

February 2, 2004

Dear Advisory Committee Members and Guests:

Thank you for agreeing to participate in the upcoming joint meeting of the Drug Safety and Risk Management and the Dermatologic and Ophthalmic Drug Advisory Committees on February 26 and 27, 2004. Your discussion at the meeting is important to FDA, as it will focus on the critical public health issue of minimizing isotretinoin exposure in pregnancy. The purpose of the meeting is to fully discuss data available for existing isotretinoin fetal exposure risk management programs, determine what elements have worked, and identify needs and regulatory options for further improvement.

Accutane (isotretinoin) was approved in 1982 for the treatment of severe recalcitrant nodular acne. Isotretinoin remains the only approved entity for this indication and has been the subject of numerous advisory committee meetings since approval, most of which have focused on its teratogenicity and continuing efforts to minimize fetal exposure during therapy.

Most recently, in September 2000, the Dermatologic and Ophthalmic Drugs Advisory Committee convened to review the adequacy of Hoffman-LaRoche, Incorporated's Pregnancy Prevention Program (PPP) for Accutane. At that time, FDA had determined that there were an unacceptable number of reports of pregnancy occurring at the time of initiating and during Accutane treatment. The Committee agreed and recommended that additional program improvements, including options of a patient and prescriber registry, be developed. In October 2000, based on the Committee's discussion, a letter to the company from Janet Woodcock, M.D., Director, Center of Drug Evaluation & Research, articulated FDA's goals for improving Accutane's risk management. A copy of that letter is included in your background packet.

Over the course of the next year, a revised program, the System for Minimizing Accutane Risk of Teratogenicity (SMART), was developed by Hoffman-La Roche in discussion and negotiation with the FDA. The program attempted to meet the goals outlined by the Advisory Committee and FDA in a manner that was manageable for a product that had been the standard of clinical practice in treating severe acne for two decades. For example, the program did not incorporate a mandatory patient or prescriber registry, but it did add significant risk management elements designed to minimize the possibility of drug being dispensed to pregnant women. Specifically, it improved strategies to educate prescribers and patients and, most importantly, required use of a yellow sticker on all prescriptions in order for a pharmacist to dispense the product. The sticker was the vehicle through which the prescriber would attest to having counseled the patient, obtained written informed consent and documented a negative pregnancy test in all female patients of childbearing potential. Further, prescriptions could not be filled for

more than a 30-day supply and no automatic refills were to be allowed. The SMART program was approved by FDA in October 2001, along with expected performance metrics by which the effectiveness of the program in leading to meaningful reductions in fetal exposure could be assessed periodically by the Agency. SMART was implemented in April, 2002. At the upcoming meeting the findings from these metrics and FDA's assessment will be presented. This background package includes a written assessment of the metrics. In the sponsor's background packages for this meeting, you will receive one or more proposals for more constrained distribution of isotretinoin. The Agency has encouraged sponsors of the drug, innovator or generic firms, to work together to devise such a plan that could unify all current, independent risk management programs for isotretinoin. Due to the close proximity in time of submission of the proposal(s) and the February meeting, a review of the plan by FDA is not included in this packet. However, we plan to address it at the meeting.

Since implementation of SMART, generic manufacturers of isotretinoin have entered the market. Each company is required to have an equivalent risk management program to SMART as a condition of marketing. Therefore, you will also be asked to consider early data from these programs, which are not in the background package, but will be presented.

Based on our review of all of risk management program data, we have asked the manufacturers to work together in preparing for this meeting. Specifically, we have requested that they jointly address the adequacy of the current revised program and provide the committee with a proposal for discussion of possible changes. In light of the complexity attendant to this deliberation, other risks associated with the use of isotretinoin will not be addressed in detail at the meeting.

In reading through the background materials (see attached content guide) provided by the sponsors of isotretinoin and by FDA, please keep in mind the following general areas that we may request that the Committee discuss:

1. Whether the SMART and equivalent generic programs have demonstrated:
 - Low potential for program misuse by patients, pharmacists and prescribers
 - An acceptable risk reduction profile for fetal exposures, based on prior prescription marketing experience of the Roche Pregnancy Prevention Program (PPP)
2. Whether, based on the data presented, the manufacturers' proposal (s):
 - Adequately address deficiencies of the current risk management program
 - The benefits of the proposed changes outweigh the risks of change
3. Whether the proposed program can reasonably be implemented based on the realities of clinical practice (e.g., office based healthcare)
4. What modifications to the current or proposed program would further ensure safe use and better meet program goals

Again, thank you for your willingness to participate in the meeting. If you have any questions or need for clarification regarding the meeting content or logistics, please contact Mary Gross at 301-827-3216. We are looking forward to seeing you at 8:00 AM on February 26, 2004.

Sincerely,

Jonca Bull, M.D.
Director
Office of Drug Evaluation V
Office of New Drugs
Center for Drug Evaluation and Research

Anne Trontell, M.D., MPH
Deputy Director
Office of Drug Safety
Office of Pharmacoepidemiology and
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Center for Drug Evaluation and Research

Attachment

Contents of Package

Office of Drug Evaluation V Division of Dermatologic and Dental Drug Products

Tab A

- Isotretinoin Historical Summary
- Letter, Dr. Janet Woodcock, dated October 6, 2000, subject: Need for registry, linkage of pregnancy status with drug dispensing
(Note to Committee: registry not implemented per innovator due to HIPAA and other constraints, so SMART program evolved over 1 year prior to implementation)
- Letter, Dr. Jonathan Wilkin, dated October 30, 2001, subject: Approval Letter, NDA 18-662/S-044
Enclosure to Letter - Final printed labeling (FPL) – 108 pages

Office of Pharmaceutical Science Office of Generic Drugs

Tab B

- Letter, Dr. Janet Woodcock, dated November 8, 2002, subject: Citizen Petition Response – Procedures and Standards; Abbreviated New Drug Applications

Office of Pharmacoepidemiology and Statistical Science Office of Drug Safety

Executive Overview - Office of Drug Safety

Combined Review - Division of Drug Risk Evaluation and Surveillance, Research, and Communications Support, Office of Drug Safety

Tab C

- Overview of the 1st of the Isotretinoin Risk Management Program
- Overview of the First Year Evaluation of the Isotretinoin Risk Management Program
- PID D030417, Drug: Isotretinoin, Topic: Pregnancy Exposures
- PID D030471, Drug: Isotretinoin, Topic: Isotretinoin Utilization
- PID D030471, Drug: Isotretinoin, Topic: Prescription Compliance Survey to Measure Compliance with Isotretinoin Qualification Stickers
- PID D030471, Drug: Isotretinoin, Topic: Review of Isotretinoin Patient Survey Materials and Data with Interest in Compliance During the First Year of the System to Manage Accutane Related Teratology (SMART) Program
- Synopsis of the elements of the *System for Thalidomide Education and Prescribing Safety™ (S.T.E.P.S.)*