CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

SUMMARY REVIEW

Division Director Summary Review of a New Drug Application

NDA: 20-981
Drug: HYCAMTIN® (topotecan) Capsules
Applicant: GlaxoSmithKline
Date: October 11, 2007

HYCAMTIN® is a topoisomerase I inhibitor. HYCAMTIN® for Injection is approved for the treatment of metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, small cell lung cancer sensitive disease after failure of first-line chemotherapy, and stage IVB, recurrent or persistant carcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiotherapy.

This application seeks approval of a new formulation, HYCAMTIN® Capsules, for the indication of "...treatment of relapsed small cell lung cancer in patients with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy." The safety and efficacy data supporting approval are summarized in the following excerpts from the agreed upon package insert:

> HYCAMTIN capsules were studied in patients with relapsed SCLC in a randomized, comparative, open label trial. The patients were prior responders (complete or partial) to first-line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and had relapsed at least 45 days from the end of first-line chemotherapy. Seventy-one patients were randomized to HYCAMTIN capsules (2.3 mg/m^2/day administered for 5 consecutive days repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to BSC alone. The primary objective was to compare the overall survival between the 2 treatment arms. Patients in the HYCAMTIN capsules plus BSC group received a median of 4 courses (range 1 to 10) and maintained a median dose intensity of HYCAMTIN capsules, 3.77 mg/m^2/week. The median patient age in the HYCAMTIN capsules plus BSC arm and the BSC alone treatment arm was 60 years and 58 years while the percentage of patients $\geq$65 years of age was 34% and 29%, respectively. All but 1 patient were Caucasian. The HYCAMTIN capsules plus BSC treatment arm included 68% of patients with extensive disease and 28% with liver metastasis. In the BSC alone arm, 61% of patients had extensive disease and 20% had liver metastases. Both treatment arms recruited 73% males. In the HYCAMTIN capsules plus BSC arm, 18% of patients had prior carboplatin and 62% had prior cisplatin. In the BSC alone arm, 26% of patients had prior carboplatin and 51% had prior cisplatin.
>
> The HYCAMTIN capsules plus BSC arm showed a statistically significant improvement in overall survival compared with the BSC alone arm (Log-rank p = 0.0104). Survival results are shown in Table 2 and Figure 1.

Table 2. Overall Survival in Small Cell Lung Cancer Patients With HYCAMTIN Capsules Plus BSC Compared With BSC Alone

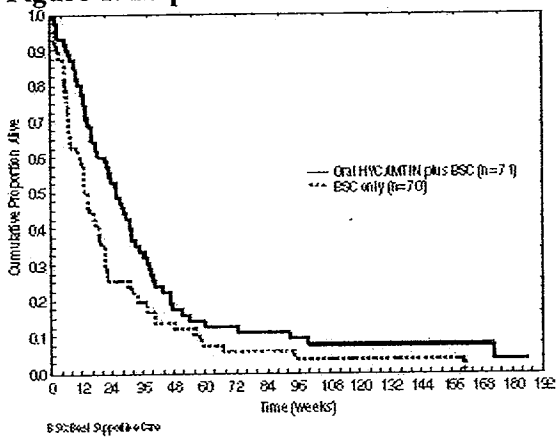
	Treatment Group	
	HYCAMTIN Capsules + BSC (N = 71)	**BSC (N = 70)**
Median (weeks) (95% CI)	25.9 (18.3, 31.6)	13.9 (11.1, 18.6)
Hazard ratio (95% CI)	0.64 (0.45, 0.90)	
Log-rank p-value	0.0104	

BSC = Best Supportive Care.

N = total number of patients randomized.

CI = Confidence Interval.

Figure 1. Kaplan-Meier Estimates for Survival



The safety of HYCAMTIN capsules was evaluated in 682 patients with thoracic cancer (3 recurrent small cell lung cancer [SCLC] studies and 1 recurrent non-small cell lung cancer [NSCLC] study) who received at least one dose of HYCAMTIN capsules.

