FDA Briefing Document

Risk Evaluation and Mitigation Strategy (REMS) for Isotretinoin Products "iPLEDGE REMS"

Combined Meeting of the Drug Safety and Risk Management Advisory Committee and Dermatologic and Ophthalmic Drugs Advisory Committee

March 28-29, 2023

Division of Risk Management/Office of Risk Management and Medication Error Prevention

and

Division of Dermatology and Dentistry/Office of Immunology and Inflammation

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Glossary

AC	Advisory Committee
BD	Briefing Document
CDER	Center for Drug Evaluation and Research
CLIA	Clinical Laboratory Improvement Amendments of 1988
DODAC	Dermatologic and Ophthalmic Drugs Advisory Committee
DSaRM	Drug Safety and Risk Management Advisory Committee
ETASU	Elements To Assure Safe Use
FDA	Food and Drug Administration
FCBP	Females of Childbearing Potential
FRP	Females of Reproductive Potential
FNCP	Females Not of Childbearing Potential
FNRP	Females of Non-Reproductive Potential
hCG	Human Chorionic Gonadotropin
HCP	Healthcare Provider
iPLEDGE	Isotretinoin REMS
IPMG	Isotretinoin Products Manufacturer Group
KAB	Knowledge Attitude and Behavior survey
PHE	Public Health Emergency
RCA	Root Cause Analysis
REMS	Risk Evaluation and Mitigation Strategy
RMA	Risk Management Authorization number

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA) is convening this joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) to discuss proposed changes to the isotretinoin (iPLEDGE) Risk Evaluation and Mitigation Strategy (REMS) requirements to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of isotretinoin oral capsules for patients.

The focus of the meeting is not to discuss whether the iPLEDGE REMS continues to be necessary or other serious risks associated with isotretinoin. Rather, information from our assessment of the iPLEDGE REMS is provided to inform the Committee about the overall status of the REMS and provide context for the discussion on how to minimize burden while maintaining a comparable level of safe use. We ask the Committee, which includes subject matter experts on optimal risk mitigation strategies to prevent fetal exposure, to focus the discussion on this risk, though we acknowledge that there are other important, serious risks associated with isotretinoin.

1.2 Context for Issues to Be Discussed at the AC

Isotretinoin, a retinoid indicated[1] for the treatment of severe recalcitrant nodular acne in non-pregnant patients 12 years of age and older with multiple inflammatory nodules with a diameter of 5 mm or greater, is a potent human teratogen. The iPLEDGE REMS is a restricted distribution program designed to reduce the risk of embryo-fetal toxicity associated with isotretinoin use. The iPLEDGE REMS requires prescriber and pharmacy certification, enrollment of all patients, confirmation of a negative pregnancy test in patients who can become pregnant at initiation of treatment and monthly, and a pregnancy registry. The iPLEDGE REMS is the largest REMS program approved by the FDA with more than 20,000 active, enrolled prescribers; more than 50,000 active, enrolled pharmacies; and more than 300,000 new patients enrolled annually.[2] This REMS is complex because of the scale coupled with the number of requirements and the time-sensitive nature of completing those requirements in specific sequence to prevent fetal exposure to isotretinoin. This inherently leads to stakeholder burden, including treatment delays imposed by documentation of the safe use requirements on participants.

Optimizing the benefit-risk balance of isotretinoin through the iPLEDGE REMS is a continual process of evaluating the REMS requirements and the effectiveness of those requirements, and making adjustments to further improve the benefit-risk balance taking into consideration the impact of those requirements on the burden to the healthcare delivery system and patient access to the drug. This process has resulted in multiple REMS modifications since its first approval in 2005, with the last REMS modification occurring in October 2021.

In October 2021, FDA approved a REMS modification[a] that changed how the iPLEDGE REMS verifies that the safe use requirements have been met before isotretinoin is dispensed. This change was necessitated by a change in vendor. This transition to the new vendor that administers the iPLEDGE REMS system did not go as planned and there were significant implementation challenges. Concerns raised during this transition led the Agency's review team to complete a systematic evaluation of the iPLEDGE REMS

[a] This modification also included a change in the number of patient risk categories from three (males, females of reproductive potential, and females of non-reproductive potential) to two (patients who can become pregnant and patients who cannot become pregnant.

requirements to identify potential, additional modifications to reduce the burden[3] to the health care delivery system and improve access - without compromising patient safety. The review team focused on requirements that we determined impose or may be perceived to impose excessive burden and, in particular, those that may impede patient access or delays in treatment.

1.3 Brief Description of Issues for Discussion at the AC

The iPLEDGE REMS remains necessary to ensure the benefits of isotretinoin outweigh the risk of embryo-fetal toxicity. The review team has determined that the iPLEDGE REMS has consistently met its REMS goals for the last five REMS assessment reporting periods (from March 1, 2017 to December 10, 2021); however, there is opportunity to reduce burden of the program while still maintaining patient safety. The review team has focused on four topic areas for the AC.

1. Documentation of Monthly Counseling for Patients Who Cannot Become Pregnant
Currently, prescribers must access the iPLEDGE REMS system monthly to document monthly counseling for each patient in order for a patient to be authorized to receive isotretinoin. Lack of this documentation is responsible for the majority of prescription authorization denials for patients who cannot become pregnant.[4] The review team recommends that the requirement for prescribers to access the iPLEDGE REMS system to ***document*** monthly counseling for patients who cannot become pregnant be extended to every 120 days or be removed. If this requirement is eliminated, there will be no need for either the patient or the prescriber to interact with the REMS system monthly, therefore alleviating significant administrative burden and treatment delays while continuing to ensure safe use.

2. Pregnancy Testing | At Home Testing
All but the initial screening pregnancy test must use a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. During the public health emergency (PHE), patients were allowed to complete pregnancy testing "at home." The number of pregnancies reported from 2020 through 2022 (i.e., during the PHE) remained stable compared to previous years. However, there are reports in the literature of patients falsifying the results of home pregnancy tests.[5-7] Further, we do not have data that informs us of the extent home pregnancy testing was used in the iPLEDGE REMS during the PHE or if there was a difference in the use of home pregnancy tests between patients who experienced a pregnancy and those who did not. The review team does not recommend the continued use of home pregnancy tests in the iPLEDGE REMS. The review team recommends pregnancy testing, with a sensitivity detection limit of at least 25 mIU/mL, be administered in a providers' office as an alternative to a CLIA-certified laboratory.

3. Pregnancy Testing | 19-day Lockout Period When the Initial 7-day Prescription Window is Missed
Patients who can become pregnant are required to take two pregnancy tests at least 19 days apart prior to initiating treatment, as well as pregnancy tests monthly during treatment, after the last dose, and one month after completing treatment. Additionally, patients who can become pregnant must pick up their prescription within 7 days from when the pregnancy test specimen was collected. Patients who can become pregnant who miss the initial 7-day prescription window (who are receiving their first prescription for isotretinoin) are required to wait an additional 19 days (referred to as the "19-day lockout period") from the date of their last pregnancy test before re-taking a pregnancy test and beginning a new 7-day prescription window. This 19-day lockout period has resulted in delays in therapy in patients who can become pregnant. Over the last five assessment reporting periods, approximately 15-20% of patients who can become pregnant missed obtaining their medication within the 7-day prescription window and were required to wait 19 days before their next pregnancy test.[8] Since Year Twelve, the iPLEDGE REMS reports 12 pregnancies that were detected during the 19-day lockout period,

thus preventing fetal exposure to isotretinoin.[9] In addition to treatment delays, published literature describe additional burden for patients including higher overall treatment costs due to additional follow-up prescriber visits and repeat pregnancy test administration.[10]

The 19-day lockout requirement, although affecting a notable number of patients, continues to provide an opportunity to detect pregnancies and prevent fetal exposure in patients who can become pregnant who have not yet begun isotretinoin therapy. The review team seeks the input from the Committee on the benefits and burden associated with this requirement including whether alternative time frames could be considered.

4. Pregnancy Registry

The objectives of the iPLEDGE REMS pregnancy registry are to 1) determine isotretinoin exposure status for each reported pregnancy, 2) document the outcome of each isotretinoin exposed pregnancy, and 3) determine, document, and analyze causes contributing to fetal exposure (i.e., root case analysis (RCA)).[11] For objectives one (exposure status) and three (root cause), the review team finds value in continuing to obtain data that support these objectives as they inform whether the REMS is meeting its goals as well as if changes to the program are necessary to consider. With regard to objective two (pregnancy outcomes), data on pregnancy and fetal outcomes are often incomplete or absent and, at least one third of pregnancies are lost to follow-up. Given the extensive knowledge of teratogenic effects of isotretinoin, the review team questions the continued value of collecting this information.

The review team is seeking input on how the pregnancy registry could be streamlined to encourage more participation to yield high quality data and in particular, to elucidate the Committee's opinions on the value of continuing to collect data specifically on pregnancy outcome and fetal outcome for a product with a well-established safety profile.

1.4 Draft Points for Consideration

As you review the AC briefing materials, we ask that you consider the following points in advance of the meeting:

- For patients who *cannot* become pregnant, should the REMS require the prescriber to ***document*** counseling the patient in the iPLEDGE REMS system:
    - Only with the first prescription as part of patient enrollment
    - Monthly (current required frequency)
    - Every 120 days
    - Some other frequency (and provide the frequency)

- Discuss whether the REMS should require that pregnancy tests be completed in a medical setting (e.g., office, laboratory) rather than at home.

- The REMS currently requires a 19-day lockout period for patients who can become pregnant and who do not pick up their first prescription of isotretinoin within the 7-day prescription window. Should the iPLEDGE REMS retain the 19-day lockout period requirement before patients can take an additional pregnancy test to be eligible to receive isotretinoin?
    - If no, do not retain the 19-day lockout period: Provide your rationale and recommendations on when the additional pregnancy test should occur before starting treatment.

- The iPLEDGE Pregnancy Registry collects information on fetal exposure, pregnancy outcome, fetal outcome, and root cause analysis. Provide recommendations on the value of the pregnancy registry requirement and ways in which it could be for streamlined to encourage more participation to yield high quality data.

- Provide any additional recommendations to reduce burden in the iPLEDGE REMS.

2 Introduction and Background

FDA is convening this joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) and the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) is to discuss proposed changes to the requirements of the isotretinoin Risk Evaluation and Mitigation Strategy (REMS), also known as the iPLEDGE REMS, to minimize burden on patients, pharmacies, and prescribers while maintaining safe use. All REMS with elements to assure safe use (ETASU), by their nature, impose some level of burden[b,12] on the healthcare delivery system by requiring healthcare providers, pharmacists, manufacturers, and patients to take additional steps to help assure safe use of the medication.

Accutane (isotretinoin) was approved on May 7, 1982 and is indicated for the treatment of severe recalcitrant nodular acne in non-pregnant patients 12 years of age or older with multiple inflammatory nodules, with a diameter of 5 mm or greater. Isotretinoin is associated with a high risk of embryo-fetal toxicity that can lead to life-threatening birth defects. Isotretinoin is contraindicated in pregnancy and is available only through a restricted distribution program called the iPLEDGE REMS. The original approval of the iPLEDGE REMS was as a risk minimization action plan (RiskMAP) in August 2005 under 21 CFR 314.520 (Subpart H). Isotretinoin was identified as a product deemed to have a REMS in effect following passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007. The iPLEDGE Program was approved as a REMS on October 22, 2010 to ensure that the benefits of the drug outweigh the risk of embryo-fetal toxicity.

2.1 Background of the Condition and Standard of Clinical Care

Acne vulgaris is a common dermatological condition that affects an estimated 85% of persons aged 12 to 24 years, and approximately one-quarter of women in their 30s.[13] The disease manifestations include open and closed comedones and inflammatory papules. In severe cases, nodules and cysts develop. Scarring may be a consequence of acne lesions, even in mild cases. Acne vulgaris usually occurs on the face, and may be seen in sebaceous areas including the neck, chest, back, and upper arms. While the pathogenesis is not completely understood, contributing factors to acne development are follicular hyperkeratinization, Cutibacterium acnes colonization, sebum production, genetic and other immune factors. Acne may be exacerbated by or as a consequence of certain medications, such as systemic corticosteroids and androgen or hormone treatments and products.

Acne treatment uses multiple modalities; therapeutic options include over-the-counter and prescription keratolytic products, topical and oral antibiotics, and topical and oral retinoids that may be used alone or in combination.[14] Many cases of acne are mild and respond well to basic hygiene, lifestyle changes, and over-the-counter products. A smaller subgroup of patients is affected by severe, nodular acne requiring intervention to treat inflammatory lesions and prevent scarring. Isotretinoin is the FDA-

[b] Burden reflects the additional effort that healthcare professionals and other stakeholders expend in complying with the REMS requirements beyond what is required for good clinical care. See draft *Guidance for Industry: REMS Assessment: Planning and Reporting*. January 2019. Accessed on February 21, 2023 at https://www.fda.gov/media/119790/download

approved drug indicated for the treatment of *nodular acne*. Isotretinoin is available as capsules for oral use and dosed according to weight (mg/kg/day) in two divided doses. In most cases, patients require a single course of isotretinoin for 15 to 20 weeks.

In addition to acne, important off-label uses for isotretinoin include treatment for certain malignancies, including high-risk neuroblastoma.[15] Isotretinoin is also used to treat some disorders of keratinization such as inherited ichthyosis.

2.2 Embryo-Fetal Toxicity

At the time of approval, isotretinoin was labeled as "Pregnancy: Category X" based on animal teratogenicity and the expected high likelihood of human teratogenicity. A boxed warning in the prescribing information[1] includes the following:

> *[Isotretinoin] can cause life-threatening birth defects and is contraindicated in pregnancy. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking [isotretinoin] in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.*

Additionally stated in the iPLEDGE REMS Prescriber Guide[16]:

> ***Documented external abnormalities*** *include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate.* ***Documented internal abnormalities*** *include: central nervous system (CNS) abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency.*

The isotretinoin prescribing information also states that "cases of IQ scores less than 85 with or without other abnormalities have been reported in children exposed in utero to isotretinoin. An increased risk of spontaneous abortion and premature births have been reported with isotretinoin exposure during pregnancy."[1]

2.3 History of Risk Management for Isotretinoin

To minimize the risk of fetal exposure, a series of risk management efforts have been implemented over the years. At the time of approval in 1982, risk messages were conveyed to patients and prescribers through labeling and letters to prescribers.

In 1988, the sponsor implemented the Accutane Pregnancy Prevention Program. The program included strengthened labeling, targeted education, reminder tools, patient informed consent forms, and patient and prescriber surveys to assess compliance with the program. In 1990, the prescribing information was revised to recommend that providers prescribe no more than a one-month supply of the drug. In May 2000, the prescribing information was revised with a recommendation that two negative pregnancy tests be obtained prior to the initial prescription. These changes were implemented in response to reports of fetal exposure to isotretinoin.

In September 2000, data from the Accutane Pregnancy Prevention Program were presented to a meeting of the DODAC. The assessment stated that 36% of females of childbearing age did not undergo a pregnancy test prior to treatment with isotretinoin.[17] The Advisory Committee members recommended modifying the program to include the registration of all patients, prescribers, implementation of a pregnancy registry, and the linkage of prescriptions to pregnancy testing.

In October 2001, the sponsor implemented a revised risk management program called the System to Manage Accutane-Related Teratogenicity (SMART). The SMART program provided expanded risk information in labeling and recommended a second pregnancy test within 5 days of menses. SMART also introduced the use of a yellow sticker applied by prescribers to all isotretinoin prescriptions and signified to pharmacists that the necessary prescriber-patient counseling and pregnancy testing had occurred.

In February 2004, the assessment findings from the SMART program were reviewed by the sponsor and FDA and were presented at a joint DSaRM and DODAC meeting. It was determined that the program was not meeting the goal of minimizing fetal exposures. While well over 90% of prescriptions contained a sticker, among women who reported receiving a prescription with a sticker, approximately 9% of indicated that they had not received a pregnancy test. DSaRM and DODAC Committees recommended strengthening and consolidation of the isotretinoin pregnancy prevention programs, registration of all patients, prescribers and pharmacies, a strict pregnancy testing requirement, and a pregnancy registry that would allow for root-cause analyses.

The Agency worked with the sponsors to develop a program that incorporated the recommended changes. That revised program, called iPLEDGE, was approved under Subpart H[c] on August 12, 2005 and included all formulations of isotretinoin. Stakeholder registration began in September 2005, and patient enrollment in late December 2005. Full transition from the previous programs to iPLEDGE was completed on March 1, 2006. During implementation, issues and concerns from stakeholders emerged, such as slow registration and activation of stakeholders, call center overload, and prescriber non-receptivity. Additionally, iPLEDGE included a requirement for all patients to pick up their prescription within 7 days of the office visit and many patients had prescriptions denied and treatment postponed because the iPLEDGE system locked out patients for an additional 23 days if they did not fill their prescription within 7 days of the office visit. Based on stakeholder feedback and at FDA's direction, the sponsors removed the 23-day lockout for males and females not of childbearing potential (FNCBP) in October 2006. This change eventually extended the prescription window from 7 days to 30 days for males and females not of childbearing potential. In October 2007, for females of child-bearing potential (FCBP), the 7-day prescription window start date was changed from the office visit to the date of specimen collection of the pregnancy test. The 23-day lockout after missing the 7-day prescription window was removed for FCBP to allow them to immediately take another pregnancy test, except for the initial prescription. For FCBP obtaining an initial prescription, failure to pick up the prescription within the 7-day window required another negative pregnancy test that is obtained 19 days after the initial confirmatory test. These changes were done with the goal of reducing interruptions in treatment and reduced burden to stakeholders.

