Pediatric Oncology Subcommittee Meeting
March 14, 2006

Summary Minutes of the Pediatric Oncology Subcommittee of the
Oncologic Drugs Advisory Committee
meeting on March 14, 2006

The committee discussed (1) clinical studies of methotrexate and daunomycin to be conducted under the Best Pharmaceuticals for Children Act (BPCA) ; (2) phase 4 requirements for Deferasirox (Exjade®), Novartis Pharmaceuticals, as mandated under Accelerated Approval;and (3) CDER's process for handling drug shortages.

The summary minutes for the March 14th meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee were approved on Arpil 6, 2006.

I certify that I attended the March 14, 2006 meeting of the Pediatric Oncology Subcomittee of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Johanna Clifford, M.Sc., RN
Executive Secretary, ODAC

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Gregory Reaman, M.D.
Acting Chair, Pediatric Oncology Subcommittee
of the
Oncologic Drugs Advisory Committee

The meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee was held in the Ballrooms at the Gaithersburg Hilton, 920 Perry Parkway, Gaithersburg, MD. Approximately 100 people were in attendance. The meeting was chaired by Gregory Reaman, M.D.

The committee met to discuss: (1) clinical studies of methotrexate and daunomycin to be conducted under the Best Pharmaceuticals for Children Act (BPCA) ; (2) phase 4 requirements for Deferasirox (Exjade®), Novartis Pharmaceuticals, as mandated under Accelerated Approval; (3) CDER's process for handling drug shortages.

Session I:

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Pamela Haylock, R.N., Gregory Reaman, M.D. (Chair)

Oncologic Drugs Advisory Committee Consultants (voting):
Peter Adamson, M.D. Stacy Berg, M.D., Susan Blaney, M.D., Barry Anderson, M.D., Victor Santana, M.D., George Schrieber, M.D., Malcolm Smith, M.D., Marilyn Eichner (patient representative), Jerry Finklestein, M.D., Ralph D'Agostino, Ph.D., Charles Reynolds, Ph.D., Cathy O'Connell (patient representative)

FDA Participants:
Richard Pazdur, M.D., Karen Weiss, M.D., Robert Justice, M.D., Ramzi Dagher, M.D.

Guest Speaker:
Daniel Armstrong, M.D., University of Miami

The agenda proceeded as follows:

Opening Comments	**Karen Weiss, M.D.** Office of Oncology Drug Products, CDER, FDA
Daunomycin: Pharmacokinetics in Children	**Stacy Berg, M.D.** Texas Children's Cancer Center Baylor College of Medicine
Overview of Methotrexate: Clinical Evaluations	**Malcolm Smith, M.D., Ph.D.** Associate Branch Chief, Pediatrics Cancer Therapy Evaluation Program (CTEP) National Cancer Institute (NCI), NIH
Cognitive Neurotoxicities in Children Treated for Acute Lymphoblastic Leukemia Using High Dose Methotrexate	**Daniel Armstrong, Ph.D.** University of Miami School of Medicine

Questions to the Subcommittee

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.

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?

The panel suggested that, in addition to the data already being collected that white count data be included as well. In reference to Dr. Berg's proposal, the panel expressed some concern about the sampling strategy used, specifically with respect the number of continuous samples that are needed to collect the necessary data. The committee was in favor of a more limited sampling methodology than what is currently being used.

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).

The panel noted that the Children's Oncology Group is currently conducting a planned correlative study in pediatric patients with ALL.

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.

In the leukemia studies, the dose is 25mg/m2 with a short infusion. The committee noted that with this pharmacokinetic modeling approach, the infusion rate and dosing are already incorporated and fairly standard according to treatment.

Session II

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.

The general sense among the panel was that there would be heightened neurocognitive effects in the HD MTX vs. Capizzi. The panel suggested that, regardless of the strength of the regimen used that the study results will prove to be beneficial in terms of defining a population of children who are most susceptible to the neurotoxicity.

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

- *The panel agreed that the study endpoints identified by Dr. Armstrong (neurocognitive function in the two age cohorts) in his presentation are relvant to assessing HD methotrexate related toxicity.*

- *The panel noted that there are currently studies being conducted recognizing treatment intervention as a potential outcome complication. However, identifying and categorizing the distinct groups with respect to treament intervention and collecting the data from these groups could be useful in identifying prevention and treatment of cognitive effects.*
- *Dr. Armstrong emphasized that the study will include a gender variable as there are currently theories recognizing a higher incidence of cognitive effects among girls than boys.*

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

The panel agreed with the timing and frequency of evaluation of the two cohorts. Dr. Armstrong emphasized that the T3 (off treatment 3 year evaluation) would be the most critical endpoint, however, the timing intervals were origninally designed to look at the neurodevelopmental pathways.

