DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Memorandum

Date: July 18, 2007

To: Dermatologic and Ophthalmic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Members and Consultants

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Subject: FDA Background Package for August 1, 2007 Meeting

Thank you for agreeing to participate in the joint session of the DODAC/DSaRM Advisory Committees that will be convening on 01 August 2007 to be briefed on iPLEDGE, the risk management program for isotretinoin products.

In 2005, FDA approved a new, single risk management program for all isotretinoin products (both innovator and generic) called iPLEDGE. Transition from the previous program to iPLEDGE was completed on March, 1, 2006 and the isotretinoin sponsors have now submitted to FDA the one year data from the iPLEDGE program.

This half day meeting will provide updates on risk management activities for isotretinoin since the full implementation of iPLEDGE on March 1, 2006. The program performance parameters and outcomes collected by iPLEDGE are of interest to a wide variety of stake holders. In the interest of providing full information to stakeholders as early as possible, the iPLEDGE one year data will be presented at this meeting. As further information is obtained form the iPLEDGE program, we anticipate that discussion of the implementation of risk management strategies for isotretinoin will be an ongoing dialogue with the DODAC/DSaRM Advisory Committees at future meetings.

The specific purpose of the advisory committee meeting on 01 Aug 07 is two-fold: First, to place the iPLEDGE one-year data in the public domain and to seek the committee's advice on future possible enhancements and secondly, to discuss the acceptability of various planned programmatic changes to the iPLEDGE program. These changes derive from user experience and are directed primarily towards improving patient access and relieving stakeholder burden. We will be seeking your input on future enhancements to the risk management functions of the iPLEDGE program, and the acceptability of the pending programmatic changes.

We look forward to your attendance at this meeting and as always, we very much appreciate your time and commitment.

FDA Briefing Document
01 August 2007

Regulatory History

Accutane (isotretinoin), indicated for treatment of severe recalcitrant nodular acne, was approved for marketing on May 7, 1982, followed by generics Amnesteem in November 2002, Sotret in December 2002, and Claravis in April of 2003. Isotretinoin is the only drug product approved for the treatment of severe recalcitrant nodular acne and is a uniquely effective therapeutic option for physicians and their patients. However, isotretinoin is highly teratogenic, contraindicated in pregnancy, and labeled as Pregnancy Category X. Risk management strategies to prevent fetal exposure to isotretinoin have been in place since the original approval, with warnings about teratogenicity included in the original approved label, and a boxed warning added in February 1984. In 1988, the "**Accutane Pregnancy Prevention Program**" **(APPP)** was introduced, which included strengthened labeling and added new educational and reminder tools, a patient informed consent form, and voluntary patient and prescriber surveys designed to assess patient and prescriber compliance with APPP. In April 1990, the labeling was updated to include a description of isotretinoin-associated birth defects and a recommendation to prescribe no more than one month supply of isotretinoin. Obtainment of two negative pregnancy tests prior to the initial prescription was recommended in labeling after May 2000.

In September 2000, the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) met and concluded that the APPP was not sufficiently effective in minimizing pregnancy exposure to isotretinoin. DODAC recommended strengthening of the APPP by augmentation of patient education, mandatory registration of patients and prescribers, implementation of a pregnancy registry and linkage of prescription dispensing to negative pregnancy test results. In response to the DODAC recommendations, a sticker-based program, **System to Manage Accutane Related Teratogenicity (S.M.A.R.T.),** was approved in October 2001 and implemented in early 2002. Similar programs followed for the generic products: S.P.I.R.I.T. (Amnesteem), I.M.P.A.R.T. (Sotret), and A.L.E.R.T. (Claravis), each of which were essentially identical to S.M.A.R.T. except for tradename and logo.

In February 2004, a joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and DODAC was convened to review data from the first year following implementation of S.M.A.R.T. A number of topics, including pregnancy exposure reports, patient survey data, and the need to adequately monitor the isotretinoin pregnancy prevention risk management program, were discussed. The committee recommended strengthening and consolidation of the isotretinoin pregnancy prevention programs, to include registration of all patients, prescribers and pharmacies, tighter linkage of pregnancy test results to prescription dispensing, implementation of a pregnancy registry (for root cause analysis), and participation of all manufacturers in a single risk minimization action plan.

Following the recommendations from the joint committee, a labeling supplement for a risk minimization action plan was submitted in June 2005, and a new, single, program for all isotretinoin products (both innovator and generic) called **iPLEDGE** was approved by FDA on August 12, 2005.

