Clinical Review for NDA 21-029

Executive Summary

This multidisciplinary medical-statistical review addresses a supplement to NDA 21-029/S-005 for use of Temodar for the treatment of pediatric patients with recurrent malignant brain tumors.

The current supplement presents the results of two Phase 1 and one Phase 2, open-label, multicenter studies of Temodar administered to this patient population. Phase 1 Study I93-125 was a dose escalation study in 27 pediatric patients with advanced non-CNS and CNS cancers. Phase 1 Study 193-125 Extended was actually a Phase 2 Study in 63 pediatric patients with recurrent brain stem glioma and high grade astrocytoma.

Phase 2 study H97-017 was a Cooperative Group-Sponsored Study in 122 pediatric patients with various recurrent CNS tumors. The primary objective for the Phase 2 study was assessment of the response rate of Temodar in patients with recurrent CNS tumors.

Submission of results of these studies meets the FDA Written Request for pediatric studies. On this basis Pediatric Exclusivity has been granted.

In this application it is not completely clear whether the sponsor is making any specific efficacy claims. Labeling changes proposed by Schering-Plough include the addition of pharmacokinetics data, dosage information, and results from the clinical studies in children (efficacy and safety data).

TEMODAR is approved by the FDA for “the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.”

I. Recommendations

A. Recommendation on Approvability

The Supplemental Application can be approved, providing the Applicant agrees with the FDA’s proposed labeling revisions. Otherwise the Supplemental Application is approvable, pending the required labeling revisions.

No indication for use in children will be added to the label. No dosage information, pharmacokinetic data or efficacy data from the clinical studies in children will be added to the label. To do so would imply a pediatric use where efficacy for a pediatric use has not been demonstrated. Safety results from the clinical studies in children will be added

to the Pediatric subsection of the PRECAUTIONS section of the label.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In the absence of clinical efficacy, there are no recommended Phase 4 studies of the use of Temodar in pediatric patients with recurrent brain tumors.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Temozolomide (TEMODAR) Capsules was granted marketing accelerated approval in the United States (NDA 21-029) for treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. Approval was based on the complete response rate and duration in a single-arm, multicenter study.

The primary source for this sNDA review consisted of data submitted to the original NDA 21-029 from Phase 1 Study 193-125 in pediatric patients with advanced cancers, and previously unsubmitted Phase 1 Study 193-125/Extended study of Temozolomide in pediatric patients with recurrent cancers, and previously unsubmitted Phase 2 Study H97-017 in children and adolescents with recurrent CNS tumors.

It is not completely clear whether this submission makes specific efficacy claims. SPRI proposes labeling changes including an addition of pharmacokinetics data, dosage information, and results from the clinical studies in children (efficacy and safety data) in the Clinical Studies Section of the labeling.

B. Efficacy

Temodar Capsules have been studied in 2 open-label Phase 1 Studies (Study 193-125 and Study 193-125/Extended), and Phase 2 Study H97-017 in children and adolescents with recurrent non-CNS and CNS tumors. The primary endpoint for the Phase 2 Study and for the Extended Phase 1 Study was tumor response rate. Assessment of the response was a secondary endpoint for the initial Phase 1 Study.

The analysis of efficacy showed that in the Study 193-125 there were only one confirmed complete response and three partial responses among 27 patients with advanced non-CNS and CNS cancers.

In Study 193-125 Extended in 63 patients with recurrent CNS tumors the response rates were 0% complete response, 0% partial response, and 0% complete response and 12% partial response in BSG and HGA population, respectively.

In Phase 2 Study H97-017 in 122 children with recurrent CNS tumors the overall response rate (CR+PR) was 5%. Only one patient achieved CR, and 5 patients had PR's.

C. Safety

Safety was assessed at a doses of 100-240mg/m2 daily for 5 days every 28 days, in 204 pediatric patients with recurrent primary brain tumors and some non-CNS tumors The toxicity profile in children was similar to that of the adult patients. The most common adverse events were dizziness, neuropathy, paresthesia, nausea, vomiting and constipation.

D. Dosing

Study 193-125 Dose Escalation Part.

Twenty seven pediatric patients with advanced cancers, most with primary CNS tumors (high-grade astrocytoma or brain stem glioma), participated in this study. The ages of the patients ranged from 3 to 17 years, with the majority of the patients between 6 and 12 years of age. Patients were stratified for previous treatment with either nitrosurea therapy or craniospinal irradiation (poor risk) versus no such previous treatment (good risk). Patients were randomized to one of the Temodar dose levels (100, 120, 160 or 240mg/m2) given daily for 5 days every 28 days.

Study 193-125 /Extended.

In Extension Part of Study 193-125, 63 pediatric patients with recurrent CNS tumors (brain stem glioma or high-grade astrocytoma) received Temodar daily for 5 days every 28 days. The ages of the patients ranged from 4 to 15 years. Patients were given either 160mg/m2/day if they had prior therapy, or 200mg/m2/day if no prior therapy was received.

Study H97-017.

One hundred twenty two pediatric patients with recurrent CNS tumors (113 patients), and tumor histology categorized by the sponsor as "Other" (9 patients) were enrolled in this Phase 2 Study. Category "other" includes: neuroblastoma, osteosarcoma, Ewing's sarcoma, malignant meningioma, and alveolar soft part sarcoma.

The ages of the patients ranged from 1 to 23 years. Temodar was administered at the dose of 180mg/m2/day to patients previously treated with cranio-spinal irradiation, and 200mg/m2/day to patients who did not receive radiation treatment.

E. Special Populations

Both Phase 1 Studies (Study 193-125 and Study 193-125 Extended) and Phase 2 Study H97-017 were conducted solely in children and adolescents with recurrent CNS tumors and a few non-CNS tumors. Patients range in age from 1 to 23 years old. The majority of patients were between 3 to 17 years.