Initial REMS Approval: 10/2010
Most Recent Modification: 7/2016

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

The iPLEDGE Program

Single Shared System for Isotretinoin

Reference ID: 3956479

1. GOALS

The goals of the isotretinoin risk evaluation and mitigation strategy are:

1. To prevent fetal exposure to isotretinoin
2. To inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions

2. REMS ELEMENTS

2.1. Medication Guide

A Medication Guide for isotretinoin is dispensed with each prescription for isotretinoin in accordance with 21 CFR 208.24, as described below.

A Medication Guide is enclosed with each blister package of isotretinoin to ensure that the Medication Guide is given to each patient with each prescription.

The currently approved isotretinoin Medication Guide is part of this REMS.

2.2. Elements to Assure Safe Use

2.2.1. Healthcare providers who prescribe isotretinoin are specially certified in the iPLEDGE Program.

a. Isotretinoin sponsors will ensure that healthcare providers who prescribe isotretinoin are specially certified in the iPLEDGE Program. To become certified, each prescriber must activate registration, by completing the Prescriber Enrollment Form, via the iPLEDGE Program website or the automated phone system. The registration and activation requires each prescriber to agree to do the following:

   i. Register each patient in the iPLEDGE Program via the iPLEDGE Program website or automated phone system.
   ii. Understands the risks of fetal exposure to isotretinoin and the risk factors for unplanned pregnancy.
   iii. Correctly identify and document patients as females of reproductive potential, females of non-reproductive potential, or males.
   iv. Provide contraception counseling to females of reproductive potential prior to and during isotretinoin treatment, or refer females of reproductive potential to an expert for such counseling.

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v. Provide scheduled pregnancy testing for females of reproductive potential and then verify and document the negative pregnancy test result prior to writing each prescription.

vi. Document the two chosen forms of contraception for each female of reproductive potential prior to writing each prescription.

vii. Prescribe no more than a 30-day supply of isotretinoin with no refills.

viii. Report any pregnancies in patients prescribed isotretinoin to the iPLEDGE Program.

b. Isotretinoin sponsors will ensure the iPLEDGE Program documents that certified prescribers/designees have performed the following responsibilities prior to initiating isotretinoin treatment and monthly prior to providing each prescription:

i. Counseled the patient about isotretinoin risks.

ii. Determined the reproductive status of all female patients prior to initiating treatment, and determined whether the reproductive status of female patients has changed.

iii. For patients who are females of reproductive potential, provide evidence or other documentation that prescribers/designees have:

a. Obtained a negative CLIA-certified pregnancy test result.

b. Determined that each female of reproductive potential has appropriate contraception and has been re-counseled about the importance of complying with contraceptive methods.

c. Isotretinoin sponsors will:

i. Maintain a validated and secure database of all iPLEDGE Program registered and activated prescribers, designees, and delegates.

ii. Monitor to ensure that only iPLEDGE Program certified prescribers are prescribing isotretinoin.

iii. Monitor to ensure that iPLEDGE Program certified prescribers correctly identify patients who are females of reproductive potential. A female of reproductive potential is defined as a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

iv. Monitor certified prescriber compliance with the iPLEDGE Program. Certified prescriber compliance with the iPLEDGE Program includes categorizing female patient risk (females of reproductive potential vs. females of non-reproductive potential), providing counseling as required, documenting contraception forms as required, and providing pregnancy testing for all females of reproductive potential treated with isotretinoin.

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v. Institute appropriate corrective action according to the Non-Compliance Action Policy if the prescriber is found to be non-compliant with the iPLEDGE Program.

d. The following materials are part of the REMS and are appended:

i. *The Guide to Best Practices For the iPLEDGE Program*

ii. *Prescriber Contraception Counseling Guide*

iii. DVDs for prescriber use in patient counseling: *Be Prepared, Be Protected* and *Be Aware: The Risk of Pregnancy While on Isotretinoin.*

iv. Recognizing Psychiatric Disorders In Adolescents And Young Adults

v. Request for Exemption for Patients with Serious Medical Reasons

vi. Office Staff Designee Registration/Activation Form

vii. Instructions for Managing Office Staff Designees

viii. Prescriber Enrollment Form

2.2.2. Isotretinoin will only be dispensed by pharmacies that are specially certified in the iPLEDGE Program.

a. Isotretinoin sponsors will ensure isotretinoin is only dispensed by pharmacies that are certified. To become certified, the pharmacy must become registered and activated in the iPLEDGE Program. To become registered and activated, each pharmacy must identify a "responsible site pharmacist" who completes the Pharmacy Enrollment Form and agrees to do the following before dispensing an isotretinoin prescription:

i. Affirm that all pharmacists will comply with all iPLEDGE Program requirements**:**

