**DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

**DERMATOLOGIC AND OPTHALMIC DRUGS ADVISORY COMMITTEE**

**MARCH 28-29, 2023**

**BRIEFING DOCUMENT**

**IPLEDGE**

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**ADVISORY COMMITTEE BRIEFING MATERIALS:**
**AVAILABLE FOR PUBLIC RELEASE.**

**ABSORICA®, ABSORICA LD™, AND ISOTRETINOIN, SUN PHARMACEUTICAL INDUSTRIES, INC.**

**AMNESTEEM®, MYLAN PHARMACEUTICALS INC.**

**CLARAVIS™, TEVA PHARMACEUTICALS USA, INC.**

**ISOTRETINOIN, AMNEAL PHARMACEUTICALS LLC**

**ISOTRETINOIN, UPSHER-SMITH LABORATORIES, LLC**

**MYORISAN®, AKORN INC.**

**ZENATANE™, DR. REDDY'S LABORATORIES, LTD.**

# 1.0 EXECUTIVE SUMMARY

## 1.1 Introduction

Isotretinoin is an oral prescription medication that belongs to the retinoid drug class and was first approved by the United States Food and Drug Administration (US FDA) in 1982 for the treatment of severe recalcitrant nodular acne unresponsive to conventional therapy, including systemic antibiotics. Isotretinoin is highly effective and demonstrates complete and prolonged disease remission.

However, it is a known teratogen and when taken during pregnancy can cause serious side effects, including fetal malformations, increased risk of spontaneous abortions, and premature birth. It is associated with an extremely high risk of life-threatening birth defects if pregnancy occurs while taking isotretinoin in any amount, even for short periods of time. Therefore, isotretinoin must not be used by patients who are or may become pregnant.

In 1984, a risk management program for isotretinoin was implemented to minimize the risk of these birth defects. Over the years, that program has evolved from labeling to a Risk Management Action Plan and finally to a Risk Evaluation and Mitigation Strategy (REMS). The isotretinoin REMS, known as iPLEDGE, is a computer-based, centralized registry of Prescribers, Patients, Pharmacies, and Wholesalers that provides a closed-loop system for prescribing, dispensing, and distributing isotretinoin. iPLEDGE was developed by the isotretinoin Sponsors (Barr Laboratories, a wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.; Genpharm ULC; Mylan Pharmaceuticals Inc.; Ranbaxy Laboratories Limited, which was subsequently acquired by Sun Pharmaceutical Industries Limited, a parent company of Sun Pharmaceutical Industries, Inc.; and Roche Laboratories Inc.) in collaboration with FDA during 2004 and 2005.

There are currently 7 Sponsors with at least 1 approved New Drug Application or Abbreviated New Drug Application for an isotretinoin product: Absorica®, Absorica LD™, and isotretinoin distributed by Sun Pharmaceutical Industries, Inc.; Amnesteem® distributed by Mylan Pharmaceuticals Inc.; Claravis™ manufactured by Teva Pharmaceuticals USA, Inc.; isotretinoin distributed by Amneal Pharmaceuticals LLC; Myorisan® distributed by Akorn Inc.; isotretinoin distributed by Upsher-Smith Laboratories, LLC; and Zenatane™ distributed by Dr. Reddy's Laboratories, Ltd. These 7 Sponsors are collectively referred to as the Isotretinoin Product Manufacturer Group.

## 1.2 Goals of iPLEDGE REMS

The goals of the isotretinoin REMS are

1. To prevent fetal exposure to isotretinoin
2. To inform Prescribers, Pharmacists, and Patients about isotretinoin's serious risks and safe-use conditions

These goals are intended to underscore the foundational principles of iPLEDGE, which are to prevent pregnant Patients from receiving a prescription for isotretinoin and to prevent Patients from becoming pregnant while taking isotretinoin.

### 1.2.1 Key Components for Safe Use of Isotretinoin

The iPLEDGE REMS is required by FDA to ensure the benefits of isotretinoin outweigh its risks.

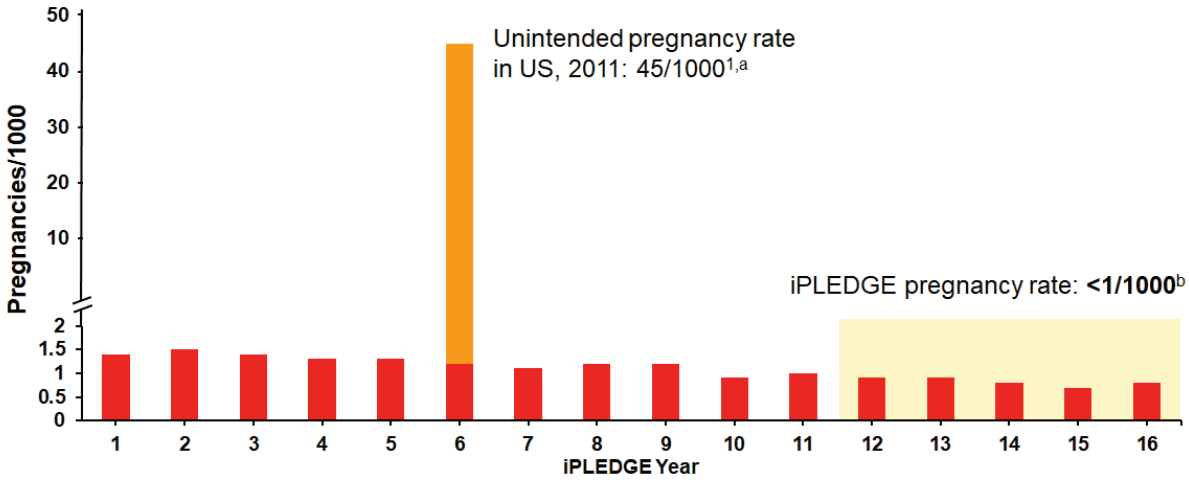
Isotretinoin Sponsors must ensure that healthcare providers (HCPs), Patients, Pharmacies, and Wholesalers-distributers comply with the required elements to assure safe use (ETASUs). These include

- HCPs who prescribe isotretinoin are specially certified in the iPLEDGE REMS.
- Isotretinoin will only be dispensed by Pharmacies specially certified in the iPLEDGE REMS.
- Isotretinoin Sponsors will ensure that isotretinoin will only be dispensed to Patients enrolled in the iPLEDGE REMS with evidence or other documentation of safe-use conditions.
- Isotretinoin Sponsors will maintain a centralized pregnancy registry for Patients enrolled in the iPLEDGE REMS who become pregnant and consent to participate in a root cause analysis.

### 1.2.2 Evidence That iPLEDGE Is Meeting Its Goals

The pregnancy rate for Patients who can become pregnant (PWCBP) enrolled in iPLEDGE has remained consistently low over a period of 16 years (Figure A).[1] Since iPLEDGE Year 12, there has been less than 1 pregnancy per 1000 PWCBP who have received at least 1 Risk Management Authorization for isotretinoin through iPLEDGE. The Risk Management Authorization is the authorization for a Pharmacist to dispense a prescription and is the last iPLEDGE REMS system interaction prior to a Patient being dispensed isotretinoin.

**Figure A: Pregnancy Rates From 2006-2021 (iPLEDGE Years 1-16)**




Abbreviations: PWCBP=Patients who can become pregnant; RMA=Risk Management Authorization; US=United States.
[a] Women and girls 15-44 years of age in the US.
[b] PWCBP enrolled in iPLEDGE with at least 1 RMA.
[1] Finer LB and Zolna MR. *N Engl J Med*. 2016;374(9):843-852.

The overall rate of unintended pregnancies in the United States calculated by Finer and Zolna was 45 unintended pregnancies per 1000 women and girls 15-44 years of age.[1] While direct comparisons are not possible, these data are from individuals of a similar age to iPLEDGE Patients and suggest that the iPLEDGE pregnancy rate is far lower than the unintended pregnancy rate in the general US population.

In addition, the iPLEDGE REMS has detected and prevented at least 516 pregnancies from exposure to isotretinoin during iPLEDGE Years 1-16. In all cases, those PWCBP were registered in iPLEDGE, had negative screening pregnancy tests, but had positive pregnancy tests at the confirmation visits after the initial 30-day wait before drug was dispensed.

When a PWCBP misses their first prescription because the 7-day prescription window has expired, the Patient is required to wait at least 19 days before their next confirmatory pregnancy test. This second confirmatory pregnancy test must be negative to proceed with the subsequent requirements that then allow the Patient to become qualified to receive drug. This ensures the Patient does not receive and start taking drug during their most fertile period. Since iPLEDGE Year 12, 12 pregnancies have been detected during the 19-day wait, preventing fetal exposure to isotretinoin. Importantly, the 19-day wait requirement is essential to prevent fetal exposure to isotretinoin at the time when the Patient is most fertile.

Data collected by the iPLEDGE Pregnancy Registry indicate that the majority of pregnancies are being detected within the first 29 days of conception and that Patients are discontinuing isotretinoin on suspicion or detection of pregnancy. Among 184 exposed or indeterminately exposed iPLEDGE pregnancies in Year 16, 124 had data on duration of exposure, and the median duration of exposure to isotretinoin was 16.5 days.

Metrics to assess Patient knowledge of the risks of isotretinoin indicate that in iPLEDGE Year 16, >95% of non-pregnant and >96% of pregnant PWCBP demonstrated an understanding of the need to use contraception and of the risk of birth defects for isotretinoin-exposed pregnancies by passing the monthly comprehension test on the first attempt.

### 1.3 Modifications to iPLEDGE

In December 2021, the iPLEDGE REMS transitioned to a new REMS administrator, website host, and contact center. The transition did not go as planned and there were several challenges, including stakeholders not being able to log in to the new website and a massive influx of calls to the newly established call center. Efforts to get stakeholders updated passwords or to use a secondary identifier (Date of Personal Significance) to enable a stakeholder to log in were only marginally successful.

The departure of the legacy system vendor with relatively short notice and encryption of passwords that could not be transferred to the new system were contributing factors to the issues with the transition, and actions were taken that addressed these challenges. Discussions with FDA and stakeholders identified further opportunities for improvement.

The iPLEDGE Sponsors submitted a Major REMS Modification in November 2022 that included proposed changes based on stakeholder feedback. Modifications to iPLEDGE to reduce stakeholder burden must be carefully weighed against the potential impact on the safe use of isotretinoin. A negative impact on safety is defined as any change that has the potential for an

increased risk of fetal exposure to isotretinoin. Any proposed change must preserve the foundational principles of iPLEDGE to prevent pregnancies in Patients taking isotretinoin and to prevent pregnant Patients from receiving a prescription for isotretinoin.

The iPLEDGE Sponsors identified 4 potential REMS modifications that will reduce stakeholder burden while maintaining the goals of the safe use of isotretinoin:

1. **Change in confirmation interval for Patients who cannot become pregnant (PWCNBP):** The iPLEDGE Sponsors propose to extend the confirmation interval for these Patients to every 120 days, rather than monthly.

   The prescription for PWCNBP will still be no more than a 30-day supply. Prescribers who want to confirm their PWCNBP will still have the ability to do so for each prescription, but it will not be required. At each confirmation, the timing for the next required confirmation for PWCNBP will be 120 days. All other REMS requirements for both the Patient and the Prescriber remain unchanged. This proposed change will reduce the burden for both PWCNBP and Prescribers.

2. **Enhanced enrollment process:** The iPLEDGE Sponsors propose that a Designee will be able to log in and enter all enrollment information (including pregnancy test results and Patient categorization) on behalf of the Prescriber. This information can be saved at any time in the process. To complete the process, the Prescriber will need to log in and attest that the information is correct, complete the informed consent(s) with the Patient, and provide an electronic signature.

   Additionally, the Prescriber will have the ability to access pending Patient enrollments, review and confirm the Designee's entries, complete informed consent(s), and save and continue entries for completion later. This proposed change will substantially reduce the burden for Prescribers.

3. **Reinstate calendar functionality to improve the iPLEDGE REMS user interface for PWCBP:** The iPLEDGE Sponsors plan to reinstate calendar functionality to better communicate the Patient's course of treatment (COT).

   A Patient Calendar will be added to the Patient Profile screen for PWCBP, which will provide a graphical view of the COT and requirements for individual Patients. This will be visible to Patients, Prescribers, and their Designees. This proposed change will make it easier for both Patients and Prescribers to quickly see where they are in the COT and upcoming requirements.

4. **Website updates for Prescribers and Designees:** The iPLEDGE Sponsors propose website updates that will be made to reduce data entry errors and help to reduce delays in delivery of isotretinoin to Patients. This proposed change will benefit both Patients and Prescribers.

### 1.4 Benefit/Risk Summary

The iPLEDGE REMS is meeting its goals of preventing fetal exposure to isotretinoin and informing Prescribers, Pharmacists, and Patients about the serious risks and safe-use conditions of isotretinoin. The iPLEDGE REMS helps to ensure that the benefits of isotretinoin outweigh its risks. Based on stakeholder feedback, the iPLEDGE Sponsors identified 4 potential

modifications that should reduce stakeholder burden while maintaining the safe use of isotretinoin and submitted a Major REMS Modification in November 2022 that included these proposed changes. Any proposed modification must be carefully weighed against the potential impact on the safe use of isotretinoin and must preserve the foundational principles of the iPLEDGE REMS, which are to prevent pregnancies in Patients taking isotretinoin and to prevent pregnant Patients from receiving a prescription for isotretinoin.

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## KEY TERMS AND ABBREVIATIONS

| Key Terms/ Abbreviations | Definitions and Notes |
|---|---|
| β-HCG | Beta human chorionic gonadotropin |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CLIA | Clinical Laboratory Improvement Amendment |
| COT | Course of treatment |
| Designee | Staff member in a certified Prescriber's office who may perform most Patient activities in the iPLEDGE REMS system on behalf of the Prescriber |
| DO | Doctor of Osteopathic Medicine |
| DOP | Date of Personal Significance |
| DSaRM | Drug Safety and Risk Management |
| ETASU | Elements to Assure Safe Use |
| FCBP | Female Patients of Childbearing Potential |
| FDA | Food and Drug Administration |
| FNBC | Female Patients of Non-Childbearing Potential |
| FRP | Females of reproductive potential |
| FNRP | Females of non-reproductive potential |
| HCP | Healthcare provider |
| iPLEDGE pregnancy | An isotretinoin-exposed or indeterminate-exposure pregnancy, whether medically confirmed or unconfirmed, in a Patient who was registered in iPLEDGE |
| IPMG | Isotretinoin Product Manufacturer Group |
| IQ | Intelligence quotient |
| IVRS | Interactive Voice Recognition System |
| KAB | Knowledge, Attitudes, and Behaviors |
| Max | Maximum |
| MD | Doctor of Medicine |
| Min | Minimum |
| 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 |
| PDF | Portable document format |
| PHE | Public Health Emergency |
| PPP | Pregnancy Prevention Program |
| Prescriber | Healthcare providers who prescribe isotretinoin |
| PWCBP | Patients who can become pregnant |
| PWCNBP | Patients who cannot become pregnant |
| QR | Quick reference (code) |
| REMS | Risk Evaluation and Mitigation Strategy |
| RMA | Risk Management Authorization |
| SD | Standard deviation |
| US | United States |

# 2.0 BACKGROUND

## 2.1 Overview of Isotretinoin

Isotretinoin is an oral prescription medication that belongs to the retinoid drug class. Isotretinoin is used in patients 12 years of age and older and is efficacious for the treatment of severe recalcitrant, nodular acne in patients who are unresponsive to conventional therapy. However, it is a known teratogen and when taken during pregnancy can cause serious side effects, including fetal malformations, increased risk of spontaneous abortions, and premature birth. It is associated with an extremely high risk of life-threatening birth defects if pregnancy occurs while taking isotretinoin in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected, and there is no accurate means of determining whether an exposed fetus has been affected.

