Isotretinoin Update: iPLEDGE

In February 2004, data from the first year following implementation of the sticker-based isotretinoin risk minimization action plan (riskMAP) was presented to a joint meeting of the Drug Safety and Risk Management (DSaRM) and Dermatologic and Ophthalmic (DODAC) Advisory Committees. At that time, the committees recommended implementation of a single, consolidated mandatory riskMAP incorportating the following elements:

- registration of all patients, both males and females
- registration of prescribers
- registration of pharmacies
- tightened linkage between pregnancy testing and isotretinoin dispensing
- establishment of a pregnancy registry for root cause analysis of pregnancy exposures

On August 12, 2005, the Agency approved iPLEDGE, a strengthened, consolidated riskMAP based on the committees' recommendations. On February 10, 2006, the committee will receive an update on the progress that has been made toward implementing these recommendations. To assist the committee, this document will review the regulatory history of isotretinoin, describe iPLEDGE, and discuss implementation.

Regulatory History:

Accutane (isotretinoin), indicated for the treatment of severe, recalcitrant nodular acne, was approved for marketing on May 7, 1982. Because of a non-clinical signal for teratogenesis, Accutane was labeled as Pregnancy Category X and contraindicated for women who were or might become pregnant; information about the risk and prevention of fetal exposure was included in the CONTRAINDICATIONS, WARNINGS and PRECAUTIONS sections. The label was successively updated as human teratogenesis data accrued. A boxed warning was added on February 20, 1984, which recommended pregnancy testing prior to Accutane initiation and use of contraception for the month prior to initiating therapy. Education and reminder tools such as Dear Doctor and Dear Pharmacist letters were issued, and pharmacists were instructed to affix red warning stickers to all Accutane prescriptions dispensed and to include a patient information brochure with the prescription. In 1986, instruction to begin Accutane therapy on the second or third day of the next menses following obtainment of a negative pregnancy test was added to the boxed warning.

In 1988, the sponsor introduced the Accutane Pregnancy Prevention Program (APPP), a risk management program that strengthened the content of labeling and added new education and reminder tools as well as assessment surveys. In the APPP, the boxed warning advised obtainment of a negative serum pregnancy test within two weeks prior to onset of therapy, use of two reliable forms of contraception simultaneously for one month before, during, and one month following discontinuation of therapy, initiation of therapy on the second or third day of the next menses following confirmation of non-pregnant status, monthly repetition of contraception counseling and pregnancy testing,

and use in women of child bearing potential only if the patient had severe disfiguring cystic acne recalcitrant to standard therapies and was reliable in understanding and carrying out instructions. Education tools and targeted outreach included two Dear Doctor letters and patient brochures. New reminder tools were introduced: the blister pak with the "Avoid Pregnancy" icon, a limitation of amount dispensed to 30-days supply, and patient informed consent forms. A voluntary patient survey and a prescriber survey were instituted to assess prescriber and patient compliance with the APPP.

In September 2000, the Dermatologic and Ophthalmologic Drugs Advisory Committee (DODAC) convened to discuss risk minimization of fetal exposure to Accutane. DODAC articulated two goals: 1) that no woman should begin isotretinoin therapy if pregnant, and 2) that no woman becomes pregnant while being treated with isotretinoin. DODAC recommended strengthening of the APPP by augmenting patient education, registering patients and prescribers, implementing a pregnancy registry, and linking prescription dispensing to adequate pregnancy testing.

In response to the DODAC recommendations, a sticker-based riskMAP, SMART, was approved for the innovator on October 30, 2001, and fully implemented as of April 14, 2002. Over the next year, three generic isotretinoin products (Amnesteem, Sotret, Claravis) were approved with three separate riskMAPs for the respective generic products (SPIRIT, IMPART, and ALERT). These programs were essentially identical to SMART but differed in tradename and logo. In addition to continuing the content and tools of the APPP, the sticker-based riskMAPs added a requirement for a second pregnancy test within the first five days of menses prior to starting therapy, and a new reminder tool -- a qualification sticker, intended to link prescribing of isotretinoin to demonstration of adequate pregnancy testing. A Medication Guide was introduced to be dispensed with the drug. The voluntary patient survey was continued, and a pharmacy survey replaced the prescriber survey.

