Medical Officer's Review of
Pediatric Exclusivity Request

NDA:	20,571
Drug:	Camptosar (Irinotecan, CPT-11)
Serial no.:	SE8- 021-PM
Sponsor:	Pfizer Pharmaceuticals
Medical Reviewer:	Amna Ibrahim MD
Team Leader:	John Johnson MD
Letter date:	December 22, 2003

Recommendation:

The Applicant seeks to obtain pediatric exclusivity for irinotecan by submitting study reports in response to a written request. The Applicant has met all the requirements of the written request, except that children younger than one year were not enrolled. This was discussed at the pediatric exclusivity board and was found to be acceptable.

In the Study P9761, 16% (n=3) responses were observed in the Rhabdomyosarcoma subgroup (n=19). The numbers of patients in this stratum are too small to allow definitive conclusions. In the second phase 2 study, D9802, 9 of 21 patients (43%) had a PR as the best response to irinotecan. However, the irinotecan window was closed to accrual due to 14% early deaths. Although irinotecan demonstrates some promise, no overall efficacy was demonstrated.

No efficacy claim is made. Changes to the label have been proposed by the applicant. These include description of the two phase II studies and safety of study COG 9761. There should be no change in the label as no efficacy has been observed. No unexpected adverse event findings have been noted. Biopharmaceutics review is pending at this time.

Executive Summary:

Four phase 1 and two phase 2 study reports have been submitted to support a response to the written request for pediatric exclusivity. Please see table 1. Three schedules were tested in the phase 1 trials. Two of the phase I studies evaluated daily x 5, q 3 weeks schedule (POG 9571 and P9871). Another studied [daily x 5] x 2, q 3 weeks (St. Judes Study). The last one mimicked the adult schedule of weekly x 4, q 6 weeks (H6957). Daily x 5, q 3 weeks schedule and [daily x 5] x 2, q 3 weeks were studied in two phase II trials.

Three phase I studies and one phase II study were completed. Interim reports have been submitted for two phase I studies (H6957, a phase 1 study and P9761, a phase 2 study). One study (P9871, a phase 1 study) was closed early due to insufficient and slow accrual. DSMB closed the single agent irinotecan window for D9802, a phase 2 study because of the numbers of PD and early death.

Studies H6957 (although patients were enrolled after cut-off date), POG 9571 and St. Judes Studies are adequate for analysis of phase 1 studies. The following observations are made after analyzing the phase I studies:

-Twenty mg/m^2 [daily x 5] x 2, q 3 weeks evaluated in the St. Judes study appears to be too toxic, although it was thought to be appropriate as a phase 2 dose by the investigator. This high toxicity was again observed in the phase II trial (D9802) that employed this regimen.

-For heavily treated patients in POG9571, 39 mg/m^2, for less heavily treated patients 50 mg/m^2 and for children less than 6 years of age 30 mg/m^2 administered daily x 5 q 3 weeks is an appropriate phase 2 regimen. The 50 mg/m^2 daily x 5, q 3 regimen was used in phase II study, P9761. The toxicity was acceptable, but the response rate was too low at 5%.

-The investigators of study H6957 concluded that 125 mg/m^2 of irinotecan is an appropriate phase 2 dose, although by FDA assessment, this dose is too high. It should be noted that 125 mg/m^2 was initially thought to be the dose for adult patients. In a large NCI trial, an increased number of early deaths were observed at this dose in adult patients.

-P9871 closed early prior to MTD determination.

Two phase II studies were submitted. Conclusions for the phase II studies are as follows:

-P9761 accrued 170 patients and was ongoing at the time of cut-off date. A 5% RR was observed with acceptable toxicity.

-In the other phase II study D9802, single agent irinotecan (SAI) was administered prior to a multi-agent regimen. The SAI window was closed early due to high rate of early disease progressions and deaths.

Two studies were designed to study the interaction of irinotecan with anticonvulsants (AC). One of them was H6957. The 3rd stratum of this study which was designed to evaluate interaction with anticonvulsants was closed with out accruing any patients. In the second study P9871, a total of 9 patients were accrued to all 3 strata (6 in enzyme-inducing ACs, 1 in valproic acid and 2 in other AC strata). This study was closed early due to slow accrual. The sponsor compared the pharmacokinetics of the EIAC patients to a control group who were not on any anticonvulsants. The control group was from another concurrent study (P9761). The demographics, regimens and pharmacokinetic sampling and analysis methods were comparable between the two studies. In the assessment of the Biopharmaceutics reviewer, Dr. Roshni Ramchandani, the studies appear to fulfill the PK requirements of the Written Request.

Table 1: Summary of results of submitted studies

FDA table

	Schedule	**Number enrolled**	**Study completed**	**Result**
Phase 1 studies				
H6957	weekly x 4, q 6 weeks	16	Interim report. 8 pts. enrolled after cut-off date	MTD of 125 mg/m^2 probably too high by FDAs definition for strata 2 & 3.
P9871	daily x 5, q 3 weeks	9	Closed early	Study closed early due to slow accrual
POG9571	daily x 5, q 3 weeks	33	Yes	The MTD for stratum 1 =39 mg/m^2, stratum 2 =50 mg/m^2 (<6 years age) stratum 3 = 30 mg/^{2}
St. Jude Study	[daily x 5] x 2, q 3 weeks	22	Yes	55% experienced DLT at the starting dose
Phase 2 Studies				
P9761 Refractory pts. <2 prior Rx	50 mg/m2 qd x 5, q 3 weeks	170	3 strata still open	5% RR with acceptable toxicity
D9802 Newly diagnosed rhabdomyosarcoma	20 mg/m^2 qd x 5, wks 0 & 1, 3&4	21	Yes	High rate of early PDs and deaths. SAI window closed by DSMB

SAI: single agent irinotecan

The applicant states the following in the summary of the clinical document:
"*The results of these phase II studies, confirm that single- agent irinotecan is generally tolerable and provides an early indication of clinical activity in children with refractory tumors (solid tumors or CNS tumors) or with metastatic untreated rhabdomyosarcoma. Combinations of irinotecan with other anticancer drugs are critical for the development of new treatments for the pediatric population.*"

However, the applicant states in the proposed label *"The effectiveness of CAMPTOSAR in pediatric patients has not been formally established."* This reviewer agrees with this preceding statement. A description of PK findings, of the two phase II studies and a table that represents

the adverse events in 170 previously treated patients in the COG 9761 phase 2 study has been included in the proposed package insert. However, because the efficacy of irinitecan has not been demonstrated, and because there is no new, meaningful safety information, no changes should be made to the approved label.

Interim reports from phase I and phase II trials have been submitted instead of final reports. However sufficient numbers of patients were enrolled in the phase I and phase II studies. Other than children over 1 year were enrolled into the studies, instead of over 1 month in age, all conditions of the written request have been met.

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/s/

Amna Ibrahim

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