Documented external abnormalities include abnormalities of the skull, ear (including anotia, micropinna, and small or absent external auditory canals), eye (including microphthalmia), facial dysmorphia, and cleft palate. Documented internal abnormalities include abnormalities of the central nervous system (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, and cranial nerve deficit), cardiovascular and thymus gland abnormalities, and parathyroid hormone deficiency. In some cases, death has occurred with certain of the abnormalities previously noted. Cases of intelligence quotient (IQ) scores <85, with or without other abnormalities, have been reported.[2]

Therefore, isotretinoin must not be used by patients who are or may become pregnant. If pregnancy does occur during treatment with isotretinoin, isotretinoin must be discontinued immediately, and the patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

## 2.2 History of Isotretinoin Risk Management Programs

The risk management strategies for isotretinoin have evolved for nearly 40 years (Table 1). They began in February 1984, when a Boxed Warning for pregnancy was added to the label. In 1988, the Pregnancy Prevention Program was initiated, and the label was strengthened to contain the need for pregnancy testing, 2 forms of contraception, and monthly negative pregnancy tests before starting therapy. Because of continued unacceptable levels of fetal exposure to isotretinoin, risk labeling and mitigation strategies were progressively made stronger based on United States Food and Drug Administration (US FDA) and Advisory Committee feedback.

In 2000, the label was updated with a requirement for 2 negative pregnancy tests prior to the initial prescription, and the Drug Safety and Risk Management (DSaRM) Advisory Committee articulated 2 goals: no woman should begin isotretinoin therapy if pregnant, and no woman becomes pregnant while being treated with isotretinoin.

In January 2002 the SMART Risk Minimization Action Plan was initiated, which was the first isotretinoin program linking dispensing of drug to confirmed negative pregnancy status. Multiple similar programs were implemented by Sponsors of generic isotretinoin products.

In 2004, the DSaRM Advisory Committee recommended the initiation of a unified, mandatory isotretinoin Risk Management program with a single centralized pregnancy registry. iPLEDGE

was approved by FDA in August 2005, stakeholder registration began in September 2005, and patient enrollment began in late December 2005. On March 1, 2006, participation of stakeholders became mandatory. In October 2010, iPLEDGE was deemed a formal Risk Evaluation and Mitigation Strategy (REMS).

**Table 1: Timeline of Key Isotretinoin Regulatory Events (1982-2010)**

| Date | Type of Event | Regulatory Event |
|---|---|---|
| June 1982 | FDA approval | US approval of Accutane™ with pregnancy contraindication. |
| August 1983 | Label Change | Bold print pregnancy warnings in Contraindications, Warnings, and Precautions sections. |
| February 1984 | Label Change | Boxed Warning pregnancy warnings added:<br>• Recommendation for pregnancy testing<br>• Use of contraception for the month prior to therapy |
| August 1988 | Label Change | Avoid pregnancy logo inserted. |
| October 1988 | Risk Management Program | Pregnancy Prevention Program (PPP) initiated. |
| April 1990 | Label Change | Birth defects information included in Boxed Warning. Recommendation to prescribe only 1 month supply added. |
| December 1993 | Label Change | Requirement for pregnancy testing added to Boxed Warning. |
| January 1994 | Label Change | Updated Patient consent form to include additional requirements. |
| May 2000 | Label Change | Two negative pregnancy tests required 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 | FDA Advisory Committee meeting | DSaRM Advisory Committee. |
| October 2001 | Label Change | Pregnancy test of at least 25 mIU β-HCG required. |
| January 2002 | Risk Management Program | System to Manage Accutane Related Teratogenicity™ (SMART) initiated.<br>In addition to components of PPP: Link dispensing of drug to negative pregnancy testing (via Accutane Qualification Sticker). |
| November 2002<br>December 2002<br>April 2003 | Risk Management Program | SPIRIT Risk Management Program (Amnesteem)<br>IMPART Risk Management Program (Sotret)<br>ALERT Risk Management Program (Claravis) |

| Date | Type of Event | Regulatory Event |
|---|---|---|
| February 2004 | FDA Advisory Committee meeting | DSaRM Advisory Committee to discuss SMART Year 1 results and a Sponsor proposal for an isotretinoin registry.<br>A unified, mandatory, isotretinoin pregnancy risk management program, iPLEDGE, with a single centralized pregnancy registry was recommended. |
| August 12, 2005 | FDA Advisory Committee meeting | iPLEDGE Approved by FDA: stakeholder registration began in September 2005 and Patient enrollment in late December 2005. |
| December 2005 | Risk Management Program | Launch of iPLEDGE. |
| February 2006 | FDA Advisory Committee meeting | DSaRM Advisory Committee meeting to discuss the operational aspects of iPLEDGE. |
| March 1, 2006 | Risk Management Program | iPLEDGE mandatory participation. Transition to iPLEDGE was completed and all other sticker programs were discontinued. |
| October 22, 2010 | Approval of the REMS | Approval of the iPLEDGE REMS. |

Abbreviations: β-HCG=beta human chorionic gonadotropin; DSaRM=Drug Safety and Risk Management; FDA=Food and Drug Administration; REMS=Risk Evaluation and Mitigation Strategy; US=United States.

# 3.0 SCOPE OF IPLEDGE

## 3.1 iPLEDGE Overview

### 3.1.1 iPLEDGE Goals

The iPLEDGE REMS is a set of steps that all Patients, Prescribers, and Pharmacists must follow. The iPLEDGE REMS is designed to prevent pregnancies in Patients taking isotretinoin and to prevent pregnant Patients from taking isotretinoin.

The goals of the isotretinoin REMS[2] are

1. To prevent fetal exposure to isotretinoin
2. To inform Prescribers, Pharmacists, and Patients about isotretinoin's serious risks and safe use conditions

### 3.1.2 Elements to Assure Safe Use

Elements to Assure Safe Use (ETASUs) are intended to provide safe access for Patients to drugs with known serious risks that would otherwise be unavailable.

The iPLEDGE REMS Sponsors must ensure that Healthcare Providers (HCPs), Patients, Pharmacies, and Wholesalers-distributers comply with the required ETASUs. These include

- HCPs who prescribe isotretinoin are specially certified in the iPLEDGE REMS.
- Isotretinoin will only be dispensed by Pharmacies specially certified in the iPLEDGE REMS.
- Isotretinoin Sponsors will ensure that isotretinoin will only be dispensed to Patients enrolled in the iPLEDGE REMS with evidence or other documentation of safe-use conditions.
- Isotretinoin Sponsors will maintain a centralized pregnancy registry for Patients enrolled in the iPLEDGE REMS who become pregnant and consent to participate in a root cause analysis.[2]

### 3.1.3 Structure and Organization of iPLEDGE

Table 2 lists all current and previous Sponsors in the iPLEDGE REMS.

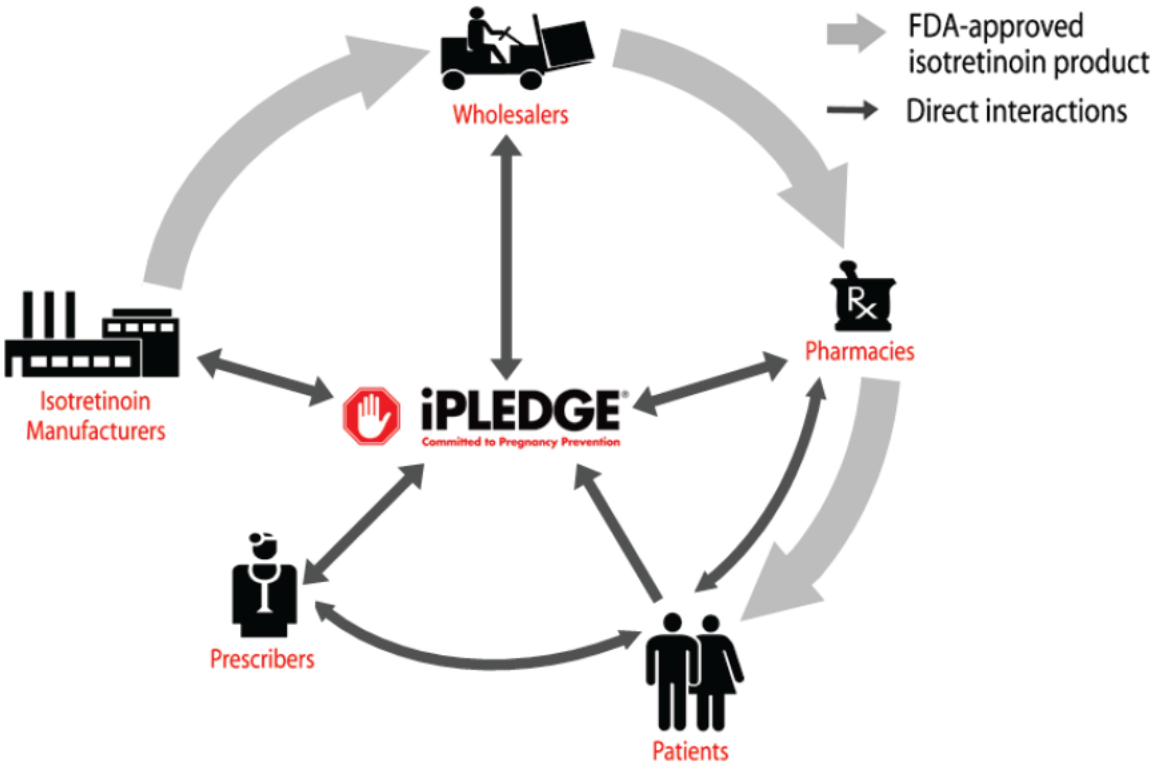
**Table 2: iPLEDGE REMS Sponsors (Current and Previous)**

| Isotretinoin Product | Manufacturer | Approval Date |
|---|---|---|
| Accutane® | Hoffmann-La Roche Inc. | May 1982<br>Withdrawn December 2010 |
| Amnesteem® | Mylan Pharmaceuticals Inc./Genpharm | November 2002 |
| Sotret® | Sun Pharmaceutical Industries, Inc.<br>(formerly Ranbaxy/Cipher) | December 2002<br>Withdrawn January 2017 |
| Claravis™ | Teva Pharmaceuticals USA, Inc.<br>(formerly Barr Laboratories, Inc.) | April 2003 |

| Isotretinoin Product | Manufacturer | Approval Date |
|---|---|---|
| Myorisan® | Akorn Inc. (formerly VersaPharm Inc.) | January 2012 |
| Absorica® | Sun Pharmaceutical Industries, Inc. (formerly Ranbaxy/Cipher) | May 2012 |
| Zenatane™ | Dr. Reddy's Laboratories, Ltd. | March 2013 |
| Amneal isotretinoin | Amneal Pharmaceuticals LLC | September 2017 |
| Absorica LD™ | Sun Pharmaceutical Industries, Inc. | November 2019 |
| isotretinoin | Sun Pharmaceutical Industries, Inc. | Authorized Generic |
| isotretinoin | Upsher-Smith Laboratories, LLC | April 2021 |
| isotretinoin | Actavis Labs FL | March 2021 |

The iPLEDGE REMS is a single, centralized program for all isotretinoin products and includes enrollment of all HCPs prescribing or dispensing isotretinoin (Figure 1). This is a restricted distribution model in which manufacturers ship isotretinoin only to registered Wholesalers who then ship only to enrolled and activated Pharmacies. Requirements for each stakeholder are detailed in Table 3.

**Figure 1: Structure of iPLEDGE REMS (IPMG & Partners)**




Abbreviations: FDA=Food and Drug Administration; IPMG=Isotretinoin Product Manufacturer Group.

**Table 3: Key iPLEDGE REMS Requirements by Stakeholder**

| iPLEDGE REMS Stakeholder | Requirement |
|---|---|
| Wholesalers | • Mandatory annual registration with iPLEDGE REMS.<br>• Distribution of only FDA-approved isotretinoin product.<br>• Shipping isotretinoin only to Wholesalers registered with the iPLEDGE REMS with the prior written consent of the manufacturer and to Pharmacies licensed in the United States that are enrolled and activated with the iPLEDGE REMS.<br>• Wholesaler to Wholesaler Shipment Request Form provided.<br>• Comply with audits carried out by the Isotretinoin Applicants, or a third party acting on behalf of the Isotretinoin Applicants to ensure that all processes and procedures are in place and are being followed. |
| Prescribers | • Mandatory annual reactivation of registration in iPLEDGE REMS.<br>• Know the risk and severity of fetal injury/birth defects from isotretinoin.<br>• Know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy.<br>• Have the expertise to provide the Patient with detailed pregnancy counseling or refer the Patient to an expert for such counseling, reimbursed by the manufacturer.<br>• Comply with the iPLEDGE REMS requirements described in the booklet entitled *iPLEDGE REMS Prescriber Guide.*<br>• Understand and comply with the Non-Compliance Action Policy.<br>• Before beginning treatment with isotretinoin, obtain the Patient's informed consent using the Patient Enrollment Form.<br>• Provide the Patient with their ID.<br>• Before beginning treatment with isotretinoin for Patients who can become pregnant and on a monthly basis, the Patient will be counseled to avoid pregnancy by using 2 forms of contraception simultaneously and continuously 1 month prior to initiation of isotretinoin treatment, during isotretinoin treatment and for 1 month after isotretinoin treatment unless the Patient commits to continuous abstinence.<br>• Not prescribe isotretinoin to any Patient who can become pregnant until verifying a negative Clinical Laboratory Improvement Amendment (CLIA)-certified pregnancy test. Patients should have a pregnancy test at the completion of the entire course of isotretinoin and another pregnancy test 1 month later. |

