Food and Drug Administration
Center for Drug Evaluation and Research
Hilton, The Ballrooms, 620 Perry Parkway, Gaithersburg, MD

Summary Minutes of the Pediatrics Subcommittee of the Anti-Infective Drugs Advisory Committee October 29 & 30, 2003

AntiInfective Drugs Advisory Committee Members Present

Mary Glode, M.D. Steven Ebert, Pharm. D.

Consultants

Patricia Chesney, M.D.	Victor Santana, M.D.	Norman Fost, M.D.
David Danford, M.D.	Robert Fink, M.D.	Richard Gorman, M.D., FAAP
Roselyn Epps, M.D.	Thomas Ten Have, Ph.D.	Sharon Raimer, M.D.
Elizabeth Andrews, Ph.D.	Bruce Schneider, M.D.	Robert Stern, M.D.

HHS Guests

Don Mattison, M.D.	Benjamin Wilfond M.D.	Constantine Stratakis, M.D.
Charles Rabkin, M.D.	Phyllis Wingo, M.D.	Lois Travis, M.D.

International Guest

Patrick Salmon, M.D., European Medical Evaluation Authority

FDA Participants

Dianne Murphy, M.D.	Jonathan Wilkin, M.D.	Anne Trontell, M.D.
Shirley Murphy, M.D.	Susan Cummins, M.D.	Lois LaGrenade, M.D.

Solomon Iyasu, M.D. Denise Cook, M.D.

These summary minutes for the October 29 & 30, 2003 meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee were approved on November 7, 2003.

I certify that I attended the October 29 & 30, 2003 meeting of the Pediatric Subcommittee of the Anti-Infective 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

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Patricia Chesney, M.D.
Chair

The Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee, of the Food and Drug Administration, Center for Drug Evaluation and Research met October 29 & 30, 2003 at the Hilton, The Ballrooms, 620 Perry Parkway, Gaithersburg, MD

On October 29, 2003 the Subcommittee meeting began with a discussion of Clinical Risk Management of HPA Axis Suppression in Children with Atopic Dermatitis being treated with Topical Corticosteroids. On October 29, 2003 beginning at 3:30 p.m. the agency reported to the subcommittee on Adverse Event Reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act. The products discussed during this portion of the meeting included Zyrtec (cetirizine), Busulfex (busulfan), Cozaar (losartan), Nolvadex (tamoxifen), Accupril (quinapril), and Serzone (nefazodone).

The Subcommittee and invited guests received a briefing document from the FDA in preparation for this meeting.

There were approximately 80 persons present at the meeting on October 29. The meeting was called to order at 8:10 a.m. by the Chair, Joan Chesney, M.D. The Subcommittee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee read the Meeting Statement. A welcome and opening comments were provided by Dianne Murphy, M.D., Director, Office of Counterterrorism and Pediatric Drug Development, and Jonathan Wilkin, M.D., Director, Division of Dermatologic and Dental Drug Products.

Presentations began at 8:25 a.m. and proceeded as follows.

Atopic Dermatitis: Its Clinical Course and Therapeutic Options	Bindi Nikhar, M.D. Division of Dermatologic and Dental Drug Products
Overview of HPA Axis Suppression	Jean Temeck, M.D., Division of Pediatric Drug Development
FDA Experience: Topical Corticosteriods and HPA Axis Suppression	Denise Cook, M.D. Division of Dermatologic and Dental Drug Products
Post Marketing Adverse Event Reports	Claudia Karwoski, Pharm.D. Division of Drug Risk Evaluation

At 10:05 the subcommittee began a question and answer period of the prior presentations. After a 15 minute break the following presentation began at 11:05 a.m.

Framework for Risk Assessment & Management	Anne Trontell, M.D., Deputy Director, Office of Drug Safety

At 11:30 the subcommittee continued with a question and answer period, and at 12:00 the subcommittee broke for lunch, and reconvened at 1:05 p.m., with the open public hearing portion of the meeting. The subcommittee heard from one presenter, Jerry Roth, President, Hill Dermaceuticals.

