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iPLEDGE®
Committed to Pregnancy Prevention

The iPLEDGE REMS

Prescriber Guide

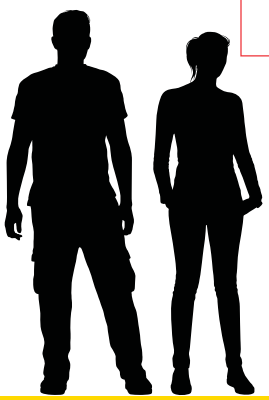


This guide is for healthcare providers who prescribe isotretinoin. It contains resources to help you understand the iPLEDGE REMS requirements. It will also help you guide your patients to prepare, plan treatments, and prevent pregnancies during the course of isotretinoin treatment.

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What is Isotretinoin?

Isotretinoin is used to treat severe recalcitrant nodular acne. Isotretinoin belongs to a class of drugs known as retinoids, commonly understood to include all natural and synthetic analogues of vitamin A. Treatment with isotretinoin should not be undertaken before conventional treatment has been tried first, including the use of systemic antibiotic therapy, and the patient has been fully counseled about the warnings and precautions in the isotretinoin package insert.

What is the Most Important Information I Should Know About Isotretinoin?



Isotretinoin is teratogenic and must not be used when pregnant. Patients should not get pregnant while taking isotretinoin and for 1 month after treatment is discontinued. A patient who gets pregnant during treatment should stop taking isotretinoin and immediately contact the prescriber.

All patients should be counseled on the following:

- to not donate blood at any time while taking isotretinoin and for 1 month after the last dose
- to not breastfeed while taking isotretinoin and for 1 month after the last dose
- to never share your isotretinoin with anyone else.

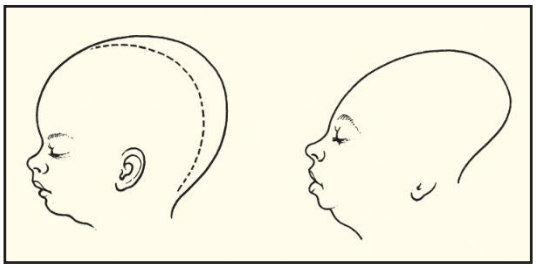
Birth Defects

There is an extremely high risk that a deformed infant will result if pregnancy occurs while patients who **can** get pregnant are taking isotretinoin in any amount, even for short periods of time. Potentially, any fetus exposed during pregnancy can be affected. Not every fetus exposed to isotretinoin has resulted in a deformed child. However, there are no accurate means of determining which fetus has been affected and which fetus has not been affected.

When isotretinoin is taken during pregnancy, it has been associated with fetal malformations, and there is an increased risk for spontaneous abortions and premature birth. **The following human fetal abnormalities have been documented.**

External Abnormalities

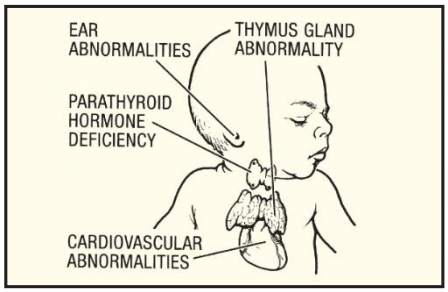
Skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate.



Line drawing represents the possible abnormalities of the low-set, deformed, or absent ears; wide-set eyes; depressed bridge of nose; enlarged head; and small chin.

Internal Abnormalities

CNS abnormalities including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit; cardiovascular abnormalities; thymus gland abnormalities; parathyroid hormone deficiencies. In some cases, death has occurred with certain of the abnormalities noted.



Line drawing represents the possible abnormalities of the brain, heart, and thymus gland that may occur

Pregnancy After Isotretinoin Treatment

The terminal elimination half-life of isotretinoin varies but is generally within 10 to 20 hours. The elimination half-life of 1 of the isotretinoin metabolites, 4-oxoisotretinoin, is approximately 25 hours. Since plasma elimination is host dependent, prescribers should warn patients not to get pregnant for 1 month post treatment. Women who get pregnant during this month should be counseled as to the outcome data. In 1989, Dai et al reported the results of an epidemiologic study of pregnancies that occurred in women who conceived after discontinuing isotretinoin.[2] They studied women from 5 days to more than 60 days between the last dose of isotretinoin and conception. The incidence of birth defects in former isotretinoin patients was not significantly different from the rate in the general population.

Isotretinoin is found in the semen of male patients taking isotretinoin, but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin-induced embryopathy is unknown, 20 years of post-marketing reports include 4 with isolated defects compatible with features of retinoid-exposed fetuses; however, 2 of these reports were incomplete, and 2 had other possible explanations for the defects observed.

