Food and Drug Administration
Center for Drug Evaluation and Research
ACS Building, 5630 Fishers Lane, Rockville, MD

Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee July 15, 2003

Members Present

Jody Pelusi, R.N., Ph.D. Gregory Reaman, M.D.

Consultants

Victor Santana, M.D.	C. Patrick Reynolds, M.D.	Susan Weiner, Ph.D.
James Boyett, Ph.D.	Susan Cohn, M.D.	Nancy Keene
Howard McLeod, Pharm.D.	David Poplack, M.D.	Naomi Winnick, M.D.
Susan Shurin, M.D.		

Guests

Malcolm Smith, M.D.	Barry Anderson, M.D.	Leslie Ball, M.D.
Richard Weinshilboum, M.D.	Bruce Morland, M.D.	Joachim Boos, M.D.
Gilles Vassal, M.D.	Riccardo Riccardi, M.D.	Ursula Kern, M.D.
Hugh Davies, M.D.	Mark Bernstein, M.D.	

Industry Guest Attendees

George Ohye, J.D.

FDA Participants

Murray Lumpkin, M.D. Grant Williams, M.D.
Dave Maybee, M.D. Steven Hirschfeld, M.D.

These summary minutes for the July 15, 2003 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee were approved on July 31, 2002.

I certify that I attended the July 15, 2003 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

Victor Santana, M.D.,
Chair

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, of the Food and Drug Administration, Center for Drug Evaluation and Research met July 15, 2003 at the FDA's Advisors and Consultant Staff conference facility at 5630 Fishers Lane, Rockville, MD

During the morning session the Subcommittee discussed the pharmacogenetic testing for thiopurine methyltransferase (TPMT) deficiency in patients for whom treatment with Purinethol (6-mercaptopurine, 6MP) is being considered. During the afternoon session the Subcommittee discussed overcoming challenges in pediatric oncology product development: regulatory oversight of multi-national clinical studies.

The Committee had received a briefing document from the FDA.

There were approximately 40 persons in the audience. The meeting was called to order at 8:10 a.m. by the Chair, Victor Santana, M.D. The subcommittee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee read the Meeting Statement for the mornings session. A welcome was provided by Grant Williams, M.D., Deputy Director, Division of Oncology Drug Products.

The scheduled presentations began at 8:20 a.m. and proceeded as follows.

Introduction to Topics of Day	Steven Hirschfeld, M.D, Ph.D., Medical Officer Division of Oncology Drug Products
Description of CDER Office of Drug Safety Programs	Victor Raczkowski, M.D., Director, Office of Drug Safety

Introduction to Thiopurine Methyltransferase Deficiency and Testing
Larry Lesko, Ph.D., Director, Office of Clinical Pharmacology and Biopharmaceutics, FDA
Richard Weinshilboum, M.D., Dept. of Molecular Pharmacology, Mayo Clinic
Howard McLeod, Pharm.D., Washington University, School of Medicine

Perspective of Children's Oncology Group on the use of 6-Mercaptopurine
Naomi Winick, M.D., University of Texas Southwestern Medical Center

The subcommittee paused for a brief Break at 10:30 a.m. and reconvened at 10:50 with the Open Public Hearing. There was one participant present for the Open Public Hearing, Mark W. Russo, M.D., GlaxoSmithKline. Additionally, a statement received from Peter C. Adamson, M.D., Children's Oncology Group, was read into the record.

The subcommittee began its discussion of the presentations at 10:55 a.m. followed by a discussion of the questions presented by the FDA. The morning session was adjourned for lunch at 12:30 p.m.

At 1:20 p.m. the afternoon session of the meeting began with a reading of the meeting statement into the record by Thomas H. Perez, Executive Secretary. This was followed by the following scheduled presentations.

Overview of Research Oversight	
United States Perspective	Leslie Ball, M.D., Office of Human Research Protection, DHHS
United Kingdom Perspective	Hugh Davies, M.B. ChB, Central Office of Research Ethics Committee
German Perspective	Ursula Kern, Ph.D., Federal Institute for Drugs and Medical Devices

There were no participants for the Open Public Hearing, and at 2:50 p.m. the subcommittee began a discussion of the presentations and the questions presented by the FDA on this topic.
The meeting was adjourned at 4:05 p.m. Transcripts of the meeting will be placed on the web when they become available, in approximately 2 to 3 weeks.

The subcommittee discussed the following questions to which no votes were requested or taken.