At 1:15 p.m. Dianne Murphy, M.D. introduced the questions, and the subcommittee began their discussion. This portion of the meeting was concluded at 3:10 p.m., and the subcommittee took a break.

The subcommittee reconvened at 3:30 p.m. with the reading of the meeting statement for the Adverse Event Reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act portion of the meeting. The subcommittee was then provided with a report by Solomon Iyasu, M.D., and ShaAvhree Buckman, M.D., members of the Division of Pediatric Drug Development

There were no participants for the Open Public Hearing. The chair, Dr. Joan Chesney provided the final comments, and the meeting was adjourned at 4:15 p.m.

On October 30, 2003 the Subcommittee discussed how to approach long term monitoring for cancer occurrence among patients treated for atopic dermatitis with topical immunosuppressants.

The Subcommittee and invited guests received a briefing document from the FDA in preparation for this meeting.

There were approximately 75 persons present at the meeting on October 30. The meeting was called to order at 8:10 a.m. by the Chair, Joan Chesney, M.D. The Subcommittee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee read the Meeting Statement. A welcome and opening comments were provided by Dianne Murphy, M.D., Director, Office of Counterterrorism and Pediatric Drug Development, and Jonathan Wilkin, M.D., Director, Division of Dermatologic and Dental Drug Products.

Presentations began at 8:15 a.m. and proceeded as follows.

Review of Topical Calcineurin Inhibitors	Bindi Nikhar, M.D. Division of Dermatologic and Dental Drug Products
Topical Immunosuppressants (Calcineurin Inhibitors) – Animal Toxicology	Barbara Hill, Ph.D. Division of Dermatologic & Dental Drug Products
Post Marketing Adverse Event Reports	Marilyn Pitts, Pharm. D. Division of Drug Risk Evaluation

At 8:55 the subcommittee began a question and answer period of the prior presentations. After a 15 minute break the following presentation began at 10:05 a.m.

Studying the Risk of Cancer with Topical Calcineurin Inhibitor Use in Children: Design Issues	Lois LeGrenade, M.D., Office of Drug Safety
Practical and Methodological Issues in Long Term Follow-up Studies	Elizabeth Andrews, Ph.D., RTI Health Solutions
The Role of Cancer Registries in Long Term Follow-up Studies	Phyllis Wingo, Ph.D., Centers for Disease Control Cancer Registry Program

At 11:40 the subcommittee continued with a question and answer period, and at 12:00 the subcommittee broke for lunch, and reconvened at 1:05 p.m., with the open public hearing portion of the meeting. The subcommittee heard from one presenter, David J. Margolis, M.D., Ph.D., University of Pennsylvania School of Medicine.

At 1:15 p.m. Shirley Murphy, M.D., and Susan Cummins, M.D., introduced the questions, and the subcommittee began their discussion. The meeting was adjourned at 3:05 p.m.

On October 29, the Subcommittee discussed the following questions to which no votes were requested or taken. The discussion will be made available through the meeting transcripts and placed on the web in approximately three weeks. Transcripts may be accessed at: www.fda.gov/ohrms/dockets/ac/acmenu.htm.

Questions to the Subcommittee

Questions to the Committee for October 29, 2003

1) Clinical trials have demonstrated Hypothalamic–Pituitary–Adrenal axis (HPA axis) suppression using the cosyntropin stimulation test with the use of topical corticosteroids. Is the cosyntropin testing performed during drug development sufficient to determine the risk? Are there additional specific tests that the Subcommittee would recommend to measure this risk?

The Subcommitee's consensus was that the cosyntropin test is a reasonable screening test to determine if there is an effect on the adrenals. It also elaborated that the tests should be prioritized. The peak value 18 mcg/dl, considered the most valuable followed by increment, and baseline tests. In addition the following tests were discussed; tests of absorption during early and late drug development, individual and population PK/PD.

