases of over exposure.
ANTIDOTES:
None known.

5.FIRE-FIGHTING MEASURES

FIRE CONTROL:
Toxic or corrosive gases are expected from fires involving this material. Use water, carbon dioxide, foam or dry chemical extinguishers.
SPECIAL FIREFIGHTING PROCEDURES:
Toxic or corrosive gases including oxides of carbon and nitrogen together with chlorine and hydrogen chloride are expected in fires involving this material. Self contained breathing apparatus and full protective equipment are recommended for firefighters. Move containers from fire area if possible without increased personal risk. Dike area if possible to contain water for later disposal.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:
For all spills, isolate the spill area, restrict access, post the area for a carcinogen and immediately implement emergency procedures for cleanup and control of occupational carcinogens. All materials, both decontaminated solution and solid wastse, should be disposed of as hazardous waste.
DECONTAMINATION PROCEDURES:
The contaminated surfaces should be thoroughly rinsed with water and the wash waters collected. The pH of the collected wash waters should be adjusted with base, such as sodium hydroxide, to a pH greater than 8. Then approximately 250 ml of commercial bleach solution, containing approximately 5% hypochorite, should be added to the wash water. The bleach will oxidise any residual Topotecan in solution immediately. The

decontaminated surfaces should be wiped down with water and, if possible, bleach solution followed by another water wipe. It is recommended that work surfaces be decontaminated if levels exceed 300 ng Topotecan/square metre.

7. HANDLING AND STORAGE

HANDLING:
Isolation and enclosure are recommended when working with dust or mist.

STORAGE:
Avoid prolonged storage at elevated temperatures (greater than room temperature, approximately 20 degrees C).

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:
TOPOTECAN:
SmithKline Beecham(PEL):
30 NG/M3 (CONTROL LEVEL)
INDUSTRIAL HYGIENE METHOD:
SB/1246 analytical method.

PERSONAL PROTECTION:

RESPIRATORS:
If dust or mist is present, a laboratory glove box or equivalent isolation system is recommended. When isolation is not possible, respirators must be combined with applicable protective equipment. The type of respirator used will depend on the dust or mist concentrations present. Follow local regulations for respirator use in the workplace.

GLOVES:
When isolation is not possible, impervious gloves must be used with other applicable protective equipment.

EYE PROTECTION:
When isolation is not possible, chemical splash goggles or equivalent eye protection must be used with other applicable protective equipment.

OTHER PROTECTIVE EQUIPMENT:
In laboratories, wear lab coat or other protective clothing with long sleeves and applicable protective equipment. When complete isolation is not possible in production areas, applicable protective equipment must be used. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:
Yellow to yellow orange solid.

FLASH POINT:
Expected to be greater than 55 degrees C.

AUTOIGNITION TEMPERATURE:
Not determined.

LOWER EXPLOSIVE LIMIT
Not applicable for solids.

UPPER EXPLOSIVE LIMIT:
Not applicable for solids.

MELTING POINT:
Greater than 145 degrees C (decomposes).

BOILING POINT:
Not applicable, decomposes at elevated temperatures.

VAPOUR DENSITY:
Expected to be negligible.

VAPOUR PRESSURE:
Expected to be negligible.
EVAPORATION RATE:
Expected to be negligible.
VOLATILE COMPONENTS (%):
None expected.
VISCOSITY:
Not applicable for solids.
PH OF AQUEOUS SOLUTIONS:
Acidic (pH was approximately 4 for a 10% solution in isotonic saline).
RELATIVE DENSITY:
Not determined.
CONDUCTIVITY:
Not applicable for solids.
OCTANOL/WATER DISTRIBUTION COEFFICIENT:
0.46 (calculated).
DISSOCIATION CONSTANT (pKA):
Two values are a1 = 6.35 and a2 = 10.1.
SOLUBILITY:
Soluble in water.
Insoluble in methylene chloride and 1-propanol.
OXYGEN BALANCE:
This material is considered to be of low energy hazard potential based on oxygen balance calculated as minus 185.
TRAIN FIRE TEST:
Since this material has not been train fire tested, it should be assumed to support combustion in bulk quantities.
DUST EXPLOSIVITY:
Classification: Not determined.
Minimum explosive concentration (grams/cubic metre): Not determined.
Minimum ignition temperature - cloud (degrees C): Not determined.
Minimum ignition temperature - layer (degrees C): Not determined.
Minimum oxygen concentration (% v/v): Not determined.
Explosion characteristics:
Pmax (bar): Not determined.
dP/dT (bar/second): Not determined.
Kst (bar metre/second): Not determined.
St class: Not determined.
DUST ELECTRICAL PROPERTIES:
Minimum ignition energy (mjoules): Not determined.
Resistivity at ambient humidity (ohm meter): Not determined.
Charge decay time at ambient humidity (seconds): Not determined.
Resistivity at low humidity (ohm metre): Not determined.
Charge decay time at low humidity (seconds): Not determined.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:
Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.
INCOMPATIBILITY:
Not identified.
STABILITY:
This material is expected to be stable.
THERMAL STABILITY:
Capillary tube test: Not determined.
Differential scanning calorimetry: Not determined.
Accelerating rate calorimeter: Not determined.

HAZARDOUS POLYMERIZATION:
Not expected to occur.
HAZARDOUS DECOMPOSITION PRODUCTS:
Not identified.
FIRE AND EXPLOSION HAZARDS:
Not identified. As with many organic dusts, explosions might result when excessive dust concentrations are present.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:
The estimated oral LD50 is between 5 and 50 mg/kg in rats.
INHALATION TOXICITY:
Not determined.
SKIN IRRITATION:
Not determined.
EYE IRRITATION:
Not determined.
SENSITIZATION:
Not determined.
MUTAGENICITY:
This material is anticipated to be mutagenic based on its pharmacologic effect.
CARCINOGENICITY:
This material is categorised as a known or probable human carcinogen (category 1) according to SB criteria. It is not listed as a carcinogen by IARC, NTP or US OSHA.
REPRODUCTIVE EFFECTS:
Not determined for this material. Other cytotoxic drugs produced adverse effects on developing offspring or on reproduction.
OTHER EFFECTS:
This material is a potential anticancer agent that affects genetic material and dividing cells. Relatively small doses, as low as 25 mg/kg, produced lethality in mice following a single, intravenous administration.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
48-hour EC50 for Daphnia magna (data currently under review).
48-hour no-observed-effect-concentration for Daphnia magna (data currently under review).
96-hour EC50 for Fathead Minnows (data currently under review).
96-hour no-observed-effect-concentration for Fathead Minnows (data currently under review).
BIODEGRADATION:
Not determined.
ACTIVATED SLUDGE RESPIRATION INHIBITION (OECD 209 PROTOCOL):
Not determined.
SOIL ADSORPTION:
Not determined.
OTHER EFFECTS:
Not determined.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or

permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

The MSDS should accompany all shipments for reference in the event of spillage or accidental release.

FOR AIR TRANSPORT (IATA REQUIREMENTS):
Proper Shipping Name: Toxic Solids, organic, N.O.S. (Not Otherwise Specified)
Technical Name (for n.o.s., not otherwise specified): (Topotecan)
UN/Identification Number: UN2811
Class/Division: 6.1
Sub Risk: Not applicable
Packing Group: II
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: 53

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):
Proper Shipping Name: Toxic Solid, organic N.O.S. (Not Otherwise Specified)
Technical Name: (for n.o.s., not otherwise specified): (Topotecan)
UN/Identification Number: UN2811
Class: 6.1
Sub Risk: Not Applicable
Packing group: II
IMDG page number: 6236
MFAG number: see Section 4.2 of IMDG Code
EMS number: 6.1-04
Marine Pollutant: No
Emergency Response Guide Number: 53

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIPEMENTS):
Proper Shipping Name: Toxic Solid, organic, N.O.S. (Not Otherwise Specified)
Technical Name: (for n.o.s., not otherwise specified): (Topotecan)
UN/Identification Number: UN2811
Class/Division: 6.1
Sub Risk: Not applicable
Packing Group: II
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: 53

FOR EUROPEAN GROUND TRANSPORT (ADR/RID/ROAD/RAIL REQUIREMENTS):
Not determined. Hazards according to ADR/RID requirements not identified.

EMERGENCY INFORMATION:
HAZCHEM code: Not identified.
TREMCARD number: Not identified.

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE:
Not classified as a significant fire hazard
HEALTH:
Toxic

ENVIRONMENTAL:
(Leave blank)

RISK PHRASES:
May cause cancer. (R45)
Possible risk of irreversible effects.(R40)
SAFETY PHRASES:
Avoid exposure - obtain special instruction before use. (S53)
Wear suitable protective clothing and gloves. (S36/37)
SYMBOL:
Skull and cross bones.(T)

16. OTHER INFORMATION

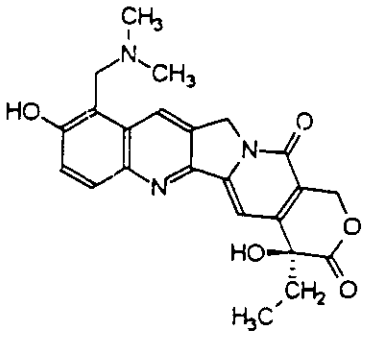
INFORMATION ON HAZARD LABELLING:
**** NOT CLASSIFIED AS A SIGNIFICANT FIRE HAZARD ****
**** TOXIC ****
**** CAUTION - ENVIRONMENTAL HAZARD NOT FULLY IDENTIFIED ****
** MAY CAUSE CANCER.
** POSSIBLE RISK OF IRREVERSIBLE EFFECTS.
** AVOID EXPOSURE - OBTAIN SPECIAL INSTRUCTION BEFORE USE.
** WEAR SUITABLE PROTECTIVE CLOTHING AND GLOVES.
** TARGET ORGAN- CYTOTOXIC AGENT THAT AFFECTS GENETIC MATERIAL AND DIVIDING CELLS.
** SYMBOL: SKULL AND CROSS BONES.(T)

REFERENCES:
SB HAZARD DETERMINATION

OTHER INFORMATION:
SMITHKLINE BEECHAM CONTROL MEASURES FOR CARCINOGENS AND MUTAGENS (ADOPTED 30 NOVEMBER 1991).
IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = U FIRE= 1 REACTIVITY = 0

SUMMARY OF TOPOTECAN (SK&F 104864A)
ENVIRONMENTAL FATE AND EFFECT DATA
last revised: 17 November 1995

STRUCTURE



SMILES NOTATION CCC1(O)C(=O)OCc5c1cc3n(Cc4cc2c(cN(C)C)c(O)ccc2nc34)c5=O

MOLECULAR FORMULA $C_{23}H_{23}N_3O_5 \cdot HCl \cdot 2.5\ H_2O$

MOLECULAR WEIGHTS free base 421.5, HCl salt 457.9, hydrated HCl salt 503.0

CAS# 119413-54-6

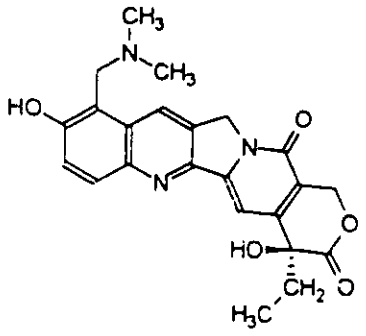
ENVIRONMENTAL FATE

Hydrolysis

Topotecan undergoes a pH-dependent, reversible hydrolysis reaction between lactone and carboxylate species. The equilibrium point, where both species are present in equal amounts, is at pH ~6.8 (SB, 1993). The carboxylate species does not exhibit topoisomerase activity (Underberg *et al.*, 1990).

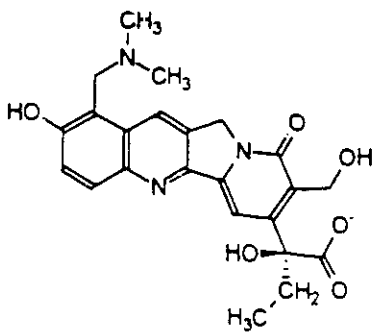
Hydrolysis of Topotecan (SK&F S-104864)

SK&F S-104864 (lactone)



$+ H_2O$ ⇌ $- H_2O$

SK&F S-105992 (carboxylate)



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Dissociation Constants
Topotecan has two basic and one acidic pK_a values (Fassberg and Stella, 1992).

pK_a	group	type
0.60	quinoline N	basic
6.99	phenol	acidic
10.5	benzyldimethylamine N	basic

Assuming a pK_a of ~4 for the COOH group of the carboxylate hydrolytic species, this group is extensively ionized at all pH values where the carboxylate species occurs.

