DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

BRIEFING DOCUMENT

FOR

iPLEDGE YEAR ONE UPDATE

AMNESTEEM® produced by Genpharm Inc; distributed by Mylan Pharmaceuticals

SOTRET® produced by Ranbaxy Laboratories Limited

Claravis™ produced by Barr Laboratories

ACCUTANE® produced by Roche Laboratories Inc

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1. EXECUTIVE SUMMARY

1.1 Background

The isotretinoin pregnancy risk management program, iPLEDGE, is a computer-based, restrictive distribution program and pregnancy registry which provides a closed-loop system for prescribing, dispensing, and distributing isotretinoin. The program's goals are to ensure that no woman starts isotretinoin therapy if she is pregnant and that no woman on isotretinoin therapy becomes pregnant during therapy and for 1 month after discontinuing isotretinoin treatment. iPLEDGE was developed by the isotretinoin sponsors (Barr Laboratories, Genpharm Inc., Mylan Pharmaceuticals Inc., Ranbaxy Laboratories Limited, and Roche Laboratories Inc.) in collaboration with the Food and Drug Administration (FDA) during 2004 and 2005. The iPLEDGE program began accepting patient registrations on December 30, 2005 and became mandatory as of March 1, 2006.

Key elements of iPLEDGE include:

- Single, centralized program for all isotretinoin products
- Registration of all healthcare professionals prescribing or dispensing isotretinoin
- Mandatory, monthly, laboratory-based, pregnancy tests for females of childbearing potential before each new prescription is authorized
- Mandatory, monthly, patient-education questions via an interactive web/phone based system
- A centralized pregnancy registry with root cause analysis for all pregnancies
- A technical infrastructure to support the above registrations, collection of laboratory pregnancy test results, and verification of patient qualifications

The remainder of this document reviews components of the iPLEDGE program, summarizes the changes implemented in the program after launch and the plan for additional program changes to meet the stakeholder needs for efficiency, and provides data from the first year of iPLEDGE (March 1, 2006 through February 28, 2007) including user compliance and pregnancies.

1.2 iPLEDGE Year 1 Update

The main highlights from the iPLEDGE Year One update are as follows:

- The iPLEDGE program is a risk management program of unprecedented size and scope with over 189 wholesalers, 42,362 pharmacies, 15,742 prescribers, and 305,366 patients registered during Year One.
- The majority of the recommended stakeholder changes to increase stakeholder efficiency have been or are in the process of being implemented into the program.
- A centralized isotretinoin pregnancy registry was established and data from its first year provide a baseline for subsequent comparisons.
- Educational messages about the need to avoid pregnancy and to use two forms of contraception for 1 month before, during, and 1 month after isotretinoin therapy are

being communicated by prescribers and are reaching female patients of childbearing potential.

- Overall, 137,415 females of childbearing potential were registered during Year One and 91,894 of these patients had an isotretinoin prescription authorized through the iPLEDGE system. A total of 122 pregnancies were reported. The majority of these pregnancies occurred after isotretinoin therapy was initiated. Most pregnancies were associated with contraceptive noncompliance.
- Almost all pregnant and nonpregnant women demonstrated an understanding of both the need to use contraception and the risk of birth defects for isotretinoin-exposed pregnancies.

2. EVOLUTION OF RISK MANAGEMENT INITIATIVES FOR PREGNANCY PREVENTION

Isotretinoin is a human teratogen that is uniquely efficacious for the treatment of severe recalcitrant, nodular acne in patients who are unresponsive to conventional therapy, including systemic antibiotics. The safe use of isotretinoin in women requires that every effort be made to 1) prevent pregnant women from taking isotretinoin; and 2) prevent women of childbearing potential from becoming pregnant 1 month before initiation of isotretinoin therapy, during therapy, and for 1 month after discontinuing isotretinoin treatment.

The innovator isotretinoin drug, ACCUTANE® was introduced to the United States in 1982 with a Category X pregnancy designation, the designation for drugs that must be avoided under all circumstances during pregnancy. Over the years, the strategies to prevent maternal/fetal exposure to isotretinoin have included both warnings in the product label, focused educational materials for prescribers and patients, and risk management programs for pregnancy prevention, the first of which, the Pregnancy Prevention Program, was introduced by Roche in 1988 (Appendix 1). This was followed by an enhanced risk management program, the System to Manage Accutane Related Teratogenicity® (S.M.A.R.T.®) in 2002, which was based in part on data generated from the Pregnancy Prevention Program. Risk management programs with the same components of S.M.A.R.T. were introduced with the approval of generic versions of isotretinoin beginning in November 2002.

On February 26 and 27, 2004, a joint advisory committee meeting was held between the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee to discuss the first year results of S.M.A.R.T. The discussion focused on whether changes were necessary to S.M.A.R.T. and its generic equivalents. At this meeting, the sponsors presented a proposal for a single, enhanced isotretinoin pregnancy risk management program, which included mandatory registration of prescribers, patients, and pharmacies, automatic system verification of pregnancy test results, and a centralized pregnancy registry for reporting and follow-up of pregnancies.

Based on the recommendations of the Advisory Committees and the FDA White Paper (issued July 2004), the sponsors developed a unified, mandatory, isotretinoin pregnancy

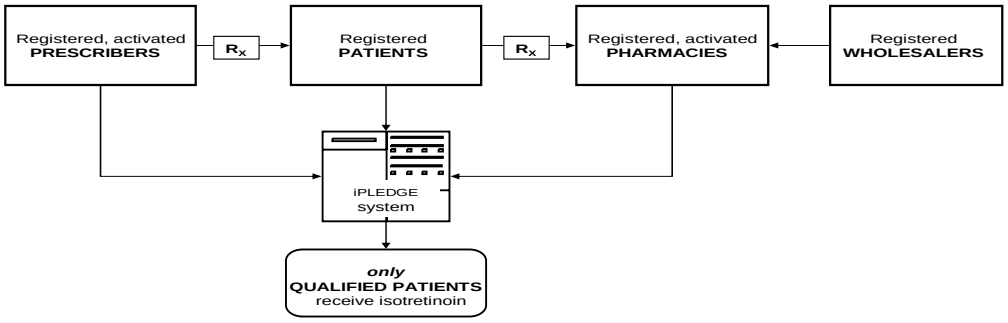
risk management program, iPLEDGE, with a single centralized pregnancy registry to replace all previous isotretinoin risk management programs.

3. iPLEDGE

3.1 Program Overview

The iPLEDGE program is a computer-based, centralized registry of prescribers, patients, pharmacies, and wholesalers, that provides a closed-loop system for prescribing, dispensing, and distributing isotretinoin (Figure 1). The public health goal of the iPLEDGE program is to eliminate fetal exposure to isotretinoin by ensuring that: 1) no female patient starts isotretinoin therapy if pregnant; and 2) no female patient on isotretinoin therapy becomes pregnant.

Figure 1 iPLEDGE System



Key elements of iPLEDGE include:

- Mandatory registration of wholesalers
- Mandatory registration and education of all isotretinoin prescribers
- Mandatory registration of all dispensing pharmacies via a responsible site pharmacist
- Mandatory registration and education of all patients prescribed isotretinoin
- Mandatory, laboratory-based, pregnancy tests for females of childbearing potential prior to authorization for each new prescription
- Mandatory, interactive-educational questions about contraception and birth defects prior to each new prescription for females of childbearing potential
- Authorization for isotretinoin to be dispensed only after a patient has met all iPLEDGE requirements
- A centralized pregnancy registry
- A technical infrastructure to support the above registrations, collection of laboratory pregnancy test results, and verification of patient qualifications

The iPLEDGE program began accepting patient registrations on December 30, 2005 and became mandatory as of March 1, 2006. This document reviews components of the iPLEDGE program, summarizes the changes implemented in the program after launch and the plan for additional program changes to meet the stakeholders needs for efficiency, and provides data from the first year of iPLEDGE (March 1, 2006 through February 28, 2007) including user compliance and pregnancies.

3.2 iPLEDGE Requirements and Processes

iPLEDGE has specific processes and requirements that target all aspects of the isotretinoin prescribing chain which includes wholesalers, prescribers, pharmacies, and patients. Many of these iPLEDGE processes have been designed to address gaps identified in the previous risk management programs for isotretinoin (Table 1). A brief description of the specific iPLEDGE processes and requirements is provided below for each of the iPLEDGE stakeholders.

