Clinical Pharmacology and Biopharmaceutics
Executive Summary

NDA	20,671/SE8 010
Drug Name	Hycamtin
Generic Name	topotecan
Date of Submission	August 29, 2002
Dosage form	4 mg/vial or 5 mg/vial lyophilized powder for injection
Route of administration	IV Injection
Sponsor	GlaxoSmithKline 1250 South Collegeville Rd Collegeville, PA 19426-0989
Reviewer	Anne Zajicek, M.D., Pharm.D.
Team Leader	N.A.M. Atiqur Rahman, Ph.D.
Pharmacometrics Reviewer	Carl-Michael Staschen, M.D.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Submission Type	NDA-Supplement

I. Executive Summary

The sponsor has submitted three pediatric studies in response to a written request by the FDA. There are two Phase 1 studies, one in children with leukemias and one in children with a variety refractory solid tumors, and one Phase 2 study in patients with various tumor types.

The Phase 1 study in children with leukemia (9275L) enrolled 14 patients, and the study for children with solid tumors (9275) enrolled 36 patients. Pharmacokinetic studies were performed, and the blood was assayed for both lactone (active) and total topotecan concentrations. Results showed similar pharmacokinetic parameters across age groups from 2-16 years. These parameters include (mean ± standard deviation) clearance of 8.02 ± 3.32 L/hr/m2, steady-state volume of distribution of 32.64 ± 12.37 L/m2, and half-life of 4.19 ± 1.62 hr. These parameters were similar to reported adult values. No pharmacokinetic-pharmacodynamic relationship for drug exposure and nadir of the white blood cell (WBC) count, as there was maximal suppression of the WBC at the lowest dose.

The pharmacokinetic parameters presented by the applicant were derived from a Bayesian analysis. The applicant has not provided adequate supporting data for the prior pharmacokinetic estimates used in the analysis; therefore, the analysis could not be verified.

No labeling changes for pediatric indications or dosing will be made at this time due to inadequate efficacy data generated in the preliminary Phase 2 study report.

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Clinical Pharmacology Reviewer	Team Leader
DPE 1	DPE 1

CC: NDA 20,671/SE8 010
HFD-150/ Division File
HFD-150/HirschfeldS
HFD-860/MehtaM, SahajwallaC, RahmanNAM, GobburuJ, StaschenCM,ZajicekA
CDR/Biopharm