Octanol/Water Partitioning and Bioaccumulation Potential
Octanol/water distribution ratios (D_{ow}) were determined at three pH values as shown below (SB, 1993).

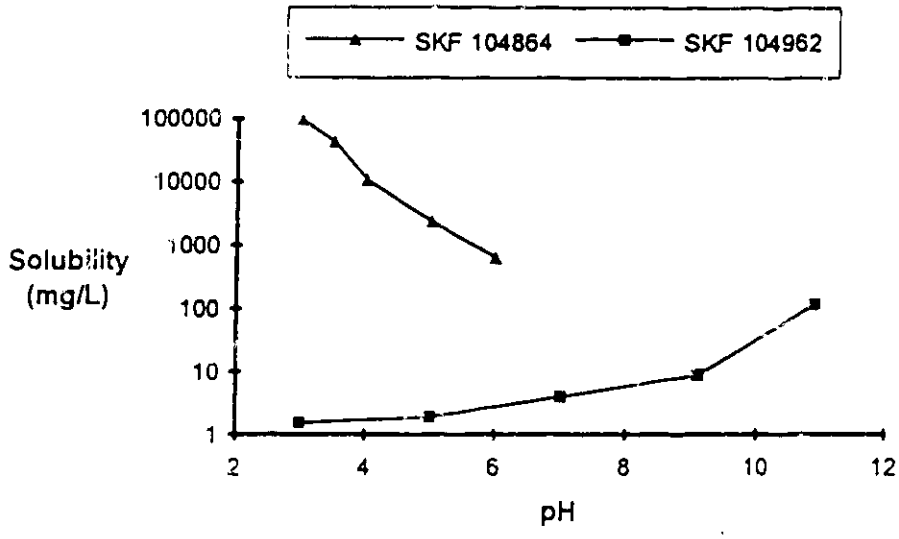
Measured Octanol/Water Distribution Ratios.

pH	buffer ionic strength	mean D_{ow}	log Dow
5.1	0.005	0.60	-0.22
7.4	0.005	0.50	-0.30
9.3	0.005	0.26	-0.59

The log octanol/water partition coefficient of topotecan (P_{ow}) estimated using the Daylight (Pomona) computer program was 0.46 (P_{ow} = 2.9). In reality, this calculated P_{ow} value has little relevance since topotecan is ionized in aqueous solution at all pH values. The D_{ow} data strongly suggest that topotecan is not likely to bioconcentrate.

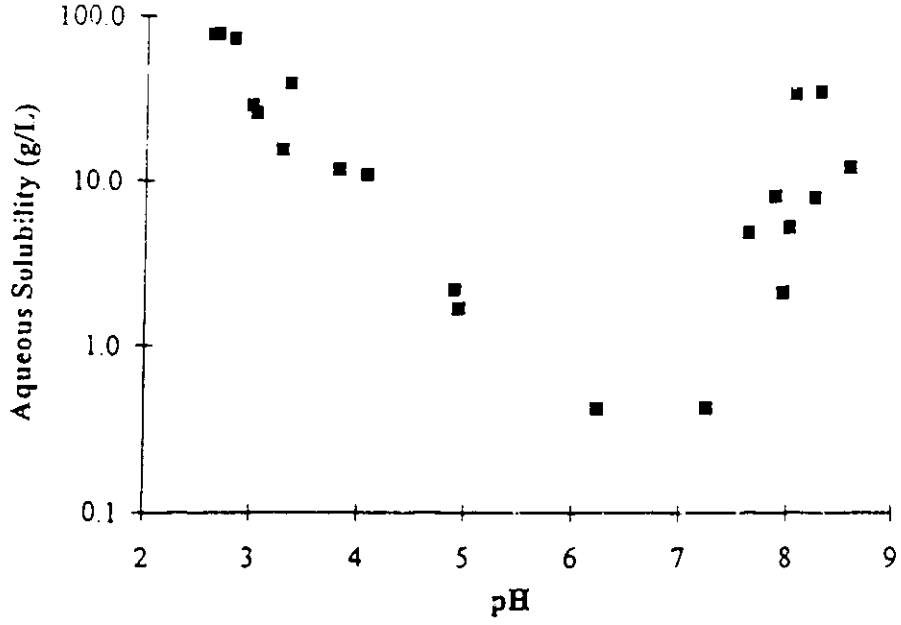
Aqueous Solubility
Camptothecin (topotecan starting material) is relatively insoluble in water. Topotecan is produced via synthetic addition of dimethylamine and hydroxyl groups at positions 9 and 10 on the camptothecin molecule, respectively. These functional groups substantially increase the solubility of topotecan compared to camptothecin.

Aqueous Solubility of SK&F 104864 (Topotecan) and SK&F 104962 (Camptothecin) as a Function of pH (SB, 1993).



Aqueous solubility data obtained by ERL are shown below.

Aqueous Solubility of Topotecan (ERL study S93019P).



Based on previously reported pK_a values (Fassberg and Stella, 1992), SK&F 104864 exists as a charged species over the entire pH range of 0 to 14. At the solubility minima at pH ~6-7, topotecan is zwitterionic, containing ionized carboxylate (-1) and benzyltrimethylamine (+1)

GCC084

groups simultaneously. However, the solubility is still quite high in this pH range: the lowest observed solubility was 420 mg/L. At low and high pH values, the solubility of SK&F 104864 increases as cationic or anionic species become more predominant.

Adsorption to Soil, Sediment, and Activated Sludge

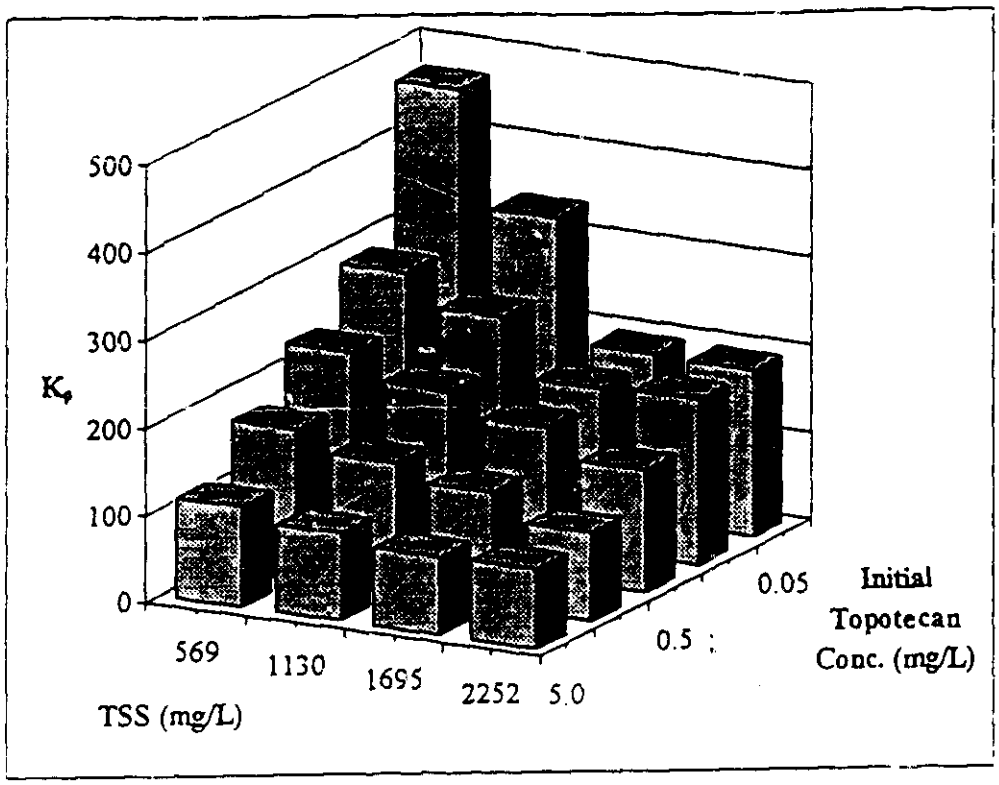
Three experiments were conducted to determine the extent of topotecan adsorption to activated sludge solids. The results are summarized below.

Experiment A: preliminary K_p determination

adsorbent phase:	authentic activated sludge solids
aqueous phase:	authentic activated sludge supernatant
equilibration time:	20 hours
initial aqueous topotecan concentration:	10.3 mg/L
total suspended solids concentration:	1800 ± 92 mg/L
mean K_p:	361 ± 14.8 mL/g (log K_p 2.56)
mean percent adsorbed:	38.0 ± 0.93 %

Experiment B: two-variable (adsorbent and topotecan concentrations) isotherm determination.

adsorbent phase:	lyophilized activated sludge solids
aqueous phase:	pH 7 phosphate buffer, 0.05 M ionic strength
equilibration time:	3.9, 23.4, 26.4 hours; equilibrium attained by 3.9 hours
initial aqueous topotecan concentration:	0.05, 0.15, 0.50, 1.5, 5.0 mg/L
total suspended solids concentration:	569, 1126, 1695, 2252 mg/L
K_p:	89 to 466 mL/g, inversely related to adsorbent and topotecan concentration



Freundlich isotherm values (sampling #1):

Initial TSS (mg/L)	log K	1/n	n	R^2
569	2.25	0.736	1.36	0.988
1126	2.19	0.777	1.29	0.998
1695	2.10	0.846	1.18	0.986
2252	2.06	0.825	1.21	0.996

Experiment C: isotherm determination to compare adsorption characteristics of lyophilized sludge solids and authentic activated sludge.

adsorbent phase:	lyophilized and authentic activated sludge solids
aqueous phase:	mineral salts medium (MSM)
equilibration time:	23.0, 47.6, 119.3 hours
initial aqueous topotecan concentration:	17.2 ug/L
total suspended solids concentration:	authentic sludge 3050 ± 31 mg/L, lyophilized sludge 2510 ± 70 mg/L

results: slope and elevation of Freundlich isotherms for authentic and lyophilized activated sludge were not statistically different at the 95% confidence level.

No data are available regarding the adsorption of topotecan to soil or sediment. Using a regression equation that predicts the carbon-normalized soil partition coefficient (K_{oc}) from aqueous solubility (log K_{oc} = 0.44 - 0.54 log WS (mole fraction), Kenaga and Goring, 1980), the

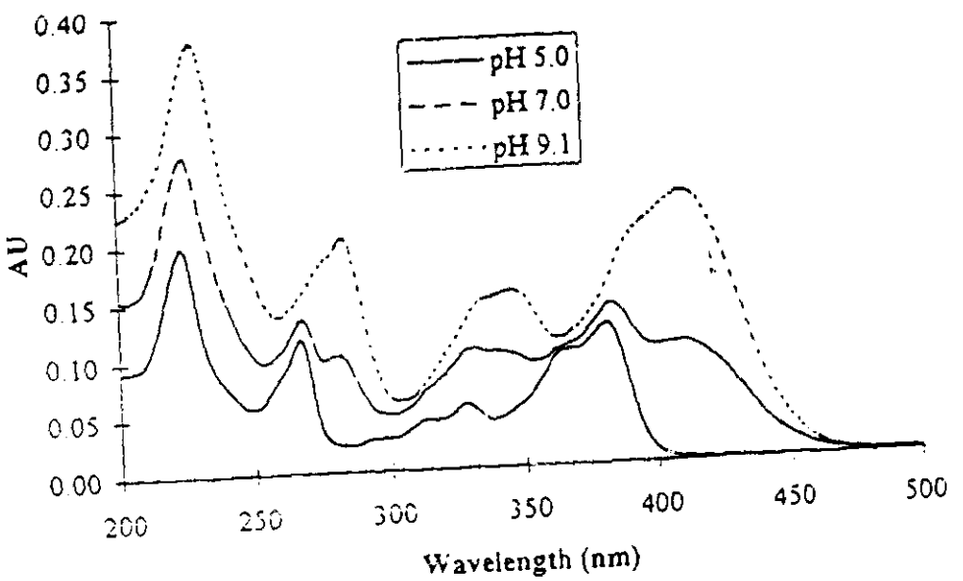
000086

solubility data in Table 2 predict log K_{oc} values of 1.7 to 2.9 over the pH range of 3 to 6 (K_{oc} ~ 50 to 800)

Photolysis

The UV/vis spectrum of topotecan shows significant absorption at wavelengths greater than 290 nm, suggesting the potential for direct photolytic degradation.