1. Know the risk and severity of fetal injury/birth defects caused by isotretinoin.
2. Dispense only FDA-approved isotretinoin products and obtain isotretinoin only from the iPLEDGE Program registered wholesalers.
3. Do not sell, borrow, loan, or otherwise transfer isotretinoin in any manner to or from another pharmacy.
4. Dispense only to qualified patients determined via authorization from the iPLEDGE Program web- or voice-based system for every isotretinoin prescription.
5. Document the Risk Management Authorization (RMA) number on each prescription.
6. Dispense no more than a 30-day supply (no refills).

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7. Dispense the isotretinoin Medication Guide with each prescription.
8. Dispense prior to the "do not dispense to a patient after" date provided by the iPLEDGE Program.
9. Return to the manufacturer (or delegate) any unused product if registration is revoked or if the pharmacy chooses to not reactivate.

ii. Re-activate pharmacy iPLEDGE Program registration annually.

b. The following materials are part of the REMS and are appended:

i. Pharmacist Guide for the iPLEDGE Program

ii. Pharmacy Enrollment Form

2.2.3. Isotretinoin sponsors will ensure that isotretinoin will only be dispensed to patients enrolled in the iPLEDGE Program with evidence or other documentation of safe-use conditions.

a. Isotretinoin sponsors will ensure that all patients treated with isotretinoin are enrolled in the iPLEDGE Program by a registered prescriber, before isotretinoin is dispensed to them. To become enrolled, each patient or guardian must sign the appropriate Patient Information/Informed Consent form acknowledging that:

i. He or she understands the potential fetal harm with female patient exposure to isotretinoin.

ii. Enrollment in the iPLEDGE Program is required.

iii. Isotretinoin must not be shared with anyone, even someone with similar symptoms.

iv. He or she cannot donate blood while on isotretinoin and for 1 month after treatment has ended.

v. He or she must obtain the prescription within specified time frames.

b. Isotretinoin sponsors must ensure that isotretinoin is dispensed to females of reproductive potential only if there is evidence or other documentation that they meet the following safe-use conditions:

i. Are not pregnant or breastfeeding.

ii. Comply with the required pregnancy testing as ordered by the certified prescriber before receiving each isotretinoin prescription follows:

1. Two urine or serum pregnancy tests before receiving the initial isotretinoin prescription. The screening test and confirmation test must be at least 19 days apart. For patients with regular menstrual

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cycles, the confirmation test should be done during the first 5 days of the menstrual period immediately preceding treatment. For patients with amenorrhea, irregular cycles, or using contraceptive methods that precludes withdrawal bleeding, the confirmation test must be immediately preceding treatment and at least 19 days after the screening test.

2. Monthly pregnancy testing done prior to receiving authorization to receive each isotretinoin prescription.

iii. Unless continuously abstinent, comply with the iPLEDGE Program requirement to use 2 forms of contraception 1 month before, during, and for 1 month after discontinuing isotretinoin treatment.

iv. Access the iPLEDGE Program system before receiving each isotretinoin prescription and 1 month after isotretinoin treatment concludes to answer questions about the program requirements and to enter 2 chosen forms of contraception.

v. Be informed of the purpose and importance of providing information about her pregnancy, should she become pregnant while taking, or within 1 month of the last dose of isotretinoin.

vi. Be informed of the need to immediately stop isotretinoin treatment if she engages in unprotected heterosexual intercourse.

c. Isotretinoin sponsors will ensure that there is evidence or other documentation that all iPLEDGE Program safe use requirements have been met for each female of reproductive potential prior to receiving isotretinoin each month:

i. The patient is registered in the iPLEDGE Program and had required pregnancy test(s).

ii. The patient entered their two chosen forms of birth control into the iPLEDGE Program.

iii. The patient answered the required questions about the iPLEDGE Program and pregnancy prevention.

iv. The prescriber entered into the iPLEDGE Program the two chosen forms of contraception after re-counseling.

v. The patient has a negative pregnancy test result entered into the iPLEDGE Program by the prescriber or designee.

d. The following materials are part of the REMS and are appended:

i. Guide to Isotretinoin for Female Patients Who Can Get Pregnant

ii. Guide to Isotretinoin for Male Patients and Female Patients who Cannot Get Pregnant

iii. The iPLEDGE Program Patient Introductory Brochure

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iv. Isotretinoin Educational Kit for Males and Females of Non-Reproductive Potential

v. Isotretinoin Educational Kit for Females of Reproductive Potential

vi. Patient Information/Informed Consent for all patients

vii. Patient Information/Informed Consent for Females of Reproductive Potential

viii. Patient Monthly Comprehension Questions

2.2.4 Isotretinoin sponsors will maintain a centralized pregnancy registry for the iPLEDGE Program enrolled female patients who become pregnant and consent to participate in a root cause analysis.