Table 1 describes the hematologic and non-hematologic adverse reactions in recurrent SCLC patients treated with HYCAMTIN capsules plus best supportive care (BSC) and in the overall thoracic cancer patient population.

Table 1. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated With HYCAMTIN Capsules Plus BSC and in 4 Thoracic Cancer Studies

Adverse Reaction	HYCAMTIN Capsules + BSC (N = 70)			HYCAMTIN Capsules Thoracic Cancer Population (N = 682)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	94	15	10	98	18	7
Leukopenia	90	25	16	86	29	15
Neutropenia	91	28	33	83	24	32
Thrombocytopenia	81	30	7	81	29	6
Non-hematologic						
Nausea	27	1	0	33	3	0
Diarrhea	14	4	1	22	4	0.4
Vomiting	19	1	0	21	3	0.4
Alopecia	10	0	0	20	0.1	0
Fatigue	11	0	0	19	4	0.1
Anorexia	7	0	0	14	2	0
Asthenia	3	0	0	7	2	0
Pyrexia	7	1	0	5	1	1

BSC = Best Supportive Care.

N = total number of patients treated.

Adverse reactions were graded using NCI Common Toxicity Criteria.

In the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies, 39 deaths occurred within 30 days after the last dose of study medication for a reason other than progressive disease; 13 of these deaths were attributed to hematologic toxicity, 5 were attributed to non-hematologic toxicity, and 21 were attributed to other causes. One patient death (68 years of age) was attributed to treatment-related diarrhea and one death (68 years of age) attributed diarrhea as a contributory event; both patients received HYCAMTIN capsules.

In addition to the above adverse reactions, the following adverse reactions have been reported in clinical trials with HYCAMTIN for Injection: febrile neutropenia, abdominal pain, stomatitis, constipation, sepsis, hypersensitivity (including rash), hyperbilirubinemia, malaise.

Although there is no postmarketing experience with HYCAMTIN capsules, the following adverse reactions have been identified during post-approval use of HYCAMTIN for Injection: severe bleeding (in association with thrombocytopenia), allergic manifestations, anaphylactoid reactions, abdominal pain potentially associated with neutropenic colitis, angioedema, severe dermatitis, and severe pruritus.

The package insert includes contraindications for a history of severe hypersensitivity reactions, pregnancy, breastfeeding, and severe bone marrow depression. The warnings and precautions include bone marrow suppression, neutropenia leading to neutropenic colitis, and severe diarrhea.

Clinical Review

The Clinical Review by Robert White, M.D., made the following recommendation on regulatory action:

> One non-blinded, randomized, controlled trial, demonstrating the efficacy and safety of Hycamtin capsules for the treatment of patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are > 45 days post cessation of first-line chemotherapy has been submitted and reviewed. The pivotal trial was multicenter with only non-United States sites. The data submitted demonstrated that Hycamtin capsules has a survival benefit in small cell cancer patients (who have had a complete or partial response to first-line chemotherapy and who are > 45 days post cessation of first-line chemotherapy) in comparison to a best supportive care control arm.
>
> Hycamtin capsules showed a consistent improvement in survival in comparison to best supportive care across the stratification factors (i.e., cessation from prior chemotherapy (days) (< 60 or > 60), liver metastases (absence or presence), performance status (ECOG) (0/1 or 2) and gender (male or female). Also, Hycamtin capsules showed improvement in survival with regard to age, stage of SCLC, and cessation from prior chemotherapy (days) (< 90 or > 90).
>
> Based on the data submitted, Hycamtin capsules has satisfactorily demonstrated a consistent survival advantage compared to best supportive care in patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are > 45 days post cessation of first-line chemotherapy in a randomized, non-blinded study.
>
> In the Hycamtin capsules group, the frequency of grade 3 or 4 hematological toxicities followed the known profile of Hycamtin capsules: grade 3 or 4 neutropenia occurred in 61.2% of patients, grade 3 or 4 leukopenia in 40.6% of patients, grade 3 or 4 thrombocytopenia in 37.7% of patients and grade 3 or 4 anemia in 24.6% of patients. Similarly, the incidence of fever, febrile neutropenia, infection and sepsis were as expected following treatment with topotecan: fever or infection proximate to grade 4 neutropenia occurred in 4 (5.8%) patients. Sepsis was reported for 3 (4.3%) patients. The numbers of patients who experienced adverse events during the study was similar in each treatment group: 46 patients (68.7%) in the best supportive care group and 50 patients (71.4%) in the Hycamtin capsules group. The adverse events observed in the Hycamtin capsules group in study #478 study were consistent with other studies of Hycamtin capsules. A total of 18 patients (26.9%) in the best supportive care group and 18