Table 1 Risk Management Enhancements with iPLEDGE

Gaps Identified From Previous Risk Management Programs	Risk Management Enhancements in iPLEDGE
• Strengthen the verifiable link between pregnancy testing and dispensing of isotretinoin • Reinforce pregnancy testing requirements with patients and prescribers	• Monthly pregnancy tests (either serum or urine) must be conducted in an accredited laboratory (CLIA certified) • Automatic system verification of negative pregnancy test results that are entered by the prescriber before a pharmacist can dispense isotretinoin • A formalized process for following-up with prescribers and patients if expected pregnancy test results are not entered into the system (lost to follow-up procedure)
• Reinforce patient contraception requirements	• Patient and prescriber entries for the primary contraceptive form must match • Patients must answer education questions each month (tailored to the patient's selected methods of contraception)
• Multiple risk management programs for isotretinoin are a source of confusion for patients and prescribers	• Single pregnancy risk management program
• Limited participation with voluntary patient surveys	• Automatic system check to verify patients interact with the system and answer first month questions
• Improve the method for capturing pregnancy reports and the information collected to better evaluate isotretinoin-exposed pregnancies	• A centralized pregnancy exposure registry with root cause analysis for each pregnancy • A formalized process for following-up with prescribers and patients if expected pregnancy test results are not entered into the system (lost to follow-up procedure) to ensure that a potential pregnancy does not go unreported
• Reinforce education of all patients and healthcare providers*	• Mandatory registration and education of all patients prescribed isotretinoin • Automatic system check to verify patient counseling by the prescriber and that the patient answers educational questions correctly each month • Mandatory registration and education for pharmacies

*Mandatory prescriber registration and education, a component of the previous isotretinoin risk management programs, was continued with iPLEDGE.

3.2.1 Wholesalers Process and Requirements

For the purpose of the iPLEDGE program, the term wholesaler refers to wholesaler, distributor, and/or chain pharmacy distributor. To distribute isotretinoin, wholesalers must be registered with iPLEDGE and agree to meet all iPLEDGE requirements for wholesale distribution of isotretinoin products. Wholesalers must register with iPLEDGE by signing and returning the iPLEDGE wholesaler agreement form that affirms they will comply with all iPLEDGE requirements for distribution of isotretinoin. These requirements include:

- Registering prior to distributing isotretinoin and reregistering annually
- Distributing only FDA-approved isotretinoin product
- Shipping isotretinoin only to: 1) wholesalers registered in the iPLEDGE program with the prior written consent from the manufacturer; and 2) pharmacies licensed in the United States that are registered and activated in the iPLEDGE program

On a daily basis, the iPLEDGE system receives any changes in pharmacy status (openings, relocations, closings in the United States) from the National Council for Prescription Drug Programs. iPLEDGE provides to wholesalers a daily update of all registered and activated pharmacies that are eligible to receive isotretinoin shipments. Wholesalers are responsible for checking this list before distributing any isotretinoin.

3.2.2 Prescriber Process and Requirements

To prescribe isotretinoin, the prescriber must be registered and activated with iPLEDGE. Prescribers can register by signing and returning the completed, paper-based, registration form or via the internet. Prescribers can only activate their registration by affirming that they meet and will comply with all iPLEDGE requirements. This process must be completed annually.

To prescribe isotretinoin, the prescriber must:

1) Register each patient in the iPLEDGE program. Female patients of childbearing potential are registered after an initial negative pregnancy test and males and females of nonchildbearing potential are registered at the time of receiving their first isotretinoin prescription.

2) Confirm, before beginning isotretinoin treatment of female patients of childbearing potential and on a monthly basis, that each patient will be counseled to avoid pregnancy by using two forms of contraception simultaneously and continuously or commit to continuous abstinence one month before, during, and one month after isotretinoin therapy. This process was designed to remind prescribers monthly to reinforce the requirements for appropriate isotretinoin risk management.

3) Obtain a signed Patient Information/Informed Consent Form that contains warnings about the potential risks associated with isotretinoin.

4) For female patients of childbearing potential:

- Confirm that, in the prescriber's opinion, the patient can comply with the iPLEDGE requirements.
- Obtain an additional Patient Information/Informed Consent About Birth Defects Form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin.
- Enter the patient's two chosen forms of contraception each month. This process was designed to confirm the patient's contraceptive choice and that she was counseled and instructed to use two forms of contraception each month.
- Enter monthly results from laboratory-conducted (CLIA-certified) serum or urine pregnancy test. This requirement was designed to reinforce the pregnancy testing requirements with prescribers and to provide a verifiable link between a negative pregnancy test and the dispensing of isotretinoin.

To facilitate the dialogue between prescribers and females of childbearing potential about the iPLEDGE program requirements and to reinforce the educational messages about contraceptive use and the need to avoid pregnancy to female patients of childbearing potential, prescribers are provided with the following educational material:

- *The iPLEDGE Program Guide to Best Practices for Isotretinoin* that includes information on the teratogenic potential of isotretinoin, information on pregnancy testing, and the method to complete a qualified isotretinoin prescription.
- *The iPLEDGE Program Prescriber Contraception Counseling Guide* that includes specific information about effective contraception, the limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure and pregnancy, and the methods to evaluate pregnancy risk.

Prescribers are also provided with a DVD with two videos, "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin" that can be shown to the female patients of childbearing potential during the first office visit. Prescribers are also reminded to offer to all female patients of childbearing potential a referral for specialized contraceptive counseling that may be reimbursed by the isotretinoin manufacturer.

3.2.3 Patient Process and Requirements

3.2.3.1 Females of Childbearing Potential

The iPLEDGE pathway for a female of childbearing potential to receive a 30-day supply of isotretinoin is outlined in Figure 2.

Some aspects of iPLEDGE are similar to the previous risk management programs for females of childbearing potential, but are now documented and verified by the iPLEDGE system. For example, females of childbearing potential must have monthly pregnancy tests and must use two forms of contraception 1 month before, during, and 1 month after isotretinoin therapy.

Some of the new requirements with iPLEDGE for females of childbearing potential include patient registration in iPLEDGE and patient monthly interactions with the system

to document her two chosen forms of contraception. Two appropriate forms must be selected or the patient will not be authorized to receive isotretinoin, except where abstinence is selected as the primary method. Additionally, the system verifies that the contraceptives entered into the system by the patient matches that entered by her prescriber.

To facilitate patient-prescriber conversations about the need to avoid pregnancy for 1 month before, during, and 1 month after stopping isotretinoin therapy, and the contraceptive requirements of iPLEDGE, prescribers and female patients of childbearing potential are provided with a series of educational materials. To ensure that the key educational messages in these materials were being communicated and understood, the sponsors had the educational material comprehension tested among a national sample of consumers. Educational material provided to females of childbearing potential includes:

- *The iPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant* that includes a referral program that offers female patients free (reimbursed by the manufacturer if not covered by the patient's health insurance) contraception counseling by a reproductive specialist and a second Patient Information/Informed Consent About Birth Defects form concerning birth defects.
- *The iPLEDGE Program Birth Control Workbook* that includes information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, the rates of possible contraceptive failure, and a toll-free contraception information line.
- A patient educational DVD with the videos "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin". These videos describe the birth defects that may happen if a woman takes any isotretinoin while pregnant and also reviews reasons for contraceptive failure.

In order to qualify to receive her first isotretinoin prescription, a female of childbearing potential must interact with the iPLEDGE system to answer a series of questions to determine if she received the educational material that was to be provided by her prescriber. This component of the iPLEDGE program was designed: 1) to address the limited patient participation seen in the Accutane survey of S.M.A.R.T. and similar surveys sponsored by the generic manufacturers; and 2) to allow for the collection of information on how well the iPLEDGE process is followed. These questions are only asked for the first prescription and include the following:

1. Did your doctor or anyone in your doctor's office tell you that it is important not to become pregnant while taking isotretinoin? (Yes/No)
2. Did you receive the iPLEDGE program isotretinoin educational kit for female patients who can get pregnant? (Yes/No)
   - If yes, did you read
     - The *iPLEDGE Program Guide to Isotretinoin for Female Patients who Can Get Pregnant*? (Yes/No)
     - The *iPLEDGE Program Birth Control Workbook*? (Yes/No)
3. Did you watch the video "Be Prepared, Be Protected" about birth control? (Yes/No)

4. Did you watch the video "Be Aware: The Risk of Pregnancy while on Isotretinoin"? (Yes/No)
5. Did you or anyone in your doctor's office offer to refer you to another healthcare provider for birth control counseling? (Yes/No)
6. From whom did you receive birth control counseling?
    - My doctor
    - Another healthcare provider provided
    - I did not receive birth control counseling