Questions to Subcommittee

Morning Session

Pharmacogenetic testing for thiopurine methyltransferase (TPMT) deficiency in patients for whom treatment with Purinethol (6-mercaptopurine, 6MP) is being considered

Food and Drug Administration (FDA) pediatric initiatives are directed at identifying opportunities for improving the clinical quality of therapeutics relating to the use of already-marketed drugs in pediatric patients, and developing new therapeutics for the treatment of childhood cancer. This includes updating product information in the approved package insert or product label where such data is relevant to the safe and effective use of the drug in the pediatric population. The Best Pharmaceuticals for Children Act of 2002 supports the pediatric use information of the approved package insert (product label) as one of the primary mechanisms to publicly disseminate that information.

Purinethol (6-mercaptopurine, 6MP) is a marketed product that is indicated for remission induction and maintenance therapy in acute lymphoblastic leukemia in pediatric patients as well as in adults. The Agency has reviewed recently published literature and corresponding data about the variability in the metabolism of 6MP related to pharmacogenetics. There is evidence that the administration of the usual doses of 6MP to patients with hereditary thiopurine methyltransferase (TPMT) deficiency are at a substantially increased risk of toxicity. Previously the Pediatric Subcommittee, at a meeting in November 2001, was presented clinical evidence that genotypes in the pediatric patient population having little or no TPMT activity (0.3%), or reduced TPMT activity (10%) are at risk for excessive myelosuppression.

The Agency would like the Subcommittee to provide advice on what additional information would be considered necessary or appropriate to be in the product label for 6MP regarding pharmacogenetics.

Question #1

The current product package insert states in the Warning Section:

- There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. Substantial dosage reductions may be required to avoid the development of life-threatening bone marrow suppression in these patients. This toxicity may be more profound in patients treated with concomitant allopurinol. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine, or sulphasalazine.

The Dosage Section states:

- PURINETHOL is administered orally. The dosage which will be tolerated and be effective varies from patient to patient, and therefore careful titration is necessary to obtain the optimum therapeutic effect without incurring excessive, unintended toxicity.

- Once a complete hematologic remission is obtained, maintenance therapy is considered essential. Maintenance doses will vary from patient to patient.

What additional information should be included in the product label with regard to TPMT metabolic activity and the potential for exposure to excessive bone marrow toxicity in pediatric patients with acute lymphoblastic leukemia?

Additional Information may include:

1. Prevalence of pediatric patients in the general population that have little or no TPMT activity (0.3%) and reduced TPMT activity (10%)

   Yes, should be included

2. An additional statement in the Warning section that children with hereditary deficiency of TPMT activity may be unusually sensitive to the myelosuppressive effects of 6MP and at greater risk of toxicity

   Current statement in labeling conveys the information, but language should be adjusted to convey that only persons who have the homozygous condition are at high and consistent risk of developing toxicity. Preliminary data indicate that more than half of heterozygous persons tolerate standard doses. In addition, patients with normal TPMT status could have severe toxicity, so a normal screening test does not preclude severe toxicity.

3. A statement that laboratory tests are available to determine the TPMT status of pediatric patients (genotyping or phenotyping) and some information regarding the use of these tests

   Statement that tests are available but no further recommendations on use or interpretation other than response to question # 2.

4. Recommendations for adjustment of doses in children identified as having little or no, or reduced, TPMT activity

   No, dosage adjustment recommendations should be included because insufficient data are available to make specific dose recommendations. The committee sees these as significant issues for research, and strongly recommends that such studies be undertaken by investigators. Since the drug is used in many different schedules and in combination with other agents, the combined myelosuppressive effects should also be considered.

Question #2

If pharmacogenetic information is added to the label, what other testing information, if any, about genotyping or phenotyping for TPMT activity in pediatric patients would you consider necessary or

appropriate to include in the product label?

Information may include:

1. A recommendation for testing for the status of TPMT activity in children before initiating treatment with 6MP

   No

2. A recommendation for testing for TPMT activity status in the pediatric patient within the first week of initiating treatment with 6MP

   No

3. A recommendation for testing for the status of TPMT activity if the child develops severe myelosuppression

   Yes, with the statement conditional and not a mandatory recommendation for testing.

4. A description of what information a TPMT screening test could provide.

   No further information than above.

Afternoon Session

Overcoming challenges in pediatric oncology product development: regulatory oversight of multi-national clinical studies

What core principles should be incorporated in the conduct and monitoring of multinational pediatric oncology clinical studies?

Principles of Belmont Report, those of HHS 45 CFR 46 and those contained in the European Union Directive to become effective May 2004.

What monitoring mechanism would be acceptable to assure adherence to these principles?

A mutual recognition procedure that avoids duplication and minimizes paperwork, yet that adheres to the same coherent set of standards.