patients (25.7%) in the Hycamtin capsules group had serious adverse events. The reported incidence of disease progression was higher in the best supportive care group (11 patients, 16.4%) than in the Hycamtin capsules group (5 patients, 7.1%). The incidence of serious thrombocytopenia (5 patients, 7.1%), leukopenia (3 patients, 4.3%) and neutropenia (3 patients, 4.3%) was higher in the Hycamtin capsules group, none of these events being reported in the best supportive group. In total, 1 patient (1.5%) in the best supportive care group and 11 patients (15.7%) in the Hycamtin capsules group were withdrawn from the study due to adverse events in the modified intent-to-treat population. In the best supportive group, one patient withdrew, due to a pulmonary embolism. In the Hycamtin capsules group, the events most commonly leading to withdrawal were leukopenia, thrombocytopenia, pulmonary embolism and diarrhea. In the modified intent-to-treat population, 67 patients (95.7%) in the ASC alone group and 62 patients (88.6%) in the Hycamtin capsules were known to have died at any time. In the modified intent-to-treat population, 11 patients (15.7%) in the Hycamtin capsules died within 30 days of their last receipt of study medication; 51 patients (72.9%) died more than 30 days after last receipt of study medication. Three patients died within 30 days of their last receipt of study medication due to hematological toxicity and one due to nonhematological toxicity. Monitoring of non-hematological laboratory data and measurement of vital signs showed no results of clinical significance for the Hycamtin capsules group.

However, the demonstration of the survival benefit is based on only one randomized, control trial. Study #478 was not conducted under an IND; the FDA did not have knowledge about the study until notified about the pre-NDA meeting in August 2006. The study was conducted in Europe (and one site in Canada) and was under European authority. Study #478 did have challenges with regard to certain aspects of conduct of the trial (i.e., discrepancies in time to progression from the end of prior chemotherapy; liver metastases [presence or absence]; performance status; registration and randomization; and eligibility). Despite removal of 32 patients with discrepancies, the survival benefit of Hycamtin capsules in comparison to best supportive care remained. Also, on the Hycamtin capsules arm, the response rates for patients who were defined as having "sensitive" and "resistant" SCLC were the reverse of what would be expected from the literature and from the experience with intravenous topotecan; the "resistant" patients had a higher response rate than the "sensitive" patients.

Based on this review of NDA 20-981, Hycamtin capsules is clinically approvable for the treatment of patients with small cell lung cancer who have had a complete or partial response to first-line chemotherapy and who are > 45 days post cessation of first-line chemotherapy.

Medical Team Leader Memo

The Medical Team Leader Memo by Ramzi Dagher, M.D. made the following recommendation:

I recommend approval of this NDA for the following indication based on superiority in overall survival demonstrated in a randomized trial comparing oral topotecan plus best supportive care to best supportive care alone:

"patients with relapsed small cell lung cancer who had a complete or partial response and who are at least 45 days from the end of first-line chemotherapy"

The overall survival benefit demonstrated outweighs the risks exemplified by bone marrow suppression and diarrhea in this patient population.