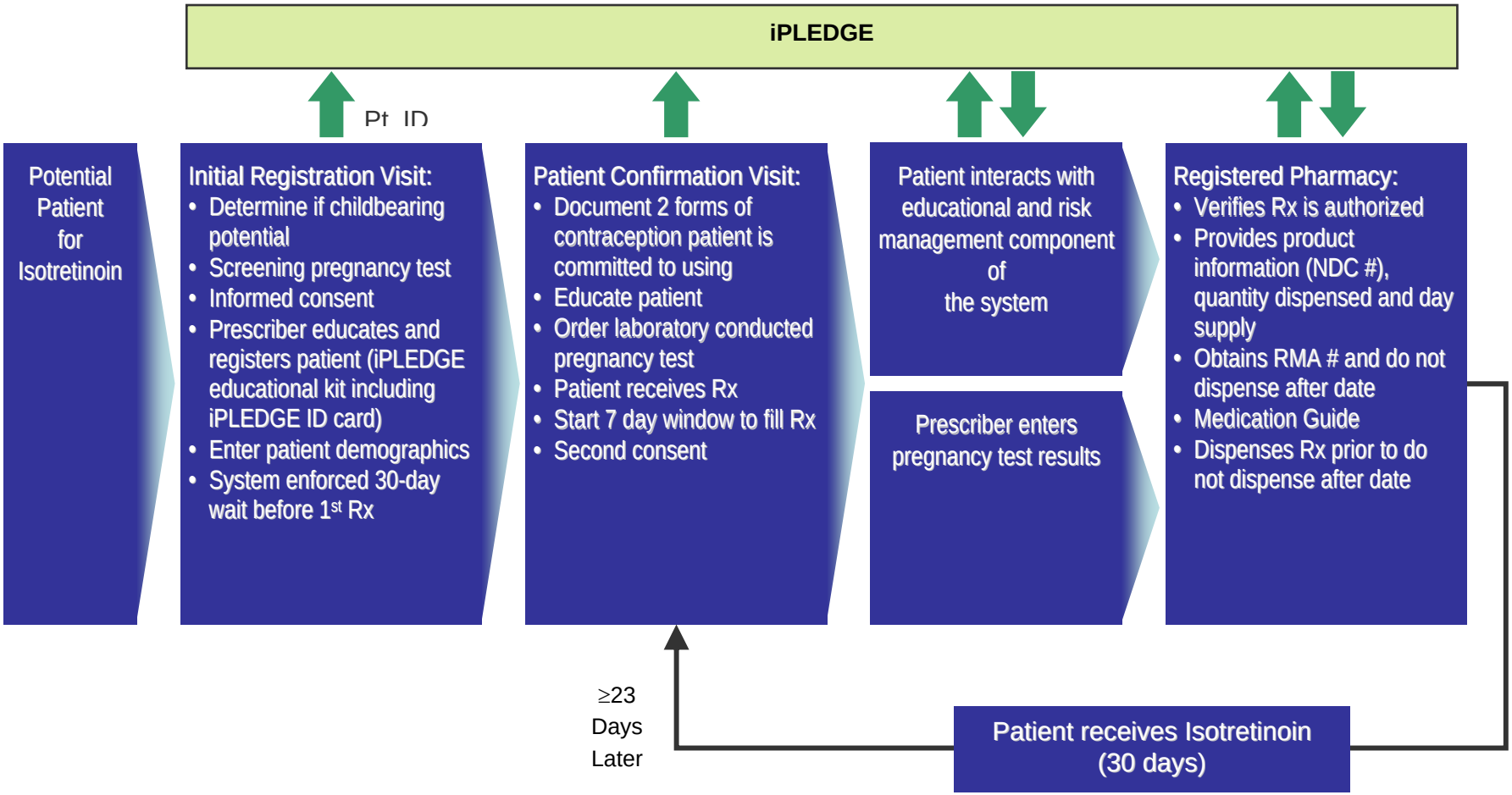
For the first and all subsequent months of isotretinoin therapy, female patients of childbearing potential must also answer a series of questions to demonstrate their understanding of the need to use contraception and the risk of birth defects. These questions can be grouped into the following categories:

- Program steps
- General contraception requirements
- Birth defects and pregnancy
- Safety information (sharing, giving blood)
- Filling a prescription
- Birth control (questions in this category are randomly selected based upon the contraceptive choices entered into the system by the prescriber and the patient)
    - Primary birth control
    - Secondary birth control

Patients must correctly answer one randomly selected question from each category (total of 6 questions). If a question is answered incorrectly, the patient is then presented with a second question from the same category. If this question is answered incorrectly, the patient fails the test and is required to take the test again. For each question that is answered incorrectly, the patient is provided with a specific reference to one of the educational materials to review. There is no time restriction on when the test can be retaken, however, the test must be passed for the isotretinoin prescription to be authorized.

Once all iPLEDGE requirements for females of childbearing potential are met, isotretinoin prescriptions can only be filled and picked up within a defined time window (within 7 days of the prescriber's office visit date). Currently, female patients of childbearing potential may not start the qualification process for another isotretinoin prescription until 23 days after the end of their 7-day window, whether a prescription was filled or not (see Section 3.6).

Figure 2 **iPLEDGE Pathway for Females of Childbearing Potential**



RMA=Risk Management Authorization; NDC=National Drug Code

3.2.3.2 Males and Females of Nonchildbearing Potential

The primary change for males and females of nonchildbearing potential compared to the previous isotretinoin risk management programs is registration in iPLEDGE. These patients are not required to interact with the system as a part of their isotretinoin treatment and participation in iPLEDGE.

All males and females of nonchildbearing potential continue to have monthly office visits, complete the informed consent process, and only receive up to a 30-day supply of isotretinoin with no refills. This requirement is the same as with the previous isotretinoin risk management programs.

Males and females of nonchildbearing potential must also fill and pickup their isotretinoin prescriptions within 7 days of the prescriber's office visit, but can start the qualification process over immediately at the end of their 7-day window, if a prescription was not filled (see Section 3.5).

The iPLEDGE Program Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant is provided to males and female patients of nonchildbearing potential. This booklet includes information about male reproduction and a warning not to share isotretinoin with others or to donate blood during isotretinoin therapy and for 1 month following discontinuation of isotretinoin.

3.2.4 Pharmacy Process and Requirements

Isotretinoin can only be dispensed by licensed pharmacies in the United States that are registered and activated with iPLEDGE. Pharmacies are the key to ensuring that the patient does not obtain isotretinoin unless all iPLEDGE requirements have been fulfilled. Each pharmacy must identify a responsible site pharmacist who must register the pharmacy by signing and returning the completed registration form. After registration, the responsible site pharmacist can only activate the pharmacy registration by affirming that all pharmacists meet and will comply with all iPLEDGE requirements. This process must be repeated annually.

To ensure that isotretinoin is dispensed only to patients who are registered in iPLEDGE and are authorized to receive product, a pharmacist must:

1) be trained by the responsible site pharmacist about the iPLEDGE program requirements.

2) obtain authorization from the iPLEDGE program via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) for every isotretinoin prescription. Authorization signifies that the patient has met all program requirements and is qualified to receive isotretinoin.

3) write the Risk Management Authorization number on the prescription.

Isotretinoin must only be dispensed in no more than a 30-day supply with an isotretinoin Medication Guide within 7 days of the prescriber's office visit. Automatic refills for isotretinoin are not allowed.

Pharmacists are provided with *The iPLEDGE Program Pharmacist Guide for Isotretinoin* that includes information about the teratogenic potential of isotretinoin and the method to obtain authorization to dispense an isotretinoin prescription.