| iPLEDGE REMS Stakeholder | Requirement |
|---|---|
| | • Report any pregnancy case while the Patient is on isotretinoin or if it occurs within 1 month after the last dose to the Pregnancy Registry. |
| Patients Who Can Become Pregnant | • Use of 2 effective methods of contraception simultaneously and continuously for at least 1 month prior to initiation of isotretinoin treatment, during isotretinoin treatment and for 1 month after discontinuing isotretinoin treatment.<br>• Monthly interaction with the iPLEDGE REMS to document 2 chosen forms of contraception. The system verifies that there is a match with the primary method of contraception entered by the Prescriber.<br>• Monthly CLIA-certified laboratory pregnancy test.<br>• Monthly interaction with the iPLEDGE REMS, referred to as monthly comprehension testing, to answer a series of questions demonstrating understanding of the need to use contraception and the risk of birth defects. Questions are asked in the categories of general iPLEDGE REMS requirements, general contraception requirements, birth defects and pregnancy, safety information about not sharing product and not donating blood, filling a prescription, and contraception questions. A Patient is asked 1 question in each category and passes the comprehension test if all questions are answered correctly. If a question is answered incorrectly, the Patient is given another question in the same category. If the second question in the category is answered incorrectly, the Patient does not pass the comprehension test and is instructed to take the comprehension test after the educational material has been re-reviewed.<br>• For the first isotretinoin prescription only, answer a series of questions to determine if the Prescriber provided information on how to access the Patient educational material, was told to avoid pregnancy and received birth control counseling.<br>• Required to obtain an isotretinoin prescription within 7 days of the specimen collection date for the confirmatory pregnancy test and for each subsequent monthly pregnancy test. |
| Patients Who Cannot Become Pregnant | • Required to obtain their isotretinoin prescription within 30 days of the Prescriber's office visit. |
| Pharmacy | • Must designate a Responsible Site Pharmacist who attests to the requirements in the iPLEDGE REMS Website on behalf of the Pharmacy. |
| Pharmacists | • Will comply and seek to ensure all Pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE REMS requirements described in the booklet |

| iPLEDGE REMS Stakeholder | Requirement |
|---|---|
| | entitled *iPLEDGE REMS Pharmacist Guide*, specifically the "Key Information for Pharmacists" section.<br>• Understand and will comply with the Non-Compliance Action Policy.<br>• Will obtain isotretinoin only from iPLEDGE REMS registered Wholesalers.<br>• Be trained by the Responsible Site Pharmacist concerning the iPLEDGE REMS requirements.<br>• Obtain authorization from the iPLEDGE REMS 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.<br>• Write and/or record the RMA on the prescription or in the Patient record in the Pharmacy system.<br>• Only dispense isotretinoin in no more than 30 day's supply.<br>• Only dispense after authorization from the iPLEDGE REMS.<br>• Only dispense isotretinoin prior to the "Do Not Dispense To Patient After" date provided by the iPLEDGE REMS system (within 30 days of the office visit for Patients who cannot become pregnant and within 7 days of the date of specimen collection for Patients who can become pregnant). Only dispense isotretinoin with a new prescription for refills and another authorization from the iPLEDGE REMS. (No automatic refills are allowed.)<br>• Comply with audits carried out by applicants or third party acting on behalf of the applicants to ensure that all processes and procedures are in place and are being followed. |

Abbreviations: FDA=Food and Drug Administration; ID=identification; RMA=Risk Management Authorization.

### 3.1.4 Risk Categorization

Before enrolling a Patient in the iPLEDGE REMS, the Prescriber must determine if this is a Patient who can become pregnant (PWCBP). In the iPLEDGE REMS, the definition of a PWCBP is

- A Patient who has not had a hysterectomy and/or bilateral oophorectomy
- A Patient who is not postmenopausal
- A Patient who has not yet started menstruating
- A Patient who has had a tubal sterilization
- A transgender male with viable female reproductive organs

Prior to the major modification in October 2021 (see Section 5.1), Patients were categorized as females of reproductive potential (FRP), females of non-reproductive potential (FNRP), or males. After the October 2021 modification, Patients were categorized as PWCBP and Patients who cannot become pregnant (PWCNBP; Table 4). In this briefing document, tables will refer to these groups using the prior classifications of FRP, FNRP, and males as they were reported in previous annual reports.

**Table 4: iPLEDGE REMS Definition of Patient Categories**

| Patients Who Can Become Pregnant (PWCBP) | Patients Who Can NOT Become Pregnant (PWCNBP) |
|---|---|
| • Cisgender females (born a female with a uterus and at least 1 ovary, aka cis-female)<br>• Transgender males (born female with a uterus and at least 1 ovary, transitioned to a male, aka trans-male) | • Cisgender male (born a male, aka cis-male)[a]<br>• Cisgender females and transgender males who have undergone a hysterectomy (surgical removal of the uterus)<br>• Cisgender females and transgender males who have undergone a bilateral oophorectomy (surgical removal of both ovaries)<br>• Cisgender females and transgender males who are postmenopausal according to the iPLEDGE REMS definition[b]<br>• Transgender female (born male and transitioned to female) |
| Prior Classification (prior to October 2021) | |
| Females of Reproductive Potential (FRP) | Females of Non-Reproductive Potential (FNRP) or Males |

Abbreviation: REMS=Risk Evaluation and Mitigation Strategy.
[a] Per a pending modification, this terminology will be updated to "Patient assigned as male at birth (born a male)."
[b] Menopause can be assumed to have occurred in a woman when there is either: 1) Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed), or 2) Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years).

### 3.1.5 Risk Management Authorization Process

The Risk Management Authorization (RMA) is the last iPLEDGE REMS system interaction prior to a Patient being dispensed isotretinoin. The RMA is the authorization for a Pharmacist to dispense a prescription. When the Patient and Prescriber have fulfilled all safe-use conditions, the Patient is qualified to receive drug. Upon receipt of a prescription, an enrolled and activated Pharmacist can enter the Patient information into the iPLEDGE REMS system to obtain an RMA. Once this has been obtained, the Pharmacist is authorized to dispense to the Patient.

#### 3.1.5.1 Patients Who Can Become Pregnant

The iPLEDGE requirements for PWCBP are intended to increase Patient safety, and a typical Patient journey is detailed in Figure 2.

Before receiving the initial isotretinoin prescription, PWCBP must have 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL: a negative screening pregnancy test and a negative confirmatory pregnancy test.

Patient enrollment includes

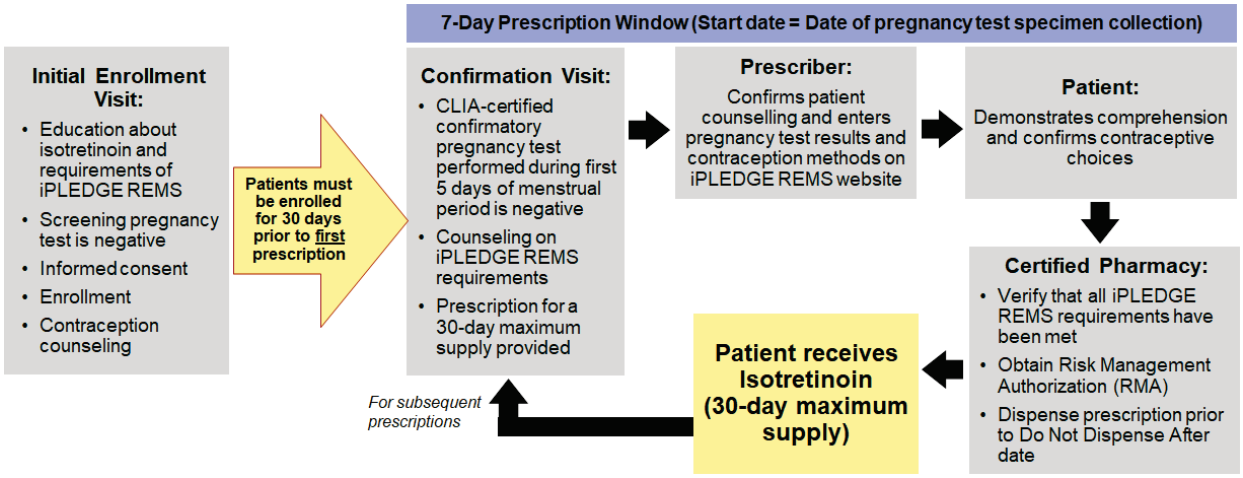
- Obtaining a screening pregnancy test, which may be completed at the Prescriber's office, and which must be negative for the Patient to be enrolled in the iPLEDGE REMS
- Obtaining Patient consents
- Counseling the Patient on either the mandatory simultaneous use of 2 effective forms of contraception, or abstinence, for at least 30 days before starting treatment, during treatment, and for 1 month after end of treatment. This counseling can be conducted by the Prescriber or a Contraception Counselor.

Once a Patient has been enrolled, the iPLEDGE REMS system enforces a 30-day wait before the first prescription. Per the Prescribing Information, a second negative confirmatory pregnancy test is required after the Patient has either used 2 forms of contraception, or remained abstinent, for 30 days. This test must be conducted during the first 5 days of the menstrual cycle that immediately precedes the beginning of isotretinoin therapy. This timing provides the greatest probability that the Patient is not pregnant when starting isotretinoin therapy.

The Prescriber confirms the Patient in the iPLEDGE REMS system by documenting the negative pregnancy test and completed contraception counseling. Isotretinoin must be dispensed to the Patient within 7 days of the specimen collection date of the second negative confirmatory pregnancy test. The Patient is then required to interact with the educational and risk management component of the iPLEDGE REMS system to demonstrate their comprehension of the Patient requirements.

When a Pharmacy receives a prescription from a certified Prescriber, the Pharmacy must interact with the system to obtain an RMA to ensure all ETASUs and safe-use conditions are in place. If not in place, the RMA is denied. When the RMA is obtained, the Pharmacist is provided with a Do Not Dispense After date. The prescription must be dispensed to the Patient by this date. These steps create a 7-day window in which to dispense up to a 30-day supply of isotretinoin to the Patient, which minimizes the chances that the Patient is pregnant before starting therapy.

**Figure 2: Patient Journey for PWCBP**



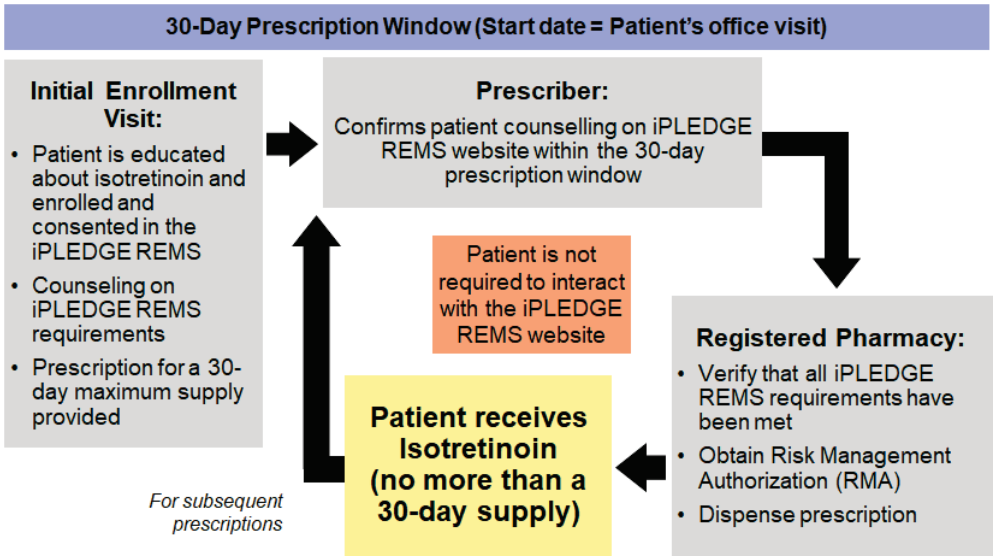

Abbreviations: CLIA=Clinical Laboratory Improvement Amendment; PWCBP=Patients who can become pregnant; REMS=Risk Evaluation and Mitigation Strategy.

[a] Patients counseled that they must either simultaneously use 2 effective forms of contraception correctly, or remain abstinent, for at least 30 days before starting treatment.
[b] For the first prescription only, a CLIA-certified confirmatory pregnancy test must be performed during first 5 days of menstrual cycle, at least 30 days after enrollment. For subsequent prescriptions, a CLIA-certified pregnancy test is required.
[c] Counseling on iPLEDGE REMS and contraception required monthly.
[d] Prior to obtaining authorization for the Pharmacy to dispense a prescription, the Prescriber and Patient must have entered their required information into the iPLEDGE REMS website.
[e] If all iPLEDGE REMS requirements have been met, this will generate an RMA number, which the Pharmacist should document prior to dispensing prescription.
[f] Do Not Dispense After date is calculated as 7 days from the date of confirmatory pregnancy test specimen collection. Patients who present a prescription after this date will not be authorized in the iPLEDGE REMS website to receive isotretinoin.

#### 3.1.5.2 Patients Who Cannot Become Pregnant

The Patient is enrolled and signs a consent form, is counseled, and is confirmed by the Prescriber. Following that, they are qualified to receive drug within a 30-day prescription window. The Patient journey for PWCNBP is shown in Figure 3.

**Figure 3: Patient Journey for PWCNBP**




Abbreviations: PWCNBP=Patients who cannot become pregnant; REMS=Risk Evaluation and Mitigation Strategy.

## 3.2 iPLEDGE Operations

The years of iPLEDGE reporting periods do not align with the calendar year; the reporting periods and corresponding iPLEDGE years are shown in Table 5.

For the first 15 iPLEDGE years, the Sponsors submitted an annual assessment report to the FDA where the reporting period ran from March through February of the next calendar year.

A bridge assessment report was submitted for Year 16, which covered the 10 months from the end of Year 15 and through the transition. This was the most recent assessment submitted to FDA. The next assessment report for the period from December 11, 2021, to December 31, 2023, is due on March 1, 2024.

**Table 5: iPLEDGE Year and Corresponding Reporting Period**

| iPLEDGE Year | Reporting Period |
|---|---|
| 1 | March 1, 2006, to February 28, 2007 |
| 2 | March 1, 2007, to February 29, 2008 |
| 3 | March 1, 2008, to February 28, 2009 |
| 4 | March 1, 2009, to February 28, 2010 |
| 5 | March 1, 2010, to February 28, 2011 |
| 6 | March 1, 2011, to February 29, 2012 |
| 7 | March 1, 2012, to February 28, 2013 |
| 8 | March 1, 2013, to February 28, 2014 |
| 9 | March 1, 2014, to February 28, 2015 |
| 10 | March 1, 2015, to February 29, 2016 |
| 11 | March 1, 2016, to February 28, 2017 |
| 12 | March 1, 2017, to February 28, 2018 |
| 13 | March 1, 2018, to February 28, 2019 |
| 14 | March 1, 2019, to February 29, 2020 |
| 15 | March 1, 2020, to February 28, 2021 |
| 16 | March 1, 2021, to December 10, 2021 |

To participate in the iPLEDGE REMS, Wholesalers must be registered in iPLEDGE REMS and must re-register in the iPLEDGE REMS annually. The number of registered Wholesalers, enrolled and activated Prescribers, activated Designees, and enrolled and activated Pharmacies in iPLEDGE Years 12, 13, 14, 15, and 16 are shown in Table 6.

