DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

DERMATOLOGIC AND OPTHALMIC DRUGS ADVISORY COMMITTEE

BRIEFING DOCUMENT

FOR

iPLEDGE

Amnesteem® (Isotretinoin Capsules, USP) produced by Mylan Pharmaceuticals Inc.

Claravis™ (Isotretinoin Capsules, USP) produced by Barr Laboratories, Inc.

SOTRET® (Isotretinoin Capsules, USP) produced by Ranbaxy Laboratories Inc.

1. EXECUTIVE SUMMARY

1.1 Historical Background

The iPLEDGE program is a computer-based risk management program designed to further the public health goal to eliminate fetal exposure to isotretinoin through a special restricted distribution program approved by the Food and Drug Administration (FDA). The program strives to ensure that:

- No female patient starts isotretinoin therapy if pregnant
- No female patient on isotretinoin therapy becomes pregnant

This enhanced program is a single pregnancy risk management program for prescribing and dispensing all isotretinoin products (brand and generic products). iPLEDGE, a performance linked access system, was developed by the isotretinoin sponsors (Genpharm Inc., now Mylan ULC, Mylan Pharmaceuticals Inc., Barr Laboratories, Inc.; a wholly owned subsidiary of Teva Pharmaceuticals USA, Inc., Ranbaxy Laboratories Inc., and Roche Laboratories Inc.) in collaboration with FDA during 2004 and 2005. The iPLEDGE program began accepting patient registrations on December 30, 2005 and became mandatory as of March 1, 2006.

On August 31, 2010, Hoffmann-La Roche voluntarily submitted a request for withdrawal of New Drug Application (NDA) 18-662 Accutane (isotretinoin) Capsules to the FDA based upon the business decision to discontinue marketing of this product. The decision to withdraw the NDA was not taken for reasons of safety or efficacy. Based upon Hoffmann-La Roche's request, the FDA accepted and acknowledged the withdrawal of NDA 18-662 effective December 22, 2010. As a result of this withdrawal approval by FDA, Hoffmann-La Roche will no longer participate in the iPLEDGE Program effective this date. The Roche exit does not affect the iPLEDGE program as the remaining isotretinoin sponsors continue to operate the program.

On October 22, 2010, the iPLEDGE Program was approved as a Risk Evaluation and Mitigation Strategy (REMS). This document summarizes the pregnancy exposure data and the results of an evaluation of the operational aspects of the iPLEDGE program, during years 3 through 5 of the program (March 1, 2008 through February 28, 2011). Additionally, this briefing document provides data on specific aspects of the behavior of female patients of childbearing potential and summarizes the pending enhancements to the current iPLEDGE program.

1.2 iPLEDGE Evaluation and Assessment

In the most recent completed year of the iPLEDGE Program (Year 5 which covers March 1, 2010 through February 28, 2011), a total of 183 wholesalers, 43,064 pharmacies and 14,444 prescribers were registered in the program. A total of 196,384 patients were newly registered in the program and 1,006,079 prescriptions were authorized for dispensing. Of the 196,384 patients that were newly registered in the iPLEDGE program in Year 5: 44.6% were females of child-bearing potential and 52.4% were males.

Adherence by prescribers with the iPLEDGE requirements to counsel female patients of childbearing potential to avoid pregnancy (99.8% non-pregnant; 100% pregnant) and to provide them with educational material (96.7% non-pregnant; 97.4% pregnant) was high. In addition, patient data for females of childbearing potential show a high degree of usage of both the isotretinoin program guide (96.2% non-pregnant; 96.8% pregnant) and the birth control workbook (92.7% non-pregnant; 95.5% pregnant).

A total of 129,554 female patients of childbearing potential with at least one Risk Management Authorization (RMA) in iPLEDGE Year 5 are considered to represent the total population at risk for isotretinoin pregnancy exposure during iPLEDGE Year 5.

During iPLEDGE Year 5, there were a total of 155 iPLEDGE pregnancies (0.12%) out of the 129,554 female patients of childbearing potential with 150 isotretinoin-exposed pregnancies and 5 pregnancies of indeterminate exposure. The majority of iPLEDGE pregnant patients (94 patients; 60.6%) conceived during isotretinoin treatment. The most common reason for iPLEDGE pregnancy as reported by the prescriber and the patient, was failure to comply with the iPLEDGE contraceptive requirements (e.g., did not use two forms of birth control, did not use contraception on the date of conception, unsuccessful at abstinence).

Nine of the pregnant patients (5.8%) initiated isotretinoin while pregnant. Of the nine patients, five had a negative pregnancy test just prior to receiving a prescription for isotretinoin. One patient initiated treatment due to an entry error by the prescriber in the iPLEDGE database. One patient initiated isotretinoin treatment while pregnant due to a laboratory error. For this patient, urine and serum pregnancy tests were conducted on the same date. The urine pregnancy test resulted negative which allowed the patient to receive a prescription. Subsequent to the negative urine pregnancy result the serum pregnancy test resulted positive. The patient ceased isotretinoin after one day of use. In the other two cases, the patients took isotretinoin outside of the iPLEDGE program and did not have pregnancy testing prior to initiating the course of treatment.

Thirteen of the pregnant patients (8.4%) conceived within 30 days after stopping isotretinoin. The timing of exposure for the remaining 39 (25.2%) pregnant patients was unknown.

Of the 155 iPLEDGE pregnancies, 83 (53.5%) resulted in elective or spontaneous abortion, 1 (0.6%) resulted in a live birth, 1 (0.6%) resulted in a stillbirth, 18 cases (11.6%) are listed as “pregnancy ongoing” and 52 cases (33.5%) are considered to be lost to follow-up.

2. BACKGROUND

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. The safe use of isotretinoin in women requires that every effort be made to prevent women of childbearing potential from initiating isotretinoin therapy while pregnant, from becoming

pregnant during therapy, and from becoming pregnant within 1 month after discontinuation of isotretinoin treatment.

The current isotretinoin pregnancy risk management program, iPLEDGE, is a computer-based, restricted distribution program and pregnancy registry to support the public health goals for isotretinoin. The iPLEDGE Program was approved as a REMS program on October 22, 2010 with the following Elements to Assure Safe Use (ETASU):

- Healthcare providers who prescribe isotretinoin are specially certified in the iPLEDGE Program.
- Isotretinoin will only be dispensed by pharmacies that are specially certified in the iPLEDGE program.
- 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.
- Isotretinoin sponsors will maintain a centralized pregnancy registry for iPLEDGE enrolled female patients who become pregnant and consent to participate in a root cause analysis.

Specific key risk management elements of iPLEDGE include:

- Single pregnancy risk management program for prescribers, patients, wholesalers, and pharmacies.
- Mandatory, monthly, laboratory-based pregnancy tests (either serum or urine) conducted in an accredited laboratory for females of childbearing potential before each new prescription is authorized
- Mandatory, monthly patient education questions via an interactive web/phone based system for females of childbearing potential
- A centralized pregnancy registry with voluntary root cause analysis (RCA) for all isotretinoin-exposed and indeterminate-exposure pregnancies
- A technical infrastructure to support the above registrations, collection of laboratory pregnancy test results, and verification of patient qualifications
- Proactive compliance monitoring and actions

Additional risk management elements of iPLEDGE are summarized in Table 1.