3.3 Patients Lost to Follow-up

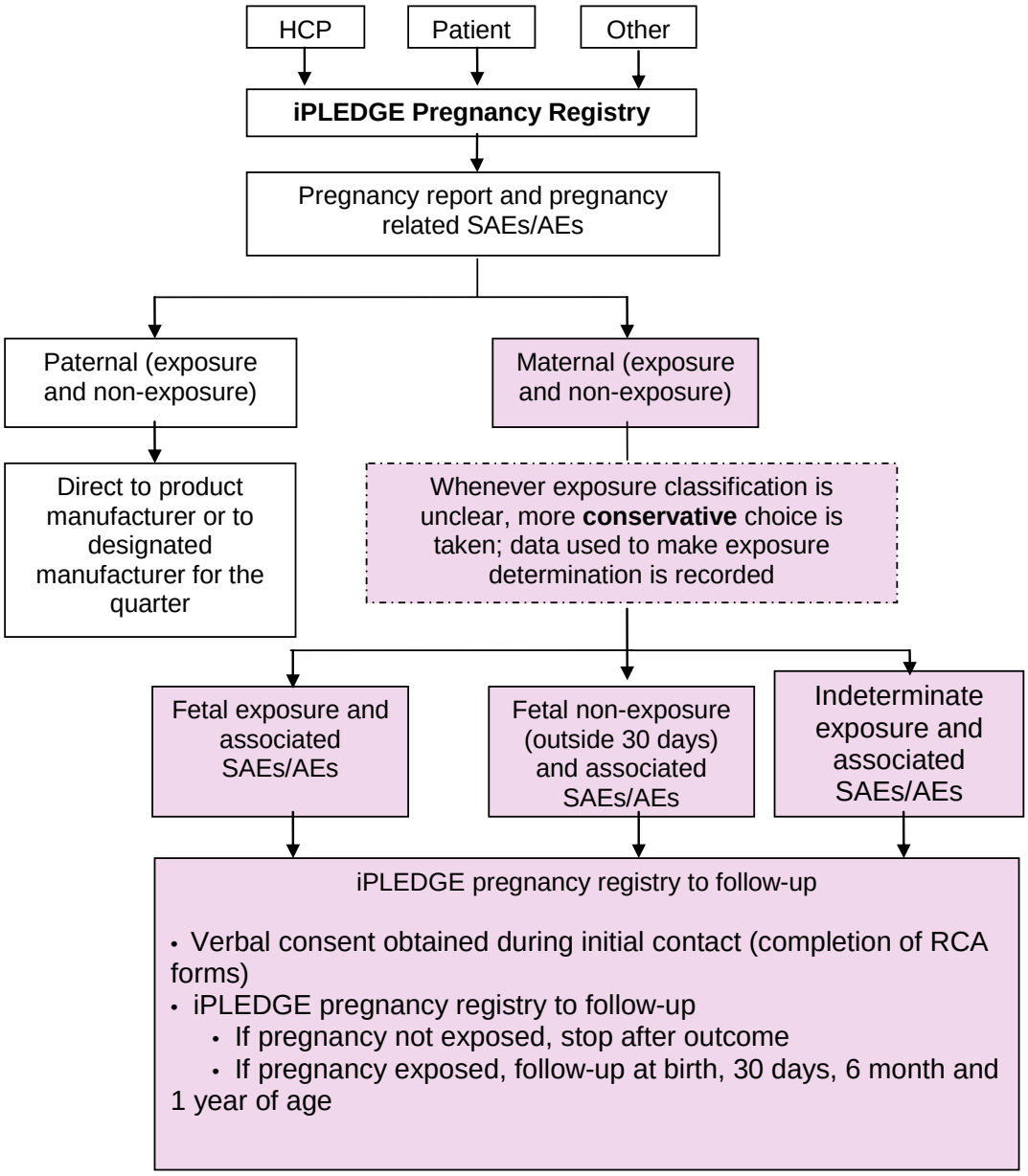
iPLEDGE includes a formal process called lost to follow-up that follows-up with prescribers and female patients of childbearing potential if expected pregnancy test results are not entered into the system. When the system detects that a patient may be lost to follow-up, iPLEDGE representatives will contact the prescriber and provide reminders about posttreatment pregnancy tests to ensure the patient has not become pregnant. Initially, two telephone attempts are made to contact the prescriber. If unsuccessful, a traceable letter is sent to the prescriber within 5 days after the second telephone attempt was made. If all attempts to reach the prescriber are unsuccessful, two telephone attempts are made to contact the patient. If unsuccessful, a traceable letter is sent to the patient, within 5 days after the second telephone attempt was made, which provides the patient with a reminder and requests the patient to contact her prescriber and iPLEDGE.

3.4 Pregnancy Registry

A centralized pregnancy registry for reporting, confirming, and follow-up of all pregnancies was established with the iPLEDGE program. The dataflow for the pregnancy registry is outlined in Figure 3. The objectives of the iPLEDGE pregnancy registry are to: 1) determine the isotretinoin exposure status for each reported pregnancy, 2) document the outcome of each isotretinoin-exposed pregnancy; and 3) provide additional information for each pregnancy to allow for evaluation of the underlying cause(s) (ie, root cause analysis). The root cause analysis questionnaire is provided in Appendix 2.

Data from the registry are reported quarterly to the FDA.

Figure 3 iPLEDGE Pregnancy Registry Dataflow



3.5 Postimplementation Program Changes

Shortly after the iPLEDGE program began accepting patient registrations, the sponsors began to receive stakeholder feedback on the operational aspects of the program. Stakeholder feedback was received: 1) through call center interactions, 2) through the iPLEDGE Scientific Advisory Board, 3) through letters to and meetings with the sponsors and FDA from various professional organizations (American Association of Dermatologists, Healthcare Distribution Management Association, National Association of Chain Drug Stores); and 4) through usability testing of the iPLEDGE system.

As a consequence of this feedback, several changes were made to the iPLEDGE program to facilitate the tasks of the various stakeholders (Appendix 3). These changes included allowing the prescriber to reset their iPLEDGE password and the removal of the 23-day lockout period for requalification for a new isotretinoin prescription, if the previous 7-day window for prescription fill was missed by male or female patients of nonchildbearing potential.

Before implementation, all changes were approved by the Agency. Some of the changes were also discussed at a Drug Safety and Risk Management Advisory Committee meeting on February 10, 2006. The Scientific Advisory Board for iPLEDGE was also involved in planning these changes and assisted in communicating these changes to their constituents.

3.6 Proposed iPLEDGE Program Changes

Several other iPLEDGE program changes have been under discussion with the Agency (supplement 58) and are currently under review, with a planned launch date of September 2007. These changes include:

- For females of childbearing potential, changing the start of the 7-day window for a prescription to be filled from the date of the prescriber's office visit to the date of specimen collection for the pregnancy test. This would allow patients to obtain all lab work prior to the prescriber's office visit and for prescribers to have the pregnancy test results at the time of the office visit, thereby mirroring the current office practices of many isotretinoin prescribers.
- Removing the 23-day lockout period after missing the 7-day window for females of childbearing potential to allow them to obtain another prescription as long as all iPLEDGE requirements are satisfied. This change is proposed because prescribers and patients are finding that the 23-day lockout period interferes with office visit scheduling, dose adjustments, vacations, and insurance practices. The exception would be for the **first** isotretinoin prescription where the next CLIA-certified pregnancy test to start the 7-day window over again would have to be at least 19 days after the pregnancy test that started the first 7-day window (the first test is to be tied to the first 5 days of the menstrual cycle).
- Modifying the list of acceptable forms of secondary contraception to allow male latex condoms to be used with or without spermicide. This was a request of the FDA because of concerns that spermicide may affect the structural integrity of condoms thereby increasing the risk of a sexually transmitted disease.

A number of other changes have been proposed to facilitate stakeholder interactions with the iPLEDGE system (Appendix 4). These proposed changes include enhancing system messages to provide greater user assistance, providing links on the iPLEDGE website to the next logical action, adding user navigation and step-by-step data entry, and providing a graphical display of patient status.

4. iPLEDGE EVALUATION

4.1 Wholesalers, Pharmacies, and Prescriber Registration

The total number of wholesalers, pharmacies, and prescribers registered in the iPLEDGE program as of February 28, 2007 is provided in Table 2.

One pharmacy was involuntarily deactivated for dispensing isotretinoin without obtaining authorization for an iPLEDGE patient in the iPLEDGE system. The responsible site pharmacist for this pharmacy stated that he did not want to comply with the iPLEDGE requirements.

Of the registered and activated prescribers, 58% were dermatologists and 23% were family/general practitioners. There were two involuntary prescriber deactivations. One involuntary deactivation was because a negative pregnancy test was entered for a female of childbearing potential without having the pregnancy test result available. The patient self-reported to be pregnant at that time. The other involuntary deactivation occurred when a prescriber gave a patient drug outside of the iPLEDGE program guidelines. This prescriber supplied the patient with Accutane samples during her 30-day waiting period for her first prescription. These samples were in the prescriber's possession and were left over from the Roche Patient Assistance Program (discontinued July 1, 2005).

