



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<sup>1</sup> 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.

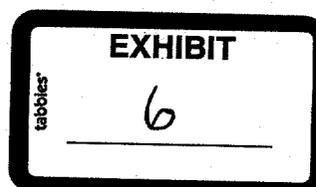
### II. Proposed Program

#### 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

<sup>1</sup> 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.