On October 22, 2010, the Agency approved the iPLEDGE program as a REMS. The iPLEDGE REMS is a shared system REMS that includes all isotretinoin products.

On December 1, 2011, FDA convened at a joint meeting with DSaRM and DODAC to solicit the Committee's views about whether the iPLEDGE REMS continues to assure the safe use of isotretinoin, whether the program is unduly burdensome, and ways to minimize burden on healthcare delivery. In general, the Committee felt that iPLEDGE REMS does assure safe use of isotretinoin; however, there was still concern about pregnancies occurring. During the meeting, the Committee Chair summarized the status of the iPLEDGE REMS as potentially having "maximized our ability to control people. And there will be failures no matter what you do, short of not allowing the drug to be used at all."[18]

[c] 21 C.F.R. Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, § 314.520 Approval with restrictions to assure safe use.

In March of 2020, the Agency released the following guidance for industry and health care professionals - *Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency*. FDA recognized that during the COVID-19 Public Health Emergency (PHE), completion of REMS-required laboratory testing or imaging studies may be difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. In response to this guidance, the iPLEDGE REMS allowed for the use of telemedicine and pregnancy testing "at home" provided the patient communicate the results and date performed to the healthcare provider. The healthcare provider remained responsible for reporting the pregnancy test results and date performed to the iPLEDGE REMS.

In October 2021, the Agency approved a modification to the iPLEDGE REMS. This modification included a change in the number of patient risk categories from three (males, females of reproductive potential, and females of non-reproductive potential) to two (patients who can become pregnant and patients who cannot become pregnant. The modification also included a change in how the program verified that the safe use requirements are met. As a result of the change - which was necessary because the previous vendor supporting the major operations of the program (iPLEDGE REMS call center and iPLEDGE REMS system) decided to discontinue support of the iPLEDGE REMS – all user data had to be transferred to a new REMS administrator's database. There were problems merging user data from the previous system into the new system. As a result, many stakeholders were unable to access their accounts in the new system without assistance from the iPLEDGE REMS call center, causing higher-than-expected call volume and long wait times, and ultimately resulting in disrupted access to treatment for many patients.

3 Summary of the iPLEDGE REMS Requirements

This section of the briefing document explains the program requirements. It does not provide the review team's analysis of the requirements. Section 5 provides a discussion of requirements and provides the review team's analysis of the possible changes that could reduce burden on participants of the iPLEDGE REMS.

All formulations of isotretinoin are currently available under the iPLEDGE REMS, a restricted distribution program designed to reduce the risk of embryo-fetal toxicity associated with isotretinoin use.[19]

The goals of the REMS[19] are:

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

The most recently approved REMS (approved October 6, 2021) for iPLEDGE consists of elements to assure safe use (ETASU), an implementation system, and a timetable for the submission of assessments of the REMS.

The iPLEDGE REMS consists of the following ETASU:

- Healthcare providers who prescribe isotretinoin must be certified (Prescriber Certification)
- Pharmacies that dispense isotretinoin must be certified (Pharmacy Certification)
- Isotretinoin must only be dispensed to patients with documentation of safe use conditions
- Patients must be monitored

- Patients who become pregnant while on isotretinoin should be enrolled in a centralized pregnancy registry

To support operations and compliance with a restricted distribution program, isotretinoin sponsors contract with wholesalers who agree to distribute isotretinoin only to certified pharmacies, train relevant staff, maintain distribution records, and comply with audits.

3.1 Prescriber Certification and Other Requirements

Healthcare providers who prescribe isotretinoin must be certified in the iPLEDGE REMS. To become certified to prescribe isotretinoin, the prescriber must review the Prescriber Guide and enroll in the REMS by completing the Prescriber Enrollment Form. The Prescriber Enrollment Form describes the requirements of the REMS and prescribers must attest to understanding the risks of isotretinoin and agree to comply with the REMS requirements. Prescribers must enroll and be certified in the program prior to prescribing isotretinoin and must also recertify (also referred to reactivate) annually. In order to recertify, prescribers must log into the iPLEDGE REMS system to review the Prescriber Guide and re-attest to the prescriber requirements.

In order to prescribe isotretinoin, prescribers must also assess and document the patient risk category based on the patient's ability to become pregnant, counsel the patient monthly, and confirm in the iPLEDGE REMS that counseling was completed. For patients who can become pregnant additional requirements include ordering pregnancy tests and assessing pregnancy status at treatment initiation and throughout treatment, and documenting patients' contraception methods. These requirements are described in more detail in subsequent sections (Section 3.3, Monitoring and Safe Use Requirements).

3.2 Pharmacy Certification and Other Requirements

Pharmacies that dispense isotretinoin must be certified in the iPLEDGE REMS. To become certified to dispense isotretinoin, pharmacies must designate an authorized representative (also referred to as the responsible site pharmacist) to review the Pharmacist Guide, enroll in the REMS by completing the Pharmacy Enrollment Form, train all relevant staff, and establish processes and procedures to comply with the REMS requirements. The pharmacy's authorized representative attests to understanding the risks of isotretinoin and to complying with the REMS requirements. Pharmacies must recertify annually in order to dispense isotretinoin. This annual recertification (also referred to reactivation) requires authorized representatives to review the Pharmacist Guide and re-attest to the pharmacy requirements.

In addition to certification, pharmacies must obtain authorization to dispense each prescription of isotretinoin, which verifies that all safe use requirements have been met and to dispense within the prescription window (see additional discussion in Section 3.2.1 below and Section 3.3.5, Verification of Safe Use Conditions | Risk Management Authorization).

Finally, pharmacies must also comply with audits to ensure all processes and procedures are in place and being followed.

3.2.1 Days' Supply and Prescription Window

A maximum 30-days' supply of isotretinoin with no refills may be prescribed and dispensed. The 30-day dispense limit serves to not only limit the amount of drug available in the community but also ensures the safe use requirements are completed and verified every month.

All patients must pick up the isotretinoin prescription within the designated timeframe (known as the prescription window). The prescription window duration is based on the assigned patient risk category. For patients who cannot become pregnant, the prescription window is 30 days and starts from the day

of the office visit. For patients who can become pregnant, the prescription window is 7 days and starts from the date of specimen collection for the pregnancy test.

If a patient fails to pick up the prescription within their designated prescription window, the pharmacy must reverse the RMA within the iPLEDGE REMS system and the product must be returned to inventory. Patients who cannot become pregnant can immediately restart the process for obtaining a new prescription. If a patient who can become pregnant fails to pick up the prescription within the 7-day prescription window, the process for obtaining a new prescription depends on whether it was the initial prescription or a continuation of treatment. These requirements, including pregnancy test timing, are discussed in Section 3.3, Monitoring and Safe Use Requirements.

3.3 Monitoring and Safe Use Requirements

3.3.1 Patient Enrollment and Risk Categorization

Before isotretinoin treatment can begin, certified prescribers must enroll all patients into the iPLEDGE REMS and they must assess patients' reproductive status using the definitions described in the iPLEDGE Prescriber Guide (Table 1 below). The purpose of this assessment is to determine their patient's ability to become pregnant.

The October 2021 iPLEDGE REMS modification changed what was historically three patient risk categories (males, females of reproductive potential (FRP), and females of non-reproductive potential (FNRP)) to two patient risk categories (patients who can become pregnant and patients who cannot become pregnant) to align the risk categories with the ability to become pregnant rather than gender assignments and/or identities. After a patient is assigned a patient risk category by the prescriber, all patients are enrolled into the iPLEDGE REMS.

Table 1. iPLEDGE REMS definitions of patient risk categories[16]

Patients who can become pregnant	**Patients who cannot become pregnant**
• Cisgender females (born a female with a uterus and at least one ovary, aka cis-female) • Transgender males (born female with a uterus and at least one ovary, transitioned to a male, aka trans-male)	• Cisgender male (born a male, aka cis-male) • Cisgender females and transgender males that have undergone a hysterectomy (surgical removal of the uterus) • Cisgender females and transgender males that have undergone a bi-lateral oophorectomy (surgical removal of both ovaries) • Cisgender females and transgender males who are postmenopausal according to the iPLEDGE REMS definition • Transgender female (born male and transitioned to female)

3.3.2 Patient Counseling

All enrolled patients must be counseled by their prescribers on the risks of isotretinoin and iPLEDGE REMS requirements using the iPLEDGE REMS educational materials (Fact Sheet and/or appropriate Patient Guide). The Patient Enrollment Form, which is signed by the prescriber and the newly-enrolled patient, is used to document that counseling took place and is sent to the iPLEDGE REMS.

After patients begin isotretinoin therapy, they must agree to return to see the prescriber every month during the course of treatment to receive counseling on the risks of isotretinoin and to receive a subsequent isotretinoin prescription.

For patients who cannot become pregnant, prescribers (or designated staff on their behalf) must document (i.e., confirm) that monthly counseling was completed. After confirmation of counseling, the enrolled patient is eligible to receive drug. Notably, patients who cannot become pregnant are not required to complete additional actions (e.g., comprehension questions) via the iPLEDGE REMS throughout therapy.

For patients who can become pregnant, prescribers (or designated staff on their behalf) must document that monthly counseling was completed, enter pregnancy test results, and confirm the patient's primary and secondary contraception (or commitment to abstinence) into the iPLEDGE REMS website.

After the prescriber documents counseling, contraception, and pregnancy test results, patients who can become pregnant must then answer a set of questions within the iPLEDGE REMS system to verify pregnancy status, contraception choices and their comprehension of the iPLEDGE REMS requirements. If patients answer a comprehension question incorrectly, a replacement question is provided. However, if the patient does not answer the replacement question correctly, the patient is directed to review the iPLEDGE REMS patient materials or contact their prescriber for program education before making another attempt. Patients who answer the comprehension questions incorrectly or choose a contraception option inconsistent with the prescriber's responses will not be eligible to receive drug until the problems are rectified.

3.3.3 Contraception Requirements

3.3.3.1 Two Forms of Acceptable Contraception

To prevent pregnancy during isotretinoin treatment, the iPLEDGE REMS requires patients who can become pregnant to use two forms of contraception for 30 days before initiation of treatment, during treatment, and for 30 days after treatment or commit to abstinence as a lifestyle choice throughout treatment.

The iPLEDGE REMS accepts the following forms of primary and secondary contraceptive methods (Table 2).[16] Patients must select one option from the primary contraceptive list and one secondary form.

Table 2. iPLEDGE approved forms of contraception[16]

Primary Contraceptive Methods
Birth control pills
Hormonal patch
Vaginal ring
Hormonal shot
Hormonal implant
IUDs (hormonal and non-hormonal)
Tubal sterilization
Male vasectomy
Secondary Contraceptive Methods
Condom
Cervical cap or diaphragm with spermicide; vaginal sponge

While continuous abstinence, defined as not having any sexual contact with a partner that could result in pregnancy, is an option for patients, it is not listed as a form of contraception because it is considered

an "acceptable lifestyle choice." For a patient who has chosen abstinence but then decides to become sexually active, there is a 30-day waiting period to be eligible to receive isotretinoin when initiating their chosen forms of contraception.

The iPLEDGE REMS considers the following forms of contraception unacceptable: progesterone only "mini-pills," female condoms, natural family planning, breastfeeding, withdrawal, and cervical shield.

3.3.3.2 Documentation of Contraception

During therapy, it is crucial for prescribers and patients to be aligned on the patient's chosen contraception methods. One of the steps in the prescription authorization process is that both the prescriber and patient must enter the 2 forms of contraception that the patient is using (or commitment to abstinence) into the iPLEDGE REMS system. The primary form of contraception reported by both the prescriber and the patient must match. If the primary forms entered by the prescriber and patient do not match, the prescription will not be authorized and an RMA will not be generated until the mismatch is rectified.

3.3.4 Pregnancy Testing Requirements

In addition to the contraception requirements, pregnancy testing is an integral part of the iPLEDGE REMS to prevent or minimize fetal exposure to isotretinoin should pregnancy occur. There are specific requirements for pregnancy tests for patients who can become pregnant prior to treatment initiation, prior to each monthly dispense, and after treatment discontinuation. Prior to treatment initiation, the iPLEDGE REMS requires two negative urine or serum pregnancy tests at least 19 days apart. The first test is a screening pregnancy test and is typically completed at the time of patient enrollment into the REMS. Although there are no specific requirements pertaining to the timing or location of the initial pregnancy test, iPLEDGE REMS requires using a CLIA-certified laboratory for the second test, also known as the confirmatory test. In addition, there are specific requirements for timing of the confirmatory pregnancy test as follows:

- For patients with regular menses, the confirmatory test must be completed during the first five days of the menstrual cycle.
- For patients with amenorrhea, irregular cycles, or using a contraceptive form that precludes withdrawal bleeding, the confirmatory test must be done immediately preceding the beginning of isotretinoin treatment and after the patient has used 2 forms of contraception for 1 month.

During treatment, patients who can become pregnant must also obtain a pregnancy test using a CLIA-certified laboratory before each monthly dispense of isotretinoin. The pregnancy test prior to each isotretinoin dispense can be completed prior to, at the time of, or after the office visit. The 7-day prescription window begins on the date of specimen collection for the pregnancy test. Additional pregnancy testing is required if patients fail to pick up the prescription within the 7-day prescription window and these requirements are outlined in Section 3.3.4.1 below.

Pregnancy testing is also required after treatment is completed as the risk of embryofetal toxicity persists for an additional month after isotretinoin is stopped. At the end of an isotretinoin course of treatment, a pregnancy test using a CLIA-certified laboratory is required and repeated 30 days after treatment discontinuation. The prescriber is responsible for documenting the results of the pregnancy tests in the iPLEDGE REMS.

As a result of the COVID-19 PHE and consistent with Agency guidance,[20] the iPLEDGE REMS allowed for pregnancy testing "at home" (i.e., not using a CLIA-certified laboratory) provided the patient

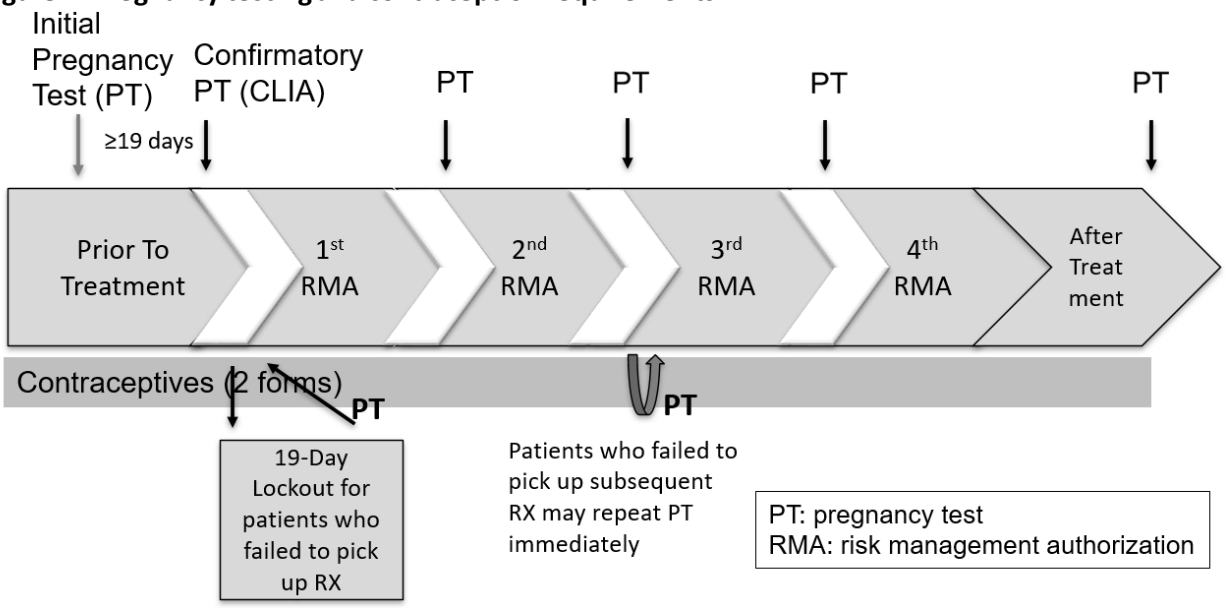
communicate the results and date performed to the healthcare provider. The healthcare provider remained responsible for reporting the results and date performed to the iPLEDGE REMS.

3.3.4.1 19-day Lockout Period When the Initial 7-day Prescription Window is Missed

If a patient who can become pregnant fails to pick up the first isotretinoin prescription within the 7-day prescription window, they enter a 19-day lockout period. The 19-day lockout period requires the patient to wait for a minimum of 19 days from the date of the confirmatory test before repeating a pregnancy test using a CLIA-certified lab and obtaining a new prescription.

As depicted in Figure 1 below, the 19-day lockout period only applies to patients who have not picked up their *first prescription* within the 7-day prescription window (see box under 1st RMA in Figure 1 below). Patients who do not pick up their subsequent isotretinoin prescription within the 7-day prescription window may repeat the pregnancy test immediately and get a new 7-day window (see arrow under 3rd RMA in Figure 1 below).