**Table 6: Numbers of Wholesalers, Prescribers, Designees, and Pharmacies Active in iPLEDGE REMS (iPLEDGE Years 12-16)**

| | Year 12 (3/1/2017-2/28/2018) | Year 13 (3/1/2018-2/28/2019) | Year 14 (3/1/2019-2/29/2020) | Year 15 (3/1/2020-2/28/2021) | Year 16 (3/1/2021-12/10/2021) |
|---|---|---|---|---|---|
| Number of registered Wholesalers at end of reporting period | 172 | 161 | 149 | 145 | 146 |
| Number of enrolled and activated Prescribers who wrote at least 1 isotretinoin prescription | 17,625 | 19,531 | 20,322 | 20,923 | 20,259 |
| Number of activated Designees | 30,703 | 26,247 | 28,353 | 28,818 | 30,303 |
| Number of enrolled and activated Pharmacies at the end of the reporting period | 47,651 | 48,935 | 50,129 | 50,895 | 51,885 |

Definition: Designee=staff member in a certified Prescriber's office who may perform most Patient activities in the iPLEDGE REMS system on behalf of the Prescriber.
Abbreviation: REMS=Risk Evaluation and Mitigation Strategy.

A total of 4,196,443 Patients have registered with iPLEDGE since its inception. Overall, 49.1% of the Patients were male, 48.2% were FRP, and 2.7% were FNRP (Table 7). These represent

prior Patient categorizations (Section 3.1.4, Table 4). A total of 297,745 Patients were newly registered for the first time during Year 16 (had not been previously enrolled). Of these newly registered Patients, 47.1% were male, 51.0% were FRP, and 2.0% were FNRP.

**Table 7: Number of Unique Patients Enrolled in the iPLEDGE REMS by Patient Risk Category Through the Reporting Period**

| Risk Category | N (%) | | | | |
|---|---|---|---|---|---|
| | Cumulative[a] Through Year 12 (3/1/2017-2/28/2018) | Cumulative[a] Through Year 13 (3/1/2018-2/28/2019) | Cumulative[a] Through Year 14 (3/1/2019-2/29/2020) | Cumulative[a] Through Year 15 (3/1/2020-2/28/2021) | Cumulative[a] Through Year 16 (3/1/2021-12/10/2021) |
| FRP | 1,365,618 (47.0) | 1,521,923 (47.3) | 1,688,605 (47.6) | 1,869,714 (48.0) | 2,020,745 (48.2) |
| FNRP | 86,246 (3.0) | 93,118 (2.9) | 100,422 (2.8) | 107,236 (2.8) | 113,821 (2.7) |
| Males | 1,451,728 (50.0) | 1,601,678 (49.8) | 1,761,670 (49.6) | 1,921,751 (49.3) | 2,061,877 (49.1) |
| Total | 2,903,592 | 3,216,719 | 3,550,717 | 3,898,701 | 4,196,443 |

Abbreviations: FRP=females of reproductive potential; FNRP=females of non-reproductive potential; REMS=Risk Evaluation and Mitigation Strategy.
[a] Includes Patients enrolled during the iPLEDGE transition period of December 30, 2005, to February 28, 2006. Patient categories may change when a Patient is re-registered; therefore, cumulative values for a Patient category do not cross-foot.

### 3.2.1 Drug Dispensed to Patients Enrolled in the iPLEDGE REMS With Evidence of Safe-Use Conditions

A prescription window is defined by the Prescriber completing a confirmation in the iPLEDGE REMS for a Patient. A course of treatment (COT) is considered complete if the Prescriber completes the Patient in the iPLEDGE system or if the Patient is discontinued by the system for inactivity. In comparing the COTs in which a Patient became pregnant to a completed COT, pregnant FRP averaged 4.0 prescription windows compared to 5.8 for non-pregnant FRP. Males and FNRP averaged 4.4 and 3.2 prescription windows per completed COT, respectively (Table 8).

**Table 8: Average Number of Prescription Windows in a Completed Course of Treatment (iPLEDGE Year 16)**

| | Completed COTs | Average Prescription Windows |
|---|---|---|
| Pregnant FRP | 183 | 4.0 |
| Non-Pregnant FRP | 170,633 | 5.8 |
| FNRP | 9,917 | 3.2 |
| Males | 188,210 | 4.4 |

Abbreviations: COT=course of treatment; FRP=females of reproductive potential; FNRP=females of non-reproductive potential.

A total of 1,833,708 prescriptions were authorized (Table 9) during iPLEDGE Year 16. The majority of prescriptions were authorized for FRP (927,284, 50.6%) and males (871,769, 47.5%). Similar results were seen during previous years.

**Table 9: Number of Prescriptions Authorized by Patient Risk Category**

| Risk Category | Year 12 (3/1/2017-2/28/2018) | Year 13 (3/1/2018-2/28/2019) | Year 14 (3/1/2019-2/29/2020) | Year 15 (3/1/2020-2/28/2021) | Year 16 (3/1/2021-12/10/2021) |
|---|---|---|---|---|---|
| FRP | 734,089 | 849,673 | 928,529 | 1,032,124 | 927,284 |
| FNRP | 31,635 | 35,462 | 38,369 | 37,161 | 34,655 |
| Males | 784,505 | 875,668 | 949,633 | 980,694 | 871,769 |
| Total | 1,550,229 | 1,760,803 | 1,916,531 | 2,049,979 | 1,833,708 |

Abbreviations: FRP=females of reproductive potential; FNRP=females of non-reproductive potential.

### 3.2.2 Changes Due to COVID-19 Pandemic

Due to the COVID-19 pandemic, FDA responded to the many queries concerning REMS that include laboratory monitoring requirements and the impact these requirements have on patient access to certain REMS drugs when patients self-isolate or are subject to quarantine.

Effective March 13, 2020, in response to FDA's draft guidance document (Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency, Guidance for Industry and Health Care Professionals, March 2020), the iPLEDGE REMS allowed at-home pregnancy tests to be performed by the Patient. After the Patient takes the home pregnancy test, the Patient must communicate to the Prescriber the results of the test. The Prescriber is then responsible to enter the results in the iPLEDGE REMS and continue to confirm the Patient per the requirements.

## 3.3 Contraceptive Data

PWCBP are required to enter their contraceptive choices during the interaction with the iPLEDGE REMS system for each prescription window. The Patient's primary contraception choice must match the primary contraception choice entered into the system by their Prescriber. Previously in the iPLEDGE REMS system, a Patient could select abstinence and birth control pills as their primary and secondary methods of contraception. To reinforce the message that a Patient choosing abstinence must not have sex or sexual contact (penis-vaginal) with any partner 24 hours a day, 7 days a week, the iPLEDGE REMS Sponsors implemented a change in the iPLEDGE REMS system on March 13, 2016 (iPLEDGE Year 11) that disabled the selection of a second contraceptive method when abstinence has been selected.

When a PWCBP enters abstinence into the iPLEDGE REMS system as the method of birth control, the Patient is presented with a message stating that the Patient has chosen abstinence and agrees to not have sex or sexual contact (penis-vaginal) with any partner 24 hours a day, 7 days a week. The PWCBP is told that if the Patient cannot commit completely to abstinence (not having sex) while taking isotretinoin the Patient is to contact their Prescriber before engaging in sexual activity. The PWCBP is also told that one of the most common reasons that a Patient gets pregnant is that they engage in sexual activity when they have planned to be abstinent. The

PWCBP is then provided with options to commit to abstinence or inform the Prescriber that the Patient is not able to commit to abstinence.

The Prescriber receives a pop-up alert that the PWCBP has chosen abstinence as the method of contraception. The Prescriber is then asked to confirm that the Patient understands they are committed to not having any sexual contact (penis-vaginal) with any partner for 1 month before starting to take isotretinoin, while on isotretinoin, and for 1 month after stopping isotretinoin and to confirm that the Patient will tell the Prescriber immediately if they decide not to be abstinent. The Prescriber is also reminded that one of the most common reasons that Patients get pregnant is that they engage in sexual activity when they have planned to be abstinent.

The primary contraception choice entered into the system by the Patient must match the primary contraception choice entered into the system by their Prescriber. Entry of a contraception option that does not match prevents the Patient from becoming qualified to fill a prescription.

The data in Table 10 represent the first contraceptive combination reported by Patients for each prescription window. Birth control pills and male latex condoms were the most frequent primary and secondary methods of contraception for PWCBP who had iPLEDGE pregnancies during iPLEDGE Year 16, with abstinence as the second most frequent method. Conversely, abstinence was the most frequent method of contraception for non-pregnant PWCBP, with birth control pills and male latex condoms as the second most frequent methods. Similar results were seen in the reporting periods for iPLEDGE Years 12, 13, 14, and 15.

**Table 10: Most Common Contraceptive Choices for Pregnant and Non-Pregnant PWCBP[a] Based on Monthly Interactions (iPLEDGE Years 12-16)**

| Most Common Contraceptive Choices[b] | | No. of Monthly Interactions With the iPLEDGE System, N (%) | | | | |
|---|---|---|---|---|---|---|
| Primary Contraceptive | Secondary Contraceptive | Year 12 (3/1/2017-2/28/2018) | Year 13 (3/1/2018-2/28/2019) | Year 14 (3/1/2019-2/29/2020) | Year 15 (3/1/2020-2/28/2021) | Year 16 (3/1/2021-12/10/2021) |
| **Pregnant FRP** | | | | | | |
| Birth control pills | Male latex condoms | 441 (56.7) | 454 (64.5) | 389 (61.5) | 325 (55.2) | 420 (61.7) |
| Abstinence | None | 143 (18.4) | 168 (23.9) | 162 (25.6) | 142 (24.1) | 127 (18.7) |
| **Non-Pregnant FRP** | | | | | | |
| Abstinence | None | 541,027 (43.9) | 574,075 (44.0) | 618,810 (43.7) | 699,334 (44.6) | 702,676 (46.2) |
| Birth control pills | Male latex condoms | 423,552 (34.4) | 447,957 (34.4) | 484,936 (34.2) | 522,960 (33.3) | 479,309 (31.5) |

Abbreviations: FRP, females of reproductive potential; PWCBP=Patients who can become pregnant.
[a] Patients were categorized as females of reproductive potential.
[b] Defined as any combination used by ≥10%.

During iPLEDGE Year 16, a total of 285,622 PWCBP had 315,279 COTs in which the Patient was qualified to receive drug at least once during the COT. To determine a change in primary contraception method, the report compares Patient contraception method choice selections for

each Patient prescription window in the report range when the Patient demonstrated comprehension. Table 11 shows days from last change in contraceptive method to pregnancy.

Of the 184 iPLEDGE pregnancies from iPLEDGE Year 16, 15 Patients made changes to their primary contraception choice before conception and 170 Patients made no changes to their primary contraception choices before conception (Table 11). These data are based on the contraception choices the Patient reported using when they became qualified to receive drug for a prescription window.

**Table 11: Primary Contraception Changes for Pregnant Patients (iPLEDGE Year 16)**

| From | To | Days Between Contraception Change and Pregnancy | No. of Patients |
|---|---|---|---|
| Birth Control Pills \| Male Latex Condom | Abstinence \| None | 126 | 1 |
| Vaginal Ring \| Male Latex Condom | Abstinence \| None | 118 | 1 |
| Natural Family Planning \| Withdrawal | Abstinence \| None | 101 | 1 |
| Non-Hormonal IUD \| Male Latex Condom | Hormonal IUD \| Male Latex Condom | 98 | 1 |
| Hormone Shot \| Male Latex Condom | Abstinence \| None | 82 | 1 |
| Non-Hormonal IUD \| Male Latex Condom | Hormonal IUD \| Male Latex Condom | 77 | 1 |
| Birth Control Pills \| Male Latex Condom | Abstinence \| Male Latex Condom | 66 | 1 |
| Progesterone-only Mini-pills \| Male Latex Condom | Birth Control Pills \| Male Latex Condom | 50 | 1 |
| Birth Control Pills \| Male Latex Condom | Abstinence \| None | 34 | 1 |
| Non-Hormonal IUD \| Male Latex Condom | Birth Control Pills \| Male Latex Condom | 34 | 1 |
| Hormonal IUD \| Male Latex Condom | Birth Control Pills \| Male Latex Condom | 33 | 1 |
| Hormonal IUD \| Male Latex Condom | Non-Hormonal IUD \| Male Latex Condom | 32 | 1 |
| Hormonal Patch \| Male Latex Condom | Birth Control Pills \| Male Latex Condom | 29 | 1 |
| Hormonal IUD \| Birth Control Pills | Birth Control Pills \| Hormonal IUD | 23 | 1 |
| Hormonal IUD \| Male Latex Condom | Non-Hormonal IUD \| Male Latex Condom | 13 | 1 |
| Birth Control Pills \| Male Latex Condom | No contraception change | | 103 |

| From | To | Days Between Contraception Change and Pregnancy | No. of Patients |
|---|---|---|---|
| Abstinence \| None | No contraception change | | 41 |
| Male Latex Condom \| Hormonal IUD | No contraception change | | 7 |
| Hormonal Patch \| Male Latex Condom | No contraception change | | 4 |
| Hormonal Implant \| Male Latex Condom | No contraception change | | 3 |
| Vaginal Ring \| Male Latex Condom | No contraception change | | 3 |
| Birth Control Pills \| Hormonal Patch | No contraception change | | 2 |
| Hormone Shot \| Male Latex Condom | No contraception change | | 2 |
| Birth Control Pills \| Hormonal IUD | No contraception change | | 1 |
| Birth Control Pills \| Hormonal Implant | No contraception change | | 1 |
| Male Latex Condom \| Non-Hormonal IUD | No contraception change | | 1 |
| Male Vasectomy \| Male Latex Condom | No contraception change | | 1 |
| Tubal Sterilization \| Male Latex Condom | No contraception change | | 1 |

Abbreviation: IUD=intrauterine device.

## 3.4 Pregnancies

### 3.4.1 Centralized Pregnancy Registry

The iPLEDGE Pregnancy Registry is a centralized, confidential registry for reporting, confirming, and follow-up of all pregnancies that occur in Patients who become pregnant while taking isotretinoin and within 30 days of their last dose. The objectives of this registry are to

1. Determine the isotretinoin exposure status for each reported pregnancy
2. Document the outcome for each pregnancy
3. Obtain additional information for each pregnancy to allow for evaluation of the underlying root cause(s)

An interview is conducted after the Patient becomes aware of the pregnancy and grants consent. Verbal or written consent from the Patient is required for follow-up with other HCPs.

These actions fit with the larger goal of the iPLEDGE REMS to prevent pregnancies in Patients taking isotretinoin by characterizing the reasons a Patient may have taken isotretinoin while pregnant.

