FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

March 14, 2006

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting

Gaithersburg Hilton, Gaithersburg, MD

Questions for the Subcommittee

Session I: BPCA-off patent drugs

Daunomycin and methotrexate are off-patent drugs that were referred to the NICHD by the Foundation for NIH, reviewed by expert consultants, and recommended for further study in the setting of pediatric oncology. Among the goals of the studies presented are to develop additional data that could result in health benefits for children with cancer.

1. ***Daunomycin*:**

   Please discuss the ability of the proposed study to meet its objective of determining the relationship between body composition and daunomycin pharmacokinetics (PK). Specifically:

   a. The study will correlate body composition, size, age, gender, and ethnic background with daunomycin PK. Please identify any other patient or disease-specific factors for which PK correlations should be made?

   b. Should the study link the pharmacokinetic data with clinical and/or laboratory outcomes? If so, which outcomes would be most relevant? If linkage to such outcomes is not appropriate or feasible in this study, should another study(ies) be conducted in order to develop these correlations? If so, please comment on optimal study design(s).

   c. Please discuss how the varied infusion regimens (infusions of any duration < 24 hours) could affect the interpretation of any exposure-response relationships for daunomycin.

2. ***Methotrexate*:**

   An objective of the two trials in patients with leukemia is to assess efficacy and safety of high dose methotrexate (HD MTX) vs Capizzi (C) MTX. Both studies seek to evaluate and answer questions about several potentially important drugs or regimens in pediatric leukemia.

   a. Please discuss whether the study designs will enable isolation and comparison of the effects of HD MTX versus C MTX, and identify specific aspects of the designs most critical in delineating the effects of HD MTX.

   b. Please discuss which of the study outcomes are most relevant to assessing HD MTX efficacy and toxicity

   c. Please comment on the adequacy and frequency of the safety assessments to assess toxicity, particularly neuro-toxicity.

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Session II: Exjade- Phase 4 commitments

Exjade was approved under accelerated approval, a mechanism that requires additional studies to be conducted post-marketing. Of the studies required as a condition of the accelerated approval, the following are relevant to the pediatric population:

- The establishment of a registry for children aged 2 to < 6 years to enroll approximately 200 patients and follow them for 5 years to collect monthly renal function and blood pressure and growth and development yearly.

3. Please discuss additional outcomes to consider for the registry that may be able to provide meaningful evidence of long term effects (i.e., measures reflecting both efficacy/activity and safety), such as: serum ferritin levels and correlations with transfusion history, growth and development, endocrine status, hepatic and renal function, etc.

- A study to examine the effects of Exjade in patients with transfusion-dependent congenital or acquired anemias who have liver iron concentrations (LIC) < 7 mg/kg/dry weight.

4. Please discuss clinical protocol design considerations for this type of study, especially with respect to inclusion of pediatric patients. Please consider in your response the potential need for liver biopsy in order to determine the LIC, the duration of observation necessary to detect major safety concerns; the types of safety endpoints, especially with respect to the potential for "over-chelation" (iron depletion).

- A proposal to assess iron concentration and cardiac function among patients treated with Exjade.

5. Please discuss cardiac functional assessments that may be useful for the sponsor to consider when developing this proposal, especially as these assessments may apply to pediatric patients. The following are examples of assessment considerations: echocardiographic assessment of cardiac function, radionuclide and/or magnetic resonance cardiac imaging, cardiac biopsy, exercise tests.

Session III – Drug Shortages

6. Please comment on your experience with drug shortages in clinical practice.

7. Please discuss what additional actions the agency should consider in the setting of:

   a. a potential drug shortage

   b. an actual shortage