Figure 1. Pregnancy testing and contraception requirements



3.3.5 Verification of Safe Use Requirements |Risk Management Authorization

Central to the iPLEDGE REMS is the RMA. The RMA is a unique identifying number generated from the iPLEDGE REMS system and provided directly to a requesting pharmacist from a certified pharmacy when all the safe use requirements have been met (as described below). Pharmacies can dispense isotretinoin only if the iPLEDGE REMS generates a valid RMA number when the patient and the prescriber (or designated staff on their behalf) successfully document all monthly iPLEDGE REMS requirements based on the patient's risk category.

For patients who cannot become pregnant, the RMA verifies the following requirements have been met:[19]

- The prescriber is certified
- The patient is enrolled in the iPLEDGE REMS
- Counseling is complete

- Dispensing is within the designated timeframe (i.e., 30-day prescription window)

For patients who can become pregnant, the RMA verifies the following requirements have been met:[19]

- The prescriber is certified
- The patient is enrolled in the iPLEDGE REMS
- Counseling is complete
- Dispensing is within the designated timeframe (i.e., 7-day prescription window)
- Patient is not pregnant
- Patient's contraception is confirmed
- Patient's monthly comprehension questions are complete

3.4 Pregnancy Registry

The iPLEDGE REMS includes a centralized pregnancy registry for reporting, confirming, and follow-up of all pregnancies. The objectives of this registry are to, 1) determine the isotretinoin exposure status for each reported pregnancy, 2) document the outcome for each isotretinoin exposed pregnancy, and 3) determine, document, and analyze causes contributing to fetal exposure (i.e., RCA).[11] Data from the registry are reported to the FDA and are used to assess the effectiveness of the iPLEDGE REMS. The data are also used to evaluate further ways to reduce fetal exposure.

Pregnancies may be reported to the registry or may be identified by a positive pregnancy result entered into the iPLEDGE REMS system. All reports of pregnancy are investigated; however, patient and healthcare provider participation in the registry is voluntary and requires consent. A questionnaire is used to conduct the RCA interviews for pregnancies that occur. The questionnaire collects data on the patient, the reporter, and the pregnancy outcome. Data collection includes an initial interview, follow up at 30 days and each trimester, outcome of the pregnancy, and data on any live births with follow-up to 1 year of age of the infant. Refer to Section 8.5 for additional information on flow of pregnancy registry data collection.

IPMG has a due diligence process to minimize the number of pregnancies that are lost to follow-up.

4 Summary of iPLEDGE REMS Assessment Data[d]

The Agency has made a determination that the iPLEDGE REMS has met its REMS goals for the last five REMS assessment reporting periods (years 12, 13, 14, 15 and 16[e])[f], ranging from March 1, 2017 to December 10, 2021. The data in this section will be presented using the three patient risk categories, males, Females of Reproductive Potential (FRP) and Females of Non-Reproductive Potential (FNRP), as

[d] This section includes data submitted by the IPMG in the iPLEDGE assessment reports as well as other supportive data including additional supplemental information from IPMG and FDA internal analyses of drug utilization data from proprietary databases.

[e] The Year Sixteen REMS Assessment was a bridge report that had a reporting period of nine months duration. A bridging report was needed due to the transition of the iPLEDGE system with a change to the new vendor and iPLEDGE REMS platform.

[f] iPLEDGE Year Twelve: reporting period from March 1, 2017 to February 28, 2018, iPLEDGE Year Thirteen: reporting period from March 1, 2018 to February 28, 2019, iPLEDGE Year Fourteen: reporting period from March 1, 2019 to February 29, 2020, iPLEDGE Year Fifteen: reporting period from March 1, 2020 to February 28, 2021,iPLEDGE Year Sixteen: reporting period from March 1, 2021 to December 10, 2021.

the change to two patient risk categories (as described in section 3.3.1) was not implemented at the time of data collection for these REMS assessment reports.

4.1 Goal 1: Prevent Fetal Exposure to Isotretinoin[g]

The first goal of the iPLEDGE REMS, *to prevent fetal exposure to isotretinoin*, was met for the last five assessment reporting periods. We based this determination on the following:

- The iPLEDGE REMS has reported that a range of 20 to 48 pregnancies (per assessment reporting period) were detected before initiation of isotretinoin treatment (Section 8.2, Table 4. Trends in iPLEDGE REMS reported pregnancies).
- Adherence to the safe use requirements (including required pregnancy testing, documentation of chosen contraceptive choices, and dispensing by pharmacies after obtaining an RMA) prior to each isotretinoin dispense has been high (details follow).
- The number of pregnancies reported to the iPLEDGE registry has been stable, ranging between 182 to 189 pregnancies per assessment reporting period. The pregnancy rate among isotretinoin treated FRPs has remained consistent at approximately one pregnancy per 1,000 FRP patients who have had at least one RMA (Section 8.2, Table 4. Trends in iPLEDGE REMS reported pregnancies).

While the iPLEDGE REMS is operating as intended and meeting its goal to prevent fetal exposure, reports of pregnancies while on isotretinoin have occurred for various reasons (e.g. contraception failure, unsuccessful at abstinence, using leftover medication).

A more detailed summary of the assessment data is summarized below.

4.1.1 Data on Pregnancies

Pregnancies detected prior to isotretinoin treatment: Assessment data indicate that compliance with the pregnancy testing requirements resulted in the identification of pregnancies prior to initiation of isotretinoin. The IPMG reported that isotretinoin exposure was prevented and the following iPLEDGE REMS system safe use requirements had occurred; all of the identified pregnant females were registered in the iPLEDGE REMS, had negative screening pregnancy tests, and had a positive pregnancy test at their confirmation visit after the 30-day waiting period. The number of patient pregnancies detected by the iPLEDGE REMS before initiation of isotretinoin treatment over the last five REMS assessments ranged from 20 to 48 pregnancies per assessment reporting period (Section 8.2, Table 4. Trends in iPLEDGE REMS reported pregnancies).

Pregnancy isotretinoin exposure status and rates: The number of pregnancies reported to the iPLEDGE registry has been stable, ranging between 182 to 189 pregnancies per assessment reporting period. Greater than 93% (range: 169 to 182) of these reported pregnancies were classified as isotretinoin-exposed, with the remainder classified as indeterminate exposure. The pregnancy rate has remained consistent at approximately one pregnancy per 1,000 females of reproductive potential (FRPs) who have had at least one RMA, with a range over the last five assessments from 0.06% (0.6/1000) to 0.09% (0.9/1000) (Section 8.2, Table 4. Trends in iPLEDGE REMS reported pregnancies).

More than half of iPLEDGE REMS patients who became pregnant (range: 61.6% to 72%) conceived while taking isotretinoin (Section 8.2, Table 6. Timing of Conception Relative to Isotretinoin Exposure). The

[g] Data used to inform this goal included: reports on the REMS safe use requirements for pregnancy testing prior to isotretinoin initiation and with each dispense (evidenced by issuance of an RMA) for FRPs, pregnancy registry data to include results of root cause analyses (data relevant to contributing factors, timing and outcomes of pregnancy), and REMS compliance data from the Year Twelve through Year Sixteen REMS assessment reports.

mean duration of exposure to isotretinoin ranged from 16.3 to 18.3 days, and the median ranged from 16 to 17 days. The maximum known exposure was estimated at 92 days (Section 8.2, Table 7. Summary of iPLEDGE REMS pregnancies fetal exposure). Of note, there have been reports of pregnancies (range of 1 to 8 pregnancies per assessment reporting period) where the patients took left-over isotretinoin.

Pregnancy outcomes: The most frequent reported outcome for iPLEDGE pregnancies[h] over the last five assessment reporting periods was elective terminations, followed by lost to follow-up and spontaneous abortions. Since program inception, there have been a cumulative total of 2,720 reported pregnancy outcomes to include a total of 124 live births and 54 pregnancies as "still continuing" (Section 8.2, Table 14. Summary of iPLEDGE REMS pregnancy outcomes)

Over the last five REMS assessment reporting periods, the majority of the patients who had iPLEDGE pregnancies have been ≥ 20 years old. As reported by the IPMG's Year Sixteen REMS Assessment report, "the highest number of pregnancies occurred in women between the ages of 20 to 29 years; this age category also had the highest number of FRP patients and RMAs". We note that most of the non-pregnant FRPs in the program across the last five REMS assessments periods were between the ages of 16 to 19 years and 20 to 29 years (Section 8.2, Table 11. Age of pregnant and non-pregnant FRPs)

Root causes identified that contributed to fetal isotretinoin exposure: For FRPs who became pregnant the most frequent primary and secondary methods of contraception documented in the iPLEDGE REMS system were "birth control pills (BCPs)" and "male latex condoms" (Section 8.2, Table 8. Summary of the most common contraceptive choices for pregnant and non-pregnant females of reproductive potential (FRPs) based on monthly interactions with iPLEDGE REMS). Interviews were also conducted with patients who reported a pregnancy to identify the contributing factors for the pregnancy and their methods of contraception.

In Year Sixteen, RCA data was not available for the majority (n=95) of the 184 reported pregnancies. The main reasons reported by the IPMG were "lost to follow-up due to a patient not remaining under the reporting HCP's care", "patient did not provide a response", "patient did not have a pregnancy outcome", "response was not obtained from the reporting HCP", or "the patient did not agree to participate in the pregnancy registry root cause analysis interviews". The main reasons reported to the pregnancy registry by prescribers and patients for isotretinoin-exposed pregnancies included: "did not use two methods of birth control," "unsuccessful at abstinence," and/or "contraceptive failure." These main reasons have remained consistent over the past five assessment reporting periods (Section 8.2, Table 9. Summary of most common reasons for iPLEDGE REMS pregnancies as reported by prescriber and patient).

Limitations to pregnancy registry data obtained via RCA interviews: Participation in the pregnancy registry by patients and healthcare providers is voluntary and requires patient consent. Data that is collected via interviews is extensive and may be perceived by the participants as cumbersome. Patients may also be reluctant to share personal health information if complete anonymity is not possible.

Pregnancies are classified as lost to follow-up after multiple outreach attempts and, subsequently, RCA data was not available. For those who did participate in the RCA, information is generally incomplete.

[h] An iPLEDGE pregnancy is defined as a pregnancy report for a patient with documented interactions in the iPLEDGE REMS system. A non-iPLEDGE pregnancy is defined as a pregnancy report for a patient who does not have documented registration in the iPLEDGE REMS system. iPLEDGE REMS Year Sixteen Assessment Report.

4.1.2 Adherence with Safe Use Requirements

Obtaining an RMA: Data indicate that prescribers and pharmacists have adhered to the iPLEDGE REMS requirements designed to prevent and limit fetal exposure to isotretinoin. Prescribers have been compliant with fulfilling their required safe use requirements, including monthly documentation of pregnancy test results, chosen forms of contraception and patient counseling. Overall, pharmacists have been compliant with obtaining an RMA, which confirms the verification of REMS safe use requirements prior to each dispensing of isotretinoin (as described in section 3.3.5). For FRPs, this verification also includes that the patient is not pregnant prior to each dispense of isotretinoin, that pregnancy test results have been documented, the prescription is filled within the 7-day prescription window and that contraceptive forms have been documented by both prescribers and patients.

Over the last five REMS assessments, the confirmed incidents of isotretinoin prescriptions dispensed without an RMA ranged from 0.6 to 2 per 10,000 prescriptions authorized. This data indicates that most isotretinoin prescriptions are dispensed only after the safe use requirements have been verified by the iPLEDGE REMS (Section 8.2, Table 5. Confirmed incidents and rate of dispensing isotretinoin without an RMA).

The authorization process or RMA for a single prescription can include multiple denials, as a denial will be given for each requirement that has not been verified for that patient before authorization to dispense isotretinoin is granted. Subsequently, this prescription can then be authorized and dispensed when evidence of any missing requirement is obtained. These RMA denials may result in a potential delay in the patient's therapy depending upon the time needed for verification of the missing safe use requirement(s). The majority of prescription authorization attempts that were denied has remained consistent for the three patient risk categories for the last five assessment periods. The majority of denials that occurred were for FRPs followed by males (Section 8.2, Table 12. Number of iPLEDGE REMS prescription authorization attempts denied by patient risk category). Over the last five assessment reporting periods, the majority of prescriptions were denied for the reason of "required to demonstrate comprehension" followed by "requires confirmation only".

4.2 Goal 2: inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions[i]

The second goal of the iPLEDGE REMS, *to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions***,** was met, for the last five assessment reports. We based this determination on the following:

- Surveyed prescribers had a good understanding of the risk and severity of embryofetal toxicity with isotretinoin, effective measures for avoiding unplanned pregnancies, and the iPLEDGE REMS program requirements.
- Surveyed pharmacists had a good understanding of the risk and severity of embryofetal toxicity with isotretinoin, and the iPLEDGE REMS program requirements.
- All enrolled patients attest to their understanding of the serious risks and safe use requirements when enrolling in iPLEDGE REMS and over 85% of patients who can get pregnant pass the monthly comprehension exam on the first attempt.

[i] Data used to inform this goal included results of included the prescribers' and pharmacists' KAB survey results. In addition, all stakeholders attest to being aware of isotretinoin's serious risks and the specific safe use requirements applicable to them. Data used to inform this goal also included patients' enrollment data and results of their monthly comprehension tests. Patients' understanding is not assessed using a KAB survey.

A more detailed summary of the assessment data is summarized below.

4.2.1 Assessment of Prescriber Understanding

The prescribers' knowledge, attitudes, behavior (KAB) survey results data were used as measurements of prescribers knowledge of the iPLEDGE REMS key messages. Additionally, prescribers attest to being aware of isotretinoin's serious risks and the specific safe use conditions applicable to them when enrolling in the iPLEDGE REMS.

The prescriber knowledge rate is the proportion of subjects who know the key message out of all subjects that participated in the survey; it is also the chance that a given subject in the target population (prescribers) knows the key message. During Years Twelve through Sixteen, KAB surveys were conducted to assess prescribers' understanding of safe use requirements, counseling requirements, and contraceptive and pregnancy requirements. Below is a summary of the results of the prescribers' knowledge of the four key risk messages which had an 80% target knowledge rate.

- Key risk message 1: prescribers understood the risk and severity of fetal injury/birth defects with isotretinoin with a mean score that ranged from 97% to 99.1%.
- Key risk message 2: prescribers understood the iPLEDGE REMS requirements regarding pregnancies with a mean score that ranged from 84% to 93.7%.
- Key risk message 3: prescribers understood the effective measures for avoiding unplanned pregnancies with a mean score that ranged from 80% to 89.3%.
- Key risk message 4: prescribers understood they must comply with the iPLEDGE REMS requirements described in the booklets entitled *The Guide To Best Practices For the iPLEDGE Program* and *The iPLEDGE Program Prescriber Contraception Counseling Guide* with a mean score that ranged from 83.9% to 92.5%.

4.2.2 Assessment of Pharmacist Understanding

KAB survey data was used to measure pharmacists knowledge of the iPLEDGE REMS key messages. In addition, responsible site pharmacists attest to being aware of isotretinoin's serious risks and the specific safe use requirements applicable to them when enrolling in the iPLEDGE REMS.

During Years Twelve through Sixteen, KAB surveys were conducted to assess pharmacists' understanding of safe use requirements and iPLEDGE REMS requirements prior to filling and dispensing isotretinoin. Below is a summary of the results of the pharmacists' knowledge of the four key risk messages which had an 80% target knowledge rate.

- Key risk message 1: pharmacists understood the risk and severity of fetal injury/birth defects with isotretinoin with a mean score that ranged from 96.9% to 99%.
- Key risk message 2: pharmacists understood that responsible site pharmacists are responsible for training all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions at their location on the iPLEDGE REMS requirements with a mean score that ranged from 92.1% to 99.3%.
- Key risk message 3: pharmacists understood that responsible site pharmacists must comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE REMS requirements with a mean score that ranged from 91.4% to 97.9%.
- Key risk message 4: pharmacists understood that isotretinoin product should be obtained from only iPLEDGE-registered wholesalers and pharmacies must not sell, buy, borrow, loan, or otherwise transfer isotretinoin in any manner to or from another pharmacy with a mean score

that ranged from 64% to 93.1%. Surveyed pharmacists consistently scored low in Years Fourteen, Fifteen and Sixteen on the key risk message 4 question item that specifically assessed knowledge as to whether or not its permissible for a pharmacy to borrow isotretinoin from another pharmacy.[j] Of note, this question was added in Year Fourteen, and will be reviewed by IPMG prior to the launch of Year Seventeen Pharmacist KAB surveys as reported in their Year Sixteen REMS Assessment Report to see if improvements are needed.

4.2.3 Assessment of Patient Understanding

Data used to determine if patients were informed of the serious risks and safe use requirements included enrollment data and results of monthly comprehension tests. Dispensing of isotretinoin is restricted to patients who are enrolled in the iPLEDGE REMS. In order to enroll, patients must have completed the Patient Enrollment Form which identifies the serious risk and safe use requirements. The iPLEDGE REMS requires that patients attest to their understanding. FRPs must complete a baseline and monthly comprehension tests to verify that they were counseled and are aware of isotretinoin's serious risks and safe use requirements.