The iPLEDGE Pregnancy Registry is notified of pregnancies by one or more of the following ways: entry of a positive pregnancy test or diagnosis of pregnant in the iPLEDGE REMS database; a call to the call center, which is then triaged to the Pregnancy Registry; a direct call to the Pregnancy Registry; or a discontinuation of a Patient in the iPLEDGE REMS due to a reason of pregnancy. Once the Pregnancy Registry has been notified, a trained representative collects information from the reporter (Patient, HCP, parent, Pharmacist, or other such person) on the status of the pregnancy. If any reporter is a Patient and when such Patient is called, consent is always requested before information collection begins (the iPLEDGE Pregnancy Registry adheres to 45 CFR part 46 and 21 CFR parts 50 and 56). Follow-up with reporters continues with 1 outreach per trimester until either no more information is available (case becomes lost to follow-up) or contributing reasons for the pregnancy (factors that lead to contraceptive failure) and outcome (defined as live birth, still birth, spontaneous abortion, elective termination, or ectopic pregnancy) are obtained. Follow-up also continues for up to 1 year after live birth. Pregnancies, and updates to each case, are reported to the manufacturing Sponsor within 1 business day of initial receipt by the Pregnancy Registry.

The Pregnancy Registry also includes a formal process to minimize the number of pregnancies lost to follow-up. This process includes a minimum of 3 telephone attempts to contact the initial reporter of the pregnancy. If the telephone attempts to the reporter are unsuccessful, a hard copy letter is sent to the reporter via traceable carrier within 10 days after the last telephone attempt was made. If all attempts to reach the reporter are unsuccessful, the same process is repeated with the Patient's secondary contact and with all HCPs for Patients who have consented to be contacted by the Pregnancy Registry. If no response has been received within 30 days of sending the last letter and the outcome and/or reason for the pregnancy is unknown, the pregnancy case is classified as lost to follow-up.

A written narrative is prepared once a case is closed. This document details demographic information including manufacturer of the product the Patient was taking at the time of conception. Additionally, the Pregnancy Registry attempts to capture the following information from various sources: first day of last menstrual period; approximate date of conception; date of pregnancy; exposure classification; registration dates; treatment start date; pregnancy test type and results; past gynecologic, medical and medication history prior to current pregnancy; pregnancy course; root causes; and outcomes. In addition to the narrative, the Pregnancy Registry team prepares descriptive statistics for all exposed or indeterminately exposed cases (non-exposed cases are not included in this statistical analysis). Some of the endpoints include timing of isotretinoin exposure relative to conception (during treatment or after treatment [within 30 days of last dose]), source of isotretinoin, reasons for pregnancy, pregnancy outcomes, and reasons for loss to follow-up.

### 3.4.2 iPLEDGE Pregnancies

Overall, 185 iPLEDGE Year 16 reportable pregnancies were recorded by the iPLEDGE Pregnancy Registry during the reporting period (Table 12). This is consistent with the rate of pregnancy observed in iPLEDGE Years 1-15 (Figure 4). Of the 185 pregnancies reported during iPLEDGE Year 16, 1 Patient did not have documented registration in the iPLEDGE system (Case 04692) and was classified as a non-iPLEDGE pregnancy, and 184 Patients had documented interactions in the iPLEDGE system and were classified as iPLEDGE pregnancies.

The number of pregnancies during iPLEDGE Year 16 compared with the 4 previous years is provided in Table 12. The Year 16 iPLEDGE pregnancy rate for PWCBP who had at least 1 RMA was 0.6 per 1000 (Table 13).

**Table 12: Total Number of Pregnancies (iPLEDGE Years 12-16)**

| Status | Year 12 (3/1/2017-2/28/2018) | Year 13 (3/1/2018-2/28/2019) | Year 14 (3/1/2019-2/29/2020) | Year 15 (3/1/2020-2/28/2021) | Year 16 (3/1/2021-12/10/2021) |
|---|---|---|---|---|---|
| iPLEDGE pregnancy | 185 | 193 | 186 | 189 | 184 |
| Non-iPLEDGE pregnancy | 2 | 2 | 4 | 3 | 1 |
| Total | 187 | 195 | 190 | 192 | 185 |

Definitions: 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.

**Table 13: iPLEDGE Pregnancy Rate for PWCBP[a] With at Least 1 RMA (iPLEDGE Years 12-16)**

| | Year 12 (3/1/2017-2/28/2018) | Year 13 (3/1/2018-2/28/2019) | Year 14 (3/1/2019-2/29/2020) | Year 15 (3/1/2020-2/28/2021) | Year 16 (3/1/2021-12/10/2021) |
|---|---|---|---|---|---|
| Number of FRP | 199,031 | 214,984 | 232,762 | 257,876 | 285,622 |
| Number of iPLEDGE Pregnancies during the reporting year | 185 | 193 | 174 | 168 | 184 |
| Pregnancy rate, % | 0.09 | 0.09 | 0.07 | 0.07 | 0.06 |
| Pregnant Patients per 1000 FRP with ≥1 RMA | 0.9/1000 | 0.9/1000 | 0.7/1000 | 0.7/1000 | 0.6/1000 |

Abbreviations: FRP=females of reproductive potential; PWCBP=Patients who can become pregnant; RMA=Risk Management Authorization.
[a] Patients were categorized as females of reproductive potential.

Isotretinoin exposure was classified for each pregnancy into categories:

- Exposed: A pregnancy in a PWCBP who has taken isotretinoin during the pregnancy or within 30 days prior to the date of conception
- Non-Exposed: A pregnancy in a PWCBP who has either not taken isotretinoin or taken isotretinoin more than 30 days prior to the date of conception
- Indeterminate Exposure: A pregnancy where fetal exposure to isotretinoin cannot be determined because the date of conception and/or the date(s) of isotretinoin exposure are unknown

The majority of these Year 16 iPLEDGE pregnancies (177 pregnancies; 96.2%) were classified as isotretinoin exposed (Table 14). A similar proportion of exposed pregnancies was seen in previous years.

**Table 14: iPLEDGE Pregnancies by Isotretinoin Exposure (iPLEDGE Years 12-16)**

| Isotretinoin Exposure, N (%) | Year 12 (3/1/2017-2/28/2018) (N=185) | Year 13 (3/1/2018-2/28/2019) (N=193) | Year 14 (3/1/2019-2/29/2020) (N=186) | Year 15 (3/1/2020-2/28/2021) (N=189) | Year 16 (3/1/2021-12/10/2021) (N=184) |
|---|---|---|---|---|---|
| Exposed | 179 (96.8) | 179 (92.7) | 182 (97.8) | 182 (96.3) | 177 (96.2) |
| Indeterminate exposure | 6 (3.2) | 14 (7.3) | 4 (2.2) | 7 (3.7) | 7 (3.8) |

Most of the PWCBP who had iPLEDGE pregnancies during iPLEDGE Year 16 were ≥20 years of age (Table 15). The highest number of pregnancies (116 pregnancies; 63.0%) occurred in Patients between the ages of 20 and 29 years. Most of the non-pregnant PWCBP in the program during Year 16 were between the ages of 16 and 19 years (32.2%) and 20 and 29 years (37.0%).

**Table 15: Ages of Pregnant and Non-Pregnant PWCBP[a] (iPLEDGE Year 16)**

| Age (years), N (%) | Year 16 (3/1/2021-12/10/2021) | |
|---|---|---|
| | Non-Pregnant FRP N=331,338 | Pregnant FRP[b] N=184 |
| <12 | 1610 (0.5) | 1 (0.5) |
| 12-15 | 45,240 (13.7) | 1 (0.54) |
| 16-19 | 106,767 (32.2) | 25 (13.6) |
| 20-29 | 122,588 (37.0) | 116 (63.0) |
| 30-39 | 38,981 (11.8) | 38 (20.7) |
| 40-44 | 9304 (2.8) | 2 (1.1) |
| 45+ | 6848 (2.1) | 1 (0.5) |

Abbreviation: FRP=females of reproductive potential; PWCBP=Patients who can become pregnant.
[a] Patients were categorized as females of reproductive potential.
[b] Pregnancy data for each year is as of the data cut-off date for each year.

### 3.4.3 Time of Conception

The timing of the date of conception relative to isotretinoin exposure was classified for each pregnancy into categories:

- Pregnancy occurred before starting isotretinoin: Patient conceived within 30 days prior to the first dose of isotretinoin and then subsequently took isotretinoin
- Pregnancy occurred during isotretinoin therapy
- Pregnancy occurred within 30 days after last dose: Patient conceived within 30 days after taking the last isotretinoin dose
- Unknown: Exposed or indeterminately exposed pregnancy, but the exact timing of exposure cannot be determined

The majority of iPLEDGE Patients (126 Patients; 68.5%) who became pregnant during iPLEDGE Year 16 conceived while taking isotretinoin (Table 16). Fourteen Patients (7.6%)

conceived prior to starting isotretinoin, and 16 Patients (8.7%) conceived within 30 days of stopping isotretinoin. These results are similar to the previous 4 years (Table 16).

**Table 16: Timing of Conception Relative to Isotretinoin Exposure (iPLEDGE Years 12-16)**

| Timing of Conception, N (%) | Year 12 (3/1/2017-2/28/2018) (N=185) | Year 13 (3/1/2018-2/28/2019) (N=193) | Year 14 (3/1/2019-2/29/2020) (N=186) | Year 15 (3/1/2020-2/28/2021) (N=189) | Year 16 (3/1/2021-12/10/2021) (N=184) |
|---|---|---|---|---|---|
| Before the start of isotretinoin | 9 (4.9) | 10 (5.2) | 17 (9.1) | 13 (6.9) | 14 (7.6) |
| While taking isotretinoin | 114 (61.6) | 118 (61.1) | 126 (67.7) | 136 (72.0) | 126 (68.5) |
| Within 30 days after isotretinoin completion | 21 (11.4) | 18 (9.3) | 11 (5.9) | 13 (6.9) | 16 (8.7) |
| Unknown[a] | 41 (22.2) | 47 (24.4) | 32 (17.2) | 27 (14.3) | 28 (15.2) |

[a] Includes indeterminate exposures.

Table 17 is populated based on a derived variable for fetal exposure (in days). The variable was derived using the following method

1. If isotretinoin was stopped prior to the conception date, the exposure duration is set to zero
2. If a discontinuation date cannot be determined or pregnancy outcome is prior to stop date, the exposure duration is calculated using the outcome date
3. If days on treatment (measured from start and stop dates) are less than the derived exposure days, the exposure duration is set to that number

When the stop date was missing, the outcome date was used because this is a more conservative approach to calculating fetal exposure.

Data collected by the iPLEDGE Pregnancy Registry indicate that the majority of pregnancies are being detected within the first 29 days of conception and that Patients are discontinuing isotretinoin on suspicion or detection of pregnancy. The methodology employed for this analysis identified 15 pregnancies with exposure potentially equaling or exceeding 30 days. Where a precise date of conception was unavailable, maximum potential exposure was recorded.

There were 184 exposed or indeterminately exposed iPLEDGE pregnancies in iPLEDGE Year 16, of which 124 had data on duration of exposure. The mean duration of exposure to isotretinoin was 17.4 days, and the median was 16.5 days. Duration of isotretinoin exposure was unknown for 60 (32.6%) Patients. Discontinuation of isotretinoin occurred before conception in 18 (9.8%) pregnancies, 1-14 days after conception in 32 (17.4%) pregnancies, 15-29 days after conception in 59 (32.1%) pregnancies, and 30 or more days after conception in 15 (8.2%) pregnancies (Table 17). The maximum known exposure was estimated at 60 days.

Information on maximum potential exposure could not be calculated for the 60 Patients with unknown duration of isotretinoin exposure.

**Table 17: Duration of Fetal Exposure to Isotretinoin (iPLEDGE Year 16)**

| Summary of Days Between Date of Conception and Discontinuation of Isotretinoin[a]: | (N=184) |
|---|---|
| Number of cases with known duration of exposure | 124 |
| Number of days of exposure to isotretinoin | |
| Mean (SD) | 17.4 (12.7) |
| Median (Min, Max) | 16.5 (0, 60) |
| **Number of Exposures With Days Between Date of Conception and Discontinuation of Isotretinoin:** | **No. of Exposures (N, %)** |
| 1-14 days | 32 (17.4) |
| 15-29 days | 59 (32.1) |
| ≥30 days | 15 (8.2) |
| Discontinued isotretinoin before conception[b] | 18 (9.8) |
| Unknown | 60 (32.6) |

Abbreviations: Max=maximum; Min=minimum; SD=standard deviation.
[a] If isotretinoin was discontinued prior to conception, the exposure days was set to zero.
[b] Conception occurred within 30 days following last dose of isotretinoin.

### 3.4.4 Reasons for Pregnancy

Table 18 details the reasons for pregnancy as reported by both Prescribers and Patients for iPLEDGE Years 12-16. The most common reasons for an iPLEDGE pregnancy during iPLEDGE Year 16, as reported by the Prescriber and the Patient, were not using 2 forms of birth control (30.4% and 5.4%, respectively), unsuccessful at abstinence (22.3% and 3.3%, respectively), and contraceptive failure (16.3% and 4.9%, respectively).

**Table 18: Reasons Reported by Prescribers and Patients for iPLEDGE Pregnancies (iPLEDGE Years 12-16)**

| | N (%) | | | | |
|---|---|---|---|---|---|
| Reason for Pregnancy[a] | Year 12 (3/1/2017-2/28/2018) (N=185) | Year 13 (3/1/2018-2/28/2019) (N=193) | Year 14 (3/1/2019-2/29/2020) (N=186) | Year 15 (3/1/2020-2/28/2021) (N=189) | Year 16 (3/1/2021-12/10/2021) (N=184) |
| **Prescriber** | | | | | |
| Did not use 2 forms of birth control | 65 (35.1) | 70 (36.3) | 48 (25.8) | 43 (22.8) | 56 (30.4) |
| Unsuccessful at abstinence | 34 (18.4) | 50 (25.9) | 49 (26.3) | 43 (22.8) | 41 (22.3) |
| Contraceptive failure[b] | 52 (28.1) | 17 (8.8) | 26 (14.0) | 38 (20.1) | 30 (16.3) |
| Failure to use contraceptive on date of conception | 2 (1.1) | 3 (1.6) | 7 (3.8) | 8 (4.2) | 3 (1.6) |
| Used ineffective contraception | 3 (1.6) | 2 (1) | 0 | 4 (2.1) | 3 (1.6) |
| Planned pregnancy | 0 | 1 (0.5) | 0 | 0 | 0 |
| Other | 1 (0.5) | 11 (5.7) | 6 (3.2) | 5 (2.6) | 9 (4.9) |

| Reason for Pregnancy[a] | N (%) | | | | |
|---|---|---|---|---|---|
| | Year 12 (3/1/2017-2/28/2018) (N=185) | Year 13 (3/1/2018-2/28/2019) (N=193) | Year 14 (3/1/2019-2/29/2020) (N=186) | Year 15 (3/1/2020-2/28/2021) (N=189) | Year 16 (3/1/2021-12/10/2021) (N=184) |
| Unknown[b] | 14 (7.6) | 37 (19.2) | 49 (26.3) | 44 (23.3) | 43 (23.4) |
| Missing | 16 (8.6) | 9 (4.7) | 9 (4.8) | 15 (7.9) | 15 (8.2) |
| **Patient** | | | | | |
| Did not use 2 forms of birth control | 16 (8.6) | 24 (12.4) | 20 (11.8) | 20 (10.6) | 10 (5.4) |
| Contraceptive failure[b] | 13 (7) | 13 (6.7) | 8 (4.3) | 16 (8.5) | 9 (4.9) |
| Unsuccessful at abstinence | 5 (2.7) | 7 (3.6) | 5 (2.7) | 5 (2.6) | 6 (3.3) |
| Failure to use contraceptive on date of conception | 0 | 0 | 0 | 0 | 0 |
| Possible drug interaction that may decrease effectiveness of hormonal contraceptives | 0 | 1 (0.5) | 3 (1.6) | 1 (0.5) | 0 |
| Used ineffective contraception | 0 | 0 | 0 | 0 | 0 |
| Planned pregnancy | 0 | 0 | 0 | 0 | 0 |
| Other | 2 (1.1) | 8 (4.1) | 8 (4.3) | 6 (3.2) | 5 (2.7) |
| Unknown[b] | 0 | 2 (1) | 2 (1.1) | 0 | 1 (0.5) |
| Missing | 158 (85.4) | 152 (78.8) | 150 (80.6) | 152 (80.4) | 159 (86.4) |

[a] Categories are not mutually exclusive; Patients may appear in multiple categories.
[b] No additional information provided.