Clinical Inspection Summary

The Clinical Inspection Summary by Dan-My T. Chu, Ph.D., summarized the findings at the five foreign sites that were inspected. The findings were discussed with the Medical Reviewer and the Medical Team Leader. All were in agreement that the findings would not significantly impact the finding of improved overall survival or the risk:benefit ratio.

Statistical Review and Evaluation

The Statistical Review and Evaluation by Chia-Wen Ko, Ph.D., made the following conclusions and recommendations:

Results from the NDA registration trial Study 478 indicate a survival benefit from addition of oral topotecan to best supportive care in patients with relapsed small cell lung cancer (SCLC). Median survival was 13.9 weeks (95% confidence interval [CI]: 11.1, 18.6 weeks) for patients under the best supportive care only, and was 25.9 weeks (95% CI: 18.3, 31.6 weeks) for patients treated with oral topotecan plus best supportive care. The unadjusted survival hazard ratio for best supportive care plus oral topotecan (BSC+OT) relative to best supportive care alone (BSC alone) was 0.64 (95% CI: 0.45, 0.90), and the un-stratified log-rank test for comparing survival curves between the two treatment groups was significant at a p-value of 0.0104. Issues related to the conduct of Study 478 such as study was closed earlier than planned, and some study sites may have failed to follow the stratification procedure, do not appear to alter the conclusion that adding oral topotecan to best supportive care appears to provide survival benefit to patients with relapsed SCLC.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Sophia Abraham, Ph.D., made the following recommendation:

The Supplemental NDA 20-981/N-000 submitted for the use of Oral Hycamtin Capsules for the treatment of patients with relapsed small cell lung cancer is acceptable from the clinical pharmacology perspective. The Applicant should

incorporate the Clinical Pharmacology labeling recommendations as outlined in Section 3 of this review.

Please forward the above Recommendation, the general Comment below and the clinical pharmacology recommendation outlined on pp. 38 of this review to the Applicant.

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation by W. David McGuinn, Jr., M.S., Ph.D., made the following recommendation on approvability: "The available Pharmacology and Toxicology information is adequate to support the approval of HYCAMTIN™ for use in the proposed clinical indication."

Acting Pharmacology/Toxicology Team Leader Memorandum

The Acting Pharmacology/Toxicology Team Leader Memorandum stated that "I concur with Dr. McGuinn's conclusion that pharmacology and toxicology data support the approval of NDA 20-981, Oral HYCAMTIN. There are no outstanding nonclinical issues related to the approval of Oral HYCAMTIN."

Chemistry Review

The Chemistry Review by Brian Rogers made the following recommendation and conclusion on approvability:

> All CMC review issues have been resolved adequately. The Office of Compliance provided acceptable cGMP recommendation on October 10, 2007. The NDA is recommended for approval from a CMC perspective. Two comments listed at the end of the review need to be included in the action letter.

DSRCS Review of Patient Package Insert

The DSRCS Review of Patient Package Insert by Sharon Mills, BSN, RN, CCRP, had a number of recommendations that were discussed in labeling meetings and either incorporated into the PPI or resolved during the discussions.

DMETS Consultation

DMETS did not recommend the use of the proprietary name Oral Hycamtin but found the name to be acceptable from a promotional perspective. The consultation also had recommendations for revisions to the container and carton labels and the package insert. The applicant agreed to make all of the revisions.

DDMAC Labeling Review

The DDMAC consultation on the proposed labeling was completed by Kathy Oh, Regulatory Review Officer. The recommendations were discussed during the labeling meetings and were either incorporated into the revised label or were resolved during the discussions.

Conclusion

I concur with the reviewers' recommendations that the application should be approved. The improvement in overall survival in this patient population outweighs the observed toxicities. Agreement has been reached on the package insert and the carton and container labels. There are no required post-marketing commitments. All outstanding issues have been resolved.

Robert L. Justice, M.D.
Director
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/s/

Robert Justice
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MEDICAL OFFICER