UV/vis Spectra of Topotecan in Water.



Experiments were conducted to determine the direct photolysis kinetics of topotecan in pH 5, 7, and 9 buffers (ERL study S93017P). A *p*-nitroanisole-pyridine (PNA-PYR) actinometer was used to allow determination of direct quantum yields (ϕ_d) for topotecan. Results are summarized below.

Sample	pH	k_{dE} (min^{-1})	$t_{1/2}$ (min)	ϕ_d
topotecan	5	0.0389	17.8	3.55E-3
topotecan	7	0.276	2.51	2.52E-2
topotecan	9	0.518	1.34	4.72E-2
PNA-PYR	nd	0.00816	85.0	4.87E-3

k_{dE} = first-order direct photolysis rate constant

GCC087

Volatilization

No experimental data are available regarding the volatility of topotecan. Given the high aqueous solubility, ionization at all pH values, moderately high molecular weight, and the capacity to hydrogen bond with water, volatilization of topotecan from water is expected to be insignificant.

Biodegradation

The biodegradation of topotecan (SK&F 104864) was assessed in activated sludge matrices (Orvos, 1995). The experimental design utilized a batch activated sludge (BAS) test system that used freshly-collected activated sludge from a municipal wastewater treatment plant.

The solution concentration of topotecan did not significantly decrease over 28 days. The initial concentration of topotecan was 29 mg/L and 22 mg/L after 28 days. The 24% loss during this time period was attributed to biomass sorption since the loss was observed in initial samples and no further topotecan removal was observed during the course of the study. The sorption phenomena was also observed during other investigations with other sorbants.

ENVIRONMENTAL EFFECTS

Numerous mammalian toxicity studies have been conducted with topotecan in mice, rats, and dogs. In addition, aquatic toxicity studies were conducted with fathead minnow and *Daphnia magna* for topotecan (SK&F 104864), camptothecin (SK&F 104962), and 10-hydroxycamptothecin (SK&F 104961). Acute aquatic toxicity data are summarized below (SB, 1989)

compound	code#	species	duration (hrs)	LC50 (mg/L)
topotecan	SK&F 104864	*P. promelas*	96	45.7
		D. magna	48	61.8
10-OH-camptothecin	SK&F 104961	*P. promelas*	96	4.59
		D. magna	48	> 10
camptothecin	SK&F 104962	*P. promelas*	96	0.153
		D. magna	48	0.046

Since all three substances exhibit the same biological activity, topoisomerase I inhibition, the difference in toxicities may be related to the aqueous solubilities of the compounds. The compounds are listed in order of decreasing solubility in the above table.

Topotecan, 10-hydroxycamptothecin, and camptothecin are known to reversibly hydrolyze between biologically active lactone and inactive carboxylate forms. The lactone is favored at low pH and the carboxylate is favored at high pH. For topotecan, the two species are present at equal concentrations at pH ~6.8 (Underberg *et al.*, 1990). The pH values observed during the aquatic toxicology studies ranged from approximately 6.8 to 8.2 (SB, 1989). It may therefore be surmised that the test organisms were predominantly exposed to the carboxylate form of the test chemical.

Single intravenous (IV) doses of SK&F 104864-A produced lethality in mice, rats, and beagle dogs at concentrations on the order of 13 to 240 mg/m^2 (Von Hoff *et al.*, 1990). Toxic effects were observed in mice, rats, and beagle dogs at doses as low as 0.2 mg/m^2. These effects included gastrointestinal epithelial necrosis, bone marrow depression, lesions of the testes and thymus, white blood cell count reduction, and lymphoid tissue atrophy. In surviving test animals, these effects were noted to be reversible. The only known enzymatically-formed metabolite of topotecan in rats, dogs, and humans is a mono-N-desmethylated derivative, SB 209780 (Draper *et al.*, 1995). In addition, topotecan may be excreted as the (open-ring) carboxylate hydrolysis product (Von Hoff *et al.*, 1990).

LITERATURE CITED

Draper, M.A., F.J. Hollis, and S.E. Clarke, *The Metabolism of [^{14}C]SK&F 104864 in Rat Dog and Human Hepatic Microsomes*, SmithKline Beecham Pharmaceuticals, SB Report No. BF-1012/SKF-104864/1, DMPK Report No. D95122/104864, 13 October 1995.

Fassberg J. and V.J. Stella, 1992, A Kinetic and Mechanistic Study of the Hydrolysis of Camptothecin and Some Analogs, *J. Pharm. Sci.* 81: 676-684.

Orvos, D., Topotecan (SKF 104864) - Evaluation of Biodegradation in Activated Sludge, SB ERL memorandum, September 28, 1995

SB, 1987, *SK&F 104864: Aquatic Toxicity Results for SK&F S-104962, SK&F S-104961, and SK&F 104864-A*, SmithKline Beecham Environmental Research Laboratory report# ER89/10/1, 13 January 1989.

SB, 1993, Physicochemical Properties of SK&F S-104864-A, SmithKline Beecham Analytical Sciences Report 3257, SB report CP-1010/SKF-104864/1.

Underberg, WJM, RMJ Goossen, BR Smith, and JH Beijnen, "Equilibrium Kinetics of the New Experimental Anti-tumor Compound SK&F 104864-A in Aqueous Solution", *J. Pharm. Biomed. Analysis*, 8:681-683, 1990.

Von Hoff, D. *et al.*, *Phase I Trial of SK&F 104864-A Administered as a Single Intravenous Dose Every 21 Days*, SmithKline and French Laboratories report SK&F 104864/A9901/US, 8 May 1990, 34 pps

MATERIAL SAFETY DATA SHEET

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

SUBSTANCE/PREPARATION:
HYCAMTIN

CHEMICAL FAMILY:
Chemical mixture.

COMPANY:

SMITHKLINE BEECHAM, CORPORATE ENVIRONMENT & SAFETY

U.S. OFFICE:
709 SWEDELAND ROAD
KING OF PRUSSIA, PA, 19406
U.S.A.

U.K. OFFICE:
NORFOLK HOUSE, DOWNSBROOK TRADING ESTATE
SOUTHDOWNVIEW WAY, WORTHING
WEST SUSSEX, BN14 8NQ, ENGLAND

PHONE NUMBERS:
++1-610-270-7600 ++44-(0)1903-822650

EMERGENCY AND AFTER HOURS CONTACT:
++1-612-221-3999, EXTENSION 221
++1-800-228-5635, EXTENSION 221 (Toll Free USA/Canada)

2.COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENTS	CAS REGISTRY NO	PERCENT
TOPOTECAN	119413-54-6	LESS THAN 10
TARTARIC ACID	87-69-4	LESS THAN 30
MANNITOL	69-65-8	LESS THAN 70

CONTAMINANTS:
No significant hazardous contaminants.

3. HAZARDS IDENTIFICATION

SKIN CONTACT:
Measures should be taken to avoid skin contact and accidental innoculation. Irritation is not expected following direct contact. The extent of absorption after skin contact is not known.

EYE CONTACT:
Measures should be taken to avoid eye contact. Effects of direct contact with this material are not known.

INHALATION:
Measures should be taken to avoid breathing this material. Effects after overexposure are not known but might include nausea, diarrhea, vomiting or myelosuppression.

INGESTION:
Measures should be taken to avoid occupational ingestion. Effects after ingestion might include nausea, diarrhea, vomiting or myelosuppression.

CONDITIONS AGGRAVATED BY EXPOSURE:
Exposure during pregnancy might have an adverse effect on developing offspring, based on effects of other cytotoxic materials.

4. FIRST-AID MEASURES

SKIN CONTACT:
Remove contaminated clothing and immediately flush exposed area with large amounts of water. Obtain medical attention if any symptoms develop.

NOTE TO PHYSICIAN:
Refer to INGESTION, below.

EYE CONTACT:
Flush eyes continuously with water for at least 15 minutes. Do not use a chemical neutraliser. Obtain medical assistance if symptoms occur.

NOTE TO PHYSICIAN:
Refer to INGESTION, below.

INHALATION:
Not applicable for finished products.

NOTE TO PHYSICIAN:
Refer to INGESTION, below.

INGESTION:
In the event of swallowing this material, seek medical assistance. Do not induce vomiting.

NOTE TO PHYSICIAN:
This product contains a cytotoxic agent. Manifestations of overexposure might include myelosuppression or gastrointestinal toxicity. Health surveillance with monitoring of complete blood counts is recommended in cases of overexposure. In case of occupational exposure, contact the site monitor or medical monitor for the study.

ANTIDOTES:
No specific antidotes known.

5.FIRE-FIGHTING MEASURES

FIRE CONTROL:
Not applicable.

SPECIAL FIREFIGHTING PROCEDURES:
No special requirements needed. Where appropriate, collect product or firefighting water for later disposal. Refer to MSDS Section 10 for expected thermal decomposition products.

6. ACCIDENTAL RELEASE MEASURES

SPILLS:
Isolate the spill area, restrict access, post the area for a carcinogen and immediately implement emergency procedures for cleanup and control of occupational carcinogens. All materials, both decontaminated solution and solid wastse, should be disposed of as hazardous waste.

DECONTAMINATION PROCEDURES:
Work surfaces should be decontaminated if levels exceed 300 ng topotecan/square metre. Contaminated surfaces should be washed with water, then bleach solution followed by another water wash. The pH of the collected wash waters should be adjusted using base, such as sodium hydroxide, to a pH greater than 8. Then approximately 250 ml of commercial bleach solution, containing approximately 5% hypochorite, should be added to the wash water. The bleach will oxidise any residual topotecan in solution immediately. Microgram levels of surface contamination can be visualised using ultraviolet light.

7. HANDLING AND STORAGE

HANDLING:
Isolation and enclosure are recommended when working with dust or mist.

STORAGE:
The recommended temperature for storage is 15 to 30 degrees C.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE CONTROLS:
Not applicable for this product.
PERSONAL PROTECTION:
RESPIRATORS:
If dust or mist is present, a laboratory glove box or equivalent isolation system is recommended. When isolation is not possible, respirators must be combined with applicable protective equipment. The type of respirator used will depend on the dust or mist concentrations present. Follow local regulations for respirator use in the workplace.
GLOVES:
When isolation is not possible, impervious gloves must be used with other applicable protective equipment.
EYE PROTECTION:
When isolation is not possible, chemical splash goggles or equivalent eye protection must be used with other applicable protective equipment.
OTHER PROTECTIVE EQUIPMENT:
In laboratories, wear lab coat or other protective clothing with long sleeves and applicable protective equipment. When isolation is not possible in production areas, applicable protective equipment must be used. An eye wash station should be available.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE:
Lyophilised powder.
FLASH POINT:
Expected to be greater than 55 degrees C.
AUTOIGNITION TEMPERATURE:
Not determined
LOWER EXPLOSIVE LIMIT
Not applicable for solid mixtures.
UPPER EXPLOSIVE LIMIT:
Not applicable for solid mixtures.
MELTING POINT:
Decomposition is expected at temperatures greater than 145 degrees C.
VAPOUR PRESSURE:
Expected to be negligible.
PH OF AQUEOUS SOLUTIONS:
Neutral.
SOLUBILITY:
All components are soluble in water.

10. STABILITY AND REACTIVITY

CONDITIONS TO AVOID:
Avoid direct sunlight, conditions that might generate heat and dispersion as a dust cloud.
INCOMPATIBILITY:
Strong oxidisers.
STABILITY:
This material is expected to be stable.
THERMAL STABILITY:
Stable under normal temperature and pressures.

HAZARDOUS POLYMERIZATION:
Not expected to occur.
HAZARDOUS DECOMPOSITION PRODUCTS:
Toxic and/or corrosive by-products are expected during thermal decomposition. None are expected under normal conditions.
FIRE AND EXPLOSION HAZARDS:
None.