In Years Twelve through Sixteen, greater than 85% of FRPs passed the monthly comprehension test[k] on their first attempt. At the time of the initial baseline monthly comprehension test, patients are asked if they were told to avoid pregnancy, if they received the education kit for FRPs, and if they received contraception counseling. In addition, FRPs are asked monthly series of questions (prior to receiving each subsequent isotretinoin prescription) to assess their understanding of the need for contraception and the risk of birth defects if isotretinoin exposure occurs during pregnancy. Documentation of an RMA prior to dispensing ensures that the patients have understood the key risk messages. As indicated above, prescriptions that have been dispensed without an RMA has been very low, ranging from 0.6 to 2 per 10,000 prescriptions authorized over the last five assessments.

4.3 Data on REMS Burden and Patient Access

4.3.1 Assessment of Burden

Burden, with respect to REMS, has been described as, "the additional effort that healthcare professionals and other stakeholders expend in complying with the REMS requirements beyond what is required for good clinical care".[b, 12] For the iPLEDGE REMS this burden can include the additional effort needed by stakeholders to comply with the documentation and verification of the safe use requirements prior to each dispense of isotretinoin. The REMS Assessment reports provide limited data on iPLEDGE REMS burden, but do include reporting on isotretinoin prescriptions that have been denied authorization for not completing any of the REMS requirements.

RMA Denials: A denied RMA occurs when any of the monthly safe use requirements have not been documented by the prescriber and/or patient. This RMA denial might result in additional burden for stakeholders (prescriber, pharmacist and patient). For example, if an RMA is denied it may require the pharmacist to contact the prescriber or patient to have them complete the missing requirement. In addition, there can be multiple RMA denials for the same patient. Of note, FRPs have more requirements (e.g. pregnancy test results) that need verification in order to obtain an RMA than other

[j] This is an iPLEDGE REMS requirement.

[k] The iPLEDGE REMS comprehension questions are available at REMS@FDA.gov or using this link: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Isotretinoin_2022_10_6_Comprehension_Questions.pdf

risk categories (males, FNRP) (as described in 3.3.5 Verification of Safe Use Requirements | Risk Management Authorization).

Although FRPs had a similar percentage of prescriptions authorized when compared to males (51% vs. 48% for the Year Sixteen), the majority of RMA denials were for FRPs (72%) which suggests that the burden associated with obtaining an RMA is higher for FRP patients and their prescribers. While the number of reported RMA denials for males was less than that for FRPs, the data indicate that there is also potential burden associated with obtaining an RMA for males. Over the last five reporting periods, RMA denials have remained consistent across the patient risk categories, with the majority of RMA denials occurring for FRPs (range: 969,635 to 2,340,642) followed by males (range: 331,186 to 907,026). See Section 8.2, Table 12. Number of iPLEDGE REMS prescription authorization attempts denied by patient risk category.

Reasons for RMA denial: Over the last five assessment reporting periods, the most common reason (>40%) for RMA denials was "required to demonstrate comprehension" followed by "requires confirmation only." Of note, between 1.39% and 1.75% of RMAs were denied for the reason of "19-Day Wait." Only FRPs complete the monthly comprehension tests and are subject to the "19 day wait". However, the prescriber is responsible for confirming counseling was completed for all patient risk categories. Approximately a third of the total number of RMA denials were due to a missing prescriber confirmation of counseling (Section 8.2, Table 13. Summary of reasons for iPLEDGE REMS prescription denials).[2]

The Agency received supplemental information[4] for data that is not captured by Years Twelve through Year Sixteen REMS Assessment Reports. For patients who cannot become pregnant, "requires confirmation only" has been the most common reason for RMA denials. From the week ending February 26, 2022 through February 18, 2023, "prescriber did not complete counseling confirmation" accounted for 72-78% of RMA denials for patients who cannot become pregnant.

We note that a single RMA attempt may have been denied by the iPLEDGE REMS system for multiple reasons, with each reason being counted separately. The RMA denial reason "required to demonstrate comprehension" was described as occurring when a patient who can become pregnant attempted to fill a prescription without answering the monthly comprehension questions. The IPMG indicated that "It is possible that after this denial, the patient answered the comprehension questions in the iPLEDGE REMS system and was able to have the prescription authorized." The RMA denial reason "requires confirmation only" was described as occurring when a prescriber had not confirmed in the iPLEDGE REMS system that the patient had received the required monthly contraception counseling.

4.3.2 Patient Access

iPLEDGE REMS Assessment Data

The REMS Assessment reports for Year Twelve through Year Sixteen provides limited data on impact of the iPLEDGE REMS on patient access to isotretinoin or delays in treatment. Patient demographic data within the iPLEDGE REMS provides an understanding of how many patients have access to isotretinoin therapy. Across the last five REMS assessments, males and FRPs have been the top two registered patient risk categories. The lowest patient risk category has remained as FNRP. From December 30, 2005 through December 10, 2021 a cumulative total of 4,196,443 patients have been registered in the iPLEDGE REMS; of these, approximately 49% were male, 48% were FRP, and 3% were FNRPs. During Year Sixteen, a total of 297,745 patients were newly registered in the program for the first time (had not been previously enrolled). Of the newly registered patients, 47% were male; 51% were FRPs; and 2%

were FNRP. This remained consistent with the previous reporting periods. (Section 8.2, Table 10. Number of patients registered in iPLEDGE REMS by patient risk category).

FDA Internal Analyses of Drug Utilization Data from Proprietary Databases

Using proprietary databases available to the FDA, the drug use team within the Division of Epidemiology II examined utilization trends of isotretinoin prescriptions dispensed from U.S. retail and mail-order/specialty pharmacies from 2013 through 2022 (Table 3. National annual estimates of isotretinoin prescriptions dispensed from U.S. retail and mail-order/specialty pharmacies from 2013 through 2022, by patient sex and age). This information will be used for background and context for the advisory committee panel discussion. The total estimated number of isotretinoin prescriptions dispensed almost doubled from an estimated 1 million in 2013 to 2 million prescriptions dispensed in 2022. Males and females represented 50% each of total prescriptions dispensed and utilization doubled during the examined time period across both genders.

Table 3. National annual estimates of isotretinoin prescriptions dispensed from U.S. retail and mail-order/specialty pharmacies from 2013 through 2022, by patient sex and age

	Year									
	2013		2014		2015		2016		2017	
	Prescriptions	%	Prescriptions	%	Prescriptions	%	Prescriptions	%	Prescriptions	%
Total Isotretinoin Prescriptions	1,061,924	100.0%	1,181,033	100.0%	1,305,855	100.0%	1,414,599	100.0%	1,469,850	100.0%
Female	503,611	47.4%	566,263	47.9%	630,747	48.3%	691,965	48.9%	729,237	49.6%
<12 years	996	0.2%	786	0.1%	783	0.1%	929	0.1%	853	0.1%
12 - <46 years	462,956	91.9%	525,436	92.8%	584,762	92.7%	641,441	92.7%	676,887	92.8%
46+ years	36,307	7.2%	36,373	6.4%	37,583	6.0%	38,175	5.5%	37,132	5.1%
Unknown Age	3,352	0.7%	3,668	0.6%	7,619	1.2%	11,420	1.7%	14,365	2.0%
Male	553,918	52.2%	610,219	51.7%	668,151	51.2%	714,473	50.5%	734,527	50.0%
Unknown Sex	4,395	0.4%	4,551	0.4%	6,957	0.5%	8,161	0.6%	6,086	0.4%

	Year									
	2018		2019		2020		2021		2022	
	Prescriptions	%	Prescriptions	%	Prescriptions	%	Prescriptions	%	Prescriptions	%
Total Isotretinoin Prescriptions	1,578,461	100.0%	1,721,221	100.0%	1,813,902	100.0%	2,070,382	100.0%	2,006,298	100.0%
Female	795,855	50.4%	866,142	50.3%	930,704	51.3%	1,070,892	51.7%	1,018,600	50.8%
<12 years	834	0.1%	1,072	0.1%	1,170	0.1%	1,413	0.1%	1,329	0.1%
12 - <46 years	741,948	93.2%	816,573	94.3%	888,124	95.4%	1,019,043	95.2%	969,293	95.2%
46+ years	35,060	4.4%	37,838	4.4%	36,239	3.9%	40,708	3.8%	39,953	3.9%
Unknown Age	18,013	2.3%	10,659	1.2%	5,171	0.6%	9,728	0.9%	8,025	0.8%
Male	773,119	49.0%	840,205	48.8%	860,988	47.5%	974,225	47.1%	971,928	48.4%
Unknown Sex	9,487	0.6%	14,874	0.9%	22,210	1.2%	25,265	1.2%	15,770	0.8%

Source: Symphony Health Metys™, 2013 through 2022. Data extracted January 2023.

5 Evaluation of Potential Modifications to Reduce Burden

The review team completed an independent, systematic evaluation of the iPLEDGE REMS to identify if there are modifications that might reduce the burden[12] to the health care delivery system and improve access - without compromising patient safety. In the context of REMS with ETASU, burden reflects the additional effort that healthcare professionals and other stakeholders expend in complying with the REMS requirements beyond what is required for good clinical care.

We evaluated all requirements in the iPLEDGE REMS. This section focuses on requirements that we determined impose or may be perceived to impose excessive burden and, in particular, those that may impede patient access or delays in treatment.

5.1 Requirements Impacting All Patients

5.1.1 Patient Enrollment

As described in Section 3.3.1 , all patients treated with isotretinoin must be enrolled in the iPLEDGE REMS.

As part of the patient enrollment process, all patients are counseled on the risks associated with isotretinoin use, informed of the requirements of the REMS and categorized into the two patient risk categories based upon reproductive status.[19] Those who are categorized as a patient who can become pregnant must undergo additional counseling and safe use requirements.

Questions have been raised regarding the need for all patients to enroll in the iPLEDGE REMS when only patients who can become pregnant are at risk for embryofetal toxicity. While enrolling only patients who can become pregnant may reduce burden for prescribers and patients who cannot become pregnant, patient safety could be compromised for the following reasons:

- Enrollment and documentation of patients into specific risk categories ensures that prescribers have thoroughly assessed that patient's reproductive status prior to initiating therapy with isotretinoin.
- Pharmacists are not able to determine patient risk categories based on a patient's name or perceived sex.

For the reasons described above, the review team recommends continuing enrollment of all patients into the iPLEDGE REMS.

5.1.2 Limitation on Prescription Days' Supply

A maximum 30-days' supply of isotretinoin with no refills may be prescribed and dispensed. The iPLEDGE REMS 30-day dispense limit serves to limit the amount of drug available in the community. Questions have been raised regarding the need to limit the days' supply, particularly for patients who cannot become pregnant. Eliminating this requirement could increase access to isotretinoin and reduce the burden of patients needing to visit their prescriber and pharmacist monthly.

Limiting the days' supply for all patients prevents the potential sharing of extra or leftover medication among friends and family members. Use of leftover medication has been identified as a root cause of fetal exposure in a small number of cases. In Year Twelve through Year Sixteen assessment reports, 1 to 8 pregnancy exposures were reported resulting from taking leftover medication each year.[2]

Limiting the days' supply also ensures the safe use requirements are completed and verified every month since these requirements must be completed to obtain more isotretinoin.

For the reasons described above, the review team recommends continuing the 30-day supply limit as a requirement of the iPLEDGE REMS.

5.2 Requirements Impacting Patients Who Cannot Become Pregnant

Approximately 50% of the patients who are enrolled in the iPLEDGE REMS are categorized as patients who cannot become pregnant (previously categorized as females of non-reproductive potential and males).

5.2.1 Monthly Requirement for Prescribers to Document Counseling

As mentioned in section 3.3.2, the iPLEDGE REMS requires prescribers to counsel patients on the risks of isotretinoin and iPLEDGE REMS requirements at the initiation of isotretinoin therapy, monthly during treatment and when treatment is discontinued. Each month the prescriber must document (i.e., confirm) within the iPLEDGE REMS system that counseling was completed. Patients who cannot become pregnant are not required to interact with the system on a monthly basis. However, they do agree as part of the enrollment process to return to see the prescriber every month during the course of treatment to receive counseling on the risks of isotretinoin and receive a subsequent isotretinoin prescription.

If the prescriber does not document counseling in the iPLEDGE REMS system for a patient who cannot become pregnant, the patient is deemed ineligible to receive drug until the counseling is documented. When the prescription is in a denied state, actions to remedy the denial include additional contacts such as phone calls and reminders from pharmacies to patients and multiple contacts to the prescriber's office to complete the documentation step in the iPLEDGE REMS system which may result in treatment delays or gaps in therapy.[21]

Over the last five years approximately one-third of the total number of RMA denials for all patient categories were denied for dispense due to a missing prescriber confirmation of counseling (see Section 8.2, Table 13. Summary of reasons for iPLEDGE REMS prescription denials).[2] For patients who cannot become pregnant, this was the most common reason for RMA denials. Based on supplemental information requested by the review team, the IPMG has provided certain data throughout the last year. From the week ending February 26, 2022 through February 18, 2023, "Prescriber Needs to Complete Patient's Confirmation," accounts for 72-78% of the RMA denials for patients who cannot become pregnant.[4] This denial reason disproportionately impacts this patient risk category.

The review team recommends that the requirement for prescribers to access the iPLEDGE REMS system to ***document*** monthly counseling for patients who cannot become pregnant be extended to every 120 days or be removed. Prescribers must still provide monthly counseling but will not be required to access the iPLEDGE system to ***document*** the counseling. If this requirement is eliminated, there will be no need for either the patient or the prescriber to interact with the iPLEDGE REMS system monthly for this patient risk category. Discontinuation of the need to document counseling for patients who cannot become pregnant should eliminate 72-78% of the RMA denials for this group.

5.3 Requirements Impacting Patients Who Can Become Pregnant

5.3.1 Monthly Requirement for Prescribers to Document Counseling

On a monthly basis, prescribers are required to document completion of counseling in the iPLEDGE REMS in addition to documenting the pregnancy test result and the patient's two forms of contraception. Missing documentation of prescriber counseling as a reason isotretinoin was denied for dispense accounts for only a small percentage of rejections for this patient risk category. Based on supplemental information requested by the review team, the IPMG has provided certain data throughout the last year. From the week ending February 26, 2022 through February 18, 2023, this reason accounts for approximately 11-14% of RMA denials for patients who can become pregnant.[4]

Given that prescribers are already interacting with the iPLEDGE REMS system on a monthly basis to document other safe use requirements (i.e., pregnancy test results, contraception choices), the contribution of this documentation task to burden is minimal, and the importance of regular reminders about the risk and safe use behaviors are important. We recommend prescribers continue to confirm

(i.e., document) completion of counseling for patients who can become pregnant at treatment initiation and at each monthly dispense.

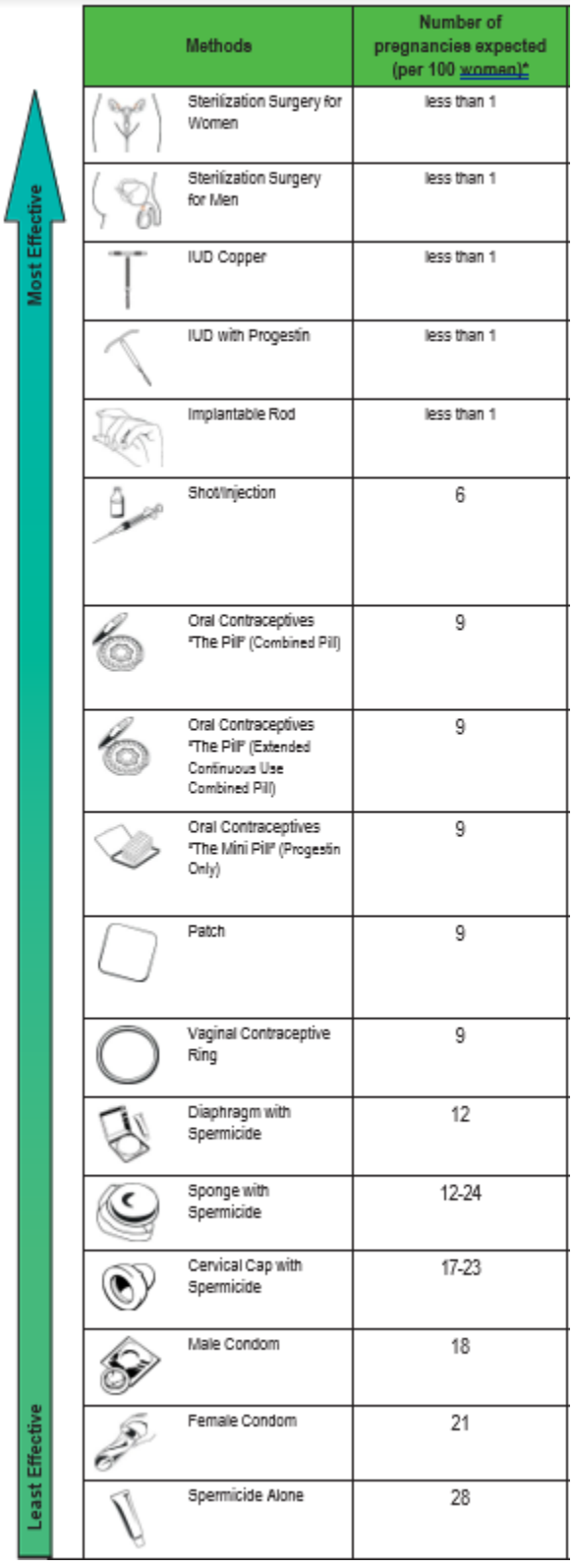
5.3.2 Contraception Requirements

5.3.2.1 Two Forms of Acceptable Contraception

As described in section 3.3.3.1, the iPLEDGE REMS requires patients who can become pregnant to use two acceptable forms of contraception. Contraceptive choice is based on many factors including the likelihood of correct and consistent use of the contraceptive method, medical conditions, previous adverse reactions, drug-drug interactions, and the patient's preference.