2) Younger pediatric patients have a larger surface area to mass ratio when compared to adults and may be at greater risk of higher systemic exposure to topically applied drugs. Because of this, the FDA has usually requested that the Sponsor conduct suppression studies in older age groups first, and if there is no evidence of suppression, to proceed in sequentially younger patients until all age groups have been studied, or until there is evidence of significant suppression. Given the data from clinical trials that was presented today, does the Subcommittee recommend continuing this sequential testing, or should the testing be performed concurrently?

If the Subcommittee recommends sequential testing, what percent of children who suppress should be utilized to determine if further studies may proceed? (e.g. should the studies be stopped if any single patient in the clinical trial group demonstrates suppression by cosyntropin testing, or 10 percent demonstrate suppression, or 50 percent demonstrate suppression, etc.)?

The Subcommittee provided a variety of responses with reasons for doing sequential and concurrent testing with an associated consistent criteria for testing. Responses included some members recommending sequential testing while testing for suppression more frequently, and others doing concurrent testing based on the evidence that suppression is occurring at a rate of 30 – 50%. Some of the recommendations hinged on the significance of suppression and evidence of resulting life threatening problems.

Background to Question 3

Fact 1: There are only a few post-marketing cases of adrenal suppression in patients using topical corticosteroids.

Fact 2: Data from clinical studies has consistently demonstrated that a percentage of pediatric patients using topical corticosteroids under the maximal labeled use conditions will experience adrenal suppression. This suppression is most likely transient in nature and related to extent of exposure to the steroid.

<u>Fact 3:</u> Patients with a post-ACTH stimulation cortisol level of = 18 mcg/dL by cosyntropin stimulation testing require corticosteroid replacement at stress doses if they experienced trauma, sepsis, or are challenged with any other cause of physiologic stress.

<u>Premise:</u> It may not be recognized that the clinical course of patients who have undergone trauma, sepsis, or major surgery is complicated by adrenal suppression from underlying topical corticosteroid use, and hence, this adverse event may go unrecognized and under-reported.

3) Given the above information, does the Subcommittee think this represents a clinically significant (or relevant) concern for pediatric patients exposed to topical corticosteroids?

If yes, should any additional risk management action be taken? Please discuss which risk management approaches listed below you think would be appropriate, and why.

- Additional studies
- A box warning
- Limiting the indication to certain age groups,
- Recommending against use in certain age groups
- Contraindicating use of the product in populations that demonstrate HPA axis suppression
- Include a Patient Package Insert to inform the patient or parent/guardian of the risk
- Require that a Medication Guide be dispensed with every prescription
- Unit of use packaging
- Issuing a "Dear Health Care Provider" letter to groups of health care providers most likely to prescribe topical corticosteroids to pediatric patients
- Education programs for providers (including emergency room physicians, anesthesiologists, dentists, practitioners who perform procedures in their office under anesthesia or heavy sedation) and patients/caregivers

The Subcommittee felt that use of topical corticosteroids was a relevant concern for pediatric patients. The following risk management approaches were discussed:
Additional studies in children: epidemiological studies relating to steroid exposure and effect on risk, study to look at cortisol levels in patients under conditions of high stress.
Educational items that provide practical information (eg., indications that reflect when specifically to treat, use of OTC topicals recommended by family members and friends), such as the Patient Package Insert, and education materials that provide information on issues on the topic that are actively being discovered.

On October 30, the Subcommittee discussed the following questions to which no votes were requested or taken. The discussion will be made available through the meeting transcripts and placed on the web in approximately three weeks. Transcripts may be accessed at: www.fda.gov/ohrms/dockets/ac/acmenu.htm.

Questions to the Subcommittee

Questions to the Committee for October 30, 2003

1) What is a clinically meaningful increase in cancer risk from a treatment for a chronic non-life threatening disease? Does the present patient package insert appropriately reflect the information concerning cancer risk? Please discuss any recommendations.