11. TOXICOLOGICAL INFORMATION

ORAL TOXICITY:
No studies have been conducted. The oral LD50 is expected to be less than 2000 mg/kg in rats, based on calculations relating to the effects of individual components and concentrations present.
INHALATION TOXICITY:
Not applicable for finished products.
SKIN TOXICITY:
Irritation is not expected based on effects of individual components.
EYE EFFECTS:
No studies have been conducted.
SENSITISATION:
No studies have been conducted.
GENETIC TOXICITY:
No studies have been conducted. This material contains components that produced genotoxicity in laboratory tests.
CARCINOGENICITY:
Topotecan is listed as a carcinogen by SB. No other components in this material are listed as carcinogens by SB, IARC, NTP or US OSHA.
REPRODUCTIVE EFFECTS:
This material is categorised according to SB criteria as follows:
Known or presumed to cause developmental toxicity in humans (category 1D).
OTHER TOXICOLOGIC OR ADVERSE EFFECTS:
This mixture contains an anticancer agent that affects genetic material and dividing cells.

12. ECOLOGICAL INFORMATION

ACUTE AQUATIC EFFECTS:
For topotecan, data are currently under review.
OTHER EFFECTS:
None known.

13. DISPOSAL CONSIDERATIONS

Collect for recycling or recovery, if possible. Dispose of material on site in a licensed chemical incinerator, if allowed by the incinerator license or permit. If no on-site incinerator is available, dispose of material in a licensed commercial chemical incinerator.

14. TRANSPORT INFORMATION

The MSDS should accompany all shipments for reference in the event of spillage or accidental release.
FOR AIR TRANSPORT (IATA REQUIREMENTS):
Proper Shipping Name: TOXIC SOLID, ORGANIC, N.O.S. (Not Otherwise

000093

Specified)
Technical Name (for n.o.s., not otherwise specified): (Topotecan)
UN/Identification Number: UN2811
Class/Division: 6.1
Sub Risk: Not applicable
Packing Group: II
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: 53

FOR MARITIME TRANSPORT (IMDG REQUIREMENTS):
Proper Shipping Name: Toxic Solid, organic , N.O.S. (Not Otherwise Specified)
Technical Name: (for n.o.s., not otherwise specified): (Topotecan)
UN/Identification Number: UN2811
Class: 6.1
Sub Risk: Not Applicable
Packing group: II
IMDG page number: 6236
MFAG number: see Section 4.2 of IMDG Code
EMS number: 6.1-04
Marine Pollutant: No
Emergency Response Guide Number: 53

FOR UNITED STATES GROUND TRANSPORT (DOT REQUIREMENTS):
Proper Shipping Name: Toxic Solid, organic , N.O.S. (Not Otherwise Specified)
Technical Name: (for n.o.s., not otherwise specified): (Topotecan)
UN/Identification Number: UN2811
Class/Division: 6.1
Sub Risk: Not applicable
Packing Group: II
RQ (Reportable Quantity): Not applicable
Emergency Response Guide Number: 53

15. REGULATORY INFORMATION

EUROPEAN UNION CLASSIFICATION AND LABELLING REQUIREMENTS:

FIRE:
(Leave blank)
HEALTH:
Toxic

ENVIRONMENTAL:
(Leave blank)
RISK PHRASES:
May cause cancer. (R45)
May cause heritable genetic damage. (R46)
SAFETY PHRASES:
Avoid exposure - obtain special instruction before use. (S53)
Wear suitable protective clothing and gloves. (S36/37)
SYMBOL:
Skull and cross bones.(T)

16. OTHER INFORMATION

INFORMATION ON HAZARD LABELLING:

DATE APPROVED: 04 January 95 DATE REVISED: 28 June 95 PRINTED: 09 August 95

MATERIAL SAFETY DATA SHEET

**** CAUTION - FIRE HAZARD NOT FULLY IDENTIFIED ****
**** TOXIC ****
**** CAUTION - ENVIRONMENTAL HAZARD NOT FULLY IDENTIFIED ****
** MAY CAUSE CANCER.
** MAY CAUSE HERITABLE GENETIC DAMAGE.
** WEAR SUITABLE PROTECTIVE CLOTHING AND GLOVES.
** AVOID EXPOSURE - OBTAIN SPECIAL INSTRUCTION BEFORE USE.
** TARGET ORGAN- POTENT PHYSIOLOGICAL AGENT. SEE MATERIAL/CHEMICAL SAFETY DATA SHEET BEFORE HANDLING.
** SYMBOL: SKULL AND CROSS BONES.(T)

REFERENCES:
SB HAZARD DETERMINATION

OTHER INFORMATION:
IF HMIS RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 1 FIRE= 1 REACTIVITY = 0
IF NFPA RATINGS ARE USED AT YOUR SITE, USE THE FOLLOWING:
HEALTH = 1 FIRE= 0 REACTIVITY = 0

APPENDIX V

Appendix V

Life History of Chinese Tree, *Camptotheca acuminata*

Part One: *Camptotheca acuminata*

A. Geographical Range and Distribution

The natural distribution of *Camptotheca acuminata* in the southeastern Provinces of China range from Szechwan's Red Basin east to southern Anhwei and northern Chekiang, and south to Yunnan, Kwangsi and Kwangtung (see Figure 1). The tree has been found-in twelve Chinese Provinces (listed below), totaling nearly 1 million square miles over which *Camptotheca acuminata* may be found.

12 Chinese Provinces in which *Camptotheca acuminata* may be found		
ANHWEI	HUPEH	KWANGTUNG
CHEKIANG	KIANGSI	KWEICHOW
FUKIEN	KIANGSU	SZECHWAN
HUNAN	KWANGSI	YUNNAN

The tree has been found at elevations ranging from 150 meters to 2400 meters; however, the majority of the population are found at elevations between 300 and 1100 meters [16]. *Camptotheca acuminata* is partial to warm, moist, temperate regions, and occurs naturally along stream banks and the edges of forests [17].

B. Physical Description and Biology

Camptotheca acuminata reaches a maximum height of 30 meters [17] with a trunk diameter of 60 centimeters. Its pale gray bark is cracked and fissured, and it has simple, alternate leaves up to 15 centimeters long. The tree flowers in July and early August and bears mature fruit as wingless samaras of 2.5 centimeters in length. Its wood is extremely soft with a curly grain, fine rays and small, numerous, evenly distributed pores. Its growth rings are moderately distinct and may be exceedingly wide. [16]

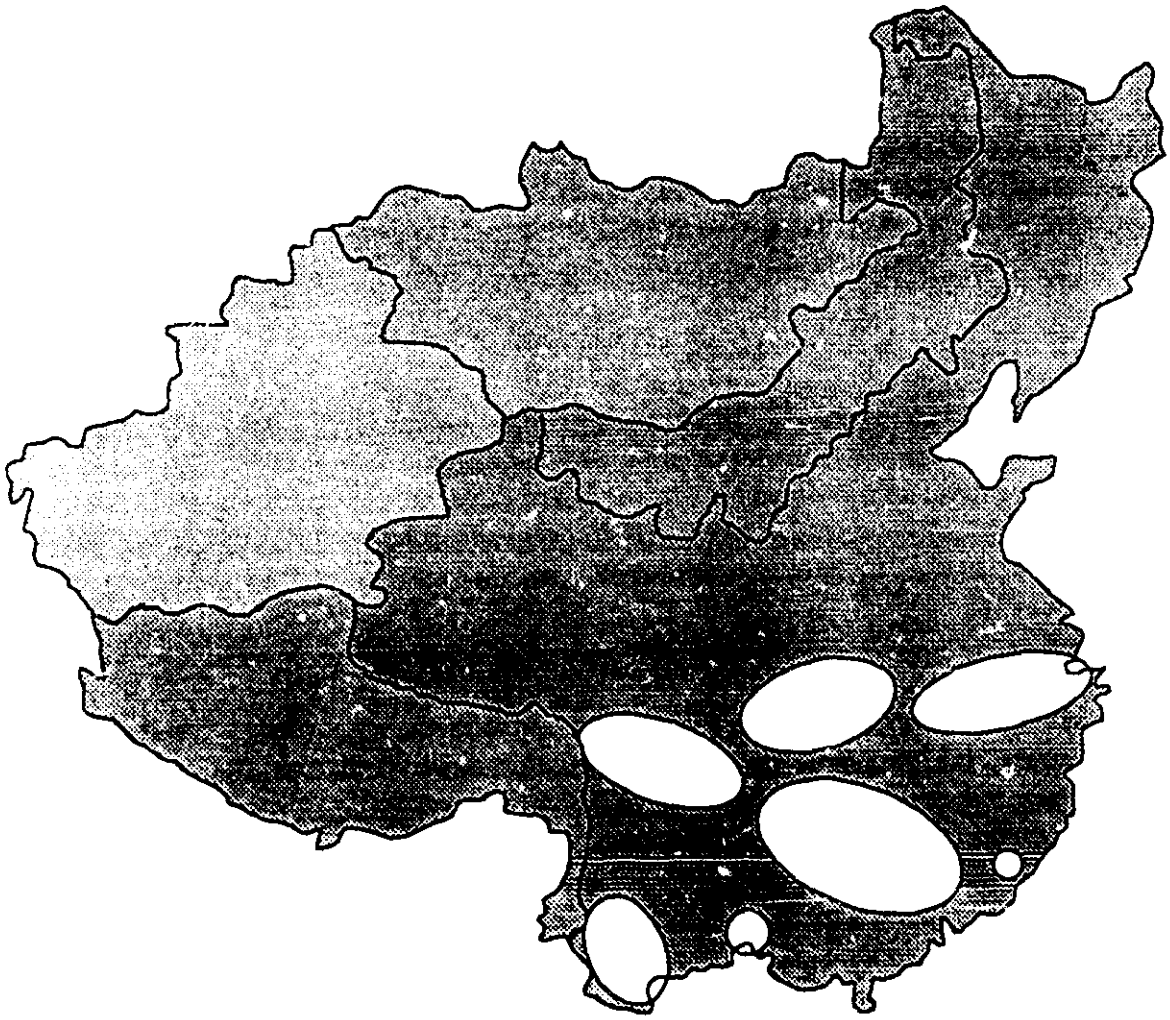
The growth rate of *Camptotheca acuminata* averages about 1.5 meters per year and a maximum height of 30 meters may be reached in approximately 20 years [17].

ENVIRONMENTAL ASSESSMENT

Hycamtin ™ (topotecan hydrochloride) for Injection

Camptotheca acuminata does not regenerate well naturally in a closed forest, however, seedlings grow well if they germinate in an open space [17]. *Camptotheca acuminata* will also produce roots from bud, root and shoot cuttings [17], which allows for successful propagation.

Figure 1. General Distribution of *Camptotheca acuminata* in Southeastern China*



* U.S. Department of Agriculture, "*Camptotheca acuminata* Decaisne (Nyssaceae): Source of Camptothecin, an Antileukemic Alkaloid", Technical Bulletin No. 1415, April 1970, 26 pp., Washington, D.C., and

Li, Shiyou and K.T. Adair, *Xi Shu - A Promising Anti-tumor Tree for the 21st Century*, The Tucker Center, College of Forestry, Stephen F. Austin State College, Nacogdoches, Texas, 1994.

C. Cultural and Natural Importance

1. Cultural Uses [17]

Camptotheca acuminata is most commonly used as an ornamental tree, planted along roadsides. It has also been planted along irrigation ditches as a firewood species due to its rapid growth and regeneration. Its branches are also reportedly used as a place for farmers to hang bundles of rice to dry.

2. Use as a Food Source for Wildlife [17]

Although there has been a lack of published data as to whether animals will feed on *Camptotheca acuminata*, there have been reports that certain species of deer and hogs may graze on the tree. Alternatively, it has been reported that the leaves of *Camptotheca acuminata* are poisonous to goats.

D. Related Species

Camptotheca acuminata is a member of the Nyssaceae family, from which two additional genus originate: *Nyssa* and *Davidia*. The species of *Nyssa* have a similar geographic distribution as *Camptotheca acuminata*, but do not occur naturally together. The only species of *Davidia* (*Davidia involucrata*) grows along the northern and northwestern perimeters of the distribution area of *Camptotheca acuminata*. [16]

E. Insects and Diseases [17]

Leaf spot is one of the most common diseases of *Camptotheca acuminata* in China, resulting in reduced yields and reduced fruit quality. Leaf pests common to *Camptotheca acuminata* include *Setora postornata, Cnidocampa flavescens, Parasa spp, Actias selene ningpoana* and the blackheaded race of the fall webworm. The latter tends to be a serious defoliator of *Camptotheca acuminata* in China. *Phassus sinifer sinensis* is a major stem pest of *Camptotheca acuminata*. Other common pests include aphids, scales and whiteflies.