Most unintended pregnancies, in general[22], result from not using contraception or from not using it consistently or correctly; this is consistent with data reported to the iPLEDGE REMS. Refer to Figure 2 below for the percentage of patients experiencing a pregnancy during the first year of typical use of each contraceptive.[23]

Figure 2. Birth Control Guide[23]



Methods	Number of pregnancies expected (per 100 woman)*
Sterilization Surgery for Women	less than 1
Sterilization Surgery for Men	less than 1
IUD Copper	less than 1
IUD with Progestin	less than 1
Implantable Rod	less than 1
Shot/Injection	6
Oral Contraceptives "The Pill" (Combined Pill)	9
Oral Contraceptives "The Pill" (Extended Continuous Use Combined Pill)	9
Oral Contraceptives "The Mini Pill" (Progestin Only)	9
Patch	9
Vaginal Contraceptive Ring	9
Diaphragm with Spermicide	12
Sponge with Spermicide	12-24
Cervical Cap with Spermicide	17-23
Male Condom	18
Female Condom	21
Spermicide Alone	28

Contraceptive methods that are user independent (e.g., intrauterine device, implants and sterilization) have typical use failure rates of less than 1%.

Contraceptive methods that are user dependent have more potential for imperfect use (forgetting to take pills or failure to return on time for injections) and have higher failure rates.[24] Studies of barrier methods display an even broader range of reported failure rates because the increased potential for imperfect use.[24]

The iPLEDGE Year Sixteen Assessment Report noted that the most common contraception choices for patients who can become pregnant are those that are user-dependent: abstinence is the primary choice, with birth control pills and male condoms being the second most frequent combination of choice.[2] For patients who had unintended pregnancies during this time period, birth control pills and male latex condoms were the most frequent combination of contraception choices and second was abstinence.

It is important to acknowledge that despite requiring two forms of contraception, not using two forms of contraception (23-36%) and contraceptive failure (8-28%) are the two most common reasons cited by prescribers for unintended pregnancy (Section 8.2, Table 9).[2] Ideally, contraception with a typical use failure rate of less than 1% should be recommended when a patient is taking medications with teratogenic potential.

Given what is known about contraception failure rates and contraception choice trends specific to patients treated with isotretinoin, the review team is not recommending changes at this time.

Because information and recommendations about acceptable forms of contraception is a broader topic that can impact other products that are teratogens, this will not be a specific topic of discussion at this meeting; however, it is actively being discussed at the Agency.

5.3.2.2 Documentation of Contraception

As described in Section 3.3.3.2, prescribers and patients enter the selected contraception methods into the iPLEDGE REMS system monthly. If the prescriber and patient answers do not align, the prescription will not be authorized and an RMA will not be generated until the mismatch is rectified. This contraception mismatch, while having the potential to increase stakeholder burden and cause a delay to isotretinoin dispense,[21] enforces the compulsory re-evaluation of contraception choices and provides the important opportunity for the prescriber and patient to confirm their common and documented understanding of the chosen pregnancy prevention strategy. This opportunity for re-evaluation is particularly important with the high reliance on user-dependent contraception in isotretinoin patients.

The review team recommends continuing to require both the prescriber and patient confirm the contraception methods in the iPLEDGE REMS system monthly and to require that the primary method responses must match as a part of the RMA.

5.3.3 Pregnancy Testing Requirements

5.3.3.1 Use of CLIA-Certified Laboratories

The rationale for requiring a CLIA-certified laboratory to conduct pregnancy testing included the need for control of how and by whom the pregnancy test is performed. The requirement was reasoned to prevent the use of home pregnancy testing being ordered and not completed as well as reduce the likelihood of laboratory error.[25]

Currently, urine human chorionic gonadotropin (hCG) pregnancy tests performed at a healthcare provider's office and in CLIA-certified laboratories are typically considered "CLIA-waived." As defined by CLIA, waived tests are "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result."[26,27] All qualitative hCG assays must meet the same analytical performance requirements for accuracy, precision, specificity, and sensitivity regardless of whether they are intended to be used by lay users at home (OTC, and therefore automatically waived) or in prescriber offices or a laboratory setting (both prescription use).[28]

As urine hCG tests are considered waived tests, the review team recommends removing the requirement to perform the monthly pregnancy test using a CLIA-certified laboratory and allow for pregnancy testing with a sensitivity detection limit of at least 25 mIU/mL to be administered in a providers' office as an alternative to using a CLIA-certified laboratory.

5.3.3.2 At Home Pregnancy Testing

During the COVID-19 PHE, the iPLEDGE REMS permitted the use of over-the-counter (OTC) home pregnancy tests to verify pregnancy status in a patient who can become pregnant.[20] Patients were required to communicate home pregnancy test results and date performed to the healthcare provider so it could be entered into the iPLEDGE REMS system. This temporary allowance for home pregnancy testing during the PHE gave patients the ability to continue with their therapy while in isolation or quarantine due to COVID-19. The potential benefits of home pregnancy testing coupled with the use of telemedicine have been published and include eliminating the need for separate in-person laboratory visits and associated costs (e.g., missed work, childcare needs, etc.).[29]

Prescribers are required to enter a pregnancy test result; however, the iPLEDGE REMS system does not capture where and how the test was administered. Therefore, there was no mechanism in place to consistently capture the uptake of home pregnancy testing during the PHE, resulting in a lack of accurate and reliable data to understand the extent home pregnancy testing was used, and, in

particular, if there was a difference in the use of home pregnancy tests between patients who experienced a pregnancy and those who did not. For reported pregnancies, data on home pregnancy testing was collected. In Patient categories may change when a patient is re-registered; therefore, cumulative values for a patient category do not cross-foot. In the Year Sixteen assessment reporting period, there were 184 pregnancies reported in iPLEDGE REMS of which 177 were pregnancies exposed to isotretinoin. This is consistent with previous reporting periods.[2] Of those pregnancies, 66 patients reported using a home pregnancy test when reporting the pregnancy, of whom 6 provided the rationale that they used a home pregnancy test due to the COVID-19 PHE. There is no denominator of how many patients ultimately used a home pregnancy test during the PHE because data was only collected for reported pregnancies.

There are multiple publications regarding the use of home pregnancy tests for patients who can become pregnant who were treated with isotretinoin during the PHE. While the use of home pregnancy testing was reported to be convenient and effective, instances of intentional falsifications of pregnancy test results from a large institution were reported at 15.7% of patients using home pregnancy tests while on isotretinoin during the PHE (N=89).[7] Cases detail the use of stock images of pregnancy tests from the internet, repeated use of the same picture of the same test result, and editing a previously used photograph.[5-7] These intentional falsifications highlight concerns with allowing home pregnancy testing to continue in absence of a PHE. To mitigate some of the risks identified with home pregnancy testing during the PHE, the authors recommend that isotretinoin prescribers implement procedures to verify the patients' name, date, and the validity of the pregnancy tests results are authentic.[5,7]

At this time, the review team does not recommend the continued use of home pregnancy tests in the iPLEDGE REMS after the PHE ends. The review team recommends, as described above, that pregnancy testing with a sensitivity detection limit of at least 25 mIU/mL be administered in a providers' office as an alternative to a CLIA-certified laboratory.

5.3.3.3 7-Day Window for Prescription Pick-Up

The prescription window provides a finite time for the patient to pick up the isotretinoin prescription before the REMS requires the patient who can become pregnant to complete a new pregnancy test. During this 7-day prescription window, prescribers and patients are to complete all of the REMS safe use requirements and the patient must pick-up their prescription. For all but the initial prescription, a patient who can become pregnant may immediately take another pregnancy test and open another 7-day prescription window if they are unable to obtain their prescription within the 7-day prescription window. When a patient misses the 7-day prescription window for the initial prescription, the patient enters the 19-day lockout which is discussed more in Section 5.3.3.4 below.

Concerns have been raised that patients may have difficulty completing all requirements and picking up the prescription within this 7-day prescription window, especially for the first prescription. Over the last five assessment reporting periods, this requirement resulted in treatment delays for approximately 15–20% of patients who can become pregnant who miss obtaining their medication within the first 7-day prescription window.[30] In contrast, the median time for patients to pick up their first prescription was 2 days and the mean ranged between 2.31 and 2.44 days which indicates most patients are able to complete the program requirements within the 7-day window.[30]

The review team recommends maintaining a 7-day prescription window for picking up the prescription.

5.3.3.4 19-day Lockout Period When the Initial 7-day Prescription Window is Missed

As mentioned in Section 3.3.4.1, if a patient who can become pregnant fails to pick up the first isotretinoin prescription within the 7-day prescription window, they enter a 19-day lockout period. The

19-day lockout period requires the patient to wait for a minimum of 19 days from the date of the confirmatory pregnancy test before repeating a pregnancy test using a CLIA-certified laboratory and obtaining a new prescription. Once the test is completed, the patient has a new 7-day prescription window to obtain isotretinoin. The 19-day lockout period is intended to prevent pregnancy exposure to isotretinoin when there has been a delay in initiating isotretinoin after the confirmatory test has been obtained. There have been pregnancies detected during the 19-day lockout. Since Year Twelve, 12 pregnancies were identified during the 19-day lockout period, preventing fetal exposure to isotretinoin.[9]

In a prospective cohort study, 221 healthy females (1982-1986) with a mean age of 30 years, who were planning to get pregnant, were tested daily using a urine pregnancy test with an immunoradiometric assay with a detection limit of 0.01 ng/mL, which is comparable to the lower limit of detection in a serum pregnancy test.[31] Testing for pregnancy 19 days after conception can detect 90 to 97% of pregnancies. For patients with amenorrhea or irregular cycles, a 19 day or more wait time is an appropriate amount of time to detect a pregnancy that occurred prior to the time before the confirmatory pregnancy test. This is also true for those patients taking hormonal contraception, where the timing of ovulation due to contraceptive failure is unpredictable. Because of the unpredictability of ovulation and the time it takes for a pregnancy to develop prior to detection, pregnancy detection never reaches 100% and there will always be a gap in time in which a new pregnancy can be detected.

In patients with a regular menstrual cycle, the 19-day lockout period (i.e., repeating a pregnancy test 19 days or more after the confirmatory test), allows the earliest pregnancy testing to be done between day 20 to day 24 of the menstrual cycle (see Figure 3. 19-day lockout period). According to the study above, this would detect 40 to 66% of pregnancies.

Figure 3. 19-day lockout period

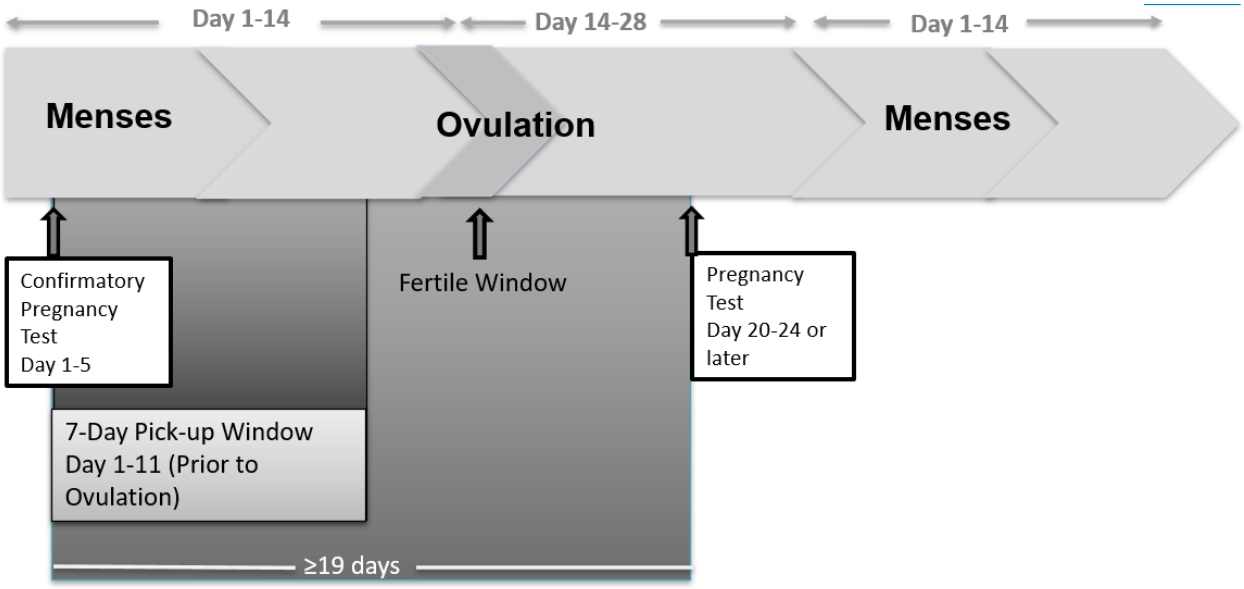


Figure 3. 19-day lockout period depicts the lockout period in the context of a regular menstrual cycle. Note that the 19-day lockout period begins from the date of the confirmatory pregnancy test.

The required 19-day lockout has affected a notable number of patients who missed the first 7-day prescription window thereby delaying the start of their treatment with isotretinoin. Cumulatively since

the Year Twelve assessment reporting period, 173,311 patients[l] who can become pregnant, missed obtaining their first prescription within the 7-day prescription window, and were required to wait 19 days before their next pregnancy test.[2,9,30] In addition to treatment delays, published literature describe additional burden for patients including higher overall treatment costs due to additional follow-up prescriber visits and repeat pregnancy test administration.[10] However, since Year Twelve, 12 pregnancies were detected during the 19-day lockout period where fetal exposure to isotretinoin was prevented.[9]

The 19-day lockout requirement, although affecting a notable number of patients, continues to provide an opportunity to detect pregnancies and prevent fetal exposure in patients who have not yet begun isotretinoin therapy. The review team seeks the input from the Committee on the benefits and burden associated with this requirement including whether alternative time frames could be considered.

5.3.3.5 Post-Treatment Pregnancy Testing

As described in Section 3.3.4, additional pregnancy tests are required after treatment is completed as the risk of embryofetal toxicity persists for one month after isotretinoin is stopped.

The majority of patients (80.2%) with a completed course of treatment during Year Sixteen did not complete the post-treatment pregnancy tests,[2] demonstrating a lack of compliance with this requirement. However, in Year Sixteen, 16 patients (N=184, 8.7%) conceived within 30 days of stopping isotretinoin. Even though patients demonstrated high levels of understanding of pregnancy testing requirements (83.4% answered a question correctly about post-treatment pregnancy tests), patients do not adhere to the post-treatment pregnancy testing requirement.

Despite the low compliance with this requirement, the review team recommends maintaining efforts to educate, monitor, and track the risk for 30 days after discontinuation of isotretinoin therapy because the risks associated with fetal exposure still remain for 30 days after completion of isotretinoin therapy.

5.3.4 Pregnancy Registry

As described in Section 3.4, the iPLEDGE REMS Pregnancy Registry is the source of the isotretinoin pregnancy data for all isotretinoin products. Participation in the registry is voluntary. The objectives of the registry are to 1) determine isotretinoin exposure status for each reported pregnancy, 2) document the outcome of each isotretinoin exposed pregnancy, and 3) determine, document, and analyze causes contributing to fetal exposure (RCA).[11] By the end of the Year Sixteen reporting period, there were 2720 reported pregnancy cases captured in the iPLEDGE REMS Pregnancy Registry.[2]

We acknowledge that the registry has limitations because it depends on the voluntary participation and the extensive data that is collected via interviews may be perceived by the participants as cumbersome. Patients may also be reluctant to share personal health information if complete anonymity is not possible.

With regard to the first objective, the review team finds the data on pregnancy exposures valuable as it allows the Agency to determine if the goal of the REMS is being met. Over the past five assessment periods the number of reported pregnancies has been consistent, ranging between 182 to 189 pregnancies per assessment reporting period and the pregnancy rate has remained stable at approximately one pregnancy per 1,000 females of reproductive potential (FRPs).

[l] This number includes patients who have had more than one course of treatment during the reporting period and would therefore have more than one first treatment window. These data count the number of patients/course of treatment combinations and not distinct patients.