The Subcommittee felt that any increase in cancer risk was unacceptable. Educational information needs to explain why these are second line drugs to physicians and patients. Underscoring the importance of what is appropriate use of the drug (including information that communicates the amount of application, duration of application, inappropriate use, in particular in children <2 years of age, not to share medication with others, and the basis for the short term use). For children under 2, because of immune system development issues and lack of understanding regarding the development of other systems in the very young a Box Warning was recommended. Additionally, the subcommittee recommended the following; a study to determine quantitatively the effect on the rate of infections and serious disease, the use of the Patient Package Insert, Dear Doctor Letters, Educational Programs, use of the Contraindications Section of Labeling. Concern was also raised about using these drugs in extemporaneous compounding and the dangers of using vehicles that may promote their absorption, the gaps in knowledge, and the level of patient understanding of information being provided to them. Also expressed was the need for cognitive testing to determine the level of patient understanding of educational materials developed.

Background to Question 2

Fact 1: *Lymphoma has been associated with systemic use of this class of immunosuppressants in both pre-clinical studies and in human use. Cutaneous malignancies are the most common malignancy associated with systemic use of this class of drugs.*

Fact 2: *Topical use of these immunsuppressants results in some, albeit modest, systemic exposure. This may be increased in pediatric patients due in part to increased body surface to mass ratio.*

Premise: *Malignancy may only be discernable via longer-term exposure, especially with modest systemic exposure.*

2) What is the best way to ascertain this clinical risk of malignancy (e.g. lymphomas or skin cancer) in clinical studies? Please discuss the merits and draw-backs of each of the following as well as study design considerations:
   - Duration of follow-up for each enrolled patient, keeping in mind that the latency period of most cancers is at least 10 years
   - Study design requirements
     - sample size needed to detect rare signals and feasibility issues

- the approach to ascertainment of skin cancers (e.g. by physical examination by physician, by physical examination by dermatologist, by interview/questionnaire)
- the role of the comparison group
- design strategies to optimize retention

- Endpoint issues
  - Specific cutaneous and systemic malignancies
  - Other biological endpoints
    - Viral infections of the skin/other (e.g. warts, EBV infection)
    - Pre-malignancy or early cancer endpoints (e.g. actinic keratoses)

The Subcommittee provided a variety of responses including; using state registries and the Children's Oncology Group, annual examinations for cancer among comparison groups, looking at information available on the systemic drug formulations.

3) FDA has not asked for such long-term studies in topical products before. To require such screening means that we are asking companies to take on very large, lengthy studies with substantial logistical challenges in patient retention, follow-up, costs, and other factors. In what situations should we require such studies? What criteria would you identify as important in deciding that this type of study be done?

The Subcommittee felt that long term studies would be needed in situations where there is evidence of systemic absorption and systemic effects with potential for serious and long term complications. Also when developmental time frames and life stages determine what changes are expressed as a result of therapy.

4) Is there a role for cancer registries and/or the SEER program in this long-term follow-up project? Please discuss how one might utilize existing registries or programs.

Existing registries and programs could play a role by identifying exposures and then ascertaining outcomes.

5) What other studies would you recommend (eg. Animal)?
What other risk management for this class would you recommend?

Systemic measure of immune response to vaccination.
Conditions placed on sponsor marketing to limit the marketing and encourage the promotion of knowledge and caution.

Risk Management Approaches

- Additional studies
- A box warning
- Limiting the indication to certain age groups
- Recommending against use in certain age groups
- Contraindicating use of the product in specific populations
- Include a Patient Package Insert to inform the patient or parent/guardian of the risk
- Require that a Medication Guide be dispensed with every prescription
- Unit of use packaging
- Issuing a “Dear Health Care Provider” letter to groups of health care providers most likely to prescribe.
- Education programs for providers and patients/caregivers