Part Two: Forests of China

A. Landscape Patterns

1. Range of *Camptotheca acuminata* [16]

Camptotheca acuminata occurs mostly within natural mixed mesophytic forests. By definition, mesophytic forests include many species, most of which are deciduous and none of which predominate. Most genera in these forests occur primarily in warm, moist, temperate regions. This forest area is intensively cultivated and forest occurs largely as remnants. On hills and mountains, this vegetation type occurs above broadleaf evergreen and below montane coniferous forests. *Camptotheca acuminata* also appears within forests consisting mostly of Evergreen oaks and Yunnan pines.

B. Soils

1. Soil Factors Influencing *Camptotheca acuminata* [16]

Camptotheca acuminata grows most commonly on deep, well-drained, friable clay soils. Though slightly acid and only of moderate fertility, granular surface layers and friable subsoils promote good plant growth.

memas

MEMO TO THE FILE

NDA #: 20-671

DATE: May 28, 1996

PRODUCT NAME: Hycamtin™ (topotecan HCl)

SPONSOR: SmithKline Beecham Pharmaceuticals

SUBJECT: Sponsor's Verbal Agreement to Phase 4 Commitments

I telephoned Richard Swenson, Ph.D. of SmithKline Beecham Pharmaceuticals, and informed him that I had prepared a draft approval letter with Phase 4 commitments for their topotecan NDA 20-671. I conveyed the following three Phase 4 commitments to Dr. Swenson over the telephone:

1) provide updated survival and other efficacy data for studies 39, 34, and 33.

2) assure that the DMF holder, will provide FDA a copy of the English translation of the master production record of in a reasonable time. The record needs to be reviewed and found acceptable by the Agency before production of new batches of camptothecin commences in (enough lead time should be allowed for necessary revisions, if any).

3) for the annual stability study of future batches of topotecan drug substance under long term storage conditions, follow the same study protocol as described in the NDA for the stability study of the validation batches.

Dr. Swenson gave me a verbal agreement that SmithKline Beecham would accept all three of the FDA's Phase 4 commitments.

Having received this verbal agreement from the sponsor, I ended the telecon and prepared the final-typed approval letter for Dr. Temple's signature.

Debra Catterson 5/28/96
Debra Catterson, Project Manager

cc:
Original NDA 20-671
HFD-150/Division File
SHirschfeld
YHsieh
DCatterson

Topotecan Review Team

Medical:	Steven Hirschfeld, M.D.
	Robert Justice, M.D. (Group Leader)
	Robert DeLap, M.D., Ph.D. (Actg. Div. Dir.)
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Biometrics:	Vance Berger, Ph.D.
	Clare Gnecco, Ph.D. (Supervisor)
Project Manager:	Debbie Catterson, R.Ph.

Hi Everyone,

Here is a copy of the draft labeling for topotecan. I have compressed the text so that you have room on the page to jot down your revisions. The labeling should be accessible in the CANDA, but I thought you might like a "compressed text" copy. I've also put this on the "N" drive (n:\ndas\n20671\draft.lab).

Debbie

11/27/95

XX:L1

Prescribing Information

HYCAMTIN™
brand of
topotecan hydrochloride
for Injection

(for intravenous use)

DESCRIPTION

Hycamtin (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 consist of 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.

Topotecan hydrochloride is a semi-synthetic product with antitumor 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 monohydrochloride.

Topotecan hydrochloride has the following structural formula:

[Place chemical structure here]

Topotecan hydrochloride is a yellow to yellow-orange powder with the molecular formula $C_{23}H_{23}N_3O_5.HCl$ and a molecular weight of 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

CLINICAL PHARMACOLOGY

Topotecan hydrochloride is a novel

chemotherapeutic agent that 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. By inhibiting topoisomerase-I, topotecan induces breaks in the protein-associated DNA single-strands, resulting in cell death.

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. The binding of topotecan to plasma proteins is 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. The metabolism of topotecan in humans has not been studied. However in rats and dogs, approximately 4% and 17% of the dose, respectively, was excreted as N-desmethy 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.

Excretion: 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

Pediatric: 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.[1] 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.

Gender: *Hycamtin* is indicated for the treatment of ovarian cancer. It has not been determined whether gender affects the pharmacokinetics of *Hycamtin*.

Geriatrics: Topotecan pharmacokinetics have 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.

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

Renal Impairment: Plasma clearance of topotecan in patients with mild renal impairment (creatinine clearance of 40 to 60 mL/min.) 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 (Cl_{cr} of 20 to 39 mL/min.), 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 (Cl_{cr} 40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment.

Hepatic Impairment: 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. Based on clinical data and total topotecan pharmacokinetics, no dosage adjustment is required in hepatically impaired patients.

Drug Interactions: Pharmacokinetic studies of the interaction of topotecan with concomitantly administered medications have not been formally investigated. However, *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.

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.

CLINICAL STUDIES:

Hycamtin (topotecan hydrochloride) was studied in four clinical trials of 445 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 5 consecutive days, starting on day one of a 21-day course.

In a randomized Phase 3 study, *Hycamtin* was compared with paclitaxel. This study treated 112 patients with *Hycamtin* (1.5 mg/m^2/d x 5 days starting on day one of a 21-day course) and 114 patients with paclitaxel (175 mg/m^2 over 3 hours on day 1 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 1.

Patients receiving *Hycamtin* achieved a higher response rate-21% vs 13%- (p=0.138) than those receiving paclitaxel; a longer duration of response: median of 32 vs. 20 weeks (hazard ratio=0.416; p=0.222); a significantly longer time to progression: median of 23 vs 14 weeks (hazard ratio=0.578; p=0.002); and a longer estimated median survival: 61 vs 43 weeks (hazard ratio=1.210; p=0.515). However, the median time to response was significantly longer with *Hycamtin* compared to paclitaxel: median of 9 vs 6 weeks (hazard ratio=0.476; p=0.041). Consequently there is a risk of underestimating the expected efficacy of *Hycamtin* if patients are withdrawn from treatment prematurely (see DOSAGE AND ADMINISTRATION).

Table 1. Comparative Efficacy Parameters of *Hycamtin* vs paclitaxel in Ovarian Cancer

Parameter	*Hycamtin* (n=112)	Paclitaxel (n=114)
Response Rate	20.5%	13.2%
95% CI	13.0 to 28.3	7.0 to 19.4
(p-value)	(0.138)	
Response Duration (weeks)		
Median	32.1	19.7
Range	5.4* to 53.1*	6.3* to 24.3*

hazard-ratio (p-value)	0.416 (0.022)	
Time to Progression (weeks)		
Median	23.1	14.0
Range	0.7* to 62.1*	0.1 to 30.9
hazard-ratio (p-value)	0.578 (0.002)	
Time to Response (weeks)		
Median	9.0	6.0
Range	3.1 to 19.0	2.4 to 12.3
hazard ratio (p-value)	0.476 (0.041)	
Survival (weeks)		
Median	61.3	42.6
Range	0.7* to 62.1*	0.1* to 75.3*
hazard-ratio (p-value)	1.210 (0.515)	

*estimate corresponds to a censored event

Patients who failed on the initial arm of this trial were allowed to switch to the alternate treatment. Five of 53 (9%) patients who received *Hycamtin* after paclitaxel have responded. One of 37 (3%) patients who received paclitaxel after *Hycamtin* responded.

Hycamtin was active in 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%. *Hycamtin* 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 product's approved labeling, the safety profile for *Hycamtin* in this study was consistent with that observed in all 445 patients from the four ovarian clinical trials (see ADVERSE REACTIONS).

The three additional studies were open-labeled and non-comparative in design. The first of these

enrolled 111 patients who had failed one prior platinum-containing regimen. The response rate was 14% (95% CI:=7.9% to 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 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 13% and 14%, respectively. Median response duration was 24 weeks (range: 1.4 - 40.7 weeks). Median time to progression was 12 weeks (range: 0.6 - 52.7 weeks). Median survival was 44 weeks (range: 2.9 - 68.7 weeks) for patients failing first-line therapy.

The third open study enrolled 30 patients 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).

INDICATIONS AND USAGE

Hycamtin (topotecan hydrochloride) is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent therapy.

CONTRAINDICATIONS

Hycamtin is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients. *Hycamtin* should not be used in patients who are pregnant or breast-feeding, or those with severe bone marrow depression.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity. The nadir for neutrophil count occurred at a median of 11 days, and the nadir for platelet and hemoglobin counts occurred at a median of 15 days. The median duration of Grade 4 neutropenia was 7 days, and of thrombocytopenia was 5 days. The median duration of Grade 3/4 anemia was 7 days. (All

grading scales reported are based on National Cancer Institute criteria.) *Hycamtin* should only be administered in patients with adequate bone marrow reserves including baseline neutrophil counts of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of blood counts should be instituted during treatment with *Hycamtin*. Patients should not be treated with subsequent courses of *Hycamtin* until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3 and hemoglobin levels recover to 9.0 mg/deciliter, using transfusion if necessary.

Hycamtin may cause fetal harm when administered to a pregnant woman. Topotecan was shown to cause embryonic and fetal lethality when given to rats and rabbits at doses less than the human clinical intravenous dose (1.5 mg/m^2). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with *Hycamtin*.

PRECAUTIONS

General: Inadvertent extravasation with *Hycamtin* has been associated only with mild local reactions such as erythema (and bruising).

Drug Interactions: In Phase I studies, myelosuppression was more severe when *Hycamtin* was given after cisplatin.

When used concomitantly with platinum compounds, the dose of *Hycamtin* must be reduced due to the observed greater incidence of myelosuppression (see DOSAGE AND ADMINISTRATION), and myelosuppression may require delay of subsequent courses (see WARNINGS).

Hematology: *Hycamtin* should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. To monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving

Hycamtin. Patients should not be retreated with subsequent courses of *Hycamtin* until neutrophils recover to a level >1,000 cells/mm^3, platelets recover to a level >100,000 cells/mm^3 and hemoglobin recovers to 9.0 mg/deciliter, using transfusion if necessary.

In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) during a course of *Hycamtin*, a reduction in dose of 0.25 mg/m^2 for subsequent courses of therapy is recommended. As an alternative, G-CSF may be administered before reducing the dose , starting from Day 6 of the course (the day after completion of topotecan administration)..

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of *Hycamtin* has not been studied. (See WARNINGS section.)

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*).

Pregnancy: Pregnancy Category D. (See WARNINGS section.) Topotecan hydrochloride was shown to cause embryo-fetal lethality when given to rats (0.59 mg/m^2) and rabbits (1.25 mg/m^2). At maternally toxic doses (0.59 mg/m^2) , topotecan caused malformations, primarily of the eye, brain, skull, and vertebrae.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving *Hycamtin* (see CONTRAINDICATIONS).

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

ADVERSE REACTIONS

Data in the following section are based on the experience of 445 patients with metastatic ovarian carcinoma treated with *Hycamtin* in Phase II/III studies.

Table 2: Summary of Hematologic Adverse Events in 445 Patients Receiving *Hycamtin*

Hematologic Adverse Events	Patients % Incidence	Courses % Incidence
Neutropenia		
<1,500 cells/mm^3	98	81
<500 cells/mm^3	79	42
Leukopenia		
<3,000 cells/mm^3	97	78
<1,000 cells/mm^3	32	12
Thrombocytopenia		
<75,000/mm^3	63	37
<25,000/mm^3	23	9
Anemia		
<10 g/dL	93	75
<8 g/dL	37	15
Sepsis and fever/infection with Grade 4 neutropenia	25	8
Platelet transfusions	12	4
RBC transfusions	54	23

Table 3: Summary of Non-hematologic Adverse Events in 445 Patients Receiving *Hycamtin*

Non-hematologic Adverse Events	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	All Patients	All Courses	All Patients	All Courses	All Patients	All Courses
Gastrointestinal						
Nausea	75	51	8	3	NA	NA
Vomiting	56	27	5	1	2	<1
Diarrhea	39	19	4	1	<1	<1
Constipation	38	19	2	<1	<1	<1
Abdominal Pain	30	13	3	<1	2	<1
Stomatitis	23	10	2	<1	<1	<1
Anorexia	17	8	2	<1	0	0
Body as a Whole						
Fatigue	36	25	5	2	0	0
Fever	32	14	1	<1	<1	<1
Asthenia	19	10	2	<1	1	<1
Skin/Appendages Alopecia	59	64	NA	NA	NA	NA

Hematologic: Neutropenia (reversible and non-cumulative over time) was the major dose-limiting toxicity. Severe (< 500 cells/mm^3) neutropenia was most common during course 1 of treatment (60% of patients). It occurred in 42% of total courses and generally resolved within one week. Neutrophil nadirs occurred at a median of 11 days.