Other Important Safety Information

Isotretinoin may cause depression, psychosis, and/or suicide. Some patients taking isotretinoin have had thoughts about hurting themselves or suicidal thoughts. Instruct the patient to stop isotretinoin and call you right away if the patient or a family member notices any signs and symptoms of depression or psychosis. Additional information is available in the REMS material **Recognizing Psychiatric Disorders in Adolescents and Young Adults.**

What is the iPLEDGE® REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a program required by the Food and Drug Administration (FDA) to help ensure that the benefits of a drug outweigh its risks.

When there is a REMS, drug companies, healthcare providers, and pharmacies must take extra steps to make sure the benefits of using the drug are greater than the risks.

Because of the serious risk of embryo-fetal toxicity, isotretinoin can only be marketed under a special restricted distribution REMS called "iPLEDGE REMS".

The iPLEDGE REMS is a computer-based risk management system that uses verifiable, traceable links between the prescriber, patient, pharmacy, and wholesaler to control prescribing, using, dispensing, and distribution of isotretinoin.

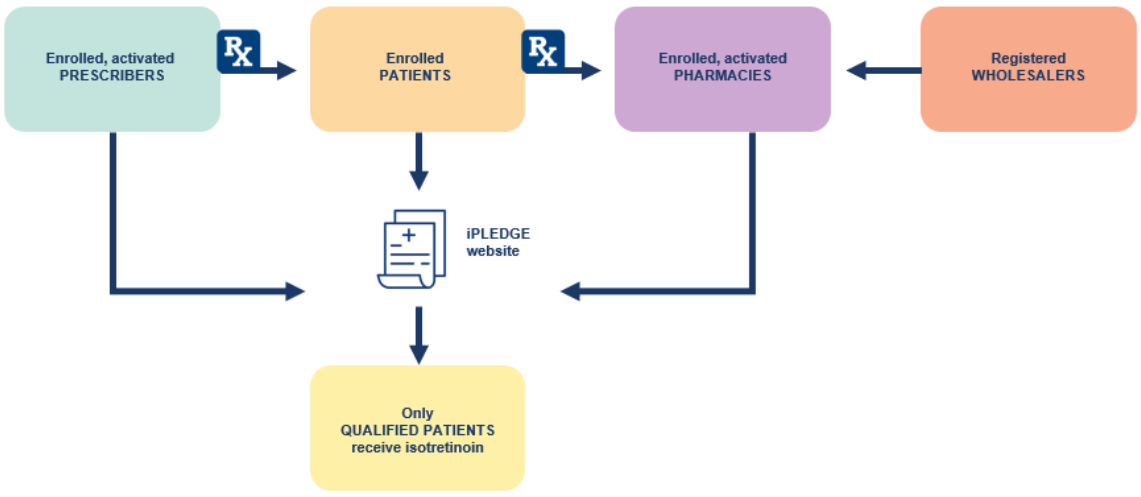
The iPLEDGE REMS is a shared (includes multiple manufacturers) Risk Evaluation and Mitigation Strategy (REMS) with requirements for prescribers, pharmacies, patients, and wholesalers. The iPLEDGE REMS also includes a pregnancy registry for patients who get pregnant.

The goal of the iPLEDGE REMS is to mitigate the risk of embryo-fetal toxicity.

a. Patients' reproductive status is assessed to determine who can get pregnant.
b. Patients who can get pregnant agree to use contraception or abstinence.
c. Before treatment initiation, patients who can get pregnant have a negative confirmatory pregnancy test.
d. During treatment, patients who can get pregnant have a pregnancy test prior to each dispense.

Isotretinoin must only be prescribed by prescribers enrolled and activated in the iPLEDGE REMS. Isotretinoin must only be dispensed by pharmacies enrolled and activated in the iPLEDGE REMS and must only be dispensed to patients enrolled and meet all the requirements of the iPLEDGE REMS.

Traceable links of the iPLEDGE REMS



How Do Prescribers Enroll in the iPLEDGE REMS?

You must enroll in the REMS by completing and submitting the **Prescriber Enrollment Form** on the iPLEDGE REMS website.

You must activate your iPLEDGE® enrollment in the **iPLEDGE REMS website** before you can prescribe isotretinoin.

You must re-activate annually to continue to be able to prescribe

The **iPLEDGE REMS website** will report the expiration date of your activation. To retrieve this information:

- On the website, log in and choose “My Profile” on the menu
- In the phone system, log in and select Additional Options then select the option to hear “Program Status”

You should review the **Prescriber Guide** to understand the REMS requirements (see Prescriber Requirements sections below).

During the enrollment and activation process, you must review and acknowledge the Prescriber Agreement found on the enrollment form.