In February 2004, a joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and DODAC convened to review data from the first year following implementation of SMART (at that time, the generic programs had not accumulated one year of data). In brief, the number of reported isotretinoin-exposed pregnancies did not decrease from the year prior to SMART's implementation. Additionally, although sticker use was high, it was an imperfect surrogate for pregnancy testing, and a 25% participation rate in the voluntary patient survey was significantly below the agreed-upon benchmark of 60%. The committees found that four separate sets of program materials were confusing and made metrics difficult to assess. They recommended strengthening and consolidation of the isotretinoin riskMAPs, to include registration of all patients, prescribers and pharmacies, tighter linkage of pregnancy testing to prescription dispensing, implementation of a pregnancy registry, and participation of all manufacturers in a single riskMAP.

In July of 2004, the FDA released a White Paper entitled Isotretinoin Teratogenicity Risk Management Program (enclosed), which amplified the elements recommended by DODAC and DSaRM at the 2004 joint meeting. The innovator and generic sponsors

jointly selected a contractor, Covance, and collaborated to design and construct a strengthened, consolidated riskMAP. In late 2004, the sponsors began to submit components of the riskMAP to the Agency for comment; the final riskMAP (less the compliance evaluation plan) was submitted as a labeling supplement on June 24, 2005, and approved by the Agency on August 12, 2005.

Because isotretinoin is indicated for the treatment of a serious condition and because safe use of the drug is predicated on the performance of specific tasks (such as pregnancy testing, contraceptive counseling), the iPLEDGE labeling supplement was approved under 21 CFR 314.500 Subpart H. Subpart H approval allows FDA to restrict distribution of a drug to ensure its safe use. FDA had previously approved thalidomide, another highly teratogenic drug with a riskMAP similar to iPLEDGE, under Subpart H.

iPLEDGE Elements

iPLEDGE builds on the prior programs by incorporating essentially all of the content and tools (education and reminder tools) of the previous riskMAPs (SMART, SPIRIT, IMPART, ALERT), and adding a performance-linked access system (PLAS) and a pregnancy registry. Embedded in the PLAS are the components of wholesaler registration, pharmacy and prescriber registration and activation, and patient registration and qualification, which comprise restricted distribution.

Performance-Linked Access System

An essential element of iPLEDGE is the iPLEDGE system, a performance-linked access system (PLAS) which tightly links the dispensing of isotretinoin (for female patients of child bearing potential) to the following elements: 1) documentation of a negative pregnancy test, 2) prescriber confirmation that contraceptive counseling has occurred, and 3) prescriber and patient identification of contraceptive methods chosen. The iPLEDGE system also provides an opportunity to reinforce patient education through testing of contraceptive knowledge. The iPLEDGE system is a technology-based construction which can be accessed either via the internet or by phone. 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 patient registered and qualified in iPLEDGE can receive isotretinoin.

Stakeholder Registration

Wholesalers, pharmacies, prescribers and patients must each register with iPLEDGE in order to distribute, dispense, prescribe or receive isotretinoin, respectively. Registration of these parties is intended to ensure that isotretinoin is not dispensed outside of iPLEDGE and hence potentially without protection against fetal exposure. Although prescribers were registered in the sticker-based riskMAPs (SMART, SPIRIT, IMPART, ALERT), registration of wholesalers, pharmacies and patients are all new elements in iPLEDGE.

Wholesalers

Wholesalers (including distributors) must register annually with iPLEDGE and agree to abide by relevant riskMAP procedures. Registration is accomplished by signing an

annual agreement that they will only ship to registered pharmacies and will provide product flow data to the sponsors. Wholesalers' participation in iPLEDGE is new; wholesalers have not been participants in prior isotretinoin riskMAPs. However, under the restricted distribution plan of iPLEDGE, wholesaler registration and participation is essential to track product and ensure that diversion of product to non-iPLEDGE participating sources does not occur.

Pharmacies

In contrast to the sticker-based riskMAPs, in which any pharmacy could dispense isotretinoin (after ensuring that a yellow sticker is in place and correctly filled out), in iPLEDGE only pharmacies that register and activate may access the iPLEDGE system, confirm patient qualification, and order, receive and dispense isotretinoin. Activation requires that the registered site pharmacist attest to possession of relevant competencies necessary to safely dispense the drug and agree to train other pharmacists at that site on iPLEDGE and compliance with iPLEDGE procedures. Pharmacy activation must be renewed annually.

