



Dear _____ :

To obtain needed pediatric information on methotrexate, 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 information from the trials in pediatric patients described below. These studies investigate use of methotrexate in the treatment of children with cancer.

Background:

Methotrexate (MTX) is an essential component of treatment for children with acute lymphoblastic leukemia (ALL). Optimal MTX dose and schedule for this indication remain the subject of considerable debate. Capizzi I methotrexate (escalating intravenous MTX without leucovorin rescue, followed by asparaginase) has been a key element of augmented BFM therapy, which is an effective strategy for treatment of higher risk childhood ALL. Recent trials for children with higher risk ALL have used components of augmented BFM, including Capizzi I methotrexate every 10 days in conjunction with vincristine and L-asparaginase during interim maintenance. On the other hand, high dose methotrexate (HD-MTX, 5 grams/m²) with leucovorin rescue has acceptable toxicity in sequential BFM trials and has also been shown to be a successful strategy in ALL. Pharmacokinetic data suggest wide variability in MTX levels and clearance. Because high risk patients with lower steady state MTX levels are at increased risk of relapse, it is reasonable to postulate high dose MTX with leucovorin rescue may be superior to Capizzi I methotrexate in preventing relapse of higher risk ALL.

In considering the relative merits of Capizzi I versus high dose methotrexate for interim maintenance of ALL, additional consideration must be given to regimen toxicity. Methotrexate has known long-term deleterious effects on neurocognitive functions such as memory, attention, language, global intellectual function, and adaptive behavior. If efficacy of the two regimens is more or less equal, then a relative advantage in late neurotoxicity would favor use of one of these regimens over the other. Thus you should determine incidence and severity of late MTX neurotoxicity associated with Capizzi I and HD-MTX treatment. In addition, your studies should seek to identify risk factors and possible mechanisms for neurotoxicity associated with MTX that lead to cognitive impairment. Enhanced understanding of risk factors for and mechanisms of late neurocognitive deficits could lead to beneficial treatment modifications, prevention strategies, and/or early identification of neurotoxicity that would facilitate implementation of preventive behavioral or educational intervention.

Design of studies for pediatric oncologic drug development is discussed in detail in the guidance for industry, *Pediatric Oncology Studies in Response to a Written Request*. Protocols for each of your studies should be submitted to the FDA for review. Each submission should review the overall development plan and justify the study design(s). Please consult the guidance for further details.

Please submit information from the following types of studies.

- *Type of studies:*

Two prospective, randomized trials to compare high dose (5 grams/m²) methotrexate with leucovorin rescue versus Capizzi escalating dose methotrexate (without leucovorin rescue) during the Interim Maintenance I phase of treatment for high risk acute lymphoblastic leukemia. Comparisons must be performed of both efficacy and neurotoxic sequelae following from use of these alternate regimens. Neurocognitive outcomes should be assessed in two age cohorts: a) patients from one to thirteen years of age and b) from thirteen to eighteen years of age. These cohorts should be stratified at study entry by age at diagnosis.

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

High risk pediatric acute lymphoblastic leukemia.

- *Age group in which studies will be performed:*

Patients from 1-18 years of age.

- *Study endpoints*

- Neurocognitive development in children with ALL at three time points: end of induction, twelve months after remission, and twelve months after treatment completion.
- Host polymorphisms that may predict increased risk for neurocognitive toxicity.
- Prognostic significance of acute, transient neurotoxicity for subsequent neurocognitive loss.
- Impact of MTX on folate dependent biochemical pathways that have been implicated in the pathophysiology of neurologic dysfunction.
- Identification of CNS areas of selective vulnerability by diffusion tensor imaging that may predict and/or correlate with neurocognitive outcome.
- Relative efficacy.

- *Drug information*

- *dosage form:* intravenous
- *route of administration:* intravenous
- *regimen:* tumor specific regimen, as determined by body surface area

- *Drug specific safety concerns:*

You must assess relative incidence of neurotoxicity following from use of high dose versus Capizzi methotrexate regimens for interim maintenance therapy of ALL. Analysis should be by age at diagnosis: 1-13 and 13-18 years. In addition, MTX is known to cause myelosuppression, mucositis, renal failure, liver damage, pneumonitis, arachnoiditis, and skin abnormalities. The latter toxicities should be compared following collection of adverse event data.

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

In your submitted protocols, you should provide power calculations for neurotoxicity endpoints. In particular, you must test the following hypotheses.

- Neurocognitive function at twelve months following treatment will be significantly lower in children treated with HD-MTX than in children treated with Capizzi I MTX.
- Neurocognitive function at twelve months following treatment will be significantly lower in the younger (1-13 years) than in the older (13-18 years) age cohort, with a significant interaction between age at diagnosis and MTX exposure (HD vs. Capizzi).
- Within the younger (1-13 years) age cohort, younger age at diagnosis will result in lower neurocognitive function at twelve months after treatment completion within both the HD and Capizzi arms.
- Children in the younger (1-13 years) age cohort will have significantly lower scores than those in the older (13-18 years) age cohort on measures of specific function, including memory, attention, language, processing speed, planning and organization, and achievement.
- Age at diagnosis, MTX dose (HD vs. Capizzi), slope of the neurocognitive function from end of induction to twelve months after remission, and neurocognitive function at twelve months after remission will be predictive of neurocognitive function at twelve months after treatment completion.
- Event-free survival will be significantly higher in children treated with HD-MTX than in children treated with Capizzi I MTX.

- *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 (including data sets and individual data listings) not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

- *Timeframe for submitting reports of the studies:*

Reports of the above studies must be submitted to the Agency within 10 years of the date of this letter. 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.

- *Response to Written Request:*

As per the Best Pharmaceuticals for Children Act, Section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an 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. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission “**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission.

Study reports should be submitted as **a supplement to an approved NDA** with proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting such 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the *Federal Register* a notification of availability.

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 any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as

well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call _____, Project Manager, at _____.

Sincerely,

CAPT Sandra L. Kweder, M.D.
Deputy Director, Office of New Drugs
Center for Drug Evaluation & Research, FDA