Prophylactic G-CSF was administered in 19% of courses.

Therapy-related sepsis associated with death occurred in 0.7% of patients. There were no episodes of serious bleeding. Severe anemia (Grade 3/4) occurred in 15% of courses. Median platelet and hemoglobin nadirs occurred on day 15 of treatment.

Gastrointestinal: (See Table 3). Prophylactic anti-emetic use was not routine in patients treated with *Hycamtin*.

Skin/Appendages: Total alopecia (Grade 2) occurred in 42% of patients.

Central and Peripheral Nervous System: Headache (19%) was the most frequently reported neurologic toxicity. Paresthesia was generally Grade 1 (8%).

Liver/Biliary: Grade 1 transient elevations in liver enzymes (5%); Grade 3/4 elevations (<1%).

Respiratory: Dyspnea (19%); Grade 3/4 dyspnea (3%).

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

OVERDOSAGE

There is no known antidote for overdosage with *Hycamtin*. The primary anticipated complication of overdosage would consist of bone marrow suppression. One patient who received a single 35 mg/m^2 infusion of *Hycamtin* showed increased neutropenia.

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

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of *Hycamtin*, patients must have a baseline neutrophil count of >1500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended

dose of Hycamtin (topotecan hydrochloride) 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. A minimum of four courses is recommended because median time to response in three clinical trials was 9 to 12 weeks. In the event of severe neutropenia, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. As an alternative, G-CSF may be administered before reducing the dose, starting from Day 6 of the course (the day after completion of topotecan administration). Routine pre-medication for non-hematological adverse events is not required with *Hycamtin*.

Patients who require concurrent cisplatin (for directions for the administration of cisplatin, refer to the cisplatin prescribing information) and *Hycamtin* may be treated as follows: 75 mg/m^2 of cisplatin administered on day one of each course of therapy, followed by 0.75 mg/m^2 of *Hycamtin* by intravenous infusion over 30 minutes for 5 consecutive days, according to the recommended regimen described above. A reported study recommended topotecan 1.0 mg/m^2/d for 5 consecutive days in combination with cisplatin 50 mg/m^2 on day 1 without G-CSF or cisplatin 75 mg/m^2 on day 1 with G-CSF support.[2]

No dosage adjustment is required for treating hepatically impaired patients (plasma bilirubin >1.5 to <10 mg/dL) _

No dosage adjustment is required for patients with mild renal impairment (Cl_{cr}40 to 60 mL/min). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20 to 39 mL/min). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

Insufficient data are available in pediatric patients to provide a dosage recommendation.

PREPARATION FOR ADMINISTRATION

Precautions: *Hycamtin* is a cytotoxic anticancer drug. As with other potentially toxic compounds, *Hycamtin* should be prepared under a vertical

laminar flow hood while wearing gloves and protective clothing. If *Hycamtin* solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If *Hycamtin* contacts mucous membranes, flush thoroughly with water.

Preparation for Intravenous Administration:
Each *Hycamtin* 4 mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Because the lyophilised dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of Hycamtin (topotecan hydrochloride) are stable until the date indicated on the package when stored between 15° and 30°C (59° and 86°F) and protected from light in the original package.

Reconstituted vials are stable for up to 24 hours when refrigerated at 5°C (41°F) or stored at 30°C (86°F). Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of *Hycamtin* diluted for infusion are stable at approximately 20° to 25°C (68° to 77°F) and ambient lighting conditions for 24 hours. If not used immediately, the diluted solution should be stored in a refrigerator in line with good pharmaceutical practice.

HOW SUPPLIED

NDC 0007-4201-05: Hycamtin (topotecan hydrochloride) for Injection is supplied in 4 mg (free base) single-dose vials, in packages of 5.

Storage: Store the vials protected from light in the original cartons between 15° and 30°C (59° and 86°F).

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.[3-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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DATE OF ISSUANCE (MONTH, YEAR)

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SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

XX:L1

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MEMORANDUM

To: Ms. Debra Catterson, CSO, HFD-150

From: Yung-Ao Hsieh, Ph.D., Review Chemist, HFD-150, through Rebecca H. Wood, Ph.D., Supervisory Chemist, HFD-150

Subject: NDA 20-671 Hycamtin

Date: February 5, 1996

Please communicate the following requests regarding the drug product stability study to the NDA applicant. We'd like to have response to request (1) at the firm's earliest convenience. Thanks.

1. Specify formulations AR and AS for the 4 mg vials and identify the formulation code for the drug product to be marketed.

2. Please provide a list of drug product batches employed in preclinic and clinic trials and identify for each lot: the lot number of the drug substance, date and site of manufacturing, batch size, formulation code, strength, container and closure system and date of the study.

3. We acknowledge the receipt of your fax, dated February, 1996, which provided the teleconference minutes between SmithKline Beecham and the agency, held on October 21, 1993. In this conference, you have agreed to submit further information on the harvesting and extraction of crude camptothecin. However, no information on the adequacy of the facility, personnel and equipment qualification of the suppliers, who extract this alkaloid from the fruit of the *Camptotheca acuminata* tree, was provided. As we have stated in our previous fax of February 2, 1996, that since topotecan hydrochloride is a semi-synthetic product derived from natural sources, the Center considers the raw natural material as the regulatory starting material for its synthesis and captothecin, a pivotal intermediate (Guideline for Submitting Documentation in Drug Applications for the Manufacture of Drug Substances, February, 1987). Please provide the names and addresses of your crude camptothecin suppliers so we can initiate the preapproval establishment evaluation process, to fulfill part of the cGMP requirements of the NDA review.

MEMORANDUM

To: Ms. Debra Catterson, CSO, HFD-150

From: Yung-Ao Hsieh, Ph.D., Review Chemist, HFD-150, through Rebecca H. Wood, Ph.D., Supervisory Chemist, HFD-150 RHW 2-2-96

Subject: NDA 20-671 Hycamtin

Date: February 2, 1996

SmithKleine Beecham sources crude camptothecin, the starting material for the synthesis of the drug substance topotecan hydrochloride, from various suppliers, who extract this alkaloid from the fruit of the *Camptotheca acuminata* tree. The Center considers the raw natural material as the regulatory starting material for the manufacture of semi-synthetic products derived from natural sources, such as topotecan hydrochloride (Guideline for Submitting Documentation in Drug Applications for the Manufacture of Drug Substances, February, 1987). Please request the firm to identify their crude camptothecin suppliers (with addresses of manufacturing sites) so we can initiate the preapproval establishment evaluation process. Thanks.

cc:
NDA 20-671
HFD-150 Div. File
HFD-150/RHWood
HFD-150/YAHsieh
[redacted]

FDA Corres

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-671

FEB 8 1996

SmithKline Beecham Pharmaceuticals
Four Falls Corporate Center
Route 23 and Woodmont Avenue
King of Prussia, PA 19406

Attention: Richard Swenson, Ph.D.
Associate Director, U.S. Regulatory Affairs

Dear Dr. Swenson:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Hycamtin™ (topotecan hydrochloride) 4 mg for Injection

Therapeutic Classification: Priority

Date of Application: December 21, 1995

Date of Receipt: December 22, 1995

Our Reference Number: NDA 20-671

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 19, 1996 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Debra Catterson, Project Manager, (301) 827-1544.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

D DeLap 2-8-96

Robert J. DeLap, M.D., Ph.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-671
HFD-150/Div. Files
HFD-80
HFD-150/CSO/DCatterson

drafted: DCatterson/January 2, 1996/20671ack.ltr
r/d init. by: DPease 1-30-96

ACKNOWLEDGEMENT (AC)

Received 4-F-96

(540) KHW 1-18-96

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: ~~Ms.~~ ~~Yana Mille~~, Chair, ~~(HFD-600) MPN II~~
MR. DANIEL BORING HFD-530

FROM: Division of Oncology Drug Products HFD-150
Attention: Yung-Ao Hsieh, Ph.D., Review Chemist Phone: 827-1523

DATE: 1-17-1996

Subject: Request for Assignment of a Trademark for a Proposed Drug Product

Proposed Trademark: Hycamtin™ (NDA # 20-671)

Established name, including dosage form: Topotecan Hydrochloride for Injection

Other trademarks by the same firm for companion products:

Indications for Use: Treatment of ovarian cancer after failure of first-line or subsequent chemotherapy

Initial comments from the submitter: (concerns, observations, etc.)
The applicant reported that the proposed trade mark, Hycamtin, was submitted to the Agency for preliminary consideration on March 30, 1995 and was informed at that time that there did not appear to be any conflicts that would prevent the firm from using the trademark Hycamtin for their brand of topoptecan hydrochloride.

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #549 (HFD-150)

HYCAMTIN topotecan hydrochloride for injection

The Committee noted some concerns with the following look alike/sound alike conflicts: HYTRIN, HYCODAN, and HYCOMINE. However, the Committee did not feel these would be significant conflicts.

The Committe has no reason to find the proposed name unacceptable.

LWBoring 4/4/96, Chair

CDER Labeling and Nomenclature Committee

Eric Tagliaferri 4/10/95

#427

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-600) MPN II

FROM: Division of Oncology HFD- 150
Attention: Michael Pelosi, CDD Phone 594-5763

DATE: 4-10-95

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: HYCAMTIN NDA/ANDA# IND

Company Name: Smith Kline Beecham

Established name, including dosage form: TOPOTECAN INJECTION

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Second line treatment for women w/ the advanced epithelial ovarian cancer

Initial comments from the submitter: (concerns, observations, etc.)

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

cc: orig IND
HFD-150/ DIV file
1 Diane Tagliaferri, Pelosi

Consult #427 (HFD-150)

HYCAMTIN

Topotecan Injection

A review revealed two names which sound or look like the proposed name: Hycomine, Hycodan. Due to differences in dosage forms, the Committee does not believe there is significant potential for confusion involving these names and the proposed name.

The Committee does note that this name is for an IND and suggests that the name be resubmitted for re-review when and if an NDA is submitted for this product.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Gloria Ruth Miller, Chair 5/15/95

COMPLETED

Co. Corres

SmithKline Beecham
Pharmaceuticals

[D[illegible]AME

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000031 - 000034

11 March 1996

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE : NDA Data on CD-ROM/Diskettes for Medical Reviewer

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND) for topotecan (SK&F S-104864-A) and to our pending New Drug Application for *Hycamtin™* (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to requests from the Medical Reviewer, Dr. Steven Hirschfeld, for NDA data (Case Report Form Tabulations [CRT]) in a format that he could analyze on his personal computer.

SmithKline Beecham Pharmaceuticals (SB) had provided Drs. Hirschfeld and Berger with portions of the reformatted CRT data on diskettes on 5 February 1996. On 12 February 1996, complete CRTs on CD-ROM (with a CD-ROM reader) were provided to Dr. Hirschfeld.

Attached with this letter, are six diskettes containing the portion of data submitted on 5 February 1996 and four compact discs with all CRT information provided FDA on 12 February 1996.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy: Drs. Hirschfeld, Berger

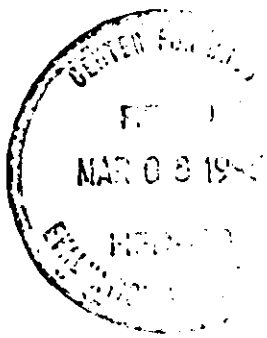
n:\topotecan\nda\rev\cover\mrg_6.doc

ORIGINAL

7 March 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 - 000001

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: Response to Medical Officer's Request for Data

NC

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S 104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a conversation I had with Dr. Steven Hirschfeld on 6 March in which SB informed Dr. Hirschfeld that his NDA dataset does not contain laboratory data for the Study 039 Alternate Phase. These laboratory data were included in the original NDA, but they were not available on the Case Report Form Tabulations.

We submit, in duplicate, diskettes with laboratory data that was missing in the original submission. These data can be inserted directly into the datasets he has already received for Study 039.