Table 2 Wholesaler, Pharmacy, and Prescriber iPLEDGE Registrations - iPLEDGE Year One

Type of Registrant	Total Number
Wholesalers	189
Pharmacies	42,362
Prescribers	15,742
Dermatologists	9,132 (58%)
Family/General Practitioners	3, 572 (23%)
Other	3,038 (19%)

4.2 Patient Registration

At the end of the first year, there were 305,366 patients registered in the iPLEDGE program. Most patients were males (50.6%) or females of childbearing potential (45%) (Table 3).

Table 3 Patients Registered in the iPLEDGE Program by Patient Risk Category [1]

Risk Category	N	%
Males	154,515	50.6
Females of childbearing potential	137,415	45
Females not of childbearing potential	13,436	4.4
Total	305,366	

[1]December 30, 2005 to February 28, 2007

4.3 Prescriptions Authorized

During the first year of iPLEDGE, there were 730,732 isotretinoin prescriptions authorized for dispensing with most authorized for males (56.4%) or females of childbearing potential (39.2%) (Table 4).

Of the 137,415 females of childbearing potential registered in iPLEDGE, 91,894 had at least one isotretinoin prescription authorized through the iPLEDGE system. A total of 286,305 isotretinoin prescriptions were authorized during the first year of iPLEDGE for female patients of childbearing potential.

Table 4 Total Number of Isotretinoin Prescriptions Authorized by Patient Risk Category - iPLEDGE Year One

Risk Category	N	%
Males	412,482	56.4
Females of childbearing potential	286,305	39.2
Females not of childbearing potential	31,936	4.4
Total	730,732	

4.4 Prescriptions Denied

During the first year of the iPLEDGE program, there were 135,926 unique patients that had at least one prescription denied (Table 5). Most of these denials were for males (52.1%) or females of childbearing potential (44%). Patients may been denied in the system for multiple reasons, with each reason (eg, counseling not entered, pregnancy test results not entered, etc) being counted in the overall total. Patients may also have been denied because they made multiple attempts to fill the same prescription. Patients who initially had a prescription denied may have subsequently had a prescription authorized if they fulfilled all iPLEDGE requirements.

The most frequent reasons for prescription fill denial for females of childbearing potential were:

- Patient was in the 7-day window and she attempted to fill a prescription without answering her monthly questions.
- Patient was in the 7-day window and she attempted to fill a prescription, but the prescriber had not entered the pregnancy test results.
- Patient missed the 7-day prescription window.

- Prescriber did not confirm patient counseling.
- Only one prescription can be filled per month.

The most frequent reasons for prescription fill denial for males and nonchildbearing females were:

- Patient missed the 7-day prescription window. Since removal of the 23-day lockout period for requalification for a new isotretinoin prescription for males and females of nonchildbearing potential, this is no longer a reason for prescription fill denial (see Section 3.5).
- Prescriber did not confirm patient counseling.
- Only one prescription can be filled per month.

These data demonstrate that pharmacists are adhering to the iPLEDGE requirements before dispensing isotretinoin.

Table 5 Number of Patients With At Least One Isotretinoin Prescription Denied by Patient Risk Category - iPLEDGE Year One

Risk Category	N	%
Males	70,850	52.1
Females of childbearing potential	59,840	44.0
Females NOT of childbearing potential	5236	3.9
Total	135,926	

4.5 Patient Behavior and Program Adherence Assessment

Specific information on patient counseling, use of the patient educational components of iPLEDGE, and contraceptive practices are captured for female patients of childbearing potential in the iPLEDGE system through their monthly input. These data have been summarized to determine patient and prescriber behavior with respect to the iPLEDGE program requirements.

4.5.1 Patient Understanding of the iPLEDGE Program

In order to qualify to receive her first isotretinoin prescription, a female of childbearing potential must also interact with the iPLEDGE system to answer a series of questions to determine if she received the educational material that was to be provided by her prescriber. Note that the numbers reported for these questions are the count of the responses provided at the time she answered her monthly questions about the need to use contraception and the risk of birth defects correctly.

Most female patients of childbearing potential indicated that they were told to avoid pregnancy and that they received an educational kit for female patients who can get pregnant (Section 4.6.2.4 - Table 10). Most also reported reading the *iPLEDGE Program Guide* to *Isotretinoin for Female Patients who Can Get Pregnant* and completing the *iPLEDGE Program Birth Control Workbook* (Section 4.6.2.4 - Table 10).

Slightly more than half of the females of childbearing potential watched the "Be Aware: The Risk of Pregnancy While on Isotretinoin" and "Be Prepared, Be Protected" videos (Section 4.6.2.4 - Table 10).

The majority of patients reported receiving birth control counseling with most receiving counseling by their doctor (Section 4.6.2.4 - Table 11). Thirteen percent of patients reported not receiving any birth control counseling. Approximately half of the patients reported that their prescriber offered to refer them to another healthcare provider for birth control counseling (Section 4.6.2.4 - Table 11).

The majority of females of childbearing potential demonstrated an understanding of the need to use contraception and the risk of birth defects for isotretinoin-exposed pregnancies by passing their monthly comprehension test the first time it was taken (Section 4.6.2.4 - Table 12).

4.5.2 Contraceptive Data

All females of childbearing potential reported compliance with the contraceptive requirements of iPLEDGE (Table 6). The most common contraceptive choices were abstinence and birth control pills and male condoms (Table 6).

Table 6 Contraception Most Frequently Used by Female Patients of Childbearing Potential - iPLEDGE Year One

Primary	Secondary	Percentage
Abstinence	-	43.1
Birth control pills	Male condom	42.0
Vasectomy	Male condom	3.3
Other combinations		11.6

4.6 Pregnancies

Information is provided for all pregnancies where:

- The patient was enrolled in iPLEDGE; and
- The pregnancy report was received by March 31, 2007; and
- Isotretinoin therapy was initiated between December 31, 2005 to March 31, 2007 with the conception date on or before February 28, 2007.

4.6.1 Case Reports

A total of 122 pregnancies were reported to the pregnancy registry and had an isotretinoin prescription authorized through the iPLEDGE program.

4.6.2 Analyses of Pregnancies

Information is provided for the iPLEDGE pregnancies reported during Year One.

4.6.2.1 Timing of Isotretinoin Exposure Relative to Pregnancy

The majority of patients became pregnant after isotretinoin therapy was initiated with 10 patients initiating isotretinoin while pregnant and 8 patients becoming pregnant within 30 days after stopping isotretinoin therapy (Table 7).

Table 7 Timing of Exposure of Isotretinoin Therapy Relative to Pregnancy- iPLEDGE Year One

	N (%)
Pregnant when isotretinoin started	10 (8.2)
Taking isotretinoin when pregnancy occurred	78 (63.9)
Became pregnant within 30 days after stopping isotretinoin therapy	8 (6.6)
Unknown	26 (21.3)
Total	122 (100)

4.6.2.2 Patient Age

Most of the women who became pregnant were over the age of 20 years (Table 8).

Table 8 Patient Age, Nonpregnant versus Pregnant Females – iPLEDGE Year One

Age Range (years)	Nonpregnant (N=97,886) n (%)	Pregnant (N=122) n (%)
< 12	116 (0.1)	-
12-15	11,579 (11.8)	2 (1.6)
16-19	30,653 (31.3)	24 (19.7)
20-29	34,550 (35.3)	68 (55.7)
30-39	14,846 (15.2)	23 (18.9)
40-44	4, 296 (4.4)	5 (4.1)
≥ 45	1,848 (1.9%)	-

4.6.2.3 Methods of Contraception

Oral contraceptives and male condoms were the most frequent primary and secondary methods of contraception for the women who became pregnant (Table 9). Abstinence was the primary method of contraception for 18.3% of the women who became pregnant.

Table 9 Methods of Contraception – Pregnancy Cases (N=112*), iPLEDGE Year One

Primary	Secondary	Percentage
Birth control pills	Male condom	72.2
Abstinence	-	18.3
Hormonal injection	Male condom	3.2
Other combinations		6.3

*10 pregnant patients did not provide their methods of contraception

4.6.2.4 Patient Understanding of the iPLEDGE Program

Almost all of the pregnant women reported that they were told to avoid pregnancy and that they had received an educational kit for female patients who can get pregnant (Table 10). Most of the pregnant women reported reading the *iPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant* and completing the *iPLEDGE Program Birth Control Workbook* (Table 10). This is similar to what the nonpregnant women reported.

More pregnant women than nonpregnant women watched the "Be Aware: The Risks of Pregnancy While on Isotretinoin" and "Be Prepared, Be Protected" videos (Table 10).