### 3.4.5 Pregnancy Outcomes

Table 19 lists the outcomes for iPLEDGE pregnancies for iPLEDGE Years 12-16 with a cumulative total since the inception of the iPLEDGE REMS.

**Table 19: Pregnancy Outcomes for iPLEDGE Pregnancies**

| Pregnancy Outcome | Year 12 (3/1/2017-2/28/2018) (N=185) | Year 13 (3/1/2018-2/28/2019) (N=193) | Year 14 (3/1/2019-2/29/2020) (N=186) | Year 15 (3/1/2020-2/28/2021) (N=189) | Year 16 (3/1/2021-12/10/2021) (N=184) | Cumulative Since iPLEDGE REMS Inception (N=2720) |
|---|---|---|---|---|---|---|
| Number of outcomes[a] | **185** | **193** | **187** | **189** | **184** | **2724** |
| Elective termination | 81 | 81 | 88 | 74 | 62 | 1263 |
| Spontaneous abortion | 14 | 18 | 18 | 22 | 15 | 262 |
| Missed abortion | 0 | 1 | 2 | 1 | 1 | 17 |
| Ectopic pregnancy | 4 | 2 | 2 | 5 | 5 | 39 |

| Pregnancy Outcome | Year 12 (3/1/2017-2/28/2018) (N=185) | Year 13 (3/1/2018-2/28/2019) (N=193) | Year 14 (3/1/2019-2/29/2020) (N=186) | Year 15 (3/1/2020-2/28/2021) (N=189) | Year 16 (3/1/2021-12/10/2021) (N=184) | Cumulative Since iPLEDGE REMS Inception (N=2720) |
|---|---|---|---|---|---|---|
| Still birth | 0 | 0 | 0 | 0 | 0 | 2 |
| Live birth | 2 | 12 | 6 | 10 | 0 | 124 |
| Still continuing | 0 | 0 | 0 | 0 | 53 | 54 |
| Unknown | 8 | 7 | 7 | 4 | 5 | 44 |
| Lost to follow-up[b] | 76 | 72 | 64 | 72 | 43 | 919 |
| No response from HCP | 7 | 11 | 8 | 9 | 4 | 76 |
| Patient did not remain under HCP's care | 44 | 58 | 47 | 49 | 35 | 547 |
| HCP left practice | 0 | 0 | 0 | 0 | 0 | 0 |
| Patient refused to participate | 8 | 1 | 3 | 3 | 0 | 67 |
| No response from Patient | 3 | 2 | 2 | 2 | 0 | 109 |
| No pregnancy outcome | 10 | 0 | 3 | 7 | 4 | 94 |
| No information provided | 4 | 0 | 1 | 2 | 0 | 26 |
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 |
| Duplicate case | 0 | 0 | 0 | 0 | 0 | 0 |
| Not pregnant/false positive | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 | 0 |

Abbreviations: HCP=healthcare provider; REMS=Risk Evaluation and Mitigation Strategy.
[a] The number of outcomes includes multiple birth outcomes. Patients with multiples: Case # 01599 had 2 outcomes in Year 3, Case # 02431 had 2 outcomes in Year 7, Case # 03162 had 2 outcomes in Year 10, Case # 04048 had 2 outcomes in Year 14.
[b] Lost to follow-up includes cases where outcome is unknown and cases where outcome is known to have occurred but specifics surrounding outcome of pregnancy are unknown.

### 3.4.6 Risk Management Authorizations in Relation to iPLEDGE Pregnancies

The majority of the iPLEDGE pregnancies (150 of 184 pregnancies; 81.5%) during Year 16 occurred in PWCBP who had between 1 and 5 RMAs for isotretinoin during the COT in which the pregnancy occurred (Table 20).

**Table 20: Number of Risk Management Authorizations During the Course of Treatment in Which the Patient Became Pregnant (iPLEDGE Year 16)**

| RMAs During Course of Treatment | No. of iPLEDGE Pregnancies (N=184) |
|---|---|
| 0 | 1 |
| 1 | 45 |
| 2 | 22 |
| 3 | 25 |
| 4 | 32 |

| RMAs During Course of Treatment | No. of iPLEDGE Pregnancies (N=184) |
|---|---|
| 5 | 26 |
| 6 | 14 |
| 7 | 9 |
| 8 | 3 |
| 9 | 3 |
| 10 or more | 4 |

Abbreviation: RMA=Risk Management Authorization.

# 4.0 EVIDENCE THAT IPLEDGE IS MEETING ITS GOALS

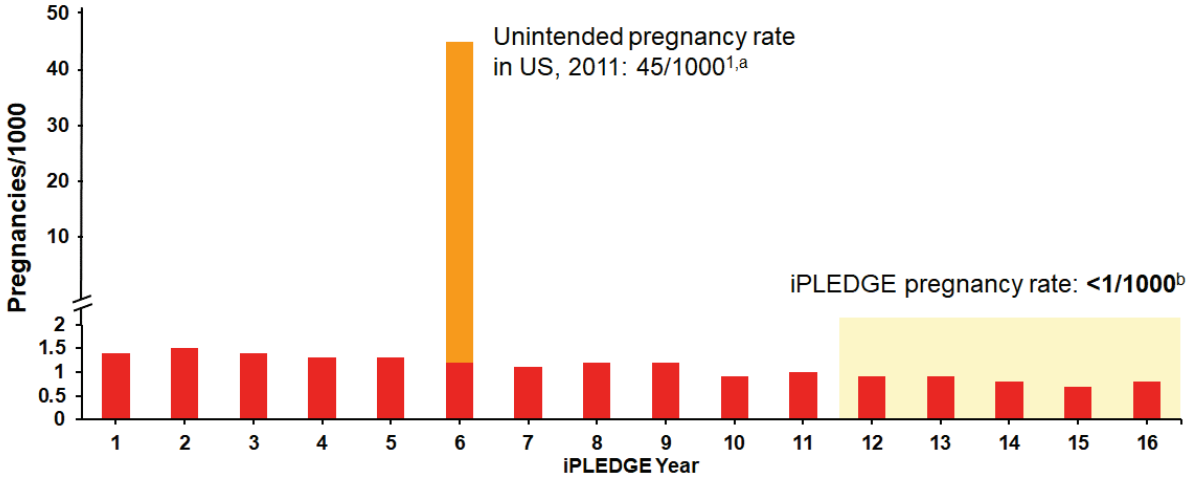
## 4.1 Pregnancy Rate Since iPLEDGE Launch

The iPLEDGE pregnancy rate for PWCBP demonstrates 16 years of consistency (Figure 4).[1] Since iPLEDGE Year 10, there has been less than 1 pregnancy per 1000 PWCBP who have received at least 1 RMA for isotretinoin through iPLEDGE.

In 2016, Finer and Zolna reported the overall rate of unintended pregnancy was 45 unintended pregnancies per 1000 women and girls (15-44 years of age) in the United States in 2011.[1] The total number of births in 2011 in the US population of women and girls aged 15-44 was obtained from the National Center for Health Statistics. Data on pregnancy intentions in this population were obtained from 2 nationally representative survey sources: the National Survey of Family Growth, and the 2008 Abortion Patient Survey conducted by the Guttmacher Institute.

While direct comparisons are not possible, the unintended pregnancy rate calculated by Finer and Zolna is based on a US study population of a similar age as those enrolled in iPLEDGE. These data suggest that the iPLEDGE pregnancy rate is far lower than the unintended pregnancy rate in the general US population.

**Figure 4: Pregnancies Per Thousand PWCBP Who Have Had at Least 1 RMA (iPLEDGE Years 12-16)**




Abbreviations: PWCBP=Patients who can become pregnant; RMA=Risk Management Authorization; US=United States.
[a] Women and girls 15-44 years of age in the US.
[b] PWCBP enrolled in iPLEDGE with at least 1 RMA.
[1] Finer LB and Zolna MR. *N Engl J Med*. 2016;374(9):843-852.

## 4.2 Occurrence of Pregnancy in Isotretinoin Users in Canada

While isotretinoin is widely used throughout the world, not all countries have adopted a program equivalent to iPLEDGE. Canada's pregnancy prevention program, for example, is education-based and is not a restricted distribution model for isotretinoin. It is less stringent than iPLEDGE in that it only requires informed written consent, 2 pregnancy tests with negative results before

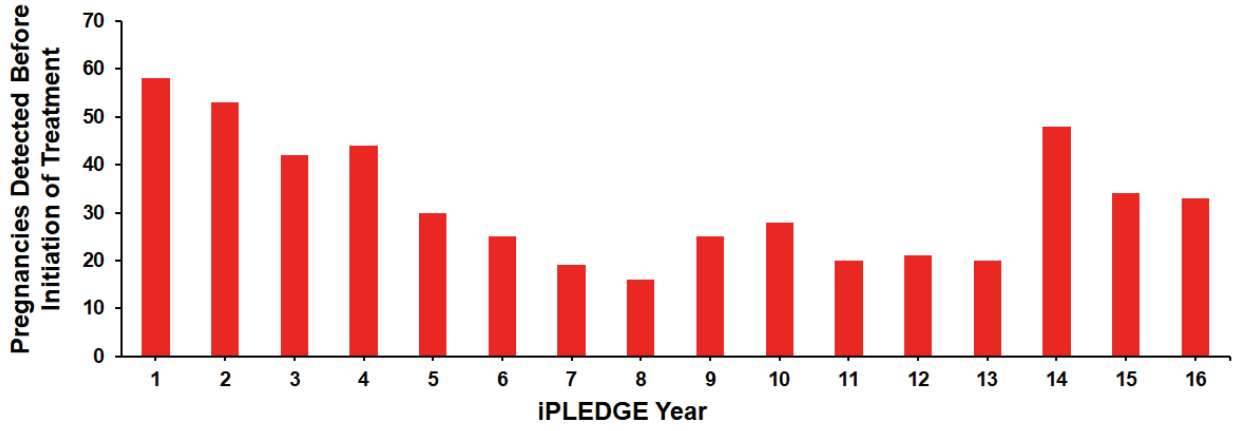
starting isotretinoin, and 2 reliable forms of contraception during treatment. Additionally, there is no system in place that monitors compliance with these requirements.

In 2016, Henry et al. published a study that estimated the frequency of pregnancy during and immediately after treatment with isotretinoin in a cohort of female isotretinoin patients aged 12-48 years in 4 provinces of Canada who had 1 or more isotretinoin prescriptions dispensed between 1996 and 2011.[3] There were 1473 pregnancies in the 59,271 female patients in the cohort (24.9/1000 users). Based on the timing of the pregnancy, pregnancy termination, or live birth, Henry et al. estimated the rate of pregnancy during isotretinoin treatment to be 16-24 pregnancies per 1000 female patients. The estimated rate of unplanned pregnancy in Canada is 50 pregnancies per 1000 female patients based on Statistics Canada data, leading the authors to conclude that the Canadian pregnancy prevention plan achieves an effectiveness of 50%-70%, which falls "short of the ideal when a potent teratogen is being ingested."[3]

### 4.3 Prevention of Fetal Exposure to Isotretinoin

A total of 33 pregnancies were detected by the iPLEDGE REMS before the initiation of isotretinoin treatment during iPLEDGE Year 16, thereby preventing isotretinoin-exposed pregnancies (Figure 5). All of these PWCBP 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. iPLEDGE has detected and prevented at least 516 pregnancies from exposure to isotretinoin during iPLEDGE Years 1-16. Note that these counts of non-exposed pregnancies may only represent a portion of the cumulative non-exposed pregnancies during this timeframe as there was no requirement for Prescribers to report non-exposed pregnancies prior to December 2021.

**Figure 5: Pregnancies Detected by iPLEDGE Before Initiation of Isotretinoin Treatment (iPLEDGE Years 1-16)**




### 4.4 Detection of Pregnancies During the 19-Day Wait

When a PWCBP misses their first prescription because the 7-day prescription window has expired, the Patient is required to wait at least 19 days between the previous pregnancy test (i.e., the beginning of the 7-day prescription window) and the next confirmatory pregnancy test

(which must also be negative) to proceed with the subsequent requirements that allow them to become qualified to receive drug. Coupled with the requirement that the Patient's first confirmatory negative pregnancy test be conducted during the first 5 days of the Patient's menstrual cycle, the 19-day wait is essential to prevent fetal exposure to isotretinoin at the time when the Patient is most fertile.

During iPLEDGE Year 16, 3 pregnancies were detected during the 19-day wait. Since iPLEDGE Year 12, a total of 12 pregnancies have been detected during the 19-day wait, preventing fetal exposure to isotretinoin (Table 21).

**Table 21: PWCBP Who Entered a 19-Day Wait and Had an iPLEDGE-Detected Pregnancy Prior to Isotretinoin Exposure (iPLEDGE Years 12-16)**

| Timing of Conception | Year 12 (3/1/2017-2/28/2018) | Year 13 (3/1/2018-2/28/2019) | Year 14 (3/1/2019-2/29/2020) | Year 15 (3/1/2020-2/28/2021) | Year 16 (3/1/2021-12/10/2021) |
|---|---|---|---|---|---|
| PWCBP who obtained an RMA | 96,956 | 105,903 | 114,550 | 127,609 | 104,571 |
| PWCBP who entered a 19-day wait | 15,467 | 16,483 | 17,234 | 18,190 | 18,506 |
| PWCBP who entered 19-day wait and had an iPLEDGE-detected pregnancy prior to isotretinoin exposure | 0 | 5 | 3 | 1 | 3 |

Abbreviations: PWCBP=Patients who can become pregnant; RMA=Risk Management Authorization.

## 4.5 Understanding of the iPLEDGE REMS

### 4.5.1 Patient Knowledge

During the first month that a PWCBP interacts with the iPLEDGE REMS system, the Patient is asked a series of questions to determine if 1) the Patient reviewed the Patient educational materials, and 2) the Patient was advised to avoid pregnancy and received birth control counseling. These questions, referred to as the baseline survey, are only asked for the first isotretinoin prescription.