Assess Reproductive Status and Determine Patient Category

Before enrolling your patient in the iPLEDGE REMS, you must assess the patient's reproductive status to determine the appropriate patient category based on the iPLEDGE REMS definitions below.

iPLEDGE REMS Definition of Patient Categories

Patient Who Can Get Pregnant	Patient Who Can NOT Get Pregnant
• Has a uterus and at least one ovary	• Born without a uterus or ovaries • Has undergone a hysterectomy (surgical removal of the uterus) • Has undergone a bilateral oophorectomy (surgical removal of both ovaries) • Is post-menopausal according to the iPLEDGE REMS definition*

* A patient is considered post-menopausal if the following criteria have been met: 12 months of spontaneous amenorrhea, or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml, or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

A patient is considered post-menopausal if the following criteria have been met:

- 12 months of spontaneous amenorrhea, or
- 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml, or
- 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

Please note that the following conditions still require a patient to be classified as a patient who can get pregnant:

- Tubal Sterilization
- Male Partner Vasectomy
- Abstinence
- Patient has not had a first menstrual period (pre-menarche)
- Patient is currently in menopause (but not yet post-menopausal)

NOTE: The iPLEDGE REMS Sponsors monitor and investigate Patient Classification, and you may be required to provide documentation to support your Patient Classification request.* Intentional falsification of Patient Classification type that is determined to be an attempt to violate REMS requirements is defined as non-compliance in the Non-Compliance Action Policy. This may result in permanent deactivation from the iPLEDGE REMS and a permanent loss of isotretinoin prescribing privilege.

Clinical documentation may be requested by the iPLEDGE REMS to support the classification of a patient who **cannot get** pregnant.

*Examples of clinical documentation include the following: healthcare professional's name, address, and date of hysterectomy, date of bilateral oophorectomy, documentation (certified laboratory tests documenting hormonal deficiency), confirming permanent cessation of previously occurring menses as a result of ovarian failure).

Prescriber Requirements for Patients Who Can Get Pregnant

- **Before initiating treatment with isotretinoin, I must:**
  - Assess the patient's reproductive status and document using the **Patient Enrollment Form for Patients Who Can Get Pregnant.**
  - Counsel the patient on the risks of isotretinoin and REMS requirements using the **Guide for Patients Who Can Get Pregnant.** Document using the **Patient Enrollment Form for Patients Who Can Get Pregnant.**
  - Counsel the patient on the pregnancy prevention requirements using the **Guide for Patients Who Can Get Pregnant** or provide the **Contraception Counseling Guide** and refer the patient for expert counseling. Document using the **Patient Enrollment Form for Patients Who Can Get Pregnant**.
  - Assess the patient's pregnancy status by reviewing a screening pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a negative result. Document and submit the result to the REMS using the **Patient Enrollment Form for Patients Who Can Get Pregnant**
  - Enroll the patient by completing and submitting the **Patient Enrollment Form for Patients Who Can Get Pregnant on the iPLEDGE website**. Provide a copy of the Informed Consent to the patient.
  - For a patient who can get pregnant with regular menstrual cycles:
    - During the first 5 days of the patient's menstrual period, immediately before starting isotretinoin treatment and after the patient has used their chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) for 1 month:
      - Assess the patient's pregnancy status by reviewing a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a second negative result. Document and submit the result to the REMS.
  - For a patient who can get pregnant with amenorrhea, irregular cycles, or using a contraceptive form that precludes withdrawal bleeding:
    - Right before starting isotretinoin treatment and after the patient has used their chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) for 1 month:
      - Assess the patient's pregnancy status by reviewing a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a second negative result. Document and submit the result to the REMS.

- For patients who can get pregnant who miss the 7-day prescription window and have not started isotretinoin:
- Assess the patient's pregnancy status by repeating a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a negative pregnancy test result. Document and submit the result to the REMS.

- **During isotretinoin treatment, before each prescription I must**
  - Assess the patient's current reproductive status.
    - If there is a change in the patient's reproductive status, follow the steps on the iPLEDGE REMS website to change the patient category before continuing.
  - Counsel the patient on the risks of isotretinoin and REMS requirements using the **Guide for Patients Who Can Get Pregnant**. Document and submit confirmation of counseling to the REMS.
  - Document and submit the patient's chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) to the REMS
  - Within 7 days before each prescription:
    - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.
  - For patients who can get pregnant who miss the 7-day prescription window:
    - Assess the patient's pregnancy status by repeating a pregnancy test and confirming a negative result. Document and submit the result to the REMS.
- **During isotretinoin treatment, on the date of the last dose, I must**
  - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.
- **After treatment discontinuation, 30 days after the date of the last dose, I must**
  - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.
- **At all times, I must**
  - Prescribe no more than a 30-day supply
  - Not prescribe refills
  - Report pregnancies to the REMS

Pregnancy Prevention Requirements and Counseling

• Contraception Counseling

- I must ensure that each individual patient receives adequate counseling about all pregnancy prevention options (including abstinence) and that the patient knows how to select and use **2** separate iPLEDGE REMS–effective forms of contraception that will give the patient the lowest failure rate.
- The patient must understand the critical responsibility assumed in electing to undertake treatment with isotretinoin and that any form of birth control, apart from complete abstinence, can fail.