Table 1 Additional Risk Management Elements of iPLEDGE

• Automatic system verification of negative pregnancy test results that are entered by the prescriber before pharmacist can dispense isotretinoin • Automatic system reminder to prescribers and patients of the pregnancy testing requirements
• Automatic system matching of the primary contraceptive choice entered by both the prescriber and patient • Automatic system check to verify patients interact with the system and answer questions each month (tailored to patients selected methods of contraception)
• 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
• Mandatory registration and education of all patients prescribed isotretinoin • Mandatory registration and education for pharmacies

The iPLEDGE program began accepting patient registrations on December 30, 2005 and became mandatory as of March 1, 2006, when any wholesaler, prescriber, pharmacy, and patient had to be registered in the iPLEDGE program in order to obtain, prescribe, or dispense isotretinoin. Pharmacies, via a responsible site pharmacist (RSP), and prescribers must attest to their understanding of and agree to comply with the iPLEDGE requirements. Female patients of childbearing potential are qualified to receive isotretinoin only after monthly interaction with the iPLEDGE system to document her two chosen forms of contraception and to demonstrate comprehension of the need to use contraception and her understanding of the risk of birth defects. Female patients must also obtain required laboratory-based pregnancy tests from a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory, which are documented in the iPLEDGE system, prior to being qualified to receive isotretinoin.

3. iPLEDGE PROGRAM ENHANCEMENTS

3.1 Implemented Enhancements

Since the launch of the iPLEDGE program in March of 2006 there has been continuous evaluation and periodic enhancement of the program. The FDA and the Sponsors receive feedback from program stakeholders (e.g., wholesalers, pharmacists, prescribers, and patients). The Scientific Advisory Board (SAB) for iPLEDGE has been actively involved in discussions regarding stakeholder feedback and proposed changes to the program. The SAB has also assisted in communicating these changes to their constituents.

Soon after the launch in 2006 a series of changes were implemented. These are summarized in Table 2.

Table 2 Early Enhancements 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 FNCBP	Changed the 23 day wait period after missing the 7 day window to allow male patients and FNCBP to start the process over immediately.	October 2006
Allow entry of 10 and 11 digit NDC 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
IVR log-in	Replaced alphanumeric user ID's; transitioned all numeric user id's and remove asterisks in data entry for IVR Log-in	January 2007

FNCBP=females not of childbearing potential; FCBP=females of childbearing potential

3.2 Phase II Program Enhancements

Once the program had been operational for a period of about a year it was clear, based on stakeholder feedback and user system interaction research, that improvements to some of the built in timing elements such as the 7-day window and user navigation were needed. A major system enhancement, deemed Phase II, that required FDA approval because it included a labeling change, was launched in December of 2007 to address these issues. These enhancements are summarized in Table 3. Of note, the following changes affected labeling:

1. For female patients of childbearing potential
    - the 7-day window starts at the time of the pregnancy test and
    - the new 7-day window starts immediately after the previous 7-day window.

2. For male patients and female patients not of childbearing potential
    - the 7-day window is now a 30-day window per FDA request.

Table 3 Phase II Enhancements—December 2007

Feedback/Suggestion	Change to iPLEDGE Program
Extend the 7-day window to be a 30-day window for male and FNCBP	Extend the window for male patients and FNCBP to be a 30 day window, which can begin again upon picking up a prescription.
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 FCBP 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 patients to start the process over immediately. The exception is for FCBP 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 male patients and FNCBP	Completion of registration for male patients or FNCBP should take a user directly to the confirmation screen.
Remove contraception bullet point for FNCBP	Remove first bullet point on Confirm Patient Counseling screen for FNCBP, which relates to the requirement to use two forms of contraception.
Enhance system messages for user assistance	Add more helpful error messages, e.g., 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 was 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.
Address various enhancements based on usability study	Various enhancements related to user navigation, system appearance, consistency, and user assistance prompts.

3.3 Pending Enhancements to Current Program

A major iPLEDGE Program system enhancement initiative is currently under review by the FDA. While this enhancement does not include labeling changes, it does improve stakeholder interactions such as the registration of female patients by prescribers and the monitoring and feedback to prescribers and patients regarding whether the system has issued a Risk Management Authorization (RMA) to dispense a prescription at a registered and activated pharmacy. Table 4 summarizes the pending enhancements to the current system.

Table 4 Pending Enhancements to Current Program

Stakeholder Category	Pending Change to iPLEDGE Program
Prescribers and Designees	Additional attestation points to assure prescriber understanding of compliance Designee attestation "Wizard"-driven categorization of female patient registration status Re-registration of existing patients Change patient risk category Correcting contraception choices Reminder regarding abstinence as contraception method Request information on previous prescription window (no RMA recorded) Reminder to get new pregnancy test to start new prescription window Allow qualitative serum pregnancy test along with quantitative test and urine test Entry of post-therapy pregnancy tests, regardless of patient status Free-form comments removed from pregnancy test entry Confirmation checkbox for pregnancy test date entry Additional discontinue reason codes Comment box for patient discontinuation only available for reason = Other New Home Page Design
Patients	Request information on previous prescription window (no fill recorded) Reminder regarding abstinence as birth control method "For Patients" button on homepage New Patient Home Page Design
Pharmacies	Visibility of Risk Management Authorization (RMA) number Display List of RMA numbers 12-digit RMA and check digit for optional use in pharmacy adjudication systems New Pharmacy Home Page Design RMA Denial Message

4. iPLEDGE EVALUATION

4.1 Wholesalers, Pharmacies, and Prescriber Registration

The total number of wholesalers, prescribers, and pharmacies registered in the iPLEDGE program at the end of iPLEDGE Year 5 (iPLEDGE Year 5: March 1, 2010 through February 28, 2011) is provided in Tables 5, 6 and 7.

Table 5 Number of Registered Wholesalers – Year 3, Year 4, and Year 5

	Year 3	Year 4	Year 5
Number of registered wholesalers at end of reporting period	184	181	183

Of the 14,444 registered and activated prescribers, 10,435 had a specialty of dermatology (72.2%) and 2,095 were family practitioners (14.5%) (Table 6). Nine prescribers have been involuntarily deactivated from the iPLEDGE Program since the inception of the iPLEDGE program through the end of iPLEDGE Year 5.

There were 43,624 registered designees in the iPLEDGE Program through the end of the iPLEDGE Year 5. A designee is a stakeholder that performs actions in iPLEDGE on behalf of a prescriber. However, a designee is not able to perform prescriber attestations or change passwords on behalf of the prescriber. A designee is enrolled in iPLEDGE and receives a unique username and password account. Twenty-four designees have been involuntarily deactivated from the iPLEDGE Program since the inception of the iPLEDGE program through the end of iPLEDGE Year 5.

Table 6 Number of Registered and Activated Prescribers Who Wrote at Least One Isotretinoin Prescription

Type of Prescriber and Medical Specialty	Year 3 N (%)	Year 4 N (%)	Year 5 N (%)
Physician			
Dermatology	8,146 (55.7)	8,463 (56.65)	8,585 (59.44)
Family practitioner/general practitioner	2,331 (15.9)	2,219 (14.85)	1,838 (12.73)
Internal medicine	534 (3.7)	537 (3.59)	408 (2.82)
Obstetrics /gynecology	68 (0.5)	71 (0.48)	63 (0.44)
Oncology	219 (1.5)	214 (1.43)	202 (1.4)
Other	566 (3.9)	558 (3.74)	494 (3.42)
Pediatrics	489 (3.3)	485 (3.25)	463 (3.21)
Nurse Practitioner			
Dermatology	399 (2.7)	438 (2.93)	465 (3.22)
Family practitioner/general practitioner	160 (1.1)	174 (1.16)	148 (1.02)
Internal medicine	9 (0.1)	5 (0.03)	5 (0.03)
Obstetrics /gynecology	2 (0)	2 (0.01)	2 (0.01)
Oncology	27 (0.2)	27 (0.18)	29 (0.2)