With regard to the second objective, data on pregnancy and fetal outcomes are often incomplete or absent and, at least, one third of pregnancies are lost to follow-up. There is extensive knowledge of the teratogenic effects of isotretinoin, including cranio-facial malformations, cardiac, thymic and central nervous abnormalities, microtia, anotia, micrognathia, aortic arch or heart defects, thymic ectopia or aplasia or cerebellar vermis agenesis.[1] According to a 2019 Draft Guidance, *Postapproval Pregnancy Safety Studies Guidance*, a pregnancy registry should be discontinued if sufficient scientific information has accumulated to meet the scientific objectives of the registry.[32]

With regard to the third objective, while RCA data is not available or complete for a majority of the pregnancies, it can still be valuable in determining changes that should be considered to the REMS to further reduce future pregnancy events. During the Year Sixteen reporting period, 59 of the 184 patients with iPLEDGE pregnancies agreed to participate in an RCA interview providing data on the pregnancy exposure root causes (e.g., what happened, why it happened, when it happened). These data identified details of the breakdowns in iPLEDGE processes or other factors (e.g., contraception failure) that may have contributed to the pregnancy exposure.

The review team is seeking input on how the pregnancy registry could be streamlined to encourage more participation to yield high quality data and in particular, to elucidate the Committee's opinions on the value of continuing to collect data specifically on pregnancy outcome and fetal outcome for a product with a well-established safety profile.

6 Summary of Issues for the AC

The purpose of this meeting is to discuss potential changes to the iPLEDGE REMS requirements to reduce burden on participants while maintaining the safe use of isotretinoin oral capsules. The review team performed an independent, systematic evaluation of the iPLEDGE REMS requirements. Specifically, we look forward to your input on the following:

- To extend or eliminate the requirement for prescribers to access the iPLEDGE REMS system to document counseling for patients who cannot become pregnant. Prescribers will still be required to counsel all patients monthly. This modification could eliminate 72-78% of the RMA denials for patients who cannot become pregnant.[4]

- During the PHE, patients were allowed to complete "at home" pregnancy testing. The number of pregnancies reported from 2020 through 2022 remained stable compared to previous years; however, we are aware of reports of falsification of pregnancy tests in the literature.[5-7] Further, we do not have data that informs us of the extent home pregnancy testing was used in the iPLEDGE REMS during the PHE or if there was a difference in the use of home pregnancy tests between patients who experienced a pregnancy and those who did not. The review team does not recommend the continued use of home pregnancy tests in the iPLEDGE REMS after the PHE ends. The review team recommends that pregnancy testing with a sensitivity detection limit of at least 25 mIU/mL be administered in a providers' office as an alternative to a CLIA-certified laboratory.

- There is currently a 19-day lockout period for patients who can become pregnant who fail to pick up their initial prescription during the 7-day prescription window. The 19-day lockout requirement, although affecting a notable number of patients who can become pregnant, continues to provide an opportunity to detect pregnancies and prevent fetal exposure in patients who have not yet begun isotretinoin therapy. The review team seeks the input from the

Committee on the benefits and burden associated with this requirement including whether alternative time frames could be considered.

- The pregnancy registry attempts to capture extensive data on fetal exposure, pregnancy outcomes, fetal outcomes and root cause analysis. The fetal exposure information and root cause analysis aspect of the pregnancy registry can inform whether REMS is meeting goals and if changes in the program are needed to prevent further pregnancies. However, the review team is seeking input on how the pregnancy registry could be streamlined and, in particular, the value of continuing to collect data specifically on pregnancy outcome and fetal outcome for a product with a well-established safety profile.

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8 Appendix

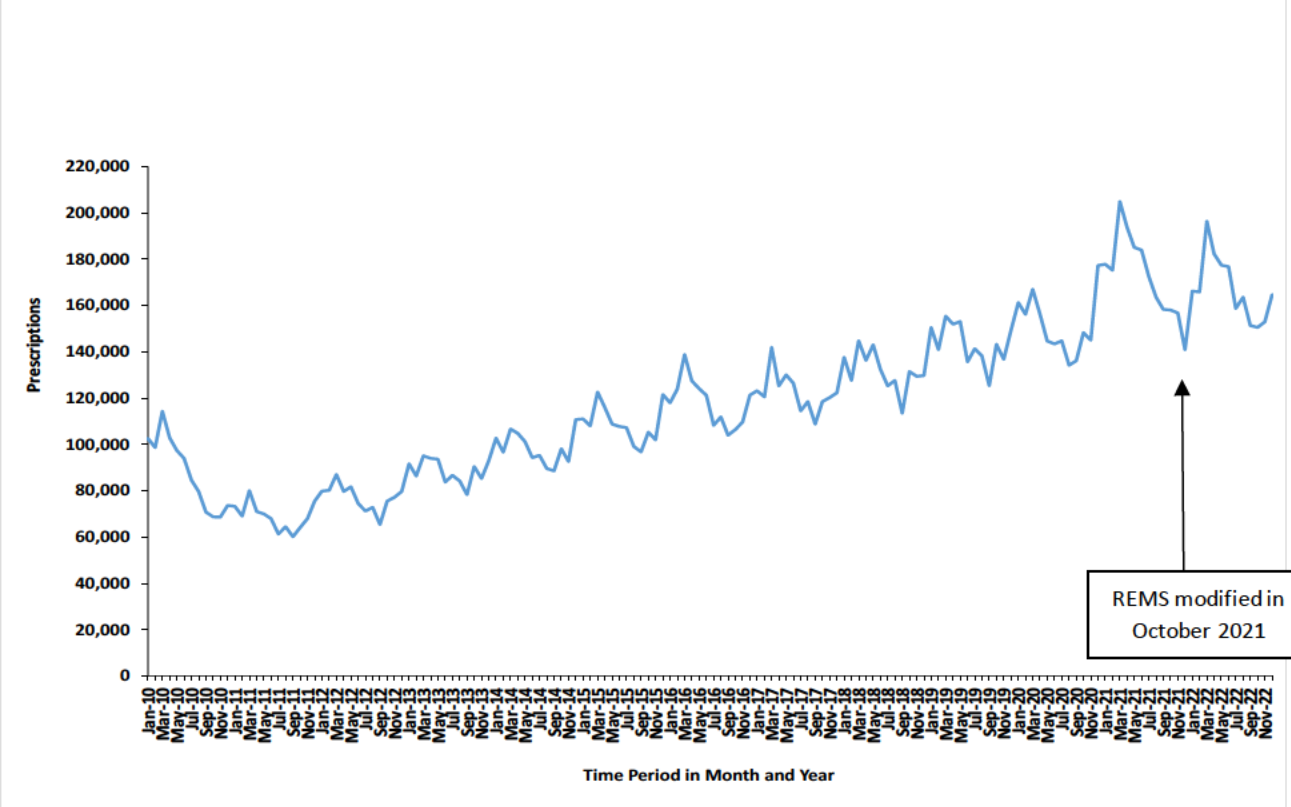
8.1 Supporting Data

8.1.1 Isotretinoin | Drug Utilization Data

The drug use team within the Division of Epidemiology II performed internal analyses to gain context on isotretinoin use over time and the impact of the REMS on isotretinoin use. Using proprietary databases available to the FDA, we examined monthly and annual isotretinoin prescription dispensing data from U.S. retail and mail-order/specialty pharmacies from 2010 through 2022.

Monthly isotretinoin prescription estimates increased from 60,000 prescriptions dispensed in September 2011 to 165,000 prescriptions dispensed in December 2022 (see Figure 4. National monthly estimates of isotretinoin prescriptions dispensed from U.S. retail and mail-order/specialty pharmacies from January 2010 through December 2022). Similarly, annual isotretinoin prescription estimates increased from 825,000 prescriptions dispensed in 2011 to 2 million prescriptions dispensed in 2022 (see Table 3. National annual estimates of isotretinoin prescriptions dispensed from U.S. retail and mail-order/specialty pharmacies from 2013 through 2022, by patient sex and age). Isotretinoin use among female and male patients was relatively equal throughout the study period. Female and male patients accounted for 51% and 48%, respectively, of total isotretinoin prescriptions dispensed in 2022. Patients aged 12- <46 years accounted for the majority of isotretinoin prescriptions dispensed to female patients throughout the study period, with 95% of prescriptions dispensed in 2022.

Figure 4. National monthly estimates of isotretinoin prescriptions dispensed from U.S. retail and mail-order/specialty pharmacies from January 2010 through December 2022



Source: Symphony Health Metys™, January 2010 through December 2022. Data extracted January 2023.

8.2 Additional iPLEDGE REMS Assessment Data

The data in the following tables are from the last five iPLEDGE REMS assessment reports (years twelve, thirteen, fourteen, fifteen and sixteen) ranging from March 1, 2017, to December 10, 2021. The Year Sixteen REMS Assessment Report was a bridge report that had a reporting period of nine months duration. A bridging report was needed due to the transition of the iPLEDGE REMS to a new vendor and iPLEDGE REMS system.

Table 4. Trends in iPLEDGE REMS reported pregnancies[m]

iPLEDGE Assessment Reports Year	Year 12 March 1, 2017 to February 28, 2018	Year 13 March 1, 2018 to February 28, 2019	Year 14 March 1, 2019 to February 29, 2020	Year 15 March 1, 2020 to February 28, 2021	Year 16[ee] March 1, 2021 to December 10, 2021
Number of Pregnancies Detected by iPLEDGE before	N=21	N=20	N=48	N=34	N=33

[m] Modified from Year Thirteen REMS Assessment Report Table 16 , 17, 18, and 19 pgs. 49-50; Year Sixteen REMS Assessment Report Table 15, 16, 17 and 18, pgs.48-49 and the updated Table 16 pg. 2 from June 24, 2022. Applicant Response to the Agency's June 2, 2022 Information Request.

Initiation of Isotretinoin Treatment[n]					
Number of FRPs**	199,031	214,984	232,762	257,876	285,622
Number of Pregnancies after initiation of isotretinoin	N = 185	N = 182	N = 186	N = 189	N = 184
Isotretinoin Exposed	*179 (96.8 %)*	*169 (92.9 %)*	*182 (97.8 %)*	*182 (96.3 %)*	*177 (96.2 %)*
Indeterminate Exposure	*6 (3.2 %)*	*13 (7.1 %)*	*4 (2.2 %)*	*7 (3.7 %)*	*7 (3.8 %)*
Pregnant Patients Per Thousand FRPs	*0.9/1,000*	*0.8/1,000*	*0.8/1,000*	*0.7/1,000*	*0.6/1,000*
Pregnancy Rate (%)	*0.09%*	*0.08%*	*0.08%*	*0.07%*	*0.06%*

*** FRP=Females of Reproductive Potential (in the approved REMS referred to patients who can become pregnant)*

[n] The Pregnancies detected by iPLEDGE system before the initiation of isotretinoin treatment for patients who had negative screening pregnancy tests, and had a positive pregnancy test at the confirmation visit after the 30-day waiting period.

Table 5. Confirmed incidents and rate of dispensing isotretinoin without an RMA [o]

	Year 12 March 1, 2017 to February 28, 2018	**Year 13** March 1, 2018 to February 28, 2019	**Year 14** March 1, 2019 to February 29, 2020	**Year 15** March 1, 2020 to February 28, 2021	**Year 16** [e] March 1, 2021 to December 10, 2021
Confirmed incidents of dispensing without an RMA	316	147	110	217	224
Total number of prescriptions authorized	1,550,229	1,760,803	1,916,531	2,049,946	1,833,708
Rate per 10,000 of Confirmed incidents of dispensing without an RMA over Total number of prescriptions authorized	2	0.8	0.6	1.1	1.2

Table 6. Timing of Conception Relative to Isotretinoin Exposure [p]

	Year 12 March 1, 2017 to February 28, 2018	**Year 13** March 1, 2018 to February 28, 2019	**Year 14** March 1, 2019 to February 29, 2020	**Year 15** March 1, 2020 to February 28, 2021	**Year 16** [ee] March 1, 2021 to December 10, 2021
Timing of Conception	**N=185** N (%)	**N=182** N (%)	**N=186** N (%)	**N=189** N (%)	**N=184** N (%)
Before start of isotretinoin	*9 (4.9%)*	*9 (4.9%)*	*17 (9.1%)*	*13 (6.9%)*	*14 (7.6%)*
While taking isotretinoin	*114 (61.6%)*	*113 (62.1%)*	*126 (67.7%)*	*136 (72.0%)*	*126 (68.5%)*
Within 30 days after isotretinoin completion	*21(11.4%)*	*15 (8.2%)*	*11 (5.9%)*	*13 (6.9%)*	*16 (8.7%)*
Unknown [q]	*41 (22.2%)*	*45 (24.7%)*	*32 (17.2%)*	*27 (14.3%)*	*28 (15.2%)*

[o] Modified from Year Thirteen REMS Assessment Report Table 54, pg. 94; Year Sixteen REMS Assessment Report Table 55, pg.90.

[p] Includes indeterminate exposures. Modified from Year Thirteen REMS Assessment Report Table 20, pg. 51; Year Sixteen REMS Assessment Report Table 19, pg.49.

[q] Includes indeterminate exposures.

Table 7. Summary of iPLEDGE REMS pregnancies fetal exposure[r]

Summary of Days Between Date of Conception and Discontinuation of Isotretinoin[a]:	**Year 12** March 1, 2017 to February 28, 2018 **N=175** N (%)	**Year 13** March 1, 2018 to February 28, 2019 **N=182** N (%)	**Year 14** March 1, 2019 to February 29, 2020 **N=174** N (%)	**Year 15** March 1, 2020 to February 28, 2021 **N=168** N (%)	**Year 16 [e e]** March 1, 2021 to December 10, 2021 **N=184** N (%)
Number of cases with known duration of exposure	102	102	122	117	124
Mean (SD) number of days of exposure to isotretinoin	18.3 (17.21%)	16.9 (12.22%)	17.8 (12.77%)	16.3 (10.5%)	17.4 (12.65%)
Median	17	16	17	16	16.5
Min, Max	0, 92	0, 49	0, 75	0, 46	0, 60
Number of Exposures with Days between Date of Conception and Discontinuation of Isotretinoin:					
1-14 days	24 (13.7%)	31 (17%)	43 (24.7%)	34 (20.2%)	32 (17.4%)
15-29 days	38 (21.7%)	42 (23.1%)	42 (24.1%)	64 (38.1%)	59 (32.1%)
≥30	19 (10.9%)	14 (7.7%)	24 (13.8%)	9 (5.4%)	15 (8.2%)
Discontinued isotretinoin before conception[b]	21 (12%)	15 (8.2%)	13 (7.5%)	10 (6%)	18 (9.8%)
Unknown	73 (41.7%)	80 (44%)	52 (29.9%)	51 (30.4%)	60 (32.6%)

[a] If Isotretinoin was discontinued prior to conception then exposure days was set to zero.

[b] Year Twelve, Thirteen, Fifteen, & Sixteen (Conception occurred within 30 days following last dose of Isotretinoin); In Year Fourteen ONLY (Conception occurred within 30 days following last dose of Isotretinoin; includes two cases (04004 and 04072) with an imputed stop date).

[r] Modified from Year Twelve REMS Assessment Report Table 24, pg. 62; Year Thirteen REMS Assessment Report Table 23, pg.56; Year Fourteen REMS Assessment Report Table 22, pg. 61; Year Fifteen REMS Assessment Report Table 22, pg.60; and Year Sixteen REMS Assessment Report Table 22, pg.56.

Table 8. Summary of the most common contraceptive choices for pregnant and non-pregnant FRPs based on monthly interactions with iPLEDGE REMS[s]

Most Common Contraceptive Choices[t]		**No. of Monthly Interactions with the iPLEDGE system N (%)**				
Primary Contraceptive	**Secondary Contraceptive**	**Year 12** March 1, 2017 to February 28, 2018	**Year 13** March 1, 2018 to February 28, 2019	**Year 14** March 1, 2019 to February 29, 2020	**Year 15** March 1, 2020 to February 28, 2021	**Year 16** [ee] March 1, 2021 to December 10, 2021
Pregnant FRPs						
Birth control pills	Male latex condoms	441 (56.68%)	454 (64.49%)	389 (61.45%)	325 (55.18%)	420 (61.67%)
Abstinence	None	143 (18.38%)	168 (23.86%)	162 (25.59%)	142 (24.11%)	127 (18.65%)
Non-pregnant FRPs						
Abstinence	None	541,027 (43.89%)	574,075 (44.02%)	618,810 (43.65%)	699,334 (44.59%)	702,676 (46.22%)
Birth control pills	Male latex condoms	423,552 (34.36%)	447,957 (34.35%)	484,936 (34.2%)	522,960 (33.34%)	479,309 (31.53%)

[s] Modified from Year Thirteen REMS Assessment Report Table 28, pg. 60; Year Sixteen REMS Assessment Report Table 28, pg.61.