SB regrets not including these data in the Case Report Form Tabulations currently under review by Dr. Hirschfeld. Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy - Dr. Hirschfeld

SmithKline Beecham
Pharmaceuticals

NDA 20-671 1 March 1996
Hycamtin™ (topotecan hydrochloride) for Injection
pp 000663 - 000664

DUPLICATE

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to Medical Officer's Request for Data

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a conversation I had with Dr. Steven Hirschfeld on 26 February 1996 at the end of our presentation to FDA of our Hycamtin NDA Overview. In our conversation, Dr. Hirschfeld stated he had difficulty confirming response to treatment based on his review of data provided in the NDA. SB offered to investigate this problem and to supply him with additional data sets that may aid him in his analysis of efficacy.

We submit, in duplicate, diskettes with reformatted data sets for **Lesion Details** from the Case Report Tabulations. The data in these files is the same as that supplied in our NDA application; the format changes to files are described in **Attachment 1**. **Attachment 2** provides replacement documentation for this section of the Case Report Tabulations that were supplied to Dr. Hirschfeld on 5 February 1996.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D
Associate Director
U.S. Regulatory Affairs

Desk Copy - Dr. Hirschfeld

SB
SmithKline Beecham
Pharmaceuticals

NDA 20-671

Hycamtin™

Topotecan Hydrochloride for Injection

Treatment of Ovarian Cancer

ITEMS 13/14: Patent Information

Pursuant to the provisions of 21 USC §355 (b) and 21 C.F.R. §314.53, particularly subsections (c) and (d), Applicant herewith submits the following patent information for each patent it believes it reasonably could assert against the manufacture, use or sale by another of certain compositions, formulations or uses of a drug or drug product for which Applicant is submitting this NDA:

(i) Patent No. 5,004,758 expiring 2 April, 2008.

(ii) Type of patent: drug, formulation and use.

(iii) SmithKline Beecham Corp.

(iv) The owner/applicant has a residence and is doing business in the United States.

The undersigned declares that Patent No. 5,004,758 covers the composition (new chemical entity), a formulation, and a method of use of topotecan hydrochloride. This product is the subject of this application for which approval is being sought.

SmithKline Beecham
Pharmaceuticals

NDA 20-671

Hycamtin™

Topotecan Hydrochloride for Injection

Treatment of Ovarian Cancer

DEBARRMENT STATEMENT

SMITHKLINE BEECHAM PHARMACEUTICALS HEREBY CERTIFIES THAT SAID APPLICANT DID NOT USE IN ANY CAPACITY THE SERVICES OF ANY PERSON DEBARRED UNDER SUBSECTION (A) OR (B) [SECTION 306(A) OR (B) OF THE ACT], IN CONNECTION WITH THE NEW DRUG APPLICATION FOR HYCAMTIN™ (TOPOTECAN HYDROCHLORIDE) FOR INJECTION. THE APPLICANT FURTHER CERTIFIES THAT NO SUCH PERSON DEBARRED BY THE FOOD AND DRUG ADMINISTRATION WILL BE USED IN ANY CAPACITY IN FUTURE INVESTIGATIONS INVOLVING THIS DRUG PRODUCT, AT SUCH TIME AS SAID DEBARRMENT BECOMES KNOWN TO THE SPONSOR.

SmithKline Beecham
Pharmaceuticals

2 May 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 - 000008

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to Outstanding Item from FDA Fax of April 23, 1996 - Chemistry

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995.

Also, reference is made to our submission dated 29 April 1996, which contained responses to a chemistry information request contained in an April 23, 1996 fax from Ms. D. Catterson. In response to question I.(4), our 29 April response committed to providing validation data by May 3.

We submit, in duplicate, the requested data. For reviewing convenience, the question is restated, in bold text, with the SB response following.

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917 7000 Fax (610) 917 7707

I. Drug Substance:

(4) Please provide method validation data for the HPLC reaction completion test for the reaction between 10-hydroxycamptothecin and TMDM.

Response: The in-process HPLC method used to test for completion of the reaction between 10-hydroxycamptothecin and TMDM has been validated with respect to linearity, precision, and limits of detection and quantitation. The information is contained herein.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy: Ms. D. Catterson

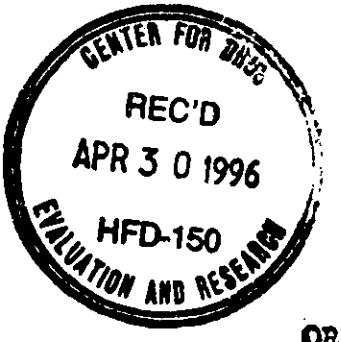
SmithKline Beecham
Pharmaceuticals

DUPLICATE

29 April 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 - 000043

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD 150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: Response to FDA Fax of April 23, 1996 - Chemistry Questions ORIG AMENDMENT

BC

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND , for topotecan (SK&F S-104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a fax from Ms. Debbie Catterson, sent April 23, 1996, which contains a draft information request from the Chemist.

We submit, in duplicate, a response to each question from the Chemist; the FDA question is presented in bold text with the SB response following

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy: Ms. D. Catterson

x \topo_nda/nda_mod/resp_cov.doc\1

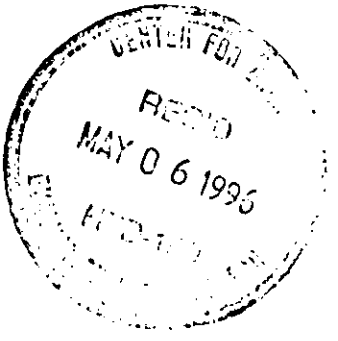
1250 S. Collegeville Road, P.O. Box 5089, Collegeville, PA 19426-0989 Telephone (610) 917-7000 Fax (610) 917-7707

Smith Kline Beecham
Pharmaceuticals

N(SU)

29 April 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Volumes 3.001 to 3.037



Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE : SAFETY UPDATE TO HYCAMTIN NDA

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995.

Submitted herewith, in duplicate, is a Safety Update to NDA 20-671; this update has been prepared after consultation with the review staff at the Division.

In NDA 20-671, SmithKline Beecham Pharmaceuticals (SB) presented safety data from 1,276 patients who received topotecan with an emphasis on the experience of 445 patients with recurrent ovarian carcinoma treated with topotecan in four Phase II/III studies (Studies 039, 034, 033, and 012) up to a clinical cutoff of 20 June 1995. In this Safety Update, we are presenting data on an additional 132 patients (a 10% increase above that reported in our NDA) up to a clinical cutoff date of 20 November 1995. In comparison with the NDA, this Safety Update contains data on 7 additional patients with ovarian cancer; the remaining data are from patients with other tumors.

Continued

The text of the Safety Update is presented in Volume 3.001 including a Summary and revised sections of the NDA Integrated Summary of Safety (ISS) related to Exposure, Adverse Experiences, Serious Adverse Experiences, Withdrawals, and Deaths. This is the only volume of the Safety Update that is printed, the remaining volumes of the update are submitted as part of our Computer Assisted New Drug Application (CANDA) and will be loaded onto the FDA computer system. Any part of this submission can be printed from the CANDA. As SB had done with our NDA 20-671, an archival copy of this submission on compact disc is included with this letter.

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

19 March 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 -000344

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation 1
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to Biopharm Request for Additional Information

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a request from Dr. Zannikos on 1 February 1996 for topotecan assay validation data.

With this letter, we are submitting copies of assay validation data, in duplicate, for Topotecan Studies 004, 005, 039, 047, and 097. An index to this submission appears on page 00005. A desk copy of these data has been submitted to Dr. Zannikos on 22 February 1996.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

000001

n:\topotecan\nda\mail_out\bio_3.doc
1250 S. Collegeville Road PO Box 5089 Collegeville PA 19426-0989 Telephone (610) 917-7000 Fax (610) 917-7637

SB
SmithKline Beecham
Pharmaceuticals

NDA 20-671 DUPLICATE 2 February 1996
Hycamtin™ (topotecan hydrochloride) for Injection
Volume 2.1: pp 000008 - 000062

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE :Response to Questions from Dr. Zannikos Dated 1 February 1996

ORIG AMENDMENT
BB

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to an Internet message from Ms. Debbie Catterson dated 30 January 1996 (**Attachment 1**) in which she forwarded to SmithKline Beecham Pharmaceuticals (SB) questions from Dr. Peter Zannikos.

SB intends to provide Dr. Zannikos with all the information he requested in his message. Attached to this letter is a statement from our pharmacokineticist, Dr. Mike Dennis, outlining our plans to answer Dr. Zannikos's questions (**Attachment 2**). Supportive data from the published literature and SB Reports, referred to in our attached response, are contained in **Attachments 3 and 4**.

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson,Ph.D
Associate Director
U.S. Regulatory Affairs

Desk Copy: Peter Zannikos, Ph.D.

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SB
SmithKline Beecham
Pharmaceuticals

my copy

NDA 20-671 ORIGINAL 11 January 1996
Hycamtin™ (topotecan hydrochloride) for Injection

Ms. Debra Catterson, Consumer Safety Officer
Division of Oncology Drug Products (HFD-150)
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, MD 20857

NEW CORR
NC

RE :Additional Copies of NDA 20-671 Volumes

Dear Debbie:

Enclosed in this box are 6 copies of the first volume (Volume 1.1) of our NDA for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671, that you requested in our telephone conversation of 18 January 1996. I am sorry that I did not include these copies at the time of the NDA submission.

For Dr. Zannikos, I have also included a copy of the clinical report for Study 010 (Volumes 1.116 to 1.119; Volume 1.120 contains laboratory data and these are available in the CANDA). Also for Dr. Zannikos, I have included a copy of the synopsis of Studies 051 and 017. Information on both studies was requested by Dr. Zannikos; the copied text from Study 017 states that blood samples were not taken and thus pharmacokinetic parameters could not be assessed. Pharmacokinetic data were presented in the study report for Study 010 and were published by the author. Pharmacokinetic data from our clinical trials on diskette, as requested by Dr. Zannikos at our Pre-NDA Meeting, will be submitted in Microsoft Excel format as soon as possible next week.

In addition, I am sending you two more copies of the diskette containing the datasets of our key clinical studies for the use of the statistical reviewer.

Should you have any questions regarding these copies from our NDA, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, PhD
Associate Director
U.S. Regulatory Affairs

JAN 22 1996
HFD-150

11 January 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Volume 2.1

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE : Diskette of NDA Data for Studies 033, 034, and 039

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995.

Enclosed with this letter is a diskette (in duplicate) containing data for our key clinical trials, Studies 033, 034, and 039 (listed as files 033.DTA, 034.DTA, and 039.DTA, respectively). In addition, this diskette contains two SAS files: INPUT.SAS reads the data files and EFFICACY.SAS provides an example of an efficacy analysis.

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 832-3705.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy: Vance Berger, Ph.D.

SmithKline Beecham
Pharmaceuticals

file copy

DUPLICATE

29 March 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 - 000006 and 000112 - 000225.01

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REC'D
APR 0 3 1996
HFD-150
EVALUATION AND

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
(BC)

RE: Response to Chemist's Request for Updated Stability Data

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a telephone conversation I had on 21 March 1996 with Ms. Debbie Catterson, wherein she relayed a request from Dr. Hsieh that we provide updated stability data for Hycamtin 4 mg vials.

We submit, in duplicate, updated stability for the 4 mg vial validation lots, and statistical analysis of these data. Data are provided through 9 months for all three lots, and through 12 months for one of these lots. In addition, updated stability data are provided for two development batches of 5 mg vials, through 36 months for one lot (previously through 24 months) and through 24 months for the second lot (previously through 18 months). Upon dat... view some errors were noted in the stability tables; corrected values are indicated in boldface type.

The information described above is provided as a complete update to Item 3.B. section 8, and maintains the page numbers of the original pages in Volume 1.4. Within the section all pages that have been revised or updated are indicated with a footnote.

NDA 20-671
Hycamtin™ (t· ›otecan hydrochloride) for Injection

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy: Ms. D. Catterson

SmithKline Beecham
Pharmaceuticals

22 February 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Volume 2.1: pp 000114 - 000118

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Overview of manufacturing of Hycamtin™ (Topotecan Hydrochloride) for Injection

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a telephone conversation I had with Ms. Debbie Catterson on 13 February 1996 in which she requested an overview of the manufacturing process for *Hycamtin*.