Session II

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Pamela Haylock, R.N., Gregory Reaman, M.D. (Chair)

Oncologic Drugs Advisory Committee Consultants (voting):
Peter Adamson, M.D. Stacy Berg, M.D., Susan Blaney, M.D., Barry Anderson, M.D., Victor Santana, M.D., George Schrieber, M.D., Malcolm Smith, M.D., Marilyn Eichner (patient representative), Jerry Finklestein, M.D., Ralph D'Agostino, Ph.D., Charles Reynolds, Ph.D., Cathy O'Connell (patient representative), Gary Brittenham, M.D. (telecon)

FDA Participants:
Richard Pazdur, M.D., Karen Weiss, M.D, Rafel Reives, M.D., Kathy Robie Suh, M.D., George Shashaty, M.D.

Open Public Hearing:
Gina Cioffi, National Executive Director, Cooleys Anemia Foundation
Harriett Lewis

The agenda continued as follows:

Overview of Exjade Approval	**George Shashaty, M.D., Medical Officer** Division of Medical Imaging and Hematology Products OODP/OND/FDA
Sponsor Presentation Post Marketing Commitments with Exjade	**Novartis Pharmceutical Corporation** Renaud Capdeville, M.D., Deputy Head Phase II/III Group – Clinical Oncology

Open Public Hearing

Questions to the Committee

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.

1. 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.

   The committee agreed that there should be additional outcomes, requirements, measures that are included as part of the registry as opposed to serum creatinine and blood pressure. In addition to incorporating these additional parameters, the panel suggested that the sponsor reconsider the frequency with which they are measured.

   Of the additional measures the following was discussed with respect to the registry.

   - *The panel noted, that with the current restrictions in place for obtaining exjade this could provide the fundamental basis for a registry*
   - *The committee noted that the registry should account for compliance*
   - *The panel agreed that it would be helpful to include ferritin as opposed to liver iron data.*

   ➢ 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.

2. 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).

   The Sponsor suggested that there were not enough incidents of hepatotoxicity to warrant the determination of a dose dependent adverse event. The panel agreed that the incidence of liver biopsies have been drastically reduced, primarily by the availability of non-invasive measures.

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

3. 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.

The committee commented that additional tests and efforts listed above haven't contributed more than what the ejection fraction shows and anything beyond this would generally be determined by a pediatric cardiologist and the age of the patient.

Session III: Drug Shortages

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Pamela Haylock, R.N., Gregory Reaman, M.D. (Chair)

Oncologic Drugs Advisory Committee Consultants (voting):
Peter Adamson, M.D. Stacy Berg, M.D., Susan Blaney, M.D., Barry Anderson, M.D., Victor Santana, M.D., Malcolm Smith, M.D., Marilyn Eichner (patient representative), Jerry Finklestein, M.D., Ralph D'Agostino, Ph.D., Charles Reynolds, Ph.D., Cathy O'Connell (patient representative).

FDA Participants:
Richard Pazdur, M.D., Karen Weiss, M.D, Robert Justics, M.D., Patricia Keegan, M.D. Mark Goldberger, M.D., M.P.H.

The agenda continued as follows:

An Industry Perspective: Drug Shortages in Pediatric Oncology	**Wayne Rackoff, M.D.** Johnson & Johnson Pharmaceutical Research And Development, L.L.C.
CDER Drug Shortages	**Mark Goldberger, M.D. M.P.H.** Drug Shortage Coordinator, CDER, FDA Director, Office of Antimicrobial Products, OND, CDER, FDA

Qeustions to the Committee:

1. Please comment of your experience with drug shortages in clinical practice.

The panel commented on their experiences with drug shortages, specifically, batch failure and rescheduling of new batches, manufacturing issues and deficiencies, communication issues with notifying physicians of shortages, generics, how the medical community is affected with respect to mergers and the acquisitions of manfacturing companies.

The role of the FDA was more clearly defined in the event of a drug shortage, i.e., tamiflu and cipro. In addition, the panel was made aware that the FDA maintains a critical products database which includes how much product is in stock, how quickly a new supply could be generated, etc.

(Please see transcript for additional details)

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

a. a potential drug shortage
b. an actual shortage

It was noted that the FDA regulations do not specifically address the issue of drug shortage management, other than to notify the agency when the product is being discontinued. Therefore the Drug Shortages Office does not have the authority to mandate procedures to address the issues associated with drug shortages. The panel discussed the following alternatives to avert the issue of a drug shortage:

- *The COG and other institutions empower a pharmacy committee to look at the resource imapct and utilization of drugs and provide this information to the agency.*
- *That a list of pediatric oncology drugs be compiled and submitted to the Office of Drug Shortages to add to their critical drugs list and further, that the COG take an active role in ensuring that the list is up to date.*
- *Introduce legislation that codifies the responsibility of drug shortages.*

The meeting adjourned at approximately 4:00 p.m.