Prescribers

Analogous to the sticker-based riskMAPs, prescribers must register in order to receive iPLEDGE materials. After reviewing the materials, attesting to possession of relevant competencies, and agreeing to comply with iPLEDGE requirements, prescibers are activated and may access the iPLEDGE system. Activation must be renewed annually. Only prescribers who are registered and activated with iPLEDGE (or their office staff designee/s) may register patients, confirm that counseling has occurred, and enter pregnancy test results. Prescribers must interact with the iPLEDGE system each month for both male and female patients in order for the patient to be qualified to receive isotretinoin.

Patients

In iPLEDGE, all patients, both males and females, must be registered as part of the qualification process order to receive isotretinoin. Registration involves assignment of an ID number, obtainment of informed consent, and input of demographic data (name, address, phone number, DOB, last four numbers of SSN, patient ID number) into the iPLEDGE system. Patient registration was not a component of the sticker-based riskMAPs.

<u>Qualification of Female Patients of Child-Bearing Potential</u>

Qualification of female patients of child-bearing potential under iPLEDGE is similar to qualification of such patients under the sticker-based riskMAPs, but differs in four ways. First, in iPLEDGE, the second confirmatory pregnancy test and each monthly follow-up pregnancy test must be performed at a CLIA-certified laboratory. The test may be performed on urine or serum samples and must have a sensitivity of 25 mIU/mL. Second, the prescriber must confirm each month in the iPLEDGE system that contraceptive counseling has occurred. Monthly contraceptive counseling was required in the sticker-based riskMAP, but documentation that it has occurred is new in iPLEDGE. Third, each month both the prescriber and the patient must enter into the

iPLEDGE system the primary and secondary forms of contraception that the patient has selected. The primary form entered by the prescriber and patient must be an acceptable form and must match or the patient will not be qualified. The secondary form must be an acceptable secondary form (or a second primary form), but concurrence is not required between the secondary forms identified by the prescriber and the patient. The iPLEDGE requirement for use of two acceptable forms of contraception, a primary and a secondary form, parallels the contraceptive requirements of the prior riskMAP, however the need for both the prescriber and the patient to document the patient's primary and secondary forms is new, as is the requirement for concurrence on the primary form identified. Fourth, the patient must correctly answer questions intended to reinforce key messages about the iPLEDGE program.

Qualification of Male Patients and Female Patients Who Cannot Get Pregnant

Unlike female patients of child-bearing potential, male patients and female patients who cannot get pregnant (nFCBP) do not need to access the iPLEDGE system each month to be qualified. Males and females not of child-bearing potential must be registered in the iPLEDGE system initially (done by the prescriber or prescriber designee), and the prescriber must interact with the iPLEDGE system each month to confirm that the patient understands iPLEDGE program requirements (such as not sharing medication, not donating blood, etc.).

Pregnancy Registry

Fetal exposures to isotretinoin will be followed through the iPLEDGE pregnancy registry to obtain information on outcomes. Additionally, root cause analysis will be conducted to identify underlying causes behind fetal exposure. As part of registration and activation in iPLEDGE, pharmacies, prescribers and patients agree to report known pregnancies to the registry.

Psychiatric Adverse Events

Although the primary focus of iPLEDGE is the prevention of fetal exposure to isotretinoin, the labeling for neuropsychiatric adverse events was revised concomitant with approval of iPLEDGE. The supportive evidence for these changes includes accrual of additional spontaneous adverse event reports for psychiatric events (including positive dechallenge and rechallenge reports) as well as non-clinical and clinical studies which demonstrate isotretinoin effects on the mammalian brain. While these data do not establish causality, they support the biologic plausibility of isotretinoin-induced neuropsychiatric adverse events. Thus, it was deemed prudent to update isotretinoin labeling to better inform prescribers and patients of the potential risk of neuropsychiatric adverse events and to provide a reminder tool to patients and their families.

Three changes were introduced. First, the back of the iPLEDGE patient identification card contains a list of symptoms of depression, with the instructions to stop isotretinoin and contact one's doctor right away if the symptoms occur. Second, the WARNINGS and Patient Information sections of the Package Insert were updated to include explicit instructions to prescribers to obtain a personal and family history for mental illness prior to initiation of isotretinoin therapy, to assess for the signs and symptoms of depression or

other mental illness during therapy, and to discontinue isotretinoin and consider further intervention if symptoms or psychiatric adverse events occur. Third, for patients who discontinue therapy prematurely, iPLEDGE will query as to the reason for premature discontinuation. Although this element of iPLEDGE was developed to identify cases of pregnancy, it will also identify other adverse events which lead to premature discontinuation of treatment.