Type of Prescriber and Medical Specialty	Year 3 N (%)	Year 4 N (%)	Year 5 N (%)
Other	73 (0.5)	73 (0.49)	69 (0.48)
Pediatrics	22 (0.2)	24 (0.16)	21 (0.15)
Physician Assistant			
Dermatology	1,143 (7.8)	1,231 (8.24)	1,297 (8.98)
Family practitioner/general practitioner	108 (0.7)	106 (0.71)	87 (0.6)
Internal medicine	12 (0.1)	10 (0.07)	7 (0.05)
Obstetrics/gynecology	0 (0)	1 (0.01)	1 (0.01)
Oncology	4 (0)	4 (0.03)	1 (0.01)
Other	112 (0.8)	113 (0.76)	103 (0.71)
Pediatrics	3 (0)	4 (0.03)	0 (0)
Unknown / Other			
Dermatology	101 (0.7)	89 (0.6)	88 (0.61)
Family practitioner/general practitioner	32 (0.2)	26 (0.17)	22 (0.15)
Internal medicine	7 (0)	6 (0.04)	5 (0.03)
Obstetrics /gynecology	1 (0)	3 (0.02)	0 (0)
Oncology	0 (0)	0 (0)	1 (0.01)
Other	47 (0.3)	51 (0.34)	36 (0.25)[a]
Pediatrics	5 (0)	4 (0.03)	4 (0.03)
Total	14,620 (100)	14,938 (100)	14,444 (100)

[a] Thirty three of these prescribers are registered in the iPLEDGE Program using a valid Drug Enforcement Administration (DEA) Number. The remaining 3 prescribers were researched to determine their professional designation and found 1 Naturopathic Doctor, 1 Nurse Practitioner, and 1 Physician's Assistant.

Table 7 Number of Pharmacies Registered and Activated at the End of the Reporting Period

	No. of Pharmacies		
	Year 3	Year 4	Year 5
Number of pharmacies registered and activated at the end of reporting period	43,477	44,962	43,064

The majority of pharmacies registered and activated were chain pharmacies (retail, grocery store, department store) (81.6%) or independent pharmacies (15.7%) (Table 8).

Table 8 Number of Pharmacies Registered and Activated in iPLEDGE by Pharmacy Type

Type of Pharmacy	Year 3 N (%)	Year 4 N (%)	Year 5 N (%)
Independent	9,615 (19.71)	7,551 (16.79)	6,776 (15.73)
Chain	37,473 (76.83)	36,192 (80.49)	35,130 (81.58)
Hospital	0 (0)	0 (0)	0 (0)
Clinic	0 (0)	0 (0)	0 (0)
Franchise	486 (1)	346 (0.77)	342 (0.79)
Government/federal	355 (0.73)	300 (0.67)	280 (0.65)
Military	37 (0.08)	27 (0.06)	27 (0.06)
Non-Pharmacy	674 (1.38)	0 (0)	0 (0)
Other	131 (0.27)	546 (1.21)	509 (1.18)

In order to dispense isotretinoin, the pharmacist must access the iPLEDGE system and obtain a Risk Management Authorization (RMA) number to verify that the patient is qualified to receive isotretinoin. The RMA is the central component to the performance linked access system. The RMA demonstrates that the prescriber and the patient have completed all the requirements necessary for the patient to be dispensed isotretinoin. Dispensing without an RMA is a non-compliant activity. Re-education is conducted for every pharmacy which has a confirmed non-compliance case. Part of this re-education activity is the verification that the stakeholder understands the iPLEDGE program requirements for pharmacies and that they agree to comply with these requirements in the future.

Two pharmacies have been involuntarily deactivated from the iPLEDGE program since the program's inception for dispensing isotretinoin without obtaining an RMA the iPLEDGE system. The first pharmacy that was deactivated for dispensing without an RMA occurred when the Responsible Site Pharmacist (RSP) refused to agree to comply with the iPLEDGE program requirements in the future after being notified of the non-compliant activity. The second pharmacy that was deactivated had 3 occurrences of dispensing without an RMA. The previous re-education conducted for the RSP at the second pharmacy was deemed ineffective and the pharmacy was deactivated due to a continued lack of understanding of the iPLEDGE program requirements.

Table 9 shows the number of reported and confirmed cases where pharmacies dispensed isotretinoin without obtaining an RMA.

Table 9 Confirmed Incidents of Dispensing Isotretinoin without an RMA

	Year 3	Year 4	Year 5
Confirmed incidents of dispensing without an RMA	1,169	1,109	932
Total number of prescriptions authorized	1,114,421	1,179,274	1,006,079

4.2 Patient Registration

Female patients of childbearing potential are registered by their prescriber after an initial negative pregnancy test. Female patients not of childbearing potential and male patients are registered at the time of receiving their first isotretinoin prescription.

By the end of iPLEDGE Year 5, there have been 1,234,881 patients registered in the iPLEDGE program. Most patients were either males (50.2%) or females of childbearing potential (46.1%) (Table 10).

Table 10 Number of Patients Registered in iPLEDGE by Patient Risk Category Through the Reporting Period

Risk Category[1]	Cumulative Through Year 3 N (%)	Cumulative Through Year 4 N (%)	Cumulative[a] Through Year 5 N (%)	Newly Registered in iPLEDGE during Year 5 N (%)
Females of child-bearing potential	362,023 (45.83)	477,948 (46.02)	569,385 (46.11)	91,556 (46.62)
Females not of child-bearing potential	31,626 (4)	39,358 (3.79)	45,484 (3.68)	6,036 (3.07)
Males	396,237 (50.16)	521,191 (50.19)	620,012 (50.21)	98,792 (50.31)
Total	789,886	1,038,497	1,234,881	196,384

[a] Includes patients enrolled during the iPLEDGE transition period of December 30, 2005 to February 28, 2006 and those enrolled in Year 1.

4.3 Prescriptions Dispensed

Each month when a patient presents an isotretinoin prescription to the pharmacy, the pharmacist must access the iPLEDGE system and obtain a Risk Management Authorization (RMA) number to verify that the patient is qualified to receive isotretinoin. As discussed earlier in this document, the RMA is the central component to the performance linked access system. The RMA demonstrates that the prescriber and the patient have completed all the requirements necessary for the patient to be dispensed isotretinoin.

During iPLEDGE Year 5, there were 1,006,079 RMAs issued to dispense isotretinoin. Most were authorized for males (52.4%) and females of childbearing potential (44.6%) (Table 11).

Table 11 Number of Prescriptions Authorized by Risk Category

	Year 3	Year 4	Year 5
Total number of prescriptions authorized	1,114,421	1,179,274	1,006,079
Females of childbearing potential	481,364 (43.19%)	519,641 (44.06%)	448,625 (44.59%)
Males	594,649 (53.36%)	622,726 (52.81%)	527,420 (52.42%)
Females not of childbearing potential	38,408 (3.45%)	36,907 (3.13%)	30,034 (2.99%)

4.4 Prescriptions Denied

If a patient does not meet the qualifications to receive isotretinoin, the pharmacist receives a denial message from the iPLEDGE system. Authorization to dispense a prescription could be denied for more than one reason. In addition, authorization to dispense a prescription could be denied several times and would continue to be denied until all qualifications are met.

During iPLEDGE Year 5, there were 408,740 unique patients that were denied a prescription (Table 12). Most of these patients were males (39.0%) or females of childbearing potential (58.9%).

Table 12 Number of Prescription Authorization Attempts Denied by Risk Category

	Year 3	Year 4	Year 5
Females of childbearing potential	229,057 (55.82%)	257,883 (57.3%)	240,570 (58.86%)
Males	170,689 (41.6%)	181,984 (40.43%)	159,354 (38.99%)
Females not of childbearing potential	10,576 (2.58%)	10,227 (2.27%)	8,816 (2.15%)
Total	410,322	450,094	408,740

For females of childbearing potential, the most common reason for denial was "Patient was in the 7-day prescription window and has attempted to fill a prescription without answering the monthly comprehension questions". There were 17 attempts to fill

prescriptions during Year 5 where the prescription was denied because the patient was reported as confirmed pregnant. These 17 attempts were performed by nine patients.

