Clinical Review of Labeling Supplement with Clinical Data
Application Number: N20671
Supplement Number: 010
Product: Hycamtin (topotecan)
Sponsor: GlaxoSmithKline
Primary Reviewer: Steven Hirschfeld, MD PhD
Secondary Reviewer: John R. Johnson, MD
Date Review Completed: February 21, 2003

Executive Summary: The Food and Drug Administration issued a Pediatric Written Request to GlaxoSmithKline on May 16, 2000 for pediatric studies using Hycamtin (topotecan). The requested studies were for a Phase I dose finding study with pharmacokinetics in at least 18 patients and Phase II or pilot studies in pediatric patients with relapsed or refractory malignancies with at least 14 patients in various tumor types. The sponsor requested an extension of the time to submit the final study reports and this was granted in the form of a revised Written Request that was issued on January 10, 2002 extending the deadline to August 31, 2002. On August 30, 2002 the final study reports in the form of a labeling supplement with clinical data were submitted.

The study reports consisted of summaries of studies previously performed by the Pediatric Oncology Group that were initiated in 1992 and 1993 but were never submitted to the FDA. GlaxoSmithKline obtained the datasets and prepared a study report. The results were that the pediatric Phase II dose was determined that was different from the approved adult dose for topotecan. The Phase II dose for pediatric patients with solid tumors on a schedule of a daily infusion for 5 consecutive days every 21 days was 1.4 mg/m ^{2} /d without Granulocyte-Colony Stimulating Factor (G-CSF) and 2.0 mg/m ^{2} /d with G-CSF. Doses up to 5.2 mg/m ^{2} /d were tolerated in pediatric patients with leukemia. The approved adult dose is 1.5 mg/m ^{2} /d for relapsed ovarian cancer or limited disease small cell lung cancer.

The Phase II study in pediatric solid tumors enrolled 108 patients less than 16 years old. The endpoint was response rate. Four tumor types, Ewing's sarcoma/Peripheral Neuroectodermal Tumor, Neuroblastoma, Osteoblastoma, and Rhabdomyosarcoma, had at least 14 patients enrolled. Of the 108 patients enrolled, 93 (86%) died with 11 patients (10%) dying within 30 days of the last dose of topotecan. Eight of the patients that died within 30 days died of progressive disease and 3 died with infection, a known complication of topotecan therapy. Forty-seven patients (44%) were hospitalized for adverse events, primarily febrile neutropenia, fever, or sepsis. The overall response rate was about 8% but in neuroblastoma patients the response rate was 18%. No patient less than 2 years old had a response.

Pediatric Exclusivity was granted on November 20, 2002 because the terms of the Written Request were fairly met. The submitted data are inadequate to independently support an indication and are in diseases that are different than the approved adult indications, therefore, extrapolation cannot be used to support a pediatric indication. If just the dosing information were to be included in the product label, pediatric use may be implied; however, safety and efficacy have not been demonstrated in pediatric cancer patients. The response data are preliminary and further studies would be required and the results would need to be submitted to the FDA and reviewed before pediatric use could be established. Response rates reported for alternative regimens using combinations of available drugs in patients with relapsed neuroblastoma are between 35 and 50%.

For these reasons the pediatric information regarding topotecan should not be incorporated into the product label.

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Steven Hirschfeld
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