For the first and all subsequent months of isotretinoin therapy, the PWCBP 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.

More than 95% of non-pregnant Patients and more than 96% of pregnant Patients 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 in iPLEDGE Year 16 (Table 22).

**Table 22: Patient Monthly Comprehension Tests: Use of Contraception and Risk of Birth Defects (iPLEDGE Years 12-16)**

| | n (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Year 12 | | Year 13 | | Year 14[a] | | Year 15[a] | | Year 16[a] | |
| | Non-Pregnant N=250,535 | Pregnant N=173 | Non-Pregnant N=161,085 | Pregnant N=106 | Non-Pregnant N=176,012[b] | Pregnant N=111[b] | Non-Pregnant N=195,544 | Pregnant N=115 | Non-Pregnant N=163,369 | Pregnant N=108 |
| Passed first time | 221,726 (88.5) | 147 (85.0) | 153,322 (95.2) | 97 (91.5) | 168,431 (95.7) | 104 (93.7) | 187,869 (96.1) | 109 (94.8) | 156,462 (95.8) | 104 (96.3) |
| No. of failures in an isotretinoin treatment course | | | | | | | | | | |
| 1 failure | 22,954 (9.2) | 22 (12.7) | 7447 (4.6) | 9 (8.5) | 7467 (4.2) | 7 (6.3) | 7613 (3.9) | 6 (5.2) | 6818 (4.2) | 4 (3.7) |
| 2 failures | 4201 (1.7) | 3 (1.7) | 263 (0.2) | 0 | 111 (0.1) | 0 | 60 (<0.1) | 0 | 79 (<0.1) | 0 |
| >2 failures | 1823 (0.7) | 1 (0.6) | 53 (<0.1) | 0 | 3 (0) | 0 | 2 (0) | 0 | 10 (<0.1) | 0 |
| Mean number of failures | 1.34 | 1.19 | 1.05 | 1 | 1.02 | 1 | 1.01 | 1 | 1.01 | 1 |

Abbreviation: COT=course of treatment.

[a] Not all Patients answered the required monthly questions.

[b] In previous reports, a first comprehension test within a COT was counted from any COT that overlapped with the assessment period, even if the comprehension test occurred in a previous assessment period. Starting with the iPLEDGE Year 14 Report, first comprehension tests were only counted if the comprehension test occurred within the assessment period. This resulted in a lower number of first comprehension tests being reported.

### 4.5.2 Prescriber Knowledge

In iPLEDGE Year 15, a survey of Prescriber Knowledge, Attitudes, and Behaviors was conducted to assess Prescribers' understanding of the iPLEDGE REMS requirements, their role in the program, and the safe use of isotretinoin. A total of 13,146 Prescribers who had registered and activated with the iPLEDGE REMS, regardless of whether their reactivation date occurred during the survey period, were identified in the iPLEDGE REMS system as of December 3, 2020. In an effort to ensure that the target sample was demographically representative of all Prescribers registered and activated in the iPLEDGE REMS (i.e., medical specialty, credentials, and geographic region), 3 stratified random samples were generated prior to survey launch. A total of 311 eligible Prescribers who made up a demographically diverse survey population completed the survey.

As shown by the high comprehension rate for each of the key risk messages, the goals of the iPLEDGE REMS were met. Correct response rates exceeded 80% for 34 of the 40 questions/items of the 4 key risk messages as shown in Table 23.

**Table 23: Prescriber Knowledge, Attitudes, and Behaviors of iPLEDGE REMS**

| Key Risk Message | Unadjusted Demonstrated Understanding Rate[a] N=311[b] n (% [95% CI])[c] |
|---|---|
| 1) The Prescriber must know the risk and severity of fetal injury/birth defects from isotretinoin. | 309 (99.4 [97.7, 99.9]) |
| 2) Prescribers should understand the iPLEDGE REMS requirements regarding pregnancies. | 262 (84.2 [79.7, 88.1]) |
| 3) Prescribers should understand the effective measures for avoidance of unplanned pregnancy. | 250 (80.4 [75.5, 84.7]) |
| 4) Prescribers must comply with the iPLEDGE Program requirements described in the booklets entitled *The Guide To Best Practices For the iPLEDGE Program and The iPLEDGE Program Prescriber Contraception Counseling Guide*. | 275 (88.4 [84.3, 91.8]) |

Abbreviations: CI=confidence interval; REMS=Risk Evaluation and Mitigation Strategy.
[a] Unadjusted rates have not been adjusted for medical specialty and geographic region.
[b] Number of eligible Prescribers completing the survey.
[c] Exact binomial 2-sided 95% CIs are calculated using the Clopper-Pearson method.

## 4.6 Prescriber Satisfaction With the iPLEDGE REMS

The iPLEDGE REMS Sponsors conducted research to assess Prescriber experience and attitudes associated with the iPLEDGE REMS requirements. This research provided qualitative feedback regarding the proposed major modifications submitted to the FDA in November 2022.

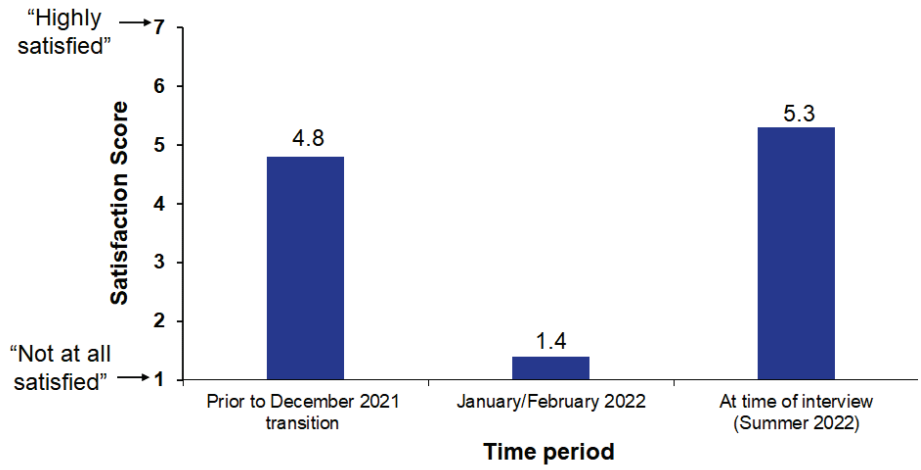
A total of 39 community-based Prescribers who actively prescribe isotretinoin were recruited, with the majority being dermatologists (n=31, Dermatologists [MD, DO]; n=4, Physician Assistants; n=4, Nurse Practitioners). All Prescribers met the criteria of working in the United States (excluding Vermont), being in practice for ≥2 years, working in a qualified role in a

dermatology practice, seeing ≥150 Patients per month, and treating ≥10 Patients per month for acne. Qualitative interviews were performed in September and October of 2022. The interviews were 45-minutes in length and conducted by telephone.

Prescribers were asked to rate the effectiveness and usability of iPLEDGE REMS on a scale of 1-7, with 1 being not at all effective and 7 being extremely effective. The Prescribers rated the effectiveness of iPLEDGE REMS in achieving its stated goals of preventing fetal exposure to isotretinoin at an average score of 5.2 and informing HCPs and Patients of isotretinoin's serious risks and safe-use conditions at an average score of 5.6. Prescribers rated the usability of the iPLEDGE REMS system at an average score of 4.5 out of 7 (data not shown).

The interviews explored Prescriber attitudes surrounding the 2021 system modification, which resulted in changes to the stakeholder-facing system and challenges with logging in and enrolling new Patients and allowing existing Patients to continue treatment. Figure 6 shows the satisfaction ratings for using the iPLEDGE REMS prior to December 2021, during the modification roll-out (January/February of 2022), and at the time of the survey (September and October of 2022). Qualitative assessment based on survey responses indicated that prior to the 2021 system modification Prescribers were familiar with the iPLEDGE REMS system and were moderately content with how it was functioning (an average score of 4.8). Satisfaction scores were much lower during the modification roll-out (January/February 2022) while implementation challenges were ongoing and actively being resolved. At the time of the survey, Prescribers rated their satisfaction with the system as comparable to before the system modification roll-out, indicating a return to normal.

**Figure 6: Prescriber Satisfaction of Using the iPLEDGE REMS Before, During, and After the 2021 System Modification**




Abbreviation: REMS=Risk Evaluation and Mitigation Strategy.

Prescribers were also surveyed on their perspective on the proposed modifications, including reinstatement of the Patient calendar functionality, addition of Designee-initiated Patient enrollment, and an extended confirmation interval of 120 days for PWCNBP. These modifications were generally characterized as positive changes that would reduce burden and improve ease of use of the iPLEDGE REMS system.

# 5.0 MODIFICATIONS TO THE IPLEDGE REMS

## 5.1 Summary of Approved iPLEDGE REMS Modifications

The ETASUs and requirements of the iPLEDGE REMS have not changed since its 2010 approval in 2010. Ongoing analysis of the REMS and consideration of stakeholder feedback have led to implementation of modifications to enhance the ease of use for stakeholders without affecting Patient safety. Table 24 outlines the details of previously approved modifications.[4]

**Table 24: Summary of Approved iPLEDGE REMS Updates (2012-2022)**

| Date | Summary of Change |
|---|---|
| October 22, 2010 | Approval of the iPLEDGE REMS Program |
| April 12, 2012 | Modified to<br>• Remove "Accutane" and "Roche" from the iPLEDGE materials<br>• Relocate the Non-Compliance Action Policy from the REMS document into the REMS supporting documents<br>• Relocate the following iPLEDGE website screen shots from the REMS document into the REMS supporting documents:<br>– iPLEDGE website Prescriber web pages<br>– iPLEDGE website Pharmacy web pages<br>– iPLEDGEprogram.com home page<br>• Relocate the "What's New" document from the REMS document to the REMS supporting document<br>• Remove references to specific brand names, and respective Sponsor names, for isotretinoin from the REMS educational materials<br>• Revise the "Effective Date" on the REMS educational materials to reflect the approved REMS modification approval date<br>• Make editorial changes to the Medication Guide |
| September 3, 2015 | Modified to<br>• Change the Request for Exemption for Patients with Serious Medical Reasons form as follows:<br>– Use of the Tanner Staging to classify Female Patients of Non-Childbearing Potential (FNCBP)<br>– Add an attestation requiring Prescribers to evaluate Patient reproductive status while receiving isotretinoin, and notify the iPLEDGE program within 10 business days of any change in the Patient's reproductive status<br>– Revise the Female Patients of Childbearing Potential (FCBP) exemption category to reflect that use of the Request for Exemption for Patients with Serious Medical Reasons is only for the first month of isotretinoin therapy<br>– Add an attestation to the monthly comprehension testing exemption category to reflect that Patients are still required to successfully complete monthly pregnancy testing |

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| | • Standardize the terminology for female Patients of childbearing potential in the REMS document, and appended REMS materials to "Females of Reproductive Potential (FRP)" and "Females of Non-Reproductive Potential (FNRP)," where applicable |
| February 4, 2016 | Modified to<br>• Add a Notice to Deter Patient Misclassification on select Prescriber and Designee screens to increase awareness and compliance with the appropriate classification of Female Patients of Reproductive Potential on the iPLEDGE Website<br>• Remove the Sponsor addresses from the Pregnancy Registry Protocol title page in the Appended Materials |
| July 8, 2016 | Modified to<br>• Make minor typographical and formatting changes<br>• Add the iPLEDGE Terms of Use text, which includes the Privacy Statement<br>• Add the following statement in the Interactive Voice Recognition System (IVRS) public prompts for all stakeholders: "I understand and will comply with the iPLEDGE Terms of Use and Non-Compliance Action Policy. The iPLEDGE Terms of Use and the Non-Compliance Action Policy are available at www.ipledgeprogram.com"<br>• Add a button to the www.ipledgeprogram.com website home page, "For Office Staff Designees"<br>• Add "Find a Patient" functionality for Pharmacies. This link will be accessible via the Pharmacy menu, post-login<br>• Change the Date of Personal Significance (DOPS) Entry to prepopulate the DOPS field with forward slashes "/" and prompt users with MM/DD/YYYY |
| June 17, 2017 | Modified to<br>• Provide for implementation of a REMS Pharmacy Network and use of an electronic verification system for iPLEDGE Program certified Pharmacies to request and receive a Risk Management Authorization (RMA) directly through the prescription claim adjudication process workflow at the point of dispensing an isotretinoin prescription<br>• Provide for the changes made to the REMS educational materials to streamline and improve clarity |
| April 23, 2018 | Modified to<br>• Add a new Sponsor<br>• Remove a product name (which is no longer available)<br>• Update a name change for a Sponsor<br>• Bold text to highlight "The Do Not Dispense After Date"<br>• Replace radio buttons and a table with drop down menus and editorial changes for consistency by aligning the list of birth control |

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| | methods options with the listing on the approved Birth Control Information Sheet |
| January 24, 2020 | Modified to make changes to the Medication Guide, an element of the iPLEDGE REMS. This modification does not provide for any changes to the REMS document, appended materials, or REMS supporting document. |
| December 9, 2020 | Modified to remove specific product information tables of currently approved isotretinoin products from the REMS@FDA Website Screenshots. |
| October 8, 2021 | Modified to<br>• Remove the Medication Guide as an element of the Risk Evaluation and Mitigation Strategy (REMS)<br>• Make changes to the REMS document and appended materials to align with labeling changes related to gender-neutral Patient risk categories<br>• Make changes to the REMS appended materials to reduce redundancy and streamline the content<br>• Make changes to the Pharmacy operations to verify safe-use conditions for the REMS Risk Management Authorization<br>• Add an optional quick reference (QR) code for use by Patients enrolled in the REMS<br>• Convert the REMS Document to the new, standardized form and modified to<br>– Make changes to the REMS document to include a requirement for Pharmacies and Wholesalers to comply with audits. This change is intended to align with the respective enrollment forms<br>– Make changes to the Non-Compliance Action Policy including updates to add a new non-compliance action for failure to comply with audit requirements for Pharmacies and Wholesalers |
| October 6, 2022 | Modified to<br>• Make changes to the REMS document to include a requirement for Pharmacies and Wholesalers to comply with audits. This change is intended to align with the respective enrollment forms<br>• Make changes to the Non-Compliance Action Policy including updates to add a new non-compliance action for failure to comply with audit requirements for Pharmacies and Wholesalers |

Abbreviation: REMS=Risk Evaluation and Mitigation Strategy.
Isotretinoin iPLEDGE REMS (Update History).[4]

## 5.2 Website Updates Implemented Following the December 2021 Transition

Following the December 2021 transition, technical enhancements were implemented to facilitate access to and use of the iPLEDGE REMS website (Table 25).