Additional Changes:
The boxed warning was simplified by removing the riskMAP program details and placing them in the PRECAUTIONS section.

iPLEDGE Implementation
The original implementation dates for iPLEDGE were for launch on November 1, 2005, and full transition by January 1, 2006. These dates were changed to launch on December 30, 2005, and full transition by March 1, 2006 to allow more time for wholesaler and pharmacy activation.

Future Input
Evaluation parameters for iPLEDGE have not yet been determined. It is anticipated that, in the near future, the Agency will seek DSaRM and DODAC input on metrics, relevant comparisons, and thresholds for success for iPLEDGE. Throughout the history of regulating this important but challenging drug, FDA has worked with all stakeholdersand the Derm AC and will continue to do so to improve the FDA oversight of isotretinoin.

July 8, 2004

Isotretinoin Teratogenicity Risk Management Program

I. Introduction

On February 26 and 27, 2004, FDA convened the Drug Safety and Risk Management and the Dermatologic and Ophthalmic Drug Advisory Committees to:

- discuss the effectiveness of the isotretinoin risk management program for the prevention of fetal exposure to ACCUTANE and its generic equivalents and
- consider whether changes to this isotretinoin risk management program would be appropriate.

This document is the Agency's "current thinking" for a new teratogenic risk management program for isotretinoin. It represents a distillation and refinement of proposals presented by the innovator and generic manufacturers at the advisory committee meeting, public comments presented during the Open Public Hearing of the advisory committee meeting, and advisory committee member recommendations.

This risk management program would replace the current risk management programs[1] SMART program. This program is being proposed voluntarily by the innovator and generic manufacturers in recognition of the public health need to eliminate fetal exposure to isotretinoin.

The central tenet of the isotretinoin risk management program is that one centralized registry, system or clearinghouse be created and that all prescribers, dispensing pharmacies, and patients participate in the risk management program in order to prescribe, dispense or receive the medication.

II. Proposed Program

A. Goals

To eliminate fetal exposure to isotretinoin by ensuring that

- No woman start isotretinoin therapy if pregnant
- No woman on isotretinoin therapy become pregnant

[1] System to Manage Accutane-Related Teratogenicity® (SMART) ™; System to Prevent Isotretinoin-Related Issues of Teratogenicity (S.P.I.R.I.T.) ™; Adverse Event Learning and Education Regarding Teratogenicity (A.L.E.R.T.)™; Isotretinoin Medication Program: Alerting you to the Risks of Teratogenicity (I.M.P.A.R.T.)™

B. Definitions

Registration – initial registration of the prescriber, patient, or pharmacies. Each patient will be registered once in the system. Registration of prescribers and pharmacies will be renewed annually.

Qualification – the monthly process occurring throughout the course of therapy to determine whether a patient is a candidate for isotretinoin.

Authorization – the process by which the pharmacist verifies with the clearinghouse that the prescription may be filled.

Clearinghouse – the single centralized system for managing the registration, qualification and authorization processes.

C. Description of Program

- All prescribers, patients and dispensing pharmacies would be registered in a single centralized "clearinghouse" (this is similar to the proposed registry).
- Before an approved pharmacy first dispenses the medication for a particular patient, the following would be required:
  - Completion of patient education by the prescriber
  - An appropriately timed negative pregnancy test within seven days prior to dispensing the medication
  - Completion of the informed consent, education and risk management component by the patient.
  - For all subsequent prescriptions, the following would be required monthly:
  - Ongoing patient education by the prescriber
  - Continued negative pregnancy tests within seven days prior to dispensing
  - Completion of the education and risk management component by the patient.

- **Sponsors Responsibilities**

1. Ship drug only to authorized distributors and registered pharmacies.
2. Establish and maintain the clearinghouse.
3. Monitor for sales of the drug outside of approved distribution channels, including via the Internet.
4. Develop procedures to monitor and evaluate each component of the risk management program (RMP) to include clearinghouse compliance with specified responsibilities, prescriber and pharmacy registration and prescribing and dispensing by non-registered prescribers and pharmacies, respectively.

5. Evaluate the effectiveness of the program in reducing and limiting pregnancy exposures.

6. Develop a single set of educational materials for all prescribers, patients and pharmacists irrespective of the brand.