The majority of pregnant women reported receiving birth control counseling with most receiving counseling by their doctor (Table 11). Approximately 13% of pregnant women reported not receiving any birth control counseling. This is similar to what was reported by nonpregnant women. A higher percentage of pregnant women compared to nonpregnant women reported that their prescriber offered to refer them to another healthcare provider for birth control counseling (Table 11).

The majority of pregnant women demonstrated an understanding of the need to use contraception and the risk of birth defects for isotretinoin-exposed pregnancies by passing their monthly comprehension test the first time it was taken (Table 12). The percentages of pregnant versus nonpregnant females who failed these tests once or twice before passing was similar.

Table 10 First Month Questions About Avoiding Pregnancy and the Educational Components of iPLEDGE (Patient Self-Reported) – Pregnancy Cases, iPLEDGE Year One[1]

	Percentage of Patients Responding Affirmatively	
	Nonpregnant N=97,151*	Pregnant N=113**
	n (%)	n (%)
Told to avoid pregnancy	96,870 (99.7)	112 (99.1)
Received educational kit for female patients who may get pregnant	95,611 (98.4)	110 (97.3)
Read guide to isotretinoin for female patients who may get pregnant	95,250 (98.0)	109 (96.5)
Read birth control workbook	93,691 (96.4)	108 (95.6)
Watched "Be Aware" video	53,922 (55.5)	77 (68.1)
Watched "Be Prepared, Be Protected" video	53,860 (55.4)	75 (66.4)

*62 nonpregnant patients did not answer the first month questions
**9 pregnant patients did not answer the first month questions
[1]Data for time period between March 1, 2006 to February 28, 2007

Table 11 First Month Questions for Females of Childbearing Potential about Contraceptive Counseling (Patient Self-Reported) - Pregnancy Cases, iPLEDGE Year One[1]

	Percentage of Patients Responding Affirmatively	
	n (%)	n (%)
	Nonpregnant N=97,151*	Pregnant N=113**
Doctor offered to refer for birth control counseling	47,695 (49.1)	62 (54.9)
Contraception counseling provided by		
My doctor	63,870 (65.7))	64 (56.6)
Another healthcare provider	19,991 (20.6)	34 (30.1)
I did not receive counseling	13,289 (13.7)	15 (13.3)

*62 nonpregnant patients did not answer the first month questions
**9 pregnant patients did not answer the first month questions
[1]Data for time period between March 1, 2006 to February 28, 2007

Table 12 Monthly Questions for Females of Childbearing Potential about the Use of Contraception and the Risk of Birth Defects – Pregnancy Cases, iPLEDGE Year One[1]

	Nonpregnant N=97,896 n (%)	**Pregnant N=112*** n (%)
Passed the first time	81,661 (83.4)	89 (79.4)
1 failure	12,179 (12.4)	21 (18.8)
2 failures	2,681 (2.7)	2 (1.8)
3 failures	780 (0.8)	-
4 failures	294 (0.3)	-
5 failures	122 (0.1)	-
6 failures	57 (< 0.1)	-
7 failures	49 (< 0.1)	-
8 failures	19 (< 0.1)	-
9 failures	14 (< 0.1)	-
10 failures	12 (< 0.1)	-
>10 failures	28 (< 0.1)	-

*10 pregnant patients never took a monthly comprehension test
[1]Data for time period between March 1, 2006 to February 28, 2007

4.6.2.5 Identification of Reasons for Pregnancies

Most of the pregnancies during isotretinoin therapy were due to patient noncompliance with birth control methods (Table 13).

Of the 10 patients who initiated isotretinoin while already pregnant, 3 patients had contraceptive failure, 2 patients were unsuccessful at abstinence, 2 patients did not use two forms of birth control, 2 patients had a prescriber or prescriber designee who falsified the pregnancy test results, and 1 patient had access to isotretinoin from a prescription filled several years earlier.

Of the 8 patients who became pregnant within 30 days of stopping isotretinoin therapy, 2 patients failed to use contraception, 1 patient did not always use two forms of contraception, 1 patient had contraceptive failure, 1 patient was unsuccessful at abstinence, and 1 patient stopped using contraception when isotretinoin therapy was stopped; the reason was unknown by the healthcare provider for 2 of these patients.

Table 13 Reasons for Pregnancies as Reported by the Health Care Provider – Pregnancies During Isotretinoin Therapy (N=87*), iPLEDGE Year One[1]

Reason for pregnancy	Number
Contraceptive failure	23
Failure to use contraceptive on date of conception	14
Did not use two forms of birth control	16
Unsuccessful abstinence	14
Used ineffective contraception	1
Planned pregnancy	0
Unknown	42

*The healthcare provider did not provide any reason for pregnancy in 35 cases.
[1]Categories for reasons for pregnancies are not mutually exclusive so one patient may be in multiple categories

5. OVERALL ASSESSMENT

The main highlights from the iPLEDGE Year One update are as follows:

- The iPLEDGE program is a risk management program of unprecedented size and scope with over 189 wholesalers, 42,362 pharmacies, 15,742 prescribers, and 305,366 patients.
- The majority of the recommended stakeholder changes to increase stakeholder efficiency have been or are in the process of being implemented into the program.
- A centralized isotretinoin pregnancy registry was established and data from its first year provide a baseline for subsequent comparisons.
- Educational messages about the need to avoid pregnancy and to use two forms of contraception for 1 month before, during, and 1 month after isotretinoin therapy are being communicated by prescribers and are reaching female patients of childbearing potential.
- Overall, 137,415 females of childbearing potential were registered during Year One and 91,894 of these patients had an isotretinoin prescription authorized through the iPLEDGE system. A total of 122 pregnancies were reported. The majority of these pregnancies occurred after isotretinoin therapy was initiated. Most pregnancies were associated with contraceptive noncompliance.
- Almost all pregnant and nonpregnant women demonstrated an understanding of both the need to use contraception and the risk of birth defects for isotretinoin-exposed pregnancies.

Appendix 1 Isotretinoin Pregnancy Risk Management Milestones

Date	Action
May 1982	US approval with pregnancy Contraindication.
August 1983	Bold print pregnancy warnings in Contraindications, Warnings, and Precautions sections.
February 1984	Black Box pregnancy warnings added.
August 1988	Avoid pregnancy logo inserted.
October 1988	Pregnancy Prevention Program (PPP) initiated Two forms of contraception Negative monthly pregnancy test "Avoid pregnancy" symbol in packaging Educational materials regarding contraceptives and pregnancy avoidance Female patient informed consent form Evaluation tools for effectiveness of PPP (Accutane Survey).
April 1990	Birth defects information included in Black Box.
April 1990	Recommendation to prescribe only one month supply added
December 1993	Need for pregnancy testing added to Black Box.
January 1994	Updated patient consent form to include additional requirements
May 2000	Two negative pregnancy tests prior to initial prescription Accutane Medication Guide distributed with the Accutane BlisterPak™. Required female patients to view a non-branded videotape on contraception.
September 2000	Drug Safety Risk Management Advisory Committee
October 2001	Pregnancy test of at least 25 mIU β-HCG required.
January 2002	System to Manage Accutane Related Teratogenicity™ initiated. In addition to components of PPP: • Link dispensing to negative pregnancy testing (via Accutane Qualification Sticker) • Enhanced educational components • Enhanced informed consent • Registration of prescribers
November 2002	S.P.I.R.I.T. Risk Management Program (Amnesteem)[1]
December 2002	I.M.P.A.R.T. Risk Management Program (Sotret)[2]
April 2003	A.L.E.R.T. Risk Management Program (Claravis)[3]
February, 2004	Drug Safety Risk Management Advisory Committee to discuss S.M.A.R.T. Year 1 results and a sponsor proposal for an isotretinoin registry
August, 2005	iPLEDGE Approved by FDA
December, 2005	Launch of iPLEDGE
February, 2006	Drug Safety Risk Management Advisory Committee meeting to discuss the operational aspects of iPLEDGE

[1]System to Prevent Isotretinoin-Related Issues and Teratogenicity
[2]Isotretinoin Medication Program Alerting You to the Risks of Teratogenicity
[3]Adverse Event Learning and Education Regarding Teratogenicity

Appendix 2 Root Cause Analysis Questionnaire

1. Patient Information:

Your name: _____

Address:_____ City_____ State____ Zip_____

Your Telephone: ____-____-_____ Your Fax: ____-____-_____

Your Email: _____ Cell Phone: ____-____-_____

The last 4 digits of your Social Security Number: _____

Date of Birth: _____ Your Age at Conception: _____

Are you enrolled in the iPLEDGE program? ___Yes ___No ___Don't know

2. Secondary Contact Information: (family member or friend who will always know how to contact you)

Name: _____

Address:_____ City_____ State____ Zip_____

Telephone: ____-____-_____ Fax: ____-____-_____

Email: _____ Cell Phone: ____-____-_____

3. Race/Ethnicity Information:

What is your race?