For males and females not of child bearing potential, the most common reason for denial was "Prescriber did not confirm patient counseling" in the iPLEDGE system (Table 13).

Table 13 Reasons for Prescription Denial

Denial Reason	Year 5 N (%)
Prescriber did not confirm patient counseling	167,524 (47.01)
Patients in prescription window and have attempted to fill a prescription without answering the comprehension questions	157,507 (44.19)
Patients attempting to fill a second prescription within a prescription window	16,621 (4.66)
Pharmacists failed to indicate multiple dosage fill for the same RMA	6,522 (1.83)
Patient missed first prescription window and must wait 19 days for next pregnancy test.	5,339 (1.5)
Prescription Dispensed at another Pharmacy	1,377 (0.39)
Patient Status is Permanently Lost to Follow Up	828 (0.23)
Patient Status is Post-therapy	412 (0.12)
Patients with requested data element change in the system which requires confirmation (i.e., FCBP to Non-FCBP)	246 (0.07)
Patient Reported/Confirmed Pregnant	17 (0)

4.5 Patient Behavior and Program Adherence Assessment

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

4.5.1 Patient Understanding of the iPLEDGE Program

During the first month that a female of childbearing potential interacts with the iPLEDGE system for a Course Of Treatment (COT), she is asked a series of questions to determine if: 1) she was told to avoid pregnancy, 2) she received the patient educational material that was to be provided by her prescriber; and 3) she received birth control counseling.

In iPLEDGE Year 5, the total number of courses of treatment started for females of childbearing potential was 163,544. Of these courses of treatment, 163,390 resulted in no pregnancies and 154 resulted in the patient becoming pregnant during the course of treatment (Table 14).

Of the non-pregnant and pregnant female patients of childbearing potential answering questions on these courses of treatment, 99.8% and 100%, respectively, indicated that they were told to avoid pregnancy and 96.7% and 97.4%, respectively, indicated that they received an educational kit for female patients who can get pregnant (Table 14). The data show a high degree of patient compliance with 96.2% and 96.8%, respectively, reporting that they read the program guide and 92.7% and 95.5%, respectively, completing the birth control workbook (Table 14).

The majority of pregnant and non-pregnant females during Year 5 reported receiving birth control counseling, with most receiving counseling by their prescriber (Table 15). A lower percentage of pregnant females (12.3%) than non-pregnant females (15.2%) during Year 5 reported not receiving any birth control counseling. A slightly higher percentage of pregnant females (57.4%) compared to non-pregnant females (43.9%) during Year 5 reported that their prescriber offered to refer them to another healthcare provider for birth control counseling. Similar results were seen during previous years.

Table 14 First Month Questions about Avoiding Pregnancy and the Educational Components of iPLEDGE

	Percentage of Patients Responding Affirmatively[a,b]					
	Year 3		Year 4		Year 5	
	Non-pregnant N = 169,037 N (%)	Pregnant N = 175 N (%)	Non-pregnant N = 182,547 N (%)	Pregnant N = 180 N (%)	Non-pregnant N = 163,390 N (%)	Pregnant N = 154 N (%)
Told to avoid pregnancy	168,534 (90.7)	173 (98.86)	182,030 (99.72)	180 (100)	163,061 (99.8)	154 (100)
Received educational kit for female patients who can get pregnant	164,497 (97.31)	172 (98.29)	177,063 (97)	175 (97.22)	158,039 (96.73)	150 (97.4)
Read guide to isotretinoin for female patients who can get pregnant	163,690 (96.84)	171 (97.71)	176,046 (96.44)	173 (96.11)	157,128 (96.17)	149 (96.75)
Read birth control workbook	158,263 (93.63)	167 (95.43)	169,728 (92.98)	170 (94.44)	151,533 (92.74)	147 (95.45)
Watched "Be Aware" video	85,989 (50.87)	104 (59.43)	94,205 (51.61)	112 (62.22)	87,818 (53.75)	102 (66.23)
Watched "Be Prepared, Be Protected" video	86,413 (51.12)	109 (62.29)	94,803 (51.93)	110 (61.11)	88,518 (54.18)	102 (66.23)

[a] Patients may have had multiple COTs represented in the data

[b] All pregnant and non-pregnant patients did not answer the required monthly questions. Some patients counted as Year 5 patients did not answer the required monthly questions for several reasons. For example, a patient that was registered on February 15, 2011 was considered a Year 5 patient, but she could not have been confirmed the first time until March 16, 2011 and would not have answered her questions during Year 5.

Table 15 First Month Questions about Contraceptive Counseling

Contraceptive Counseling[a]	Percentage of Patients Responding Affirmatively					
	Year 3		Year 4		Year 5	
	Non-pregnant N = 169,037 N (%)	Pregnant N = 175 N (%)	Non-pregnant N = 182,547 N (%)	Pregnant N = 180 N (%)	Non-pregnant N = 163,390 N (%)	Pregnant N = 154 N (%)
Doctor offered to refer for birth control counseling	75,596 (44.72)	97 (55.43)	79,945 (43.79)	94 (52.22)	71,738 (43.91)	88 (57.14)
Received specialized birth control counseling[b]	34,082 (20.16)	33 (18.86)	35,583 (19.49)	56 (31.11)	31,228 (19.11)	30 (19.48)
Received birth control counseling from my doctor	109,051 (64.51)	129 (73.71)	119,397 (65.41)	106 (58.89)	107,406 (65.74)	105 (68.18)
Did not receive birth control counseling	25,904 (15.32)	13 (7.43)	27,567 (15.1)	18 (10)	24,756 (15.15)	19 (12.34)

[a] Refers only to the initial contraceptive counseling required before therapy starts, which is different than the counseling confirmed monthly by the prescriber.

[b] Patient self reported.

For the first, and all subsequent months of isotretinoin therapy, female patients of childbearing potential must also correctly answer a series of questions to demonstrate an understanding of the need for contraception and the risk of birth defects if isotretinoin exposure occurs during pregnancy; this series of questions is collectively referred to as comprehension testing.

The majority of non-pregnant and pregnant females demonstrated an understanding of the need to use contraception and the risk of birth defects for isotretinoin-exposed pregnancies by passing the monthly comprehension test on the first attempt (Table 16).

Across all age groups, 5.9% of the non-pregnant and 7.1% of the pregnant females failed the monthly comprehension test at least one time (Table 16). Failure rates within age groups were similar with the exception of pregnant patients in the age range of 12 – 19 where 14.3% of the patients failed the monthly comprehension test at least one time.

Table 16 Monthly Comprehension Testing for Females of Childbearing Potential about the Use of Contraception and the Risk of Birth Defects

All Ages	Year 3		Year 4		Year 5	
	Non-pregnant	Pregnant	Non-pregnant	Pregnant	Non-pregnant	Pregnant
	N = 168,377 N (%)	N = 175* N (%)	N = 181,899 N (%)	N = 179* N (%)	N = 162,743 N (%)	N = 154* N (%)
Passed first time	157,634 (93.62)	160 (91.42)	170,748 (93.87)	170 (94.97)	153,132 (94.09)	143 (92.86)
Number of failures in an isotretinoin treatment course						
1 failure	9,254 (5.5)	14 (8)	9,617 (5.29)	7 (3.91)	8,360 (5.14)	8 (5.19)
2 failures	1,259 (0.75)	0 (0)	1,304 (0.72)	1 (0.56)	1,114 (0.68)	2 (1.3)
> 2 failures	385 (0.23)	1 (0.57)	399 (0.22)	1 (0.56)	315 (0.19)	1 (0.65)
Mean number of failures	1.21	1.13	1.53	1.33	1.56	1.36

* Not all non-pregnant patients answered the required monthly questions. Some patients counted as Year Five patients did not answer the required monthly questions for several reasons. For example, a patient that was registered on February 15, 2011was considered a Year Five patient, but she could not have been confirmed the first time until March 16, 2011and would not have answered her questions during Year Five. Some patients may have more than one course of treatment represented in the data.