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

Table 9. Summary of most common reasons for iPLEDGE REMS pregnancies as reported by prescriber and patient[u]

Reason for Pregnancy[v]	**Year 12** March 1, 2017 to February 28, 2018 **N=185** N (%)	**Year 13** March 1, 2018 to February 28, 2019 **N=182** N (%)	**Year 14** March 1, 2019 to February 29, 2020 **N=186** N (%)	**Year 15** March 1, 2020 to February 28, 2021 **N=189** N (%)	**Year 16** [e] March 1, 2021 to December 10, 2021 **N=184** N (%)
Prescriber					
Contraceptive Failure	52 (28.1)	15 (8.2)	26 (14.0)	38 (20.1)	30 (16.3)
Failure To Use Contraceptive On Date Of Conception	2 (1.1)	2 (1.1)	7 (3.8)	8 (4.2)	3 (1.6)
Did Not Use Two Methods Of Birth Control	64 (34.6)	65 (35.7)	48 (25.8)	43 (22.8)	56 (30.4)
Unsuccessful At Abstinence	34 (18.4)	48 (26.4)	49 (26.3)	43 (22.8)	41 (22.3)
Used Ineffective Contraception	3 (1.6)	2 (1.1)	0 (0)	4 (2.1)	3 (1.6)
Planned Pregnancy	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)
Other	1 (0.5)	10 (5.5)	6 (3.2)	5 (2.6)	9 (4.9)
Unknown**	15 (8.1)	35 (19.2)	49 (26.3)	44 (23.3)	43 (23.4)
Missing	16 (8.6)	10 (5.5)	9 (4.8)	15 (7.9)	15 (8.2)
Patient					
Contraceptive Failure	13 (7)	12 (6.6)	8 (4.3)	16 (8.5)	9 (4.9)
Failure To Use Contraceptive On Date Of Conception	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Did Not Use Two Methods Of Birth Control	16 (8.6)	20 (11)	22 (11.8)	20 (10.6)	10 (5.4)
Unsuccessful At Abstinence	5 (2.7)	7 (3.8)	5 (2.7)	5 (2.6)	6 (3.3)
Used Ineffective Contraception	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Possible Drug Interaction That May Decrease Effectiveness Of Hormonal Contraceptives	0 (0)	1 (0.5)	3 (1.6)	1 (0.5)	0 (0)
Planned Pregnancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	2 (1.1)	6 (3.3)	8 (4.3)	6 (3.2)	5 (2.7)
Unknown**	0 (0)	2 (1.1)	2 (1.1)	0 (0)	1 (0.5)
Missing	158 (85.4)	147 (80.8)	150 (80.6)	152 (80.4)	159 (86.4)

**No additional information provided.

[u] Modified from Year Thirteen REMS Assessment Report Table 31, pg. 65; Year 16 REMS Assessment Report Table 31, pgs.66-67.

[v] Categories are not mutually exclusive. Patients may appear in multiple categories.

Table 10. Number of patients registered in iPLEDGE REMS by patient risk category[w,e]

Risk Category	Cumulative Through Year 12 N (%)	Cumulative Through Year 13 N (%)	Cumulative Through Year 14 N (%)	Cumulative Through Year 15 N (%)	Cumulative Through Year 16 [e] N (%)
Females of reproductive potential	1,365,618 (47.03%)	1,521,923 (47.31%)	1,688,605 (47.56%)	1,869,714 (47.96%)	2,020,745 (48.15%)
Females of non-reproductive potential	86,246 (2.97%)	93,118 (2.89%)	100,442 (2.83%)	107,236 (2.75%)	113,821 (2.71%)
Males	1,451,728 (50%)	1,601,678 (49.79%)	1,761,670 (49.61%)	1,921,751 (49.29%)	2,061,877 (49.13%)
Total	**2,903,592**	**3,216,719**	**3,550,717**	**3,898,701**	**4,196,443**

[w] 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. Modified from Year Thirteen REMS Assessment Report Table 5, pg. 40; Year Sixteen REMS Assessment Report Table 4, pg.39.

Table **11**. Age of pregnant and non-pregnant FRPs[x]

Age (years)	**Year 12** March 1, 2017 to February 28, 2018		**Year 13** March 1, 2018 to February 28, 2019		**Year 14** March 1, 2019 to February 29, 2020		**Year 15** March 1, 2020 to February 28, 2021		**Year 16** [ee] March 1, 2021 to December 10, 2021	
	Non-Pregnant FRPs	**Pregnant FRPs[a]**	**Non-Pregnant FRPs**	**Pregnant FRPs[a]**	**Non-Pregnant FRPs**	**Pregnant FRPs[a]**	**Non-Pregnant FRPs**	**Pregnant FRPs[a]**	**Non-Pregnant FRPs**	**Pregnant FRPs[a]**
	N = 272,890 N (%)	**N = 175** N (%)	**N = 292,953** N (%)	**N = 182** N (%)	**N = 316,048** N (%)	**N = 174** N (%)	**N = 344,838** N (%)	**N = 168** N (%)	**N = 331,338** N (%)	**N = 184** N (%)
<12	533 (0.2)	0 (0)	1,119 (0.38)	0 (0)	1,337 (0.42)	0 (0)	1,453 (0.42)	0 (0)	1,610 (0.49)	1 (0.54)
12-15	33,053 (12.11)	1 (0.57)	36,143 (12.34)	5 (2.75)	39,700 (12.56)	2 (1.15)	43,668 (12.66)	2 (1.19)	45,240 (13.65)	1 (0.54)
16-19	89,705 (32.87)	26 (14.86)	96,760 (33.03)	31 (17.03)	102,544 (32.45)	38 (21.84)	112,330 (32.57)	33 (19.64)	106,767 (32.22)	25 (13.59)
20-29	100,336 (36.77)	108 (61.71)	107,820 (36.8)	109 (59.89)	117,231 (37.09)	105 (60.34)	130,780 (37.93)	96 (57.14)	122,588 (37.00)	116 (63.04)
30-39	34,230 (12.54)	36 (20.57)	35,674 (12.18)	34 (18.68)	38,656 (12.23)	25 (14.37)	40,317 (11.69)	34 (20.24)	38,981 (11.76)	38 (20.65)
40-44	8,295 (3.04)	4 (2.29)	8,674 (2.96)	1 (0.55)	9,224 (2.92)	3 (1.72)	9,245 (2.68)	1 (0.6)	9,304 (2.81)	2 (1.09)
45+	6,738 (2.47)	0 (0)	6,763 (2.31)	2 (1.1)	7,356 (2.33)	1 (0.57)	7,045 (2.04)	2 (1.19)	6,848 (2.07)	1 (0.54)

[a] Pregnancy data for each year is as of the data cut-off date for each year.

Table 12. Number of iPLEDGE REMS prescription authorization attempts denied by patient risk category[y]

Patient Risk Category	**Year 12** March 1, 2017 to February 28, 2018	**Year 13** March 1, 2018 to February 28, 2019	**Year 14** March 1, 2019 to February 29, 2020	**Year 15** March 1, 2020 to February 28, 2021	**Year 16** [e] March 1, 2021 to December 10, 2021
Females of reproductive potential	969,635	1,449,953	1,901,892	2,340,642	2,124,276
Males	331,186	609,328	797,166	907,026	777,502
Females of non-reproductive potential	12,939	23,780	31,776	33,030	31,541
Total	**1,313,760**	**2,083,061**	**2,730,834**	**3,280,698**	**2,933,319**

Note: An electronic verification system (switch solution) for the iPLEDGE Program was approved in the June 2017 REMS Major Modification and implemented March 19, 2018 which was after Year Twelve. The first REMS assessment with data from the new system was Year Thirteen.

[x] Modified from Year Thirteen REMS Assessment Report Table 27, pg. 59; Year Sixteen REMS Assessment Report Table 27, pg.60.

[y] Modified from Year Thirteen REMS Assessment Report Table 57, pg. 97; Year Sixteen REMS Assessment Report Table 60, pg.93.

Table **13**. Summary of reasons for iPLEDGE REMS prescription denials[z]

Denial Reason	Year 12 March 1, 2017 to February 28, 2018 N (%)	Year 13 March 1, 2018 to February 28, 2019 N (%)	Year 14 March 1, 2019 to February 29, 2020 N (%)	Year 15 March 1, 2020 to February 28, 2021 N (%)	Year 16 * March 1, 2021 to December 10, 2021 N (%)
Required to Demonstrate Comprehension	675,237 (64.61)	944,347 (45.33)	1,182,017 (43.28)	1,411,246 (43.02)	1,308,232 (44.60)
Requires Confirmation Only	171,087 (16 37)	775,565 (37.23)	1,008,355 (36.92)	1,138,209 (34.69)	970,496 (33.09)
Patients attempting to fill a second prescr	74,775 (7.15)	n/a	n/a	n/a	n/a
Patient Received Drug	n/a	82,266 (3 95)	166,941 (6.11)	306,833 (9.35)	257,152 (8.77)
Prescription Expired	65,827 (6.3)	96,598 (4.64)	113,792 (4.17)	116,371 (3.55)	121,046 (4.13)
Registered Only FRP	n/a	53,109 (2 55)	71,863 (2.63)	90,283 (2.75)	74,646 (2.54)
Inactive	29,875 (2.86)	47,099 (2 26)	55,700 (2.04)	65,249 (1.99)	55,006 (1.88)
19 Day Wait	18,315 (1.75)	29,008 (1 39)	40,621 (1.49)	45,503 (1.39)	46,865 (1.60)
Registered Only FNRP/Male	n/a	30,898 (1.48)	40,466 (1.48)	43,407 (1.32)	39,107 (1.33)
Prescription Dispensed at another pharm	5,998 (0.57)	n/a	n/a	n/a	n/a
Multiple Patients Found	n/a	5,763 (0.28)	22,272 (0.82)	28,734 (0.88)	31,426 (1.07)
Pharmacy Not Activated	n/a	6,914 (0.33)	16,571 (0.61)	18,853 (0.57)	15,464 (0.53)
Abstinence Switch	n/a	5,971 (0.29)	5,524 (0.2)	8,213 (0 25)	6,538 (0.22)
Post Therapy	1,678 (0.16)	3,414 (0.16)	4,579 (0.17)	5,329 (0.16)	5,358 (0.18)
Permanently Lost to Follow Up	1,966 (0.19)	1,029 (0.05)	1,424 (0.05)	1,741 (0.05)	1,346 (0.05)
Lost to Follow Up	286 (0.03)	338 (0.02)	434 (0.02)	434 (0.01)	444 (0.02)
Patients with requested data element cha	30 (0)	n/a	n/a	n/a	n/a
FNRP Wait	n/a	91 (0)	152 (0.01)	128 (0)	94 (0)
Reported Positive	14 (0) Note: reported/confirmed positive were reported as one	106 (0.01)	54 (0)	97 (0)	42 (0)
Confirmed Positive		38 (0)	46 (0)	29 (0)	26 (0)
Change FRP Neg Test Wait	n/a	92 (0)	16 (0)	21 (0)	28 (0)
Patient Not Registered	n/a	29 (0)	6 (0)	8 (0)	2 (0)
Change FRP No Test Wait	n/a	n/a	1 (0)	5 (0)	1 (0)
Unknown	n/a	3 (0)	n/a	n/a	n/a
False Positive	n/a	2 (0)	n/a	n/a	n/a
Other	n/a	1 (0)	n/a	n/a	n/a
Total	**1,045,088**	**2,083,061**	**2,730,834**	**3,280,693**	**2,933,319**

n/a- item was not reported or data was not available for the listed denial reason during the reporting year.
Note: An electronic verification system (switch solution) for the iPLEDGE REMS was approved in the June 2017 REMS Major Modification and implemented March 19, 2018 which was after Year Twelve. The first REMS assessment with data from the new system was Year Thirteen.

* The Year Sixteen REMS Assessment was a bridge report that had a reporting period of nine months duration. A bridging report was needed due to the transition of the iPLEDGE system with a change to the new vendor and iPLEDGE REMS platform.

[z] Modified from Year Twelve REMS Assessment Report Table 55, pg. 95; Year Thirteen REMS Assessment Report Table 59, pg.98; Year Fourteen REMS Assessment Report Table 61, pg. 103; Year Fifteen REMS Assessment Report Table 62, pg.106; and Year Sixteen REMS Assessment Report Table 62, pg.93.

Table **14**. Summary of iPLEDGE REMS pregnancy outcomes [aa]

Pregnancy Outcome	Year 12 March 1, 2017 to February 28, 2018 (N =185)	Year 13 March 1, 2018 to February 28, 2019 (N =182)	Year 14 March 1, 2019 to February 29, 2020 (N = 186)	Year 15 March 1, 2020 to February 28, 2021 (N = 189)	Year 16 * March 1, 2021 to December 10, 2021 (N = 184)	Cumulative Since Program Inception (N = 2,720)
Number of Outcomes [a]	**185**	**182**	**187**	**189**	**184**	**2,724**
Elective Termination	81	72	88	74	62	1,263
Spontaneous Abortion	14	14	18	22	15	262
Missed Abortion	0	1	2	1	1	17
Ectopic Pregnancy	4	2	2	5	5	39
Still Birth	0	0	0	0	0	2
Live Birth	1	4	6	10	0	124
Still Continuing	0	40	0	1	53	54
Unknown	9	6	7	4	5	44
Lost to Follow-up [b]	**76**	**43**	**64**	**72**	**43**	**919**
No response from health care provider	7	8	8	9	4	76
Patient did not remain under health care provider's care	44	33	47	49	35	547
Health care provider left practice	0	0	0	0	0	0
Patient refused to participate	8	1	3	3	0	67
No response from patient	3	1	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

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

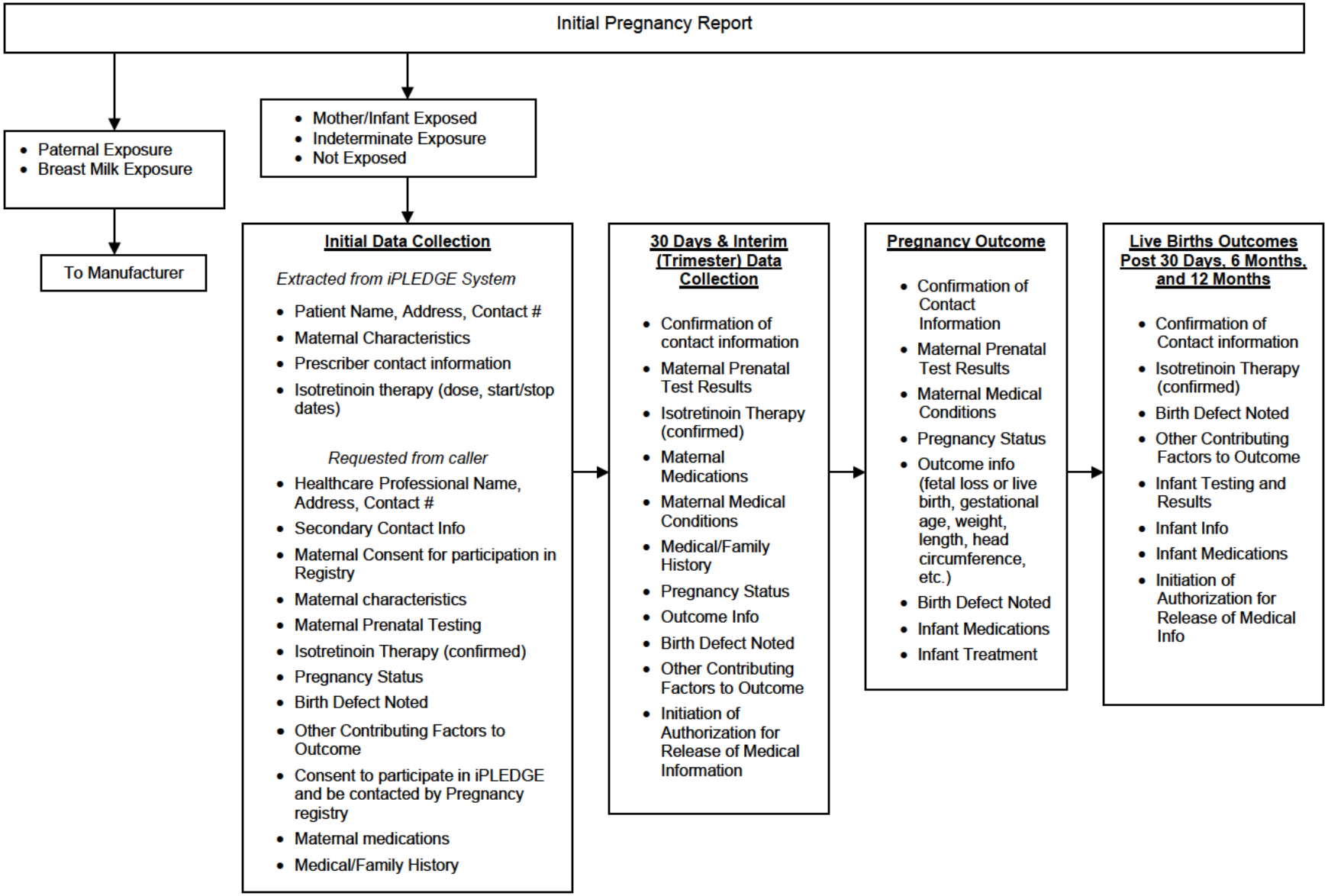
*Year Sixteen REMS Assessment was a bridge report that had a reporting period of nine months duration. A bridging report was needed due to the transition of the iPLEDGE system with a change to the new vendor and iPLEDGE REMS platform.

[aa] Modified from Year Thirteen REMS Assessment Report Table 36, pg. 73; Year Sixteen REMS Assessment Report Table 36, pg.73.

8.3 List of Approved Isotretinoin Products

Isotretinoin Product	Application Number	Manufacturer
Absorica, Absorica LD	NDA 021951 NDA 211913	Sun Pharmaceutical Industries
Amnesteem	ANDA 075945	Mylan Pharmaceuticals, Inc.
Claravis	ANDA 076356 ANDA 076135	Teva Pharmaceuticals USA, Inc.
Isotretinoin	ANDA 205063	Actavis Labs FL
Isotretinoin	ANDA 207792	Amneal Pharmaceuticals, LLC
Isotretinoin	ANDA 213571 ANDA 212333	Upsher-Smith Laboratories, LLC
Myorisan	ANDA 076485	Douglas Pharmaceuticals America LTD
Zenatane	ANDA 202099	Dr. Reddy's Laboratories, LTD.