___Caucasian ___Asian

___Black/African American ___Other, specify_____

___Native American ___Don't Know/Prefer not to answer

Are you Hispanic? ___Yes ___No

4. Language Information:

Are you comfortable speaking English? ___Yes ___No

What is your native language?

___English ___Other, specify_____

___Spanish ___Don't Know/Prefer not to answer

5. Pregnancy Information:

What was the first day of your last menstrual period? _____

What was the approximate date you became pregnant? _____

What date was your pregnancy test positive? _____

When is your approximate due date? _____

6. What was the date that the positive pregnancy test was taken?

☐☐/☐☐/☐☐☐☐

Month Day Year

What was the type of pregnancy test?

Laboratory:

☐Blood Test Serum hCG result if known: _____ ☐Urine

Non Laboratory:

☐At-home urine pregnancy test ☐Office urine pregnancy test

Other:

☐ Type Unknown ☐ Not done

7. Isotretinoin Information:

Which isotretinoin product did you use? (Product 1):

Manufacturer: Accutane® Roche ☐ Claravis® Barr ☐

Amnesteem® Mylan ☐ Sotret® Ranbaxy ☐ Unknown ☐

Have you taken isotretinoin during your pregnancy?

___Yes ___No ___Don't know

When did you begin taking isotretinoin?

___before I became pregnant

___after I became pregnant

What was the approximate date you started taking isotretinoin?
_____

What was the approximate last day you took isotretinoin? _____

Capsule Strength: _____ How often did you take isotretinoin? _____
_____

Lot#: _____ Expiration Date: ☐☐/☐☐/☐☐☐☐

Month Day Year

Which isotretinoin product did you use? (Product 2):

Manufacturer: Accutane® Roche ☐ Claravis® Barr ☐

Amnesteem® Mylan ☐ Sotret® Ranbaxy ☐ Unknown☐

Have you taken isotretinoin during your pregnancy?

___Yes ___No ___Don't know

When did you begin taking isotretinoin?

___before I became pregnant

___after I became pregnant

What was the approximate date you started taking isotretinoin?

_____

What was the approximate last day you took isotretinoin? _____

Capsule Strength: _____ How often did you take isotretinoin? _____

_____

Lot#: _____ Expiration Date: ☐☐/☐☐/☐☐☐☐

Month Day Year

_____

8. Isotretinoin Prescriber Information:

Was isotretinoin prescribed for you by a doctor? ___Yes ___No
(if no, go to question 9)

Who prescribed isotretinoin for you?

___Dermatologist ___Family Doctor

___Oncologist (cancer doctor) ___Other, specify_____

___Pediatrician ___Isotretinoin was not prescribed for me
(if checked, go to question 9)

Prescriber's Name: _____

Address:_____ City_____ State____ Zip_____

Telephone: ____-____-_____ Fax: ____-____-_____

Is your prescriber aware of your pregnancy? ___Yes ___No ___Don't know

9. Where did you obtain isotretinoin?

___Pharmacy (if checked go to question 10)

___Friend/Relative (if checked go to question 11)

___Internet (if checked go to question 12)

___Other, please specify_____
_____

10. Pharmacy Information:

Name: _____

Address:_____ City_____ State____ Zip_____

Telephone: ____-____-_____ Fax: ____-____-_____

11. If you obtained isotretinoin from a friend or relative was this person…

___male

___female

___prefer not to answer

___not applicable

Was the friend or relative participating in the iPLEDGE program? ___Yes ___No ___Don't know

Why did you obtain isotretinoin from the friend or relative? *(check all that apply)*

___I heard it was hard to get

___I didn't want to see a doctor

___I didn't want my parents to know

___Other, please specify_____
_____
_____

12. Why did you obtain isotretinoin from the internet *(check all that apply)*

___I heard it was hard to get

___I didn't want to see a doctor

___I didn't want my parents to know

___Other, please specify_____
_____
_____

13. In the ***30 days before starting isotretinoin*** did any of the following apply? *(check all that apply)*

Not sexually active, not using birth control	___Yes ___No ___Don't know/Don't remember
Not sexually active, using birth control	___Yes ___No ___Don't know/Don't remember
Sexually active, using birth control	___Yes ___No ___Don't know/Don't remember
Sexually active, not using birth control	___Yes ___No ___Don't know/Don't remember
Told or thought I was post menopausal	___Yes ___No ___Don't know/Don't remember

14. In the ***30 days before starting isotretinoin*** were you using any of the following methods of birth control? *(check all that apply)*

_____Not using birth control

___Abstinence

___Cervical Cap

___Cervical Shield

___ Combination Oral Contraceptive (birth control pills)

___Condom (Male)

___Condom (Female)

___Depo Provera (Injectable Hormones)

___Diaphragm

___Female Sterilization (tubes tied)

___Hormonal Patch

___Hormonal Vaginal Contraceptive Ring (Nuva Ring)

___Intrauterine device (IUD) LNg20 (Mirena or ParaGard T380A

___Intrauterine Device (IUD) (Progesterone T)

___Implantable Hormones (Norplant)

___Male Sterilization (partner's vasectomy)

___Mini Pills (Progestin only such as Ortho Micronor or Ovrette)

___Morning-after pill/emergency contraception

___Natural Family Planning (rhythm method)

___Vaginal Contraceptive Suppository

___Vaginal Sponge

___Withdrawal

Other, Specify_____-

15. In the ***30 days before starting isotretinoin*** did you use 2 forms of birth control together every time you had sex?

___Yes ___No ___Don't know/Don't remember

16. In the ***month before you became pregnant*** did any of the following apply? *(check all that apply)*

Not sexually active, not using birth control	___Yes ___No ___Don't know/Don't remember
Not sexually active, using birth control	___Yes ___No ___Don't know/Don't remember
Sexually active, using birth control	___Yes ___No ___Don't know/Don't remember
Sexually active, not using birth control	___Yes ___No ___Don't know/Don't remember
Told or thought I was post menopausal	___Yes ___No ___Don't know/Don't remember

17. In the ***month before you became pregnant*** were you using any of the following methods of birth control? *(check all that apply)*

_____Not using birth control	___Intrauterine device (IUD) LNg20 (Mirena or ParaGard T380A
___Abstinence	___Intrauterine Device (IUD) (Progesterone T)
___Cervical Cap	___Implantable Hormones (Norplant)
___Cervical Shield	___Male Sterilization (partner's vasectomy)
___ Combination Oral Contraceptive (birth control pills)	___Mini Pills (Progestin only such as Ortho Micronor or Ovrette)
___Condom (Male)	___Morning-after pill/emergency contraception
___Condom (Female)	
___Depo Provera (Injectable Hormones)	___Natural Family Planning (rhythm method)
___Diaphragm	___Vaginal Contraceptive Suppository
___Female Sterilization (tubes tied)	___Vaginal Sponge
___Hormonal Patch	___Withdrawal
___Hormonal Vaginal Contraceptive Ring (Nuva Ring)	Other, Specify_____

18. In the ***month before you became pregnant*** did you use 2 forms of birth control together every time you had sex?

___Yes ___No ___Don't know/Don't remember

19. ***When you became pregnant*** were you using any of the following methods of birth control? *(check all that apply)*

___Not using birth control

___Abstinence

___Cervical Cap

___Cervical Shield

___ Combination Oral Contraceptive (birth control pills)

___Condom (Male)

___Condom (Female)

___Depo Provera (Injectable Hormones)

___Diaphragm

___Female Sterilization (tubes tied)

___Hormonal Patch

___Hormonal Vaginal Contraceptive Ring (Nuva Ring)

___Intrauterine device IUD LNg20 (Mirena or ParaGard T380A

___Intrauterine Device (IUD) (Progesterone T)

___Implantable Hormones (Norplant)

___Male Sterilization (partner's vasectomy)

___Mini Pills (Progestin only such as Ortho Micronor or Orvette)

___Morning-after pill/emergency contraception

___Natural Family Planning (rhythm method)

___Vaginal Contraceptive Suppository

___Vaginal Sponge

___Withdrawal

Other, Specify_____

20. How often have you had sexual intercourse during treatment with isotretinoin ***without using any*** birth control?

___Always (did not use birth control at any time during isotretinoin therapy)

___Usually (more than half of the time)

___Sometimes (Less than half of the time)

___Never (always use birth control)

21. How often have you had sexual intercourse during treatment with isotretinoin ***using only one*** form of birth control?