Note: Not all patients who have answered their questions will have RMAs in the system. Potential reasons for this is they are still in their prescription window or because they have decided not to initiate treatment.

< 12 years	Year 3		Year 4		Year 5	
	Non-pregnant	**Pregnant**	**Non-pregnant**	**Pregnant**	**Non-pregnant**	**Pregnant**
	N = 144 **N (%)**	**N = 0*** **N (%)**	**N = 164** **N (%)**	**N = 0*** **N (%)**	**N = 145** **N (%)**	**N = 0*** **N (%)**
Passed first time	132 (91.67)	0 (0)	149 (90.85)	0 (0)	136 (93.79)	0 (0)
Number of failures in an isotretinoin treatment course						
1 failure	11 (7.64)	0 (0)	12 (7.32)	0 (0)	7 (4.83)	0 (0)
2 failures	1 (0.69)	0 (0)	1 (0.61)	0 (0)	2 (1.38)	0 (0)
> 2 failures	0 (0)	0 (0)	2 (1.22)	0 (0)	0 (0)	0 (0)
Mean number of failures	1.08	0	1.33	0	1.22	0

12 - 19 years	Year 3		Year 4		Year 5	
	Non-pregnant	**Pregnant**	**Non-pregnant**	**Pregnant**	**Non-pregnant**	**Pregnant**
	N = 71,431 **N (%)**	**N = 36*** **N (%)**	**N = 75,291** **N (%)**	**N = 48*** **N (%)**	**N = 66,596** **N (%)**	**N = 35*** **N (%)**
Passed first time	66,324 (92.85)	34 (94.44)	70,159 (93.18)	48 (100)	62,198 (93.39)	30 (85.71)
Number of failures in an isotretinoin treatment course						
1 failure	4,336 (6.07)	2 (5.56)	4,338 (5.76)	0 (0)	3,793 (5.7)	3 (8.57)
2 failures	635 (0.89)	0 (0)	656 (0.87)	0 (0)	524 (0.79)	1 (2.86)
> 2 failures	204 (0.29)	0 (0)	198 (0.26)	0 (0)	152 (0.23)	1 (2.86)
Mean number of failures	1.23	1	1.75	0	1.83	1.6

20 – 29 years	Year 3		Year 4		Year 5	
	Non-pregnant	**Pregnant**	**Non-pregnant**	**Pregnant**	**Non-pregnant**	**Pregnant**
	N = 60,769 **N (%)**	**N = 107*** **N (%)**	**N = 66,277** **N (%)**	**N = 91*** **N (%)**	**N = 59,680** **N (%)**	**N = 89*** **N (%)**
Passed first time	57,428 (94.5)	101 (94.39)	62,874 (94.87)	86 (94.51)	56,676 (94.96)	84 (94.38)
Number of failures in an isotretinoin treatment course						
1 failure	2,923 (4.81)	6 (5.61)	3,001 (4.53)	4 (4.4)	2,636 (4.42)	4 (4.49)
2 failures	366 (0.6)	0 (0)	362 (0.55)	0 (0)	334 (0.56)	1 (1.12)
> 2 failures	107 (0.18)	0 (0)	110 (0.17)	1 (1.1)	95 (0.16)	0 (0)
Mean number of failures	1.19	1	1.4	1.4	1.38	1.2

> 29 years	Year 3		Year 4		Year 5	
	Non-pregnant	**Pregnant**	**Non-pregnant**	**Pregnant**	**Non-pregnant**	**Pregnant**
	N = 36,033 **N (%)**	**N = 32*** **N (%)**	**N = 40,167** **N (%)**	**N = 40*** **N (%)**	**N = 36,322** **N (%)**	**N = 30*** **N (%)**
Passed first time	33,750 (93.66)	25 (78.13)	37,566 (93.52)	36 (90)	34,122 (93.94)	29 (96.67)
Number of failures in an isotretinoin treatment course						
1 failure	1,984 (5.51)	6 (18.75)	2,266 (5.64)	3 (7.5)	1,924 (5.3)	1 (3.33)
2 failures	257 (0.71)	0 (0)	285 (0.71)	1 (2.5)	254 (0.7)	0 (0)
> 2 failures	74 (0.21)	1 (3.13)	89 (0.22)	0 (0)	68 (0.19)	0 (0)
Mean number of failures	1.19	1.29	1.29	1.25	1.26	1

The percentage of female patients of childbearing potential who failed their monthly comprehension test on their first attempt of the month in Year 5 decreased with each additional month of therapy, ranging from approximately 6% in the first month of therapy to approximately 4% in Month 6 of therapy (Table 17). Similar results were seen during previous years.

Table 17 Number of Patients Who Passed/Failed Their Monthly Comprehension Test on the First Try of the Month

Month of Therapy	Total Patients	Patients who Passed N (%)	Patients who Failed N (%)
Year Three			
1	161,916	151,513 (93.58)	10,403 (6.42)
2	143,879	136,204 (94.67)	7,675 (5.33)
3	127,807	121,835 (95.33)	5,972 (4.67)
4	111,470	106,733 (95.75)	4,737 (4.25)
5	91,824	88,141 (95.99)	3,683 (4.01)
6	52,894	50,903 (96.24)	1,991 (3.76)
>6	47,950	46,141 (96.23)	1,809 (3.77)
Year Four			
1	174,770	164,017 (93.85)	10,753 (6.15)
2	156,184	148,185 (94.88)	7,999 (5.12)
3	140,052	133,595 (95.39)	6,457 (4.61)
4	123,278	118,166 (95.85)	5,112 (4.15)
5	102,979	98,832 (95.97)	4,147 (4.03)
6	61,192	58,826 (96.13)	2,366 (3.87)
>6	57,639	55,539 (96.36)	2,100 (3.64)
Year Five			
1	156,459	147,174 (94.07)	9,285 (5.93)
2	140,535	133,353 (94.89)	7,182 (5.11)
3	127,109	121,358 (95.48)	5,751 (4.52)
4	113,540	108,729 (95.76)	4,811 (4.24)
5	95,843	91,984 (95.97)	3,859 (4.03)
6	57,916	55,536 (95.89)	2,380 (4.11)
>6	56,816	54,748 (96.36)	2,068 (3.64)

4.5.2 Contraceptive Data

Each month, female patients of childbearing potential are required to enter their contraceptive choices during the interaction with the iPLEDGE system for each prescription window. The data in Table 18 represent the first contraceptive combination

reported by patients for each prescription window. Birth control pills (BCPs) and male condoms were the most frequent primary and secondary methods of contraception for the women who had iPLEDGE pregnancies during Year 5; these were also the most frequent primary and secondary methods of contraception for the non-pregnant females. Similar results were seen for both pregnant and non-pregnant females during previous years.

Table 18 Most Common Contraceptive Choices for Pregnant and Non-Pregnant Females of Childbearing Potential

Most Common Contraceptive Choices[a]		**No. of Monthly Interactions with the iPLEDGE system (%)**		
Primary Contraceptive	**Secondary Contraceptive**	**Year 3**	**Year 4**	**Year 5**
Pregnant FCBPs				
Birth control pill	Male latex condoms	447 (61.83)	421 (53.09)	349 (56.56)
Abstinence	None	100 (13.83)	97 (12.23)	86 (13.94)
Non-pregnant FCBPs				
Birth control pills	Male latex condoms	306,426 (39.9)	330,244 (38.8)	294,232 (37.69)
Abstinence	None	195,872 (25.51)	220,380 (25.89)	204,161 (26.15)
Abstinence	Birth control pills	83,968 (10.8)	92,748 (10.9)	82,730 (10.6)

[a] Defined as any combination used by ≥10%.