The primary objectives of the iPLEDGE Program Pregnancy Registry are to:

a. Determine isotretinoin exposure status for each reported pregnancy.
b. Document the outcome of each isotretinoin exposed pregnancy.
c. Determine, document, and analyze causes contributing to fetal exposure (root cause analysis).

2.3. Implementation System

The implementation system will include the following:

a. Isotretinoin sponsors will maintain a secure web- and voice-based interface for all certified entities as described in Sections 2.2.2 and 2.2.3. This includes a system and process to monitor pregnancy testing results, and to link monthly prescription authorization (risk management authorization) to collection of the following data:

    i. Patient age, gender, and risk category

    ii. Required counseling

    iii. Prescription data (RMA numbers, dates prescription filled, quantities dispensed)

    iv. For female patients of reproductive potential:

        a. Baseline and monthly pregnancy tests, including 30 day post-therapy test (dates and results)

        b. Chosen methods of contraception

        c. Answers to monthly comprehension questions

    v. For females who become pregnant:

        a. Maternal and fetal outcome

        b. Information from the prescriber about circumstances contributing to the fetal exposure

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b. Isotretinoin sponsors will monitor wholesaler distribution data to ensure that only registered entities distribute isotretinoin. Wholesalers who distribute isotretinoin must be registered with the iPLEDGE Program prior to distributing isotretinoin and must re-register annually thereafter. Wholesalers must register with the iPLEDGE Program by signing and returning the iPLEDGE Program wholesaler agreement. By signing the agreement, wholesalers affirm that they will comply with all of the following iPLEDGE Program requirements:

   i. Distribute only FDA-approved isotretinoin product

   ii. Only ship isotretinoin to: 1) wholesalers registered in the iPLEDGE Program with prior written consent from the manufacturer; and 2) pharmacies licensed in the US and registered and activated in the iPLEDGE Program.

   iii. Notify the isotretinoin manufacturer (or delegate) of any unregistered and/or non-activated pharmacy or unregistered wholesaler that attempts to order isotretinoin.

   iv. Return to the manufacturer (or delegate) any undistributed product if registration is revoked by the manufacturer or if the wholesaler chooses to not re-register annually.

c. Isotretinoin sponsors will maintain a secure database of all certified pharmacies to ensure compliance with the following:

   i. Obtain isotretinoin only from registered wholesalers.

   ii. Dispense isotretinoin to patients only after receiving iPLEDGE Program authorization each month for each prescription.

   iii. Fill isotretinoin within the allowed timeframes only.

d. Isotretinoin sponsors shall develop and implement a single Non-Compliance Action Policy for handling noncompliant stakeholders.

e. Isotretinoin sponsors will monitor registered wholesaler and certified pharmacy compliance, address deviations, and institute appropriate corrective actions according to the Non-Compliance Action Policy if the wholesaler/pharmacy is found to be non-compliant with the iPLEDGE Program.

f. Isotretinoin sponsors will monitor the internet to ensure isotretinoin is not prescribed, dispensed, or otherwise obtained through the internet or any other means outside of the iPLEDGE Program.

g. Based on monitoring and evaluation of the REMS elements to assure safe use, isotretinoin sponsors will take reasonable steps to work to improve implementation of these elements, as applicable.

h. Isotretinoin sponsors will maintain a call center to support prescribers, patients and pharmacies in interfacing with the iPLEDGE Program.

i. The following materials are part of the REMS and are appended:

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i. iPLEDGE Program wholesaler agreement

ii. Wholesaler to wholesaler shipment request form

2.4. Timetable for Submission of Assessments (Applicable only to drugs with an approved new drug application (NDA))

The iPLEDGE Program assessments will be submitted to FDA on May 1, 2011 and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each annual submission will conclude no earlier than 60 days before the submission date for that assessment. The iPLEDGE Program assessment will be submitted so that it is received by FDA on or before the due date.

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