8.4 iPLEDGE Pregnancy Registry Data Collection Flow


Initial Pregnancy Report
Paternal Exposure
Breast Milk Exposure
To Manufacturer
Mother/Infant Exposed
Indeterminate Exposure
Not Exposed
Initial Data Collection
Extracted from iPLEDGE System
Patient Name, Address, Contact #
Maternal Characteristics
Prescriber contact information
Isotretinoin therapy (dose, start/stop dates)
Requested from caller
Healthcare Professional Name, Address, Contact #
Secondary Contact Info
Maternal Consent for participation in Registry
Maternal characteristics
Maternal Prenatal Testing
Isotretinoin Therapy (confirmed)
Pregnancy Status
Birth Defect Noted
Other Contributing Factors to Outcome
Consent to participate in iPLEDGE and be contacted by Pregnancy registry
Maternal medications
Medical/Family History
30 Days & Interim (Trimester) Data Collection
Confirmation of contact information
Maternal Prenatal Test Results
Isotretinoin Therapy (confirmed)
Maternal Medications
Maternal Medical Conditions
Medical/Family History
Pregnancy Status
Outcome Info
Birth Defect Noted
Other Contributing Factors to Outcome
Initiation of Authorization for Release of Medical Information
Pregnancy Outcome
Confirmation of Contact Information
Maternal Prenatal Test Results
Maternal Medical Conditions
Pregnancy Status
Outcome info (fetal loss or live birth, gestational age, weight, length, head circumference, etc.)
Birth Defect Noted
Infant Medications
Infant Treatment
Live Births Outcomes Post 30 Days, 6 Months, and 12 Months
Confirmation of Contact information
Isotretinoin Therapy (confirmed)
Birth Defect Noted
Other Contributing Factors to Outcome
Infant Testing and Results
Infant Info
Infant Medications
Initiation of Authorization for Release of Medical Info

Risk Evaluation and Mitigation Strategy (REMS)

Isotretinoin (iPLEDGE®) Shared System REMS Program

I. Administrative Information

Initial Shared System REMS Approval: 10/2010
Most Recent REMS Update: 10/2022

II. REMS Goals

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

III. REMS Requirements

Isotretinoin Applicants must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare providers who prescribe isotretinoin must:	
To become certified to prescribe	1. Review the Prescriber Guide. 2. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.
Before treatment initiation (first dose)	3. Assess the patient's reproductive status using the Prescriber Guide. Document using the Patient Enrollment Form for Patients Who Can Get Pregnant or Patient Enrollment Form for Patients Who Cannot Get Pregnant. 4. For patients who cannot become pregnant: Counsel the patient on the risks of isotretinoin using the Fact Sheet. Document using the Patient Enrollment Form for Patients Who Cannot Get Pregnant. 5. For patients who can become pregnant: Counsel the patient on the risks of isotretinoin using the Fact Sheet and Guide for Patients Who Can Get Pregnant. Document using the Patient Enrollment Form for Patients Who Can Get Pregnant. 6. For patients who can become pregnant: Counsel the patient on the contraception requirements using the Guide for Patients Who Can Get Pregnant and Contraception Counseling Guide or refer the patient for expert counseling. Document using the Patient Enrollment Form for Patients Who Can Get Pregnant. 7. For patients who can become pregnant: Assess the patient's pregnancy status by ordering and confirming an initial, negative pregnancy test result. Document and submit the result to the REMS Program using the Patient Enrollment Form for Patients Who Can Get Pregnant. 8. Enroll the patient by completing and submitting the Patient Enrollment Form for Patients Who Can Get Pregnant or Patient Enrollment Form for Patients Who Cannot Get Pregnant. Provide a copy of the material to the patient.
Before treatment initiation (first dose); at least 19 days after the first pregnancy test and in the	9. For patients who can become pregnant who have regular menstrual cycles: Assess the patient's pregnancy status by ordering and confirming a second, negative, CLIA-certified

first 5 days of the menstrual period and immediately before treatment	pregnancy test result. Document and submit the result to the REMS Program.
Before treatment initiation (first dose); at least 19 days after the first pregnancy test and immediately before treatment	10. For patients who can become pregnant who have amenorrhea, irregular cycles, or use contraceptives that preclude withdrawal bleeding: Assess the patient's pregnancy status by ordering and confirming a second, negative, CLIA-certified pregnancy test result. Document and submit the result to the REMS Program.
During treatment; before each prescription	11. Assess the patient's current reproductive status. 12. For patients who cannot become pregnant: Counsel the patient on the risks of isotretinoin using the Fact Sheet. Document and submit confirmation of counseling to the REMS Program. 13. For patients who can become pregnant: Counsel the patient on the risks of isotretinoin and program requirements using the Guide for Patients Who Can Get Pregnant and Contraception Counseling Guide. Document and submit confirmation of counseling to the REMS Program. 14. For patients who can become pregnant: Document and submit the patient's contraception to the REMS Program.
During treatment, within 7 days before each prescription	15. For patients who can become pregnant: Assess the patient's pregnancy status by ordering and reviewing a CLIA-certified pregnancy test. Document and submit the results to the REMS Program.
During treatment, on the date of the last dose	16. For patients who can become pregnant: Assess the patient's pregnancy status by ordering and reviewing a CLIA-certified pregnancy test. Document and submit the results to the REMS Program.
After treatment discontinuation, 30 days after the date of the last dose	17. For patients who can become pregnant: Assess the patient's pregnancy status by ordering and reviewing a CLIA-certified pregnancy test. Document and submit the results to the REMS Program.
To maintain certification to prescribe, annually	18. Review the Prescriber Guide. 19. Re-activate in the REMS Program by completing the reactivation.
At all times	20. Prescribe no more than a 30 days' supply 21. Not prescribe refills 22. Report pregnancies to the REMS Program.

2. Patients who can become pregnant who are prescribed isotretinoin:

Before treatment initiation, for 30 days	1. Adhere to the safe use condition: use contraception and not get pregnant as described in the Guide for Patients Who Can Get Pregnant.
Before treatment initiation	2. Receive counseling from the prescriber on the risks of isotretinoin and the REMS program requirements. 3. Receive counseling from the prescriber or another expert on the contraception requirements. 4. Review the Fact Sheet and Guide for Patients Who Can Get Pregnant. 5. Enroll in the REMS Program by completing the Patient Enrollment Form for Patients Who Can Get Pregnant with the prescriber. Enrollment information will be provided to the REMS Program. 6. Get two pregnancy tests as directed by your prescriber.

During treatment; before each prescription	7. Receive counseling on the risks of isotretinoin and the REMS program requirements. 8. Get a pregnancy test as directed by your prescriber. 9. Complete the Comprehension Questions.
During treatment, within 7 days of the last pregnancy test	10. Get your isotretinoin from the pharmacy.
During treatment and after treatment discontinuation; for 30 days	11. Adhere to safe use conditions: Use contraception as described in the Guide for Patients Who Can Get Pregnant; not take isotretinoin if pregnant, breastfeeding, or not using contraception; not get pregnant; and not donate blood.
At all times	12. Inform the prescriber if you become pregnant. 13. Adhere to safe use conditions: Not share isotretinoin.

3. Patients who cannot become pregnant who are prescribed isotretinoin:

Before treatment initiation	1. Receive counseling from the prescriber on the risk of isotretinoin and the program requirements. 2. Review the Fact Sheet. 3. Enroll in the REMS Program by completing the Patient Enrollment Form for Patients Who Cannot Get Pregnant with the prescriber. Enrollment information will be provided to the REMS Program.
During treatment; before each prescription	4. Receive counseling on the risks of isotretinoin and the program requirements.
During treatment; within 30 days of your last office visit	5. Get your isotretinoin from the pharmacy.
During treatment and after treatment discontinuation; for 30 days	6. Adhere to safe use conditions: Not donate blood.
At all times	7. Adhere to safe use conditions: Not share isotretinoin.

4. Pharmacies that dispense isotretinoin must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Pharmacist Guide. 3. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program. 4. Train all relevant staff involved in dispensing using the Pharmacist Guide. 5. Establish processes and procedures to document the authorization number for each prescription. 6. Establish processes and procedures to not dispense an isotretinoin prescription after the date provided by the REMS Program, and to reverse the authorization to dispense the prescription if needed, and steps to return isotretinoin to inventory.
Before dispensing	7. Obtain authorization to dispense each prescription by contacting the REMS Program to verify the prescriber is certified, the patient is enrolled, the patient counseling is complete, and dispensing is within the designated timeframe. For patients who can become pregnant: the patient is not pregnant, the patient's contraception is confirmed, and the patient's monthly comprehension questions are complete. 8. Document the authorization number for each prescription through the processes and procedures established as a requirement of the REMS Program.

To maintain certification to dispense, annual	9. Have the authorized representative re-enroll in the REMS Program.
At all times	10. Not dispense more than a 30 days' supply. 11. Not dispense refills. 12. Not dispense after the date provided by the REMS Program, reverse the authorization to dispense, and return isotretinoin to inventory through the processes and procedures established as a requirement of the REMS program. 13. Return unused product to the manufacturer. 14. Not distribute, transfer, loan, or sell isotretinoin. 15. 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.

5. Wholesalers-distributors that distribute isotretinoin must:

To be able to distribute	1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies and authorized wholesalers with written consent from the isotretinoin manufacturer. 2. Train all relevant staff involved in distributing isotretinoin on the program requirements.
At all times	3. Distribute only to certified pharmacies and authorized wholesalers with written consent from the isotretinoin manufacturer. 4. Notify isotretinoin manufacturers of non-certified pharmacies or unauthorized wholesalers-distributors that attempt to order isotretinoin. 5. Return unused product to the manufacturer. 6. Maintain records of distribution information. 7. 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.

Isotretinoin Applicants must provide training to healthcare providers who prescribe isotretinoin.
The training must include the following educational materials: Prescriber Guide. The training must be available on the REMS Program website and available in a hardcopy format via mail.

Isotretinoin Applicants must provide training to pharmacies that dispense isotretinoin.
The training must include the following educational materials: Pharmacist Guide. The training must be available on the REMS Program website and available in a hardcopy format via mail.

To inform healthcare providers about the REMS Program and the risks and safe use of isotretinoin, Isotretinoin Applicants must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials & Dissemination Plans
Prescribers certified in the Isotretinoin REMS	**REMS Letter: Prescriber Communication Letter** 1. Email within 30 calendar days of approval of the REMS modification and again 15 calendar days later. a. Send by mail or fax within 7 calendar days of the date the second email was sent if email was reported undeliverable or unopened.
Authorized representatives for pharmacies certified in the Isotretinoin REMS	**REMS Letter: Pharmacy Representative Communication Letter** 1. Email within 30 calendar days of approval of the REMS modification and again 15 calendar days later

	a. Send by mail or fax within 7 calendar days of the date the second email was sent if email was reported undeliverable or unopened.
Healthcare providers likely to prescribe or dispense isotretinoin	**REMS Letter: Professional Organizations Communication Letter** and **Medical Organizations Communication Letter** 1. Disseminate, within 30 calendar days of the approval of the REMS modification, through the following professional societies and request the letter or content be provided to their members: a. National Community Pharmacists Association (NCPA), American Academy of Dermatology, Society of Dermatology Physician Assistants, National Association of Chain Drug Stores
Healthcare providers and patients	**Website Program Update** 1. Publish prominently on the public homepage at ipledgeprogram.com on the date of approval of the REMS modification. Display for 64 calendar days (December 10, 2021). **Website Pop-Up Message** 1. Publish prominently on the public homepage at ipledgeprogram.com on December 13, 2021 and display for 60 calendar days (February 15, 2022). The Message must appear with each visit to the homepage and require an active click to close it.

To support REMS Program operations, Isotretinoin Applicants must:

1. Establish and maintain a REMS Program website, ipledgeprogram.com. The REMS Program website must include the capability to complete prescriber and pharmacy enrollment online, to enroll and manage patients online, and the option to print the Prescribing Information, Medication Guide, and the REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
2. Make the REMS Program website fully operational and all REMS materials available through the REMS website and call center within 66 calendar days of REMS Modification (October 8, 2021).
3. Establish and maintain a REMS Program call center for REMS participants at 866-495-0654.
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
5. Ensure prescribers and pharmacies are able to enroll online and by phone.
6. Ensure prescribers are able to enroll patients online and by phone.
7. Ensure prescribers are able to report the patient's reproductive status, change in reproductive status, pregnancy test results, contraception choices to qualify patients to receive isotretinoin online and by phone.
8. Ensure prescribers are able to enroll designees online using the Office Staff Designees Activation Form.
9. Ensure prescribers are able to request an exemption on behalf of patients with a serious medical reason from the initial pregnancy testing requirements online and by fax using the Exemption for Patients with Serious Medical Reasons Who Can Get Pregnant.
10. Ensure patients who can become pregnant are able to complete the Comprehension Questions online and by phone.
11. Ensure pharmacies are able to obtain authorization to dispense online and by phone. For patients who can become pregnant, the authorization is valid for 7 days from the date of the last pregnancy test. For patients who cannot become pregnant, the authorization is valid for 30 days from the date of the last office visit and be provided with the date not to dispense isotretinoin after.
12. Ensure prescribers are able to report pregnancies online and by phone.
13. Ensure patients are able to report pregnancies by phone.
14. Provide Prescriber Enrollment Form, Prescriber Guide, and the Prescribing Information to Healthcare Providers who (1) attempt to prescribe isotretinoin and are not yet certified or (2) inquire about how to become certified.
15. Provide Recognizing Psychiatric Disorders in Adolescents and Young Adults to healthcare providers upon request.

16. Provide certified prescribers access to the database of enrolled patients and certified pharmacies.
17. Provide pharmacies access to the database of enrolled patients and certified prescribers.
18. Establish and maintain a registry which includes a reporting and collection system for all patients who become pregnant to provide information on pregnancy outcomes and root cause of pregnancy.
19. Ensure that once a report suggestive of pregnancy is received, the Isotretinoin Applicants follow up to obtain all required data for the registry.

To ensure REMS participants compliance with the REMS Program, Isotretinoin Applicants must:

20. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: isotretinoin distribution and dispensing, certification of prescribers and pharmacies, enrolled patients, and audits of REMS participants. These records must be readily available for FDA inspections.
21. Establish and maintain a plan for addressing noncompliance with REMS Program requirements, Non-Compliance Action Policy.
22. Monitor prescribers and their designees, pharmacies, patients, and wholesalers-distributors on an ongoing basis to ensure the requirements are being met. Take corrective action if noncompliance is identified, including de-certification and disenrollment.
23. Monitor and ensure that patients have been assigned correctly to one of the following patient risk categories: Confirm risk category during the patient enrollment process:
    - Patients who can become pregnant: cisgender females (born a female with a uterus and at least one ovary), transgender males (born female with a uterus and at least one ovary, transitioned to a male).
    - Patients who cannot become pregnant: cisgender male (born a male), cisgender females and transgender males that have undergone a hysterectomy, cisgender females and transgender males that have undergone a bilateral oophorectomy, cisgender females and transgender males who are post-menopausal according to the Prescriber Guide, transgender female (born male and transitioned to female).
24. Audit 10% of certified pharmacies annually (maximum 400) that have ordered isotretinoin in the previous 12 months to ensure that all processes and procedures are in place, functioning, and support the REMS Program requirements.
25. Audit wholesalers-distributors no later than 180 calendar days after the wholesaler-distributor is authorized and annually thereafter to ensure that all processes and procedures are in place, functioning, and support the REMS Program requirements. The annual audit must include all wholesalers-distributors that distributed isotretinoin in the previous 12 months.
26. Take reasonable steps to improve implementation and compliance with the requirements in the Isotretinoin REMS Program based on monitoring and evaluation of the Isotretinoin REMS Program.

IV. REMS Assessment Timetable

Isotretinoin NDA Applicants must submit REMS assessments to the FDA on March 1, 2024, and every two years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Isotretinoin NDA Applicants must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Isotretinoin REMS Program:

Enrollment Forms

Prescriber

1. Prescriber Enrollment Form

Patient

2. Patient Enrollment Form for Patients Who Can Get Pregnant
3. Patient Enrollment Form for Patients Who Cannot Get Pregnant

Pharmacy

4. Pharmacy Enrollment Form

Training and Educational Materials

Prescriber

5. Prescriber Guide

Patient

6. Guide for Patients Who Can Get Pregnant
7. Fact Sheet
8. Contraception Counseling Guide
9. Comprehension Questions

Pharmacy

10. Pharmacist Guide

Patient Care Forms

11. Exemption for Patients with Serious Medical Reasons Who Can Get Pregnant

Communication Materials

12. Prescriber Communication Letter
13. Pharmacy Representative Communication Letter
14. Professional Organizations Communication Letter
15. Medical Organizations Communication Letter
16. Website Program Update
17. Website Pop-Up Message

Other

18. REMS Program Website
19. Office Staff Designees Activation Form
20. Recognizing Psychiatric Disorders in Adolescents and Young Adults
21. Non-Compliance Action Policy