- **Clearinghouse Contractor Responsibilities**

1. Develop and maintain a secure system to register prescribers, patients and pharmacies, to gather the information necessary to qualify patients to receive the medication, and to approve dispensing by pharmacist.
2. Ensure that system is user-friendly and real-time, that input is direct and rapid, and that it is accessible via both the Internet and telephone 24 hours a day/7 days a week.
3. Ensure that health professionals and other staff are accessible to talk to patients and rapidly address any concerns or problems with the registration, qualification, or approval processes.
4. Receive all pregnancy laboratory tests.
5. Provide internet or telephone approval of prescriptions that meet the qualification criteria.
6. Develop "denial" algorithms so pharmacist can tell patient who to call if denial occurs.
7. Distribute all educational and program materials directly to prescribers and pharmacists upon registration and as needed between annual registrations.
8. Maintain a directory of registered prescribers, laboratories and pharmacies.

- **Prescriber Responsibilities**

1. Register annually and receive a prescriber number by completing the approved program of "self-attestation" of receipt of materials, possession of relevant competencies, agreement to follow RMP procedures, and signing of a Letter of Understanding. Renewal "attestation".
2. Determine the need for the drug in a patient.
3. Determine pregnancy risk category of patient (1. females of childbearing potential 2. females not of child bearing potential and males)
4. Perform screening pregnancy test for FCBP.
5. Educate patients on the risks and benefits of the drug, and obtain informed consent from the patient.
6. Order and monitor all laboratory tests in a timely fashion pertinent to the safe use of the drug (e.g., pregnancy testing, liver enzymes, etc.). Assure all pregnancy tests from FCBP are reported to the clearinghouse, including positive findings that lead to discontinuation of therapy.
7. Prescribe two simultaneous forms of contraception in females of childbearing potential including a primary form of birth control or refer patient to another prescriber for such a prescription.

8. Register the patient in the "clearinghouse," obtain a patient registration number, and provide the number to the patient on a pre-printed registration card. Record the patient registration number in the medical chart in case patient loses card.
9. Prescribe the medication to males and females of non child bearing potential.
10. Write order for confirmatory pregnancy test in FCBP and instruct patient to obtain test during menses.
11. Qualify the patient at initiation of therapy and monthly thereafter, via phone or internet, by attesting that the patient has been counseled and has selected and reports using two forms of birth control. Initial qualification should follow registration by at least 30 days for females of childbearing potential.
12. Prescribe isotretinoin to FCBP if pregnancy test results negative.
13. Follow-up monthly with the patient and communicate to the clearinghouse that the patient has received ongoing counseling.
14. Continue patient follow-up for pregnancy exposures until at least 30 days after completion of therapy.

- **Patient Responsibilities**

1. Provide the prescriber with the information needed to register the patient
2. Receive and secure the patient identification card.
3. Call the "clearinghouse" to answer questions regarding their responsibilities to take the medication using their patient identification number before receipt of the first prescription and prior to each monthly refill.
4. Adhere to all directions regarding the use of the medication, including using birth control and the completion of monthly pregnancy testing as appropriate.
5. Females of childbearing potential are required to commit to use two forms of contraception (one being primary) or abstinence during the entire course of therapy and 30 days beyond.
6. FCBP should obtain confirmatory pregnancy test in accredited laboratory during menses.

- **Pharmacy Responsibilities**

1. Register annually and receive a pharmacy authorization number by completing the approved program of "self-attestation" of receipt of materials, reading the Best Practices guide, and signing a Letter of Understanding.
2. Dispense medication after receiving authorization from the "clearinghouse" by dialing the toll-free number and entering the patient identification number.
3. Dispense only a 30-day supply of the drug at one time or in association with each prescription.
4. Ensure that all pharmacists on the pharmacy staff are familiar with the elements for the program and that pharmacists dispense only after receiving authorization.
5. Educate the patients as appropriate regarding the risks and benefits of the medication.

6. If authorization is denied, immediately refer patient to “clearinghouse” counseling number or prescriber depending on the instructions provided by the denial notice.

- **Voluntary Survey**

1. A single voluntary survey to assess patient knowledge of the program among a sample of isotretinoin recipients.

- **Pregnancy case follow-up**

1. Develop a single means for following up on cases where pregnancies occur while on medication or within 30 days after completion of therapy.

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4. Ensure that all pharmacists on the pharmacy staff are familiar with the elements for the program and that pharmacists dispense only after receiving authorization.
5. Educate the patients as appropriate regarding the risks and benefits of the medication.

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