An essential element of the iPLEDGE program is a performance-linked access system which tightly links the dispensing of isotretinoin to documentation of a negative pregnancy test, prescriber confirmation that contraceptive counseling has occurred, and prescriber and patient identification of contraceptive methods chosen.
Access to the iPLEDGE system is restricted to registered prescribers, pharmacies and patients to ensure that only prescribers registered and activated in iPLEDGE can prescribe isotretinoin, only pharmacies registered and activated in iPLEDGE can dispense isotretinoin, and only patients (both males and females) registered and qualified in iPLEDGE can receive isotretinoin.

New elements of the iPLEDGE program include documentation of monthly counseling (for all patients), documentation of monthly pregnancy testing (performed at a certified laboratory) for female patients of childbearing potential (FCBP), demonstration of comprehension by FCBPs by answering monthly questions, and implementation of a pregnancy registry for root cause analysis.

Stakeholder registration began in September 2005, and patient enrollment in late December 2005. Transition from the previous programs to iPLEDGE was completed on March 1, 2006 when the sticker programs were discontinued. During implementation, issues and concerns from stakeholders (including the prescriber community) emerged, such as slow registration and activation of stakeholders, call center overload, and prescriber non-receptivity. Additionally, many patients had prescriptions denied and treatment postponed because the iPLEDGE system locked out patients for an additional 23 days if they did not fill their prescription within 7 days of the office visit. Based on stakeholder and FDA feedback, the sponsor removed the 23-day lockout for males and females not of childbearing potential (FNCBP) in October 2006. This action, which did not require a labeling change, gave more flexibility to this subset of patients, reduced interruptions in treatment, and reduced burden to stakeholders.

<u>Proposed Revisions to the iPLEDGE Program</u>

The Agency is currently considering the proposed revisions described below. These changes are intended to enhance the flexibility of the program, reduce interruptions in treatment, and reduce the burden to stakeholders. The sponsor submitted a labeling supplement for additional iPLEDGE changes in February 2007. The major changes (and *rationale)* are:

- Elimination of the 23 day lockout for FCBP, with the exception of the first prescription to be filled
    - *eliminates unnecessary rigidity*

- Linkage of 7-day prescription window for FCBP to date of specimen collection rather than date of office visit
  - *strengthens link between pregnancy test and isotretinoin dispensing*
- Extension of prescription window from 7 days to 30 days for males and females not of childbearing potential
  - *reduces burden for patients who* cannot *become pregnant*
- Modification of the list of acceptable secondary forms of contraception to include condoms with or without spermicide
  - *conforms with current Center for Devices and Radiological Health, CDC, and WHO guidelines*
- Inclusion of Medication Guide content, rather than the shorter Safety Notice, in patient communication letters
  - *provides more complete safety information to patients*

These modifications will require changes to the isotretinoin product labeling and iPLEDGE program educational materials.

In summary, the proposed changes are anticipated to reduce system rigidity and stakeholder burden while maintaining the rigor of the iPLEDGE program.

The iPLEDGE Pregnancy Registry and Root Cause Analysis

The concept of a root cause analysis (RCA) for pregnancies occurring during isotretinoin therapy was discussed at the February 2004 Drug Safety and Risk Management/Dermatologic and Ophthalmic Drugs joint Advisory Committee (DSaRM/DODAC) meeting. The Committee expressed that the results of this analysis should be used to improve the program and prevent further pregnancy exposures, rather than to gather further information on the effects of isotretinoin on pregnancy. As a result, a detailed RCA instrument was designed and implemented as part of the iPLEDGE Pregnancy Registry. The interviews are conducted with each eligible participant and her health care provider(s) primarily via telephone, but the RCA questionnaire can be mailed to participants if they prefer. Once the RCA questionnaire has been completed, quarterly follow-up is conducted throughout the pregnancy and, in the case of a live birth, until the infant is 1 year old.

To date, patient participation in the RCA of the iPLEDGE Pregnancy Registry has been low.[1] More robust participation in the RCA would optimize identification of systemic program issues and best allow evidenced-based decisions regarding the need for program changes. The specific reasons for low participation are not known, so it is reasonable to pursue identification of potential barriers to full participation.

[1] Derived from the iPLEDGE Quarterly Reports from January 1, 2006, through March 31, 2007. iPLEDGE Program Evaluation Reports – 1st, 2nd, 3rd, 4th, 5th Quarterly Reports. Submitted by Hoffmann-La Roche, Inc., on July 24, 2006, October 19, 2006, November 15, 2006, January 31, 2007, and April 30, 2007, respectively.