A summary of the top five contraception choices by age for both pregnant and non-pregnant females is provided in Table 19. Overall, BCPs and male condoms were the most frequent primary and secondary methods of contraception among patients aged ≥16 years who became pregnant. This was similar to patients aged ≥20 who did not become pregnant; for the 16 to 19 year age group, the preferred primary and secondary contraception methods were abstinence and none, respectively.

Table 19 Top 5 Contraception Choices by Age for Pregnant and Non-Pregnant Patients

	Non-Pregnant				**Pregnant**			
Age yrs	**Primary**	**Secondary**	**Patients N (%)**	**COTs[a] N (%)**	**Primary**	**Secondary**	**Patients N (%)**	**COTs N (%)**
<12								
	Abstinence	None	104 (63.03)	112 (64.74)	N/A[b]	N/A	0 (0)	0 (0)
	Abstinence	Male Latex Condom	22 (13.33)	22 (12.72)	N/A	N/A	0 (0)	0 (0)
	Abstinence	BCPs[c]	13 (7.88)	13 (7.51)	N/A	N/A	0 (0)	0 (0)
	BCPs	Male Latex Condom	13 (7.88)	13 (7.51)	N/A	N/A	0 (0)	0 (0)
	BCPs	IUD Progesterone T	3 (1.82)	3 (1.73)	N/A	N/A	0 (0)	0 (0)

Table 19 Top 5 Contraception Choices by Age for Pregnant and Non-Pregnant Patients

	Non-Pregnant				Pregnant			
Age yrs	**Primary**	**Secondary**	**Patients N (%)**	**COTs[a] N (%)**	**Primary**	**Secondary**	**Patients N (%)**	**COTs N (%)**
12 – 15								
	Abstinence	None	9,520 (51.21)	10,197 (51.91)	Abstinence	None	1 (50)	1 (50)
	Abstinence	BCPs	2,680 (14.42)	2,811 (14.31)	BCPs	Male Latex Condom	1 (50)	1 (50)
	BCPs	Male Latex Condom	2,403 (12.93)	2,520 (12.83)	N/A	N/A	0 (0)	0 (0)
	Abstinence	Male Latex Condom	2,069 (11.13)	2,172 (11.06)	N/A	N/A	0 (0)	0 (0)
	BCPs	Natural Family Planning	457 (2.46)	460 (2.34)	N/A	N/A	0 (0)	0 (0)
16 – 19								
	Abstinence	None	19,419 (35.29)	21,319 (35.98)	BCPs	Male Latex Condom	18 (48.65)	19 (48.72)
	BCPs	Male Latex Condom	14,885 (27.05)	16,028 (27.05)	Abstinence	None	10 (27.03)	10 (25.64)
	Abstinence	BCPs	9,941 (18.07)	10,643 (17.96)	Abstinence	BCPs	4 (10.81)	4 (10.26)
	Abstinence	Male Latex Condom	4,943 (8.98)	5,285 (8.92)	Abstinence	Male Latex Condom	2 (5.41)	2 (5.13)
	Hormone Shot	Male Latex Condom	498 (0.91)	519 (0.88)	Hormonal Vaginal Ring	Male Latex Condom	1 (2.7)	2 (5.13)
20 – 29								
	BCPs	Male Latex Condom	31,395 (48.18)	34,236 (48.84)	BCPs	Male Latex Condom	60 (50)	67 (51.54)
	Abstinence	None	9,575 (14.69)	10,412 (14.85)	Abstinence	None	13 (10.83)	13 (10)
	Abstinence	BCPs	5,623 (8.63)	6,012 (8.58)	Hormonal Vaginal Ring	Male Latex Condom	9 (7.5)	10 (7.69)
	Abstinence	Male Latex Condom	3,495 (5.36)	3,702 (5.28)	Abstinence	Male Latex Condom	7 (5.83)	7 (5.38)
	IUD	Male Latex Condom	3,389 (5.2)	3,600 (5.14)	Hormone Shot	Male Latex Condom	4 (3.33)	5 (3.85)
30 – 39								
	BCPs	Male Latex Condom	9,876 (34.29)	10,825 (35.02)	BCPs	Male Latex Condom	17 (54.84)	18 (52.94)
	IUD	Male Latex Condom	3,322 (11.53)	3,536 (11.44)	Abstinence	None	6 (19.35)	6 (17.65)
	Male Latex Condom	Partner's Vasectomy	2,399 (8.33)	2,564 (8.3)	Abstinence	Male Latex Condom	2 (6.45)	3 (8.82)
	Male Latex Condom	Tying My Tubes	2,344 (8.14)	2,588 (8.37)	IUD	Male Latex Condom	1 (3.23)	2 (5.88)
	Abstinence	None	1,734 (6.02)	1,870 (6.05)	Hormonal Vaginal Ring	Male Latex Condom	3 (9.68)	3 (8.82)

Table 19 Top 5 Contraception Choices by Age for Pregnant and Non-Pregnant Patients

Age yrs	Non-Pregnant				Pregnant			
	Primary	Secondary	Patients N (%)	COTs[a] N (%)	Primary	Secondary	Patients N (%)	COTs N (%)
40 – 44								
	BCPs	Male Latex Condom	1,767 (23.28)	1,966 (23.82)	BCPs	Male Latex Condom	2 (40)	2 (40)
	Male Latex Condom	Partner's Vasectomy	1,243 (16.38)	1,369 (16.59)	Male Latex Condom	Tying My Tubes	1 (20)	1 (20)
	Male Latex Condom	Tying My Tubes	1,061 (13.98)	1,173 (14.21)	Tying My Tubes	Natural Family Planning	2 (40)	2 (40)
	IUD	Male Latex Condom	643 (8.47)	688 (8.34)	N/A	N/A	0 (0)	0 (0)
	Abstinence	None	467 (6.15)	505 (6.12)	N/A	N/A	0 (0)	0 (0)
45>								
	BCPs	Male Latex Condom	960 (20.08)	1,083 (20.74)	N/A	N/A	0 (0)	0 (0)
	Male Latex Condom	Partner's Vasectomy	878 (18.37)	982 (18.81)	N/A	N/A	0 (0)	0 (0)
	Male Latex Condom	Tying My Tubes	719 (15.04)	789 (15.11)	N/A	N/A	0 (0)	0 (0)
	Abstinence	None	410 (8.58)	446 (8.54)	N/A	N/A	0 (0)	0 (0)
	Abstinence	Male Latex Condom	300 (6.28)	326 (6.24)	N/A	N/A	0 (0)	0 (0)

[a] Course of Therapy = COT
[b] Not Applicable = N/A
[c] Birth Control Pills = BCPs.

4.5.3 FNCBP Campaigns

Since 2007 a series of iPLEDGE compliance campaigns have been conducted to ensure that female patients were being registered in the correct iPLEDGE risk category.

On average, for all prescribers in iPLEDGE, the percentage of females of childbearing potential (FCBP) and females not of childbearing potential (FNCBP) in iPLEDGE is 46% and 4%, respectively (or 92% and 8% of all female patients, respectively). It was determined that a number of prescribers had a higher than expected percentage of their female patients between the ages of 13 and 53 registered as females not of childbearing potential. These prescribers were the target of this campaign.

The activities of the FNCBP campaign included:

- Educating prescribers on the iPLEDGE criteria for FNCBP risk categorization

- Requesting prescribers to review a list of their FNCBP patients and respond with the reason for FNCBP categorization for each. (A request for reclassification of a patient to FCBP was accepted, when appropriate.)

