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. Atiquur 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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/s/
Anne Zajicek
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Atiqur Rahman
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