There are several possible explanations for less than full participation. First, participation in the RCA may be uncomfortable for patients. Both the consent process and the RCA questions can seem intrusive at a sensitive time for many women. Second, participation may be perceived to be time consuming; it involves an additional informed consent and numerous follow-up interactions. Third, the iPLEDGE prescriber may not be aware of the pregnancy and the patient thus lost to follow-up without the report of pregnancy data. Fourth, patients may not understand the purpose of the pregnancy registry and therefore decline to enroll.

Strategies to optimize participation in the RCA should be considered Both the RCA informed consent and questionnaire could be redesigned to be less intrusive and more narrowly focused on obtaining data to most accurately assess root cause. Collection of outcome information limited to that which can be used to improve the iPLEDGE program would reduce burden and intrusiveness. iPLEDGE materials could include more emphasis on the purpose of the pregnancy registry.

To better interpret the RCA information, it may be important to obtain additional comparison data from females of childbearing potential during participation in iPLEDGE. While the RCA data currently provides retrospective information obtained from telephonic interviews querying about actual contraceptive practices (as opposed to the planned contraceptive practices) for women who become pregnant, comparable information is not obtained for women who do not become pregnant. The purpose of gathering this retrospective information would be to provide a more complete understanding of how (or if) the *actual* contraceptive practices (as opposed to the planned contraceptive practices) of women who become pregnant differ from the women who do not become pregnant. Such a comparison will provide context for the RCA data and facilitate substantive program evaluation.

Observations on the Assessment of Knowledge and Behavior

Patient education and assessment of patient knowledge are key components of iPLEDGE. Currently, females of childbearing potential receive a 12-page introductory brochure, a binder containing a 20-page "Guide To Isotretinoin For Female Patients Who Can Get Pregnant," and a 34-page "iPLEDGE Program Birth Control Workbook." In addition, the prescriber may provide a DVD containing presentations on isotretinoin teratogenicity and on necessary birth control methods. Unnecessarily long or complex educational materials may impede patient comprehension.[2]

Based on initial survey responses, about 13% of females of childbearing potential reported that they did not receive birth control counseling from the prescribing doctor or

[2] Refer to Prescription Drug Product Labeling; Medication Guide Requirements; Final Rule (Federal Register: December 1, 1998, Volume 63, Number 230). The Agency recognizes that lengthy information is an ineffective communication method, "FDA is concerned that, if unrestrained, lengthy information could result in unnecessary or even dangerous barriers to the effective communication of important concepts.

contraceptive counselor.[3] However, over 99% report that they were told to avoid pregnancy[4]. Initial specialized contraceptive counseling is offered free of charge in iPLEDGE: 51% of patients recalled the offer for contraception referral and about 21% of patients reported that they elected to receive it.[2]

To assess patient knowledge and comprehension (and to reinforce safety messages), female patients of childbearing potential must correctly answer at least six questions prior to receiving each prescription. Up to 62% of patients have failed certain questions.[5] The sponsors have proposed revision of questions that were identified as consistently problematic so that the monthly patient comprehension questions will more accurately assess patient comprehension of key risk mitigation messages.

The educational plan should continue to consider the educational needs of the target audience: how and when patients prefer to receive messages, the amount of material that can be successfully reviewed, the best format for the information, the best person(s) to administer the material, and the reading level of the materials. Differences in the age, sexual knowledge, and activity of patients should also be considered. Evaluation of the educational plan should focus on assessing the patients' understanding of the key safety messages, the pregnancy prevention requirements of the iPLEDGE program, and the impact of the education on patient behaviors regarding pregnancy prevention.

[3] iPLEDGE Year 1 Report, Table 7 "Number of Female Patients of Childbearing Potential Responding to Questions About the iPLEDGE Program (Patient Self-Reported)." Submitted by Hoffmann-La Roche, Inc., on March 30, 2007.
[4] iPLEDGE Year 1 Report, Table 10 "First Month questions About Avoiding Pregnancy and the Educational Components of iPLEDGE (Patient Self-Reported)." Submitted by Hoffmann-La Roche, Inc., on March 30, 2007.
[5] iPLEDGE Program Evaluation Reports – 2nd, 3rd, 4th Quarters. Submitted by Hoffmann-La Roche, Inc., on October 19, 2006, November 15, 2006, and January 31, 2007, respectively.