___Always (never used more than one form of birth control)

___Usually (more than half of the time)

___Sometimes (Less than half of the time)

___Never (always used 2 forms of birth control)

22. If you used emergency birth control ("Morning After" pill or emergency IUD) during isotretinoin treatment, how often did this occur?

___Once

___Twice

___Three times or more

___Never

23. Please check the boxes that best describe what you think contributed to your becoming pregnant.

(check all that apply)

___Birth control failed

___Missed pills

___Did not use birth control the day I got pregnant

___Did not use 2 forms of birth control

___Partner did not use condom

___Condom broke/slipped off

___Hormone patch fell off

___Vaginal Ring fell out

___Did not get hormone injection

___Did not use spermicide with condom, cervical cap, or diaphragm

___Unsuccessful at abstinence

___Unplanned sex

___Alcohol use

___Other, specify_____

___Unknown

Please explain:_____
_____
_____

24. ***When you became pregnant*** did you use 2 forms of birth control together?

___Yes ___No ___Don't know/Don't remember

25. Do you recall if you were drinking alcohol when you got pregnant?

___Yes ___No ___Don't know/Don't remember

26. If you missed taking birth control pills in the month before you became pregnant, how often did this occur?

___One time

___Two times

___Three times or more

___Never

___NA (not taking birth control pills)

What was the greatest number of days that you missed?

___One day

___Two days

___Three days or more

___Never

___Don't know/Don't remember

27. If your hormone patch fell off in the month before you became pregnant, how often did this occur?

___One time

___Two times

___Three times or more

___Never

___NA (not using hormone patch)

What was the greatest number of days that your patch was off?

___One day

___Two days

___Three days or more

___Never

___Don't know/Don't remember

28. If your Vaginal Ring slipped out in the month before you became pregnant, how often did this occur?

___One time

___Two times

___Three times or more

___Never

___NA (not using vaginal ring)

What was the greatest number of days that your ring was out?

___One day

___Two days

___Three days or more

___Never

___Don't know/don't remember

29. If you reported using **Depo Provera® during** isotretinoin treatment, how often were any injections given more than 13 weeks apart?

___Once

___Twice

___Three or more times

___Never

___Don't know/Don't remember

___NA (Not receiving injections)

30. What is the highest level of education that you completed?

___Grades 0-8

___Grades 9-11

___High School Graduate

___Some College

___College Graduate

___Post Graduate Degree

___Don't know/Prefer not to answer

31. Were you counseled about the risk of birth defects with isotretinoin?

___Yes ___No ___Don't know/Don't remember

32. Were you instructed on how **not** to become pregnant while taking isotretinoin?

___Yes ___No ___Don't know/Don't remember

If yes, by whom: *(check all that apply)*

___Doctor who prescribed isotretinoin

___Gynecologist

___Referred to contraceptive counselor

___Other healthcare provider,
Please specify_____

___Other (such as parent, teacher, friend)
Please specify_____

33. If you were referred to a contraceptive counselor, was the counseling helpful?

___Very helpful ___Of little use

___Somewhat helpful ___Not helpful

What would make counseling better? _____
_____

34. Were you given an **iPLEDGE Program Guide for Female Patients Who Can Get Pregnant**?

___Yes ___No ___Don't know/Don't remember

If yes, did you read it?

___Yes ___No ___Don't know/Don't remember

If yes, did you understand the information in the guide?

___Yes ___No ___Don't know/Don't remember

35. Were you given an **iPLEDGE Program Birth Control Workbook**?

___Yes ___No ___Don't know/Don't remember

If yes, did you read it?

___Yes ___No ___Don't know/Don't remember

If yes, did you understand the information in the workbook?

___Yes ___No ___Don't know/Don't remember

36. Did you watch the DVD **"Be Prepared, Be Protected; Be Aware: The Risks of Pregnancy** While on Isotretinoin" about effects of isotretinoin?

___Yes ___No ___Don't know/Don't remember

If yes, did you understand the information in the DVD?

___Yes ___No ___Don't know/Don't remember

37. Which of the educational materials was most helpful?

___ iPLEDGE Program Guide for Females Who Can Get Pregnant

___iPLEDGE Program Birth Control Workbook

___DVD ("Be Prepared, Be Protected; Be Aware: The Risks of Pregnancy While on Isotretinoin")

Do you have any other comments, including comments about changes you would make in the educational materials? _____

_____

38. How often do you have a drink containing alcohol?

___Never ___Once a month or less ___Two to four times a month

___ Two to three times a week ___Four or more times a week

On Average how many drinks do you have on a typical day?

___1-2 ___3-4 ___5-6 ___7-9 ___10 or more

39. Are you still pregnant?

___Yes ___No ___Don't know

40. If you answered no to the question above, how did your pregnancy end?

___Delivered baby

___Miscarriage

___Abortion Date: ☐☐/☐☐/☐☐☐☐

Month Day Year

___Prefer not to answer

41. Your Obstetrician's Information:

Name: _____

Address:_____ City _____ State_____ Zip _____

Telephone: _____-_____-_____ Fax: _____-_____-_____

Email: _____

Comment: (please provide description of relevant events, lab test results or other findings)

_____

Date: _____

Signature of Individual Completing this Form

Thank you for your time in completing this form.

Appendix 3 Postimplementation Changes to the iPLEDGE Program

Feedback/Suggestion	Change to iPLEDGE Program	Date of Change
Ease of password	Users can now request that passwords be e-mailed to them if they forget them.	April 2006
Start new 7-day window immediately after previous 7-day window for male patients and females of nonchildbearing potential	Changed the 23 day wait period after missing the 7 day window to allow males and females of nonchildbearing potential to start the process over immediately.	October 2006
Allow entry of 10 and 11 digit National Drug Code numbers	Allowed the use of 10 or 11 digit NDC numbers for pharmacies to fill prescriptions.	January 2007
Extend one-time password usage	One-time password usage was extended to avoid password expiration upon closing the browser, and notices were added to change password prior to closing browser.	January 2007
Allow prescribers and patients to make changes to patient address and date of birth	Allowed prescribers to change patient address, date of birth, and other demographic information in iPLEDGE.	January 2007
Self-print capability for stakeholder materials	Added all materials (consent forms, educational materials, etc) in PDF format to the web site to allow stakeholders to print materials as needed.	January 2007
Update 7-day window expiration verbiage	Updated verbiage on the 7-day window calculation for the pharmacy to clarify what "midnight" on mm/dd/yy actually refers to.	January 2007
Interactive voice recognition log-in	Replaced alphanumeric user IDs; transitioned all numeric user IDs and remove asterisks in data entry for interactive voice recognition log-in	January 2007

Appendix 4 Proposed Changes to the iPLEDGE Program

Feedback/Suggestion	Planned Change to iPLEDGE Program
Replace "acne" attestation with "isotretinoin indication" attestation	Modify prescriber attestation statement from “knowing how to diagnose acne" to "knowing the indication for isotretinoin" to allow oncologists and other prescribers to complete an accurate attestation statement.
Start 7-day window at time of pregnancy test	Change the 7-day window for females of childbearing potential from date of office visit to date of pregnancy test.
Start new 7-day window immediately after previous 7-day window	Change the 23-day waiting period after missing the 7- day window to allow all patients to start the process over immediately. The exception is for females of childbearing potential who missed the 7-day window in their first month of therapy.
Enhance display of patient data, including key dates, 7-day window status, etc.	System to display upcoming key dates as well as other information regarding current status of a patient in the program (7-window expiration etc).
Remove HIPAA checkbox	Remove HIPAA check box from patient registration.
Registration navigation for males and females of nonchildbearing potential	Completion of registration for male patients or females of nonchildbearing potential should take a user directly to the confirmation screen.
Remove contraception bullet point for females of nonchildbearing potential	Remove first bullet point on Confirm Patient Counseling screen for females of nonchildbearing potential, which relates to the requirement to use two forms of contraception.
Enhance system messages for user assistance	Add more helpful error messages, eg, replace "See your doctor” or "Patient requires confirmation" and other similar messages to generally provide more information regarding the cause of certain status values and status changes as they occur.
No secondary form required when abstinence is chosen as primary (default to none)	The contraception drop down menu for secondary form should default to "None" if abstinence is selected as the primary form.
Provide "password to be mailed to patient" message to prescriber upon registration completion	At the end of registration, tell the prescriber that the patient's password will be mailed to him or her.