Table 20 summarizes the results of these campaigns and it is important to note that it was because of this high number of misclassified female patients that the "wizard"-driven categorization of female patient registration will be incorporated with the latest enhancements.

Table 20 Summary of FNCBP Campaigns

Campaign Year	# of Prescribers	# of Patients	# of Patient that Met an FNCBP Criterion	# of Patients that did not meet an FNCBP Criterion	% of Patients Requiring Re-classification
2007	198	616	469	147	23.86
2009	300	1,579	1,015	564	35.72
2010	174	817	569	248	30.35

4.6 Pregnancies

Pregnancy data have been categorized by month based on the date of pregnancy. The first day of the last menstrual period and date of conception are collected from the healthcare provider who reports the pregnancy and/or the patient. In many cases, these dates are unknown or different when collected from different sources. Thus, the following process was used to adjudicate the date of conception relative to the initiation of isotretinoin therapy:

- Date of conception, actual or estimated (first day of last menstrual period plus 14 days). Information provided by the patient was used unless it was contradicted or invalidated by objective evidence such as pregnancy test data. In these cases, the date of conception (actual or estimated) provided by the healthcare provider was used. If a logical date of conception was not provided by the patient or healthcare provider, other applicable information such as an ultrasound or serum human chorionic gonadotropin levels were used by the pregnancy registry personnel to approximate gestational age and to calculate forward to the date of conception. When using serum human chorionic gonadotropin levels to estimate date of conception (DOC), the earliest DOC is selected.
- If the conception date was unknown or could not be estimated, the pregnancy date was based on the earliest date of the first positive pregnancy test or pregnancy confirmation date.
- If the date of the first positive pregnancy test was unknown, the pregnancy date was based on the date the patient was registered in the pregnancy registry.

It is noted that the process for calculating the date of conception provides only an estimate. There is an inherent margin of error associated with each methodology and this error has the potential to impact the timing of isotretinoin pregnancy exposure (e.g., before, during, or after treatment).

When the last menstrual period is used, it assumes the woman has perfect 28-day menstrual cycles and that ovulation occurs mid cycle. Variation in the length of the menstrual cycle, use of hormonal contraception, and other physiologic changes may substantially impact the actual timing of ovulation/conception by days or even weeks. Early ultrasound measurements of gestational age offer more precision in estimating the timing of conception, but are often not reported to the Registry with precise detail. The use of quantitative serum human chorionic gonadotropin levels is one of the least precise methods for estimation due to variation in laboratory assays and wide ranging/overlapping reference values.

Every attempt is made to obtain and use all of the information reported to the Registry in the most precise and logical fashion, but a significant margin of error must be recognized in the interpretation of these estimates.

Pregnancy cases were classified based on iPLEDGE status and then within each iPLEDGE category, by isotretinoin exposure status. Medically confirmed pregnancies, defined as a pregnancy confirmed by a healthcare provider and/or a positive pregnancy test in the iPLEDGE system, and unconfirmed pregnancies, defined as pregnancies reported by patients that were not confirmed by a healthcare provider or by a positive pregnancy test result in the iPLEDGE system, were grouped for categorization.

The iPLEDGE status categories were as follows:

- iPLEDGE pregnancy: an isotretinoin-exposed or indeterminate-exposure pregnancy whether medically confirmed or unconfirmed in a patient who was registered in iPLEDGE
- Non-iPLEDGE pregnancy: an isotretinoin-exposed or indeterminate-exposure pregnancy whether medically confirmed or unconfirmed in a patient who was not registered in iPLEDGE and who became pregnant after iPLEDGE was fully implemented
- Pre-iPLEDGE pregnancy: a pregnancy that occurred before March 1, 2006

4.6.1 Case Reports

A total of 166 pregnancy case reports were received by iPLEDGE during Year 5. Of these 166 reports, 155 were iPLEDGE pregnancies, 10 were non-iPLEDGE pregnancies and 1 was pre-iPLEDGE. Of the 155 iPLEDGE pregnancies, 150 were exposed pregnancies and 5 were of indeterminate exposure (Table 21).

Table 21 iPLEDGE Pregnancies by Isotretinoin Exposure

Isotretinoin Exposure	**Year 3 (N = 190) N (%)**	**Year 4 (N = 186) N (%)**	**Year 5 (N = 155) N (%)**
Exposed	183 (96.3)	176 (94.6)	150 (96.8)
Indeterminate exposure	7 (3.7)	10 (5.4)	5 (3.2)

A total of 30 pregnancies were detected by the iPLEDGE system before the initiation of isotretinoin treatment during Year 5, thereby preventing isotretinoin-exposed pregnancies (Table 22). Similar numbers of pregnancies were detected before the initiation of isotretinoin treatment during previous years (Year 3, 42 pregnancies; Year 4, 44 pregnancies Table 22). All of these pregnant females were registered in iPLEDGE, had negative screening pregnancy tests, and had a positive pregnancy test at the confirmation visit after the 30-day waiting period.

Table 22 Pregnancies Detected by iPLEDGE Before Initiation of Isotretinoin Treatment

iPLEDGE Year 3											
Mar	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**
2	3	2	2	5	2	4	3	4	6	5	4
iPLEDGE Year 4											
Mar	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**
7	2	4	6	5	1	4	3	2	6	2	2
iPLEDGE Year 5											
Mar	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**
1	6	1	1	2	0	3	1	5	2	5	3

4.6.2 Pregnancy Rate

The rate of pregnancies reported in the general population for females in the United States who experience an unintended pregnancy is 5.1% (51/1000) *(Finer, L.B. and Henshaw, S.K. (2006). Disparities in Rates of Unintended Pregnancy in the United States, 1994 and 2001, Perspective on Sexual Reproductive Health, 38 (2): 90-96).* The average iPLEDGE unintended pregnancy rate for Years 3 through 5 was 0.127% (1.27/1000). This average was derived from FCBP Patients that had at least one RMA in iPLEDGE.

A limitation of calculating the iPLEDGE pregnancy rate is that end of therapy and post therapy pregnancy tests are often not conducted. Therefore, the rates are likely understated.

Table 23 Percentage of Pregnancies for FCBP with one Prescription Fill

iPLEDGE Year	Year 3	Year 4	Year 5
With at least 1 RMA during Report Year	140,307	149,509	129,554
iPLEDGE Pregnancies at Time of the Year 5 Report	190	186	155
% of Pregnant Pts with at least 1 RMA during Report Year	0.1354	0.1244	0.1196

The above table was calculated using data from the following sources: iPLEDGE Year 3, 4 and 5 Annual Reports, Table 5: Patients with at least One Isotretinoin Prescription Authorized through iPLEDGE by Risk Category and Age; iPLEDGE Year 5 Annual Report, Table 12: Total Pregnancies by Year of Pregnancies: iPLEDGE Year 3, Year 4, Year 5.

4.6.3 Time of Conception

Timing of conception relative to isotretinoin exposure is shown in Table 24. The majority of iPLEDGE Year 5 pregnancies (94 patients) occurred during isotretinoin treatment. Nine patients were pregnant at the start of isotretinoin treatment and 13 patients conceived within 30 days of the last dose of isotretinoin treatment. The time of conception was unknown for 39 patients.