**Table 25: Website Updates Implemented**

| Website Section | Description |
|---|---|
| Prescriber \| Patient Enrollment Screen | Addition of Informed Consent(s) PDFs for Prescribers to download/print in order to obtain signed, paper informed consents. |
| Prescriber \| Manage Patients Screen | Addition of Get Login Link function: send a login link directly to Patients and Designees to facilitate iPLEDGE REMS access. |
| Public Site \| Troubleshooting Tips | New Page after selection of Troubleshooting Tips button: PDF available for each stakeholder with most common website questions: individual documents for Patient, Prescriber, Designee, and Pharmacy. |
| Public \| Manage Account | Forgot Username? and Forgot DOPS? added to Manage Account Updates to facilitate iPLEDGE REMS access. |

Abbreviations: DOPS=date of personal significance; PDF=portable document format; REMS=Risk Evaluation and Mitigation Strategy.

## 5.3 Proposed Major REMS Modifications

After careful consideration, the iPLEDGE Sponsors submitted a Major REMS Modification in November 2022 that included 4 proposed modifications that will reduce stakeholder burden yet maintain the safe use of isotretinoin. These proposed changes are detailed in the sections below.

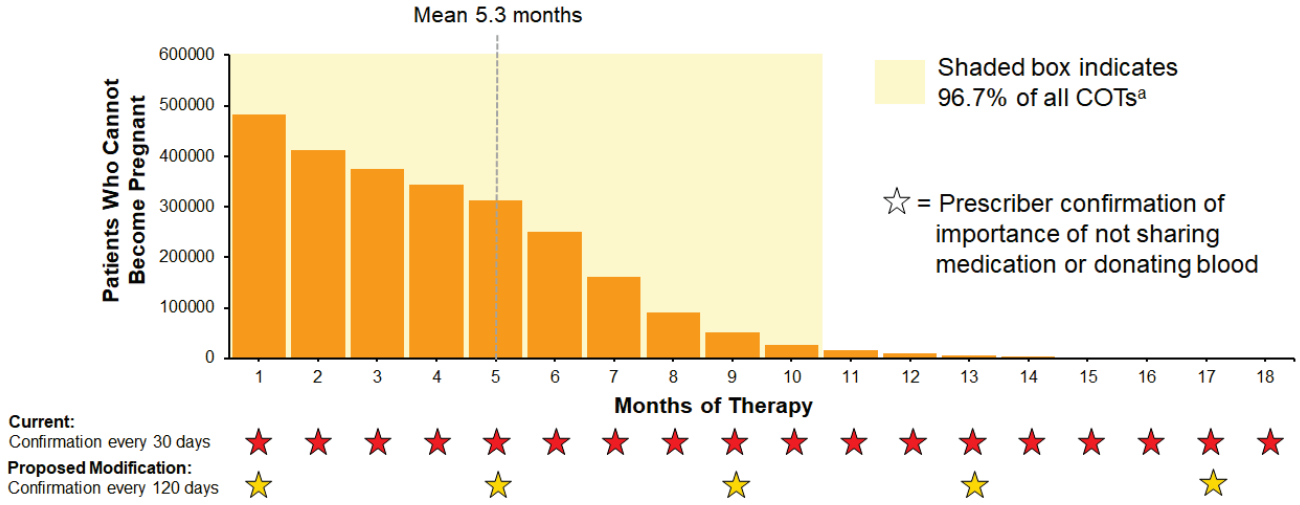
### 5.3.1 Extension of the Confirmation Interval for PWCNBP to 120 Days

The iPLEDGE Sponsors proposed to extend the confirmation interval for PWCNBP to be qualified to receive isotretinoin to every 120 days, rather than the current 30 days (Figure 3). This would relieve the Prescriber of the burden of monthly confirmations.

Figure 7 shows the number of PWCNBP and how many total months of therapy they received in iPLEDGE Year 16. Most Patients are treated for at least 1-2 months, with the mean duration of treatment being 5.3 months. In all, 96.7% of Patients complete therapy within 10 months. The current confirmation interval of every 30 days is illustrated in Figure 7 with red stars; the proposed extended confirmation interval of every 120 days is illustrated with yellow stars.

Based on isotretinoin labeling, which clearly defines the typical COT to be 15-20 weeks, the Sponsors believe a 120-day (~17-week) confirmation interval is appropriate. As stated in the INDICATIONS AND USAGE section of the label: A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many Patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that Patients may continue to improve while off isotretinoin.

**Figure 7: Proposed Extension of Confirmation Interval for PWCNBP**




Abbreviations: COT=course of treatment; PWCNBP=Patients who cannot become pregnant.
[a] COTS for PWCNBP ranged from 1 to 178 months in Year 16.

At each confirmation, the timing for the next required confirmation for PWCNBP will be 120 days. The ability to confirm PWCNBP on a monthly cadence will remain for those Prescribers who want to do so, but it will not be required. The prescription for PWCNBP will remain at no more than a 30-day supply. The requirement for Prescribers to counsel their Patients with each month's prescription will remain. All other REMS requirements for both the Patient and the Prescriber will remain unchanged.

### 5.3.2 Enrollment Enhancements for Designees and Prescribers

The iPLEDGE Sponsors proposed an enhanced enrollment process that will allow a Designee to log in and start enrollments on behalf of the Prescriber. This would relieve the Prescriber of the burden of entering all the enrollment information.

A Designee will be able to enter all enrollment information (including pregnancy test results and Patient categorization). Enrollments can be saved at any time in the process for later completion. To complete the enrollment process, the Prescriber will need to log in and attest that the information is correct, complete the informed consent(s) with the Patient, and provide an electronic signature.

The Prescriber will be able to enter all enrollment information, access pending Patient enrollments, review and confirm the Designee entries, and save and continue for later completion.

Checks will be added to the New Patient Enrollment Process to prevent the creation of duplicate Patient profiles. This will provide the end user with the ability to see previously entered Patients with matching First Name/Last Name/Date of Personal Significance associated with the Prescriber.

### 5.3.3 Calendar Functionality

The iPLEDGE Sponsors proposed to reinstate the calendar functionality on the iPLEDGE REMS website. This would improve the user interface and better communicate the COT for PWCBP.

A Patient Calendar will be added to the Patient Profile screen, which will provide a graphical view of the COT and requirements for an individual Patient. This will be visible to Patients, Prescribers, and their Designees.

### 5.3.4 Website Updates

Data entry errors can lead to delays for Patients receiving drug. The iPLEDGE Sponsors have proposed website text changes for Prescribers and Designees that are designed to help minimize these delays.

## 5.4 Elements of the iPLEDGE REMS That Should Be Preserved

The iPLEDGE Sponsors believe that the iPLEDGE REMS elements related to several "waiting periods" must be preserved to assure the safe use of isotretinoin.

### 5.4.1 30-Day Wait

The initial 30-day wait requirement prior to initiating isotretinoin therapy allows enough time for approved contraception methods to become effective and to ensure that PWCBP are not pregnant when they initiate treatment.

A PWCBP must have a negative pregnancy test and be on 2 forms of contraception, or remain abstinent, for at least 30 days prior to their first prescription. This 30-day wait provides time for the Patient to select and initiate contraception choices and provides time for these to become fully effective. After this waiting period, and during the first 5 days of the Patient's menstrual cycle, a confirmatory pregnancy test is to be obtained. If the confirmatory pregnancy test is negative, the Patient can be confirmed by the Prescriber to receive drug. Once confirmed, the Patient has 7 days to interact with the website and complete comprehension questions and confirm their 2 forms of birth control or abstinence. At that point, the Pharmacy can receive an authorization (RMA) to dispense the prescription for isotretinoin, provided the Patient is still in their 7-day window.

In iPLEDGE Year 16, 33 pregnancies were identified during the 30-day wait or with the confirmatory pregnancy test (see Section 4.3, Figure 5). Therefore, some wait period is necessary to minimize the risk of exposure. A 30-day wait has been standard, and the low rates of pregnancy in the iPLEDGE REMS support continuing this waiting period. Eliminating this waiting period will increase the risk of fetal exposure to isotretinoin.

The iPLEDGE Sponsors do not support modifying this requirement as it may increase the risk of fetal exposure to isotretinoin because not all birth control is immediately effective and because there is a risk that pregnancy tests may produce false-negative results if obtained shortly after conception. Therefore, the iPLEDGE Sponsors believe the 30-day wait must remain in place.

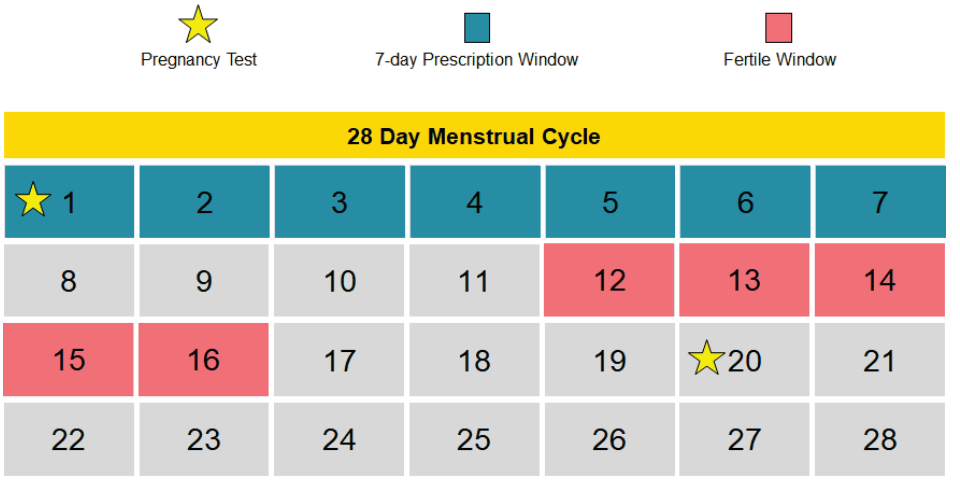
### 5.4.2 19-Day Wait

The 19-day wait requirement allows the next confirmatory pregnancy test to be completed after the most fertile period of the menstrual cycle has passed. This ensures the Patient does not receive and start taking drug during that most fertile period.

A PWCBP must have a negative pregnancy test and be on 2 forms of contraception, or remain abstinent, for at least 30 days prior to their first prescription. After this waiting period, and during the first 5 days of the Patient's menstrual cycle, a confirmatory pregnancy test is to be obtained. If the confirmatory pregnancy test is negative, the Patient can be confirmed by the Prescriber to receive drug. Once confirmed, the Patient has 7 days to interact with the website and complete comprehension questions and confirm their 2 forms of birth control or abstinence. At that point, the Pharmacy can receive an authorization (RMA) to dispense the prescription for isotretinoin provided, the Patient is still in their 7-day window.

If the Patient does not complete these activities and obtain their prescription within the 7-day window, they are required to wait 19 days after the first day of the 7-day prescription window (i.e., the most recent pregnancy test). After the 19-day waiting period, the Patient must have another negative confirmatory pregnancy test for the process to continue (Figure 8).

**Figure 8: Medical Rationale for the 19-Day Wait**




During iPLEDGE Year 16, 3 pregnancies were detected during the 19-day wait and cumulatively, 12 pregnancies were detected in iPLEDGE Years 12-16 (see Section 4.4, Table 21), preventing fetal exposure to isotretinoin. Therefore, the iPLEDGE Sponsors believe the 19-day wait must remain in place.

### 5.4.3 30-Day Abstinence Switch Wait

The Abstinence Switch wait requires a PWCBP who chooses to switch their birth control from abstinence to 2 forms of approved contraception to wait 30 days before they can continue isotretinoin. Additionally, they must have a negative confirmatory pregnancy test completed prior to receiving their next prescription for isotretinoin. This is designed to ensure that Patients who are changing their birth control methods do not become pregnant during this vulnerable transition period.

If a PWCBP chooses to switch birth control from abstinence to 2 forms of contraception, they are treated like a newly starting Patient. The Patient is required to initiate and use the 2 forms of contraception for 30 days and then have a negative confirmatory pregnancy test completed prior to receiving their next prescription for isotretinoin.

Not all birth control is immediately effective, and pregnancy tests may produce false-negative results if obtained shortly after conception. Therefore, some wait period is necessary when changing from abstinence to 2 forms of contraception. A wait period of 30 days has been the requirement since the beginning of iPLEDGE, and the low rates of iPLEDGE pregnancies support continuing this requirement. Eliminating this waiting period would increase the risk of fetal exposure to isotretinoin. Therefore, the iPLEDGE Sponsors believe the 30-day Abstinence Switch wait must remain in place.

### 5.4.4 CLIA Testing

As a result of the COVID-19 Public Health Emergency (PHE) and guidance provided by FDA, the iPLEDGE REMS relaxed the requirement for a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory confirmed pregnancy test and allowed at-home pregnancy tests to be performed by iPLEDGE Patients.

It is important to note that there have been reported limitations of at-home pregnancy tests, which include

- Deliberate falsification of results occurring at an unacceptable rate[5]
- At-home pregnancy tests and consumer interpretation of results can be unreliable[6]

A recently published survey found clinicians expressed interest in continuing to use telemedicine and home pregnancy testing to care for patients with acne treated with isotretinoin.[2] However, in that survey, 27% of clinicians expressed concern about the accuracy of the tests, 26% expressed concern about the ability to interpret the tests appropriately, and 56% expressed concern about patient deception.

The iPLEDGE Sponsors remain agreeable to allowing the use of at-home pregnancy tests as long as the declared PHE remains in effect, but do not support the use of at-home pregnancy tests beyond the PHE due to these challenges.

# 6.0 IPLEDGE REMS DEMONSTRATES A POSITIVE BENEFIT/RISK IN THE PREVENTION OF FETAL EXPOSURE TO ISOTRETINOIN

The iPLEDGE system is meeting its goals of preventing fetal exposure to isotretinoin, and informing Prescribers, Pharmacists, and Patients about the serious risks and safe-use conditions of isotretinoin. This is evidenced by very low pregnancy rates, prevention of pregnant Patients from receiving drug, and high comprehension and understanding of the safe use of isotretinoin.

Due to ETASUs in place by the iPLEDGE REMS, the overall pregnancy rate during iPLEDGE Years 1-16 was ~1/1000 PWCBP and had ≥1 RMA. Additionally, at least 516 pregnant Patients were prevented from receiving drug prior to initiation of therapy in iPLEDGE Years 1-16.

The iPLEDGE Sponsors submitted a Major REMS Modification in November 2022 that included 4 proposed modifications that will reduce stakeholder burden yet maintain the safe use of isotretinoin:

1. Extend the confirmation interval for Patients Who Cannot Become Pregnant (PWCBP) to every 120 days, rather than every 30 days
2. Implement an enhanced enrollment process that will allow Designees to enter all initial enrollment information prior to Prescriber attestation
3. Reinstate the calendar functionality to improve the Patients Who Can Become Pregnant (PWCBP) iPLEDGE REMS user interface
4. Implement iPLEDGE REMS website text changes for Prescribers and Designees designed to help minimize delays in Patients receiving isotretinoin

The iPLEDGE REMS helps to ensure that the benefits of isotretinoin outweigh its risks. Any proposed modification must be carefully weighed against the potential impact on the safe use of isotretinoin and must preserve the foundational principles of the iPLEDGE REMS, which are to prevent pregnancies in Patients taking isotretinoin and to prevent pregnant Patients from receiving a prescription for isotretinoin.

## 7.0 REFERENCES

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