Clinical Pharmacology and Biopharmaceutics Review

NDA	21,029/SE8-005
Date of Submission	September 12, 2002
Drug Name	Temodar
Generic	temozolomide
Dosage Form	oral capsule
Strength	5, 20, 100, 250 mg
Sponsor	Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033
Reviewer	Anne Zajicek, M.D., Pharm.D.
Team Leader	N.A.M. Atiqur Rahman
Type of Submission	NDA-Supplement

Executive Summary: Temozolomide is an oral alkylating agent which was approved in 1999 for treatment of adults with refractory anaplastic astrocytoma. A written request was issued for a pediatric study by the Food and Drug Administration on Jan 25, 2001 and amended on August 24, 2001. Three studies are submitted in response to the written request; the Clinical Pharmacology and Biopharmaceutics section of the application was previously submitted with the original NDA. Nineteen children, age 3-17 years with primary brain tumors, were randomized to temozolomide 100, 120, 160, 200 or 240 mg/m2 taken orally daily for five days. Pharmacokinetic sampling took place on day 5. Results showed maximum concentration (C_{max}) and area under the concentration time curve (AUC) to be somewhat higher in children than in adults given the same dose, indicating either increased bioavailability or lower clearance in children; these results, however, are difficult to interpret due to the small numbers of patients studied. There was proportionality between dose and area under the concentration-time curve, and there was no apparent relationship between clearance and age.

Comments: The previously submitted pediatric pharmacokinetic study is adequate for the purposes of the written request and the Clinical Pharmacology and Biopharmaceutics review. The remaining question is how very young children took the oral capsule formulation. In future submissions, we recommend plasma MTIC concentration measurements, since it is the active species.

Anne Zajicek, M.D, Pharm.D, Clinical Pharmacology Reviewer	N.A.M. Atiqur Rahman, Ph.D. Team Leader

CC: NDA 22,029/SE8-005

HFD-150/ Division File
HFD-150/JohnsonJ,FarrellA, ShapiroA
HFD-860/MehtaM, SahajwallaC, RahmanNAM, ZajicekA, LazorJ, SelenA, MarroumP
CDR/Biopharm

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/s/

Atiqur Rahman

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