DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-029

1/9/01

Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

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

Dear Lamendola:

Please refer to your New Drug Application (NDA) for Temodar® (temozolomide) Capsules, NDA #21-029.

The Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit pediatric studies, detailed later in the letter. These studies investigate the potential use of Temodar® in the treatment of children with various cancers.

BACKGROUND:

The development of pediatric oncology drugs merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. Because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative study group. One of the highest priorities of these groups is to develop improved novel therapies. Early access to new drugs is one mechanism to achieve this goal.

Known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. Therefore, it is usually impossible to rely on pharmacokinetic and safety data alone to guide the use of these drugs in children. It is imperative that we evaluate the effectiveness and safety of new drugs in pediatric populations. In most cases, in the absence of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to be able to use flexible regulatory approaches in developing and approving drugs for pediatric tumors [e.g., basing approval on an effect on tumor size or other surrogate marker likely to predict clinical benefit (Subpart H), and/or based on safety in smaller numbers of patients (Subpart E)].

The intent of designing studies for development of drugs for pediatric oncology is to proceed in the context of an overall development program. Drugs that lack dosing and pharmacokinetic information should begin with Phase 1 studies. Drugs that have dosing and pharmacokinetic data in pediatric patients should be tested in Phase 2 or pilot studies. Depending upon the outcome of the Phase 2 studies, Phase 3 studies may be initiated. See the **Guidance for Industry Pediatric Oncology Studies In Response to a Written Request** located on the web at www.fda.gov/cder/guidance/3756dft.htm for circumstances when it may be appropriate to request an exclusivity determination or advisory opinion at the end of either Phase 1 or 2. The FDA recommends that the rationale for the drug development plan and context in an overall pediatric oncology drug development program be included with each study.

Protocols for each of your studies should be submitted to the FDA for review, but they need not be submitted simultaneously. For example, if you begin with a Phase 1 study, initially a Phase 1 protocol should be submitted for review, but the submission of Phase 2 or pilot study protocols may be deferred.

REQUESTED STUDIES:

Please submit information from the following types of studies:

- Type of studies:

  Phase 1: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.

  Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients each with refractory or relapsed tumors. Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

- Indication(s) to be studied (i.e., objective of each study):

  Refractory or relapsed pediatric malignancies

  - Age group in which study(ies) will be performed:

    Infants > 1 month of age to adolescents

  - Study endpoints:

    The pharmacokinetic study will have maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, clearance, and distribution in

body compartments as secondary endpoints. The Phase 2 studies or pilot studies should have a disease-specific surrogate or clinically relevant endpoint.

- Drug information:

  Dosage form: *Capsule (5, 20, 100, 250mg)*

  Route of administration: *Oral*

  Regimen: *As determined by Phase 1 study*

- Drug specific safety concerns:

  Myelosuppression, nausea and vomiting

- Statistical information, including power of study and statistical assessments:

  Descriptive statistics

- Labeling that may result from the study(ies):

  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- Format of reports to be submitted:

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

- Timeframe for submitting reports of the study(ies):

  Reports of the above studies must be submitted to the Agency on or before ***December 31, 2001****. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.*

Please submit protocols for the appropriate studies to your investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports on the outcome of the studies should be submitted to a new drug application (NDA) or a supplement to an approved NDA with the proposed labeling you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC**

EXCLUSIVITY DETERMINATION REQUESTED" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send

a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if changes to this Written Request are agreed to by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you to develop additional pediatric information that may produce health benefits in the pediatric population. If you have any questions, call Sean Bradley, Regulatory Health Project Manager at 301-594-5750.

Sincerely yours,

Rachel E. Behrman, M.D., M.P.H.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research