NDA 21-029

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Attention: Joseph F. Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your new drug application (NDA) dated August 12, 1998, received August 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TEMODAR (temozolomide) Capsules.

We acknowledge receipt of your submissions dated February 11 and 22, April 23, May 19 and 24, July 19, and August 2 and 4, 1999. Your submission of June 25, 1999 constituted a complete response to our February 12, 1999 action letter.

This new drug application provides for the use of TEMODAR (temozolomide) Capsules 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.

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve TEMODAR (temozolomide) Capsules for use as recommended in the enclosed labeling text. Accordingly, the application is approved under 21 CFR Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert and text for the Pharmacist information sheet) and the draft copy of the immediate container and carton labels submitted on August 4, 1999. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-029." Approval of this submission by FDA is not required before the

labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H Phase 4 commitments) specified in your submission dated June 24, 1999 and additional requirements that you committed to on July 19 and August 2, 1999. These commitments, along with any completion dates agreed upon, are listed below.

Schering will conduct a study according to the following protocol:

"A phase I/III randomized study of radiation therapy and temozolomide versus radiation therapy and BCNU versus radiation therapy and temozolomide and BCNU for anaplastic astrocytoma". The statistical analysis plan for this study will be performed according to your submission dated July 19, 1999.

In addition, as agreed upon in your letter dated August 2, 1999, you will provide the Phase I/II safety data to support the dosing schedule in the combination arm of the trial and agree that initiation of the combination arm will be contingent on FDA approval to proceed. Furthermore, you committed to completing the two monotherapy arms of the trial in the event that the combination arm is stopped for any reason.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If

a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research