In duplicate for your files, we are presenting a copy of the fax that we sent to Ms. Catterson on 14 February 1996.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D
Associate Director
U.S. Regulatory Affairs

SB
SmithKline Beecham
Pharmaceuticals

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Volume 2.1: pp 000063-000113

8 February 1996

DUPLICATE

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
(BC)

CENTER FOR DRUG EVAL. AND RES.
REC'D
FEB 15 1996

RE: Response to Chemistry Reviewer fax of 7 February 1996

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Please also refer to a facsimile sent to SmithKline Beecham Pharmaceuticals (SB) on behalf of Dr. Hsieh on 7 February 1996.

In that fax, Dr. Hsieh stated 3 requests for additional information; our response to each request is noted following this letter. Dr. Hsieh's questions are presented in bold font with SB's response following. Most, but not all, of the information requested by Dr. Hsieh was presented in NDA 20-671, and we note in our response the location where this information can be found in the NDA.

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

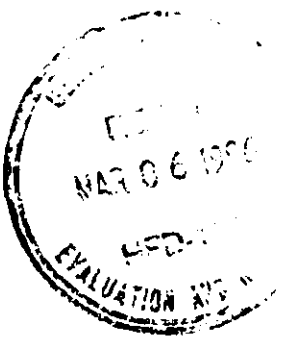
Desk Copy: Yung Ao Hsieh, Ph.D.

SmithKline Beecham
Pharmaceuticals

5 March 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 - 000129

DUPLICATE



Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
(BI)

RE: Response to Microbiologist's Request for Additional Information

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a draft letter from the FDA Microbiologist, received as a fax on 23 February 1996. In that letter, the Microbiologist requested that SmithKline Beecham (SB) file an amendment to our NDA application providing a response to each question.

We submit, in duplicate, a response to each question from the Microbiologist; the FDA question is presented in bold text with the SB response following.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D
Associate Director
U.S. Regulatory Affairs

Desk Copy: Ms. D. Catterson

D. Catterson

SB
SmithKline Beecham
Pharmaceuticals

7 February 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection

Debra Catterson, R.Ph., Consumer Safety Officer
Division of Oncology Drug Products (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20857
(302) 827-1544

RE: Additional Copies of NDA Volumes for Microbiology Reviewer

Dear Debbie:

Enclosed with this note is a copy of Volumes 1.4 and 1.5 of the Hycamtin™ (topotecan hydrochloride) New Drug Application that you requested today via the Internet.

Should you have any questions regarding these volumes, or if you need additional copies of any NDA volume, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson,Ph.D
Associate Director
U.S. Regulatory Affairs

FEB 3 1996

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 1, 1996

FROM: Robert L. Justice, M.D.
Acting Director
Division of Oncology Drug Products, HFD-150

TO: Director, Division of Scientific
Investigations, HFD-340

SUBJECT: Request for Foreign Inspections for NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection

We have identified studies 039 and 034 as being pivotal to the approval of this application. We request that the selected foreign sites be audited.

The reviewing medical officer for this application is Steven Hirschfeld, M.D. (301-594-2565).

The responsible project manager/CSO is Debra Catterson (301-827-1544).

The user fee goal date is December 22, 1996

The division's action goal date is May 15, 1996 (This application has a classification of "1P" and it has been assigned a 6 month priority review timeline.)

cc: ORIG. NDA 20-671
HFD-150/Div. File
HFD-150/SHirschfeld
HFD-150/DCatterson

SmithKline Beecham
Pharmaceuticals

EC

June 3, 1993

Miss Ellen Cutler, CSO
Division of Oncology & Pulmonary Drug Products, (HFD-150)
Document Control Room 200N
Office of Drug Evaluation I
Food and Drug Administration
Woodmont Building
1401 Rockville Pike
Rockville, Maryland 20852-1448

Subject: Topotecan End-of-Phase II Meeting (5/11/93) Minutes

Dear Ellen,

Thank you very much for the opportunity to review your minutes, we would greatly appreciate the Division's consideration of our comments outlined below:

- Under ***"Participants"***, please note that in addition to the individuals listed in our May 4th letter, Dr. Michaele Christian from NCI was also present.

- Under Page 1/last sentence , last paragraph:
  "Dr. Burke stated that the statistical criteria will be consistent with those for a randomized Phase 2 study (i.e., not an equivalency study) and that the data must support a reproducible response rate."

  We understood at the meeting that since Taxol, as a second-line ovarian chemotherapy, offers very low complete response rates, i.e., 5 to 6%, and no cures, the proposed NDA study comparing topotecan and Taxol is NOT designed to demonstrate equivalence. Thus, the sample size of this study (100 per arm or less) is NOT based on any prospective statistical considerations. The comparison

of topotecan and Taxol is only to gauge the relative efficacy and safety between the two agents ***"in the population studied"***.

Given the above, we have difficulty understanding ***"the statistical criteria will be consistent for a randomized Phase 2 study."*** Moreover, we could not recall a discussion on ***"reproducible response rates"***. While it is reasonable to seek reproducible response rates, please recognize that we are only conducting two NDA studies for second-line ovarian and the two studies are performed in different patient populations, i.e., one in platinum failures and the other in Taxol/cisplatin failures.

- Under first paragraph of Page 2: ***"A complete statistical plan should be included in the protocols."***

  As noted above, since the studies are not based on any prospective statistical considerations, please advise what will be required in the ***"statistical plan"***.

- Under third paragraph of Page 2: ***"For subsequent dosing based on neutrophil counts, the company was told to use the same limits (i.e., 1000 or 1500) for each arm."***

  We understood from both Drs. Burke and Bunn at the meeting that the company is allowed discretion in this regard. Given the observed incidences of infection and febrile neutropenia with Taxol, the current labeling stated 1500 neutrophil counts before retreatment, while the seemingly fewer cases of febrile neutropenia with topotecan led many oncologists to recommend the 1000 neutrophil counts for topotecan. We firmly believe setting the same limits for two entirely different agents with different safety profiles is not medically justified.

- Under ***"Biopharm Issues"*** on Page 2, regarding ***Emax modeling and concentration kinetics:***

  We recall that Dr. Davies of SB presented data from EORTC daily times five study and the San Antonio single dose study which demonstrated that there was only a two-fold variability in the AUC values across the dose range. Further, Dr. Davies presented graphs from the EORTC study showing the relationship between the AUC of topotecan and the % decrease on WBC, which could be characterized by an Emax model.

Dr. Burke accepted these data and stated that concentration controlled trials would not be necessary.

We will be submitting to the IND the two reports indicated by Dr. Davies, so that the Biopharm reviewers can review the data in order to confirm that indeed the variability of topotecan is small and the administered dose indeed approximate in vivo concentration in patients; thus, concentration controlled trials are not necessary and not useful in this situation.

- ***Post-meeting:***

Our consultant, Dr. Peter O'Dwyer of Fox Chase, suggested to Dr. Mehta of the Biopharm Division that the total topotecan concentration, i.e., topotecan parent molecule plus the open ring hydroxyacid, be measured in some future studies. His rationale was based on the proven relationship between total topotecan AUC and decrease in neutrophil counts and the problem of obtaining reliable topotecan parent molecule assay from multicenter studies. This appeared to be accepted by Dr. Mehta.

We would very much appreciate clarifications on the above, especially regarding the "neutrophil count" issue and the "statistical" requirements, prior to our initiation of these two NDA studies.

Your consideration in this matter will be greatly appreciated, should you have any questions please do not hesitate to contact me at (215 832-3686).

Sincerely,

Stella S. Jones

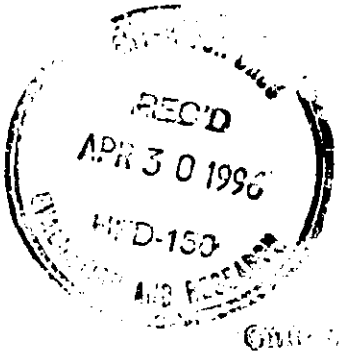
Stella S. Jones Ph.D.
Group Director,
U S. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

DUPLICATE

29 April 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages 000001 - 000305



Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Response to E-Mail of April 25, 1996 - Statistical Question on Stability

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND) for topotecan (SK&F S-104864-A) injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to an e-mail dated April 25, 1996, forwarded by Ms. Debbie Catterson, which contains a question about the statistical analysis of the stability data.

We submit, in duplicate, a response to the aforementioned e-mail question. The question is shown below, boldface, followed by our reply.

For the topotecan content assay they should provide two-sided, not one-sided, confidence bands. From the figures, for example Figure 1 on page 169, it appears that they did, in fact, do it correctly. But on page 165 it states that they will construct one-sided confidence bands. Can this be resolved?

Response: The figures referred to were generated by programs obtained from the FDA, as referenced in Volume 1.4, page 000165 (original NDA and 29 March 1996 amendment). The figures show both the upper and lower one-sided 95% confidence bands, but there is only a one-sided confidence limit.

As the assay strength can only be expected to decrease over time, testing against the one sided lower limit is the appropriate action. This is in line with the FDA's February 1987 "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics", page 31:

"An acceptable approach to drug characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided lower confidence limit (sometimes called the 95% lower confidence bound) for the mean degradation curve intersects the acceptable lower specification limit."

A two sided test would be appropriate if it were possible for the drug characteristic to increase. An example given in the FDA Guideline is concentration of a solution, where evaporation of the solvent could increase the concentration of the drug, while degradation could decrease it. As the % assay cannot increase for topotecan, the one-sided test against the lower specification is appropriate.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Debra Stevenson /for

Richard Swanson, Ph.D.
Associate Director
U.S. Regulatory Affairs

Desk Copy: Ms. D. Catterson

SmithKline Beecham
Pharmaceuticals

DUPLICATE

11 March 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Pages: 009631 - 009635

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-671
NC

RE : Response to Questions from Dr. Berger 26 February 1996

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a conversation Dr. David Fitts held with Dr. Vance Berger at the end of our NDA Overview Presentation of 26 February 1996. Dr. Berger requested additional information on the potential influence of third line therapy on survival estimates provided in the NDA.

Attached with this letter, in duplicate, is a diskette containing the information requested by Dr. Berger. The response by the SmithKline Beecham Pharmaceutical (SB) statistician, Dr. David Fitts, is included as **Attachment 1**.

Should you have any questions regarding this submission, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D.
Associate Director
U.S. Regulatory Affairs

cc: Dr. Vance Berger, Ph.D.

SmithKline Beecham
Pharmaceuticals

DUPLICATE

1 February 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Volume 2.1: pp 000002 - 000007

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE : Response to Questions from Dr. Berger Dated 30 January 1996

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND for topotecan (SK&F S-104864-A)-injection and to our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995. Also, please refer to a fax from Ms. Debbie Catterson dated 30 January 1996 in which she forwarded to SB 5 questions from Dr. Vance Berger. SB responded to these questions by facsimile on February 19 A copy of this response is attached to this letter (**Attachment 1**).

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 917-5769.

Sincerely,

Richard Swenson, Ph.D
Associate Director
U.S. Regulatory Affairs

Desk Copy: Vance Berger, Ph.D

SmithKline Beecham
Pharmaceuticals

DUPLICATE

11 January 1996

NDA 20-671
Hycamtin™ (topotecan hydrochloride) for Injection
Volume 2.1

Robert DeLap, M.D., Ph.D., Acting Director
Division of Oncology Drug Products (HFD-150)
Document Control Room
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP
NC

RE : Diskette of NDA Data for Studies 033, 034, and 039

Dear Dr. DeLap:

Reference is made to our Investigational New Drug Application (IND [redacted], for topotecan (SK&F S-104864 A)-injection and our pending New Drug Application for Hycamtin™ (topotecan hydrochloride) for Injection, NDA 20-671 submitted 22 December 1995

Enclosed with this letter is a diskette (in duplicate) containing data for our key clinical trials, Studies 033, 034, and 039 (listed as files 033.DTA, 034.DTA, and 039.DTA, respectively). In addition, this diskette contains two SAS files: INPUT.SAS reads the data files and EFFICACY.SAS provides an example of an efficacy analysis.

Should you have any questions regarding this New Drug Application, please do not hesitate to contact me at (610) 832-3705.

Sincerely,

Richard Swenson, M.D.
Associate Director for Worldwide Drug Affairs
U.S. Regulatory Affairs

JAN 16 1996

Desk Copy: Vance Berger, Ph.D