Table 24 Timing of Conception Relative to Isotretinoin Exposure

Timing of Conception	Year 3 (N=190) N (%)	Year 4 (N=186) N (%)	Year 5 (N=155) N (%)
Prior to starting isotretinoin treatment	19 (10)	16 (8.6)	9 (5.8)
During isotretinoin treatment	123 (64.7)	120 (64.5)	94 (60.6)
Within 30 days after isotretinoin treatment completion	27 (14.2)	26 (14)	13 (8.4)
Unknown[a]	21 (11.1)	24 (12.9)	39 (25.2)[b]

[a] Includes indeterminate exposures

[b] More indeterminate exposures occurred in Year 5 due to changes in the reporting period and a number of these are expected to be reclassified based on follow-up data in subsequent iPLEDGE reporting periods.

4.6.4 Identification of Reasons for Pregnancies

Overall, 48 of the 155 patients with iPLEDGE pregnancies during Year 5 agreed to participate in a voluntary Root Cause Analysis (RCA) interview. However, not all patients answered all questions.

In the RCA interview, the most frequent factors identified as contributing to becoming pregnant were: did not use two forms of birth control (11 patients), birth control failed (9 patients), missed pills (6 patients), unsuccessful at abstinence (5 patients), unplanned sex (5 patients), and partner did not use a condom (4 patients). Patients may have reported more than one contributing factor.

4.6.5 Pregnancy Outcome

Most of the iPLEDGE Year 5 pregnancies (83 cases; 53.5%) resulted in elective termination or spontaneous abortion or are listed as "pregnancy ongoing" or "still continuing" (18 cases; 11.6%) (Table 25). Fifty-two cases (33.5%) are considered lost to follow-up.

One live birth with no known congenital anomalies was reported for an iPLEDGE pregnancy in Year 5. One stillbirth with a known congenital anomaly was reported for an iPLEDGE pregnancy in Year 5.

Since the program became mandatory (March 1, 2006), there have been 47 isotretinoin exposed iPLEDGE pregnancies that resulted in either a live birth or stillbirth. Of those 47 births, 8 had significant congenital anomalies consistent with retinoid embryopathy. The birth defect/congenital anomaly status for 6 births was not reported.

Table 25 Pregnancy Outcomes for iPLEDGE Pregnancies

Pregnancy Outcome	Year 3 (N=190)	Year 4 (N=186)	Year 5 (N=155)	Cumulative Since Program Inception (N=836)
Number of Outcomes[a]	191	186	155	837
Elective Termination	92	76	78	400
Spontaneous Abortion	20	15	5	75
Missed Abortion	0	5	0	6
Ectopic Pregnancy	5	1	0	9
Still Birth	0	0	1	2
Live Birth	15	12	1	45
Still Continuing	0	0	18[b]	18
Lost to follow-up	59	77	52	282
No response from health care provider	4	5	1	19
Patient did not remain under health care provider's care	34	54	35	153
Health care provider left practice	0	0	0	0
Patient refused to participate	3	4	6	31
No response from patient	4	7	4	41
No pregnancy outcome	13	4	4	27
No information provided	1	3	2	11
Unknown	0	0	0	0
Duplicate case	0	0	0	0
Not pregnant/false positive	0	0	0	0
Other	0	0	0	0

[a] The Number of Outcomes includes multiple birth outcomes.

[b] More indeterminate exposures occurred in Year 5 due to changes in the reporting period and a number of these are expected to be reclassified based on follow-up data in subsequent iPLEDGE reporting periods.

5. OVERALL ASSESSMENT

In 2006, the isotretinoin sponsors implemented the largest restricted distribution system of its kind in the US. A performance linked access system was added to the existing Risk Minimization Action Plan (RiskMAP) tools in order to further the public health goal of preventing fetal exposure to isotretinoin. In addition, a pregnancy registry for root cause analysis of pregnancies was launched to determine, document, and analyze causes contributing to fetal exposure. The iPLEDGE RiskMAP became an approved REMS in 2010 under the FDA Amendment Act of 2007.

iPLEDGE was the first multi-sponsor program to implement a single, shared system in order to minimize the burden of REMS on the healthcare system. Stakeholder input was

sought in the development of iPLEDGE and stakeholder organizations continue to be represented through the program's Scientific Advisory Board. The number of stakeholders participating in iPLEDGE has remained stable over the life of the program. At the end of iPLEDGE Year 5 a total of 189 wholesalers, 43,064 pharmacies, and 14,444 prescribers were registered in the program. Dermatologists constitute the majority of prescribers in the program. In the first five years of the program, over 1.2 million patients have accessed isotretinoin through iPLEDGE, approximately half of which are females of child bearing potential.

iPLEDGE operations are supported by various vendors that manage the iPLEDGE database, stakeholder call center, pregnancy registry, and fulfillment of program materials to stakeholders. iPLEDGE can be accessed 24/7, 365 days a year via the internet or phone. The iPLEDGE call center is available to stakeholders Monday through Saturday, 9AM to Midnight EST. There have been no extended interruptions of iPLEDGE system functionality or call center availability. Hold times for activities have averaged less than 2 minutes and the average time for handling calls is under 5 minutes. The most common reasons for calls were requesting an override code, needing a password, getting program information and retrieving prescription data.

In iPLEDGE, prescribers, pharmacies, and patients have individual and shared responsibilities related to product distribution and to assuring that only qualified patients receive isotretinoin. Each individual isotretinoin sponsor has the responsibility to ship product only to iPLEDGE registered wholesalers. Wholesalers can only purchase isotretinoin if they are registered in the iPLEDGE system and can only sell isotretinoin to pharmacies that are registered and activated in the iPLEDGE system. Wholesaler registration is important for ensuring isotretinoin is not diverted to non-iPLEDGE participants.

In order to participate in the program, prescribers must agree to adhere to all the requirements of iPLEDGE. Regarding their female patients of childbearing potential (FCBP), prescribers may assume the responsibility for counseling patients about pregnancy avoidance and birth control, or they may also refer patients to another provider for this counseling. Most prescribers have provided this counseling without an external referral. Prescribers must obtain and enter negative pregnancy test results for those female patients of childbearing potential prior to prescribing isotretinoin and monthly after treatment is commenced.

Pharmacies must obtain authorization from the iPLEDGE system before filling any isotretinoin prescription. Pharmacies are also responsible for dispensing isotretinoin within the 7-day prescription window for females of childbearing potential and within 30 days for other patients. Pharmacies must dispense no more than a 30-day supply and provide the patient with an isotretinoin Medication Guide. Pharmacies are not permitted to sell, borrow, loan, or otherwise transfer isotretinoin in any manner to or from another pharmacy. The most common reasons for denial of dispensing authorization at the pharmacy include the prescriber not confirming counseling and the patient not answering

the comprehension questions. In the most recent year, nine patients were denied isotretinoin due to reported or confirmed pregnancy.

A total of 836 iPLEDGE pregnancies have been reported since program inception. There have been 47 isotretinoin exposed iPLEDGE pregnancies that resulted in either a live birth or stillbirth. Of those 47 births, 8 had significant congenital anomalies consistent with retinoid embryopathy. The first month of treatment has been associated with the highest number of pregnancies, with decreasing absolute counts as length of isotretinoin exposure increases.

Almost all females of childbearing potential have consistently reported receiving the iPLEDGE educational materials prior to receiving their first isotretinoin prescription. Birth control pills and male condoms were the most frequent combination of methods of contraception chosen for both pregnant and non-pregnant females. Abstinence was chosen as the primary method of contraception by an average of 13.3% of FCBPs in iPLEDGE Years 3 through 5. The majority of pregnancies occurred during isotretinoin treatment with most attributed to noncompliance with proper contraception methods. For Year 5, the most common reasons for pregnancy cited were: failure to use two forms of birth control, birth control failed, missed pills, unsuccessful at abstinence, unplanned sex, and partner did not use a condom.

Pending enhancements include the addition of a "wizard"-driven categorization of female patient registration status, availability of RMA logic checks for pharmacy software systems, and additional data collection fields to assist in identification of prescriptions dispensed outside the iPLEDGE system.