• What are the goals for counseling?

At the end of counseling, your patient should understand the following:

- Understand and commits fully to not becoming pregnant
- Understand the options to prevent pregnancy
  - Commits to using 2 forms of contraception together at all times, consistently, and correctly. The patient must use 2 forms of effective contraception for at least 1 month prior to initiation of isotretinoin treatment, during isotretinoin treatment, and for 1 month after discontinuing isotretinoin treatment OR
  - Commits fully to abstinence, not having any sexual contact (penis-vaginal) with a partner that could result in pregnancy. This commitment is required 24 hours a day, 7 days a week for 1 month before, during, and for 1 month after the patient stops taking isotretinoin
- Chooses the pregnancy prevention methods (i.e., 2 forms of contraception or abstinence) that will work best for the patient and that the patient and the partner will actually use
- If, after counseling, the patient recognizes they will not be able to commit fully to the iPLEDGE REMS pregnancy prevention requirements , encourage the patient to not take isotretinoin and do not prescribe isotretinoin to this patient
- Knows what to do if contraception failure occurs, including emergency contraception options
- Understands the risk of having a child with significant birth defects from exposure to isotretinoin

• Counseling younger teens

For younger teens, it is important to stress the following aspects of contraception for the iPLEDGE REMS during counseling:

- Why it is important to use 2 forms of birth control, 1 primary and 1 secondary, at all times. Younger teens may need more emphasis on this point to fully understand it and comply.
- Emergency contraception. Younger teens may need more explanation from you about the need to take immediate action if they have unprotected sexual contact with a partner that could result in pregnancy or if their contraception forms fail.

iPLEDGE® REMS Approved Forms of Contraception

iPLEDGE® Committed to Pregnancy Prevention

Choose 1 Primary + 1 Secondary Birth Control Form

Primary Form of Birth Control (Choose One)*	How to Use it		How Well it Works	Benefits †	Risks †
Hormonal Implant  ‡	Placed under the skin of the arm by a clinician. Works for 3 years.[1]		>99%[1]	• Nothing to do or remember • Light or no periods • May decrease acne • No increased risk of clots	• Irregular periods • Does not prevent the spread of any sexually transmitted infections (STIs) or HIV/AIDS
Hormonal IUD 	Placed in the uterus by the clinician. Self-check monthly. Works for 3-5 years.[1,2,3]		>99%[1]	• Light or no periods • No increased risk of clots	• Irregular periods • Does not prevent the spread of any STIs or HIV/AIDS
Non-Hormonal IUD 	Placed in the uterus by the clinician. Self-check monthly. Works for 10 years.[4]		>99%[1]	• No hormones • Periods remain regular • Effective immediately • No increased risk of clots	• May cause heavier periods and cramping • Does not prevent the spread of any STIs or HIV/AIDS
Tubal Sterilization 	A surgical procedure to close the tubes between the uterus and the ovaries.	MORE EFFECTIVE	>99%[5]	• It is a virtually permanent form of birth control • Nothing to do or remember	• If you want to have a child later, it is very difficult to re-open the tubes • Does not prevent the spread of any STIs or HIV/AIDS
Male Vasectomy 	A surgical procedure that closes off the tubes that carry a partner's sperm.		>99%[5]	• It is a virtually permanent form of birth control • Nothing to do or remember	• If you want to have a child later, it is very difficult to re-open the tubes • Does not prevent the spread of any STIs or HIV/AIDS
Hormonal Shot 	Given every 3 months by a clinician.		>97%[1]	• Light or no periods • No increased risk of clots	• Irregular periods • May cause weight gain • Does not prevent the spread of any STIs or HIV/AIDS
Vaginal Ring 	You place it in the vagina. Replace per prescriber's instructions.		92%[1]	• Lighter periods • May decrease acne	• Blood clots • Does not prevent the spread of any STIs or HIV/AIDS
Hormonal Patch 	You place it on the skin. Replace weekly.	MORE EFFECTIVE	92%[1]	• Lighter periods • May decrease acne	• Blood clots • Does not prevent the spread of any STIs or HIV/AIDS
Birth Control Pill (Combination Type) 	Swallow at the same time daily.		92%[1]	• Lighter periods • May decrease acne	• Blood clots • Does not prevent the spread of any STIs or HIV/AIDS

iPLEDGE® REMS Approved Forms of Contraception

iPLEDGE® Committed to Pregnancy Prevention

Choose 1 Primary + 1 Secondary Birth Control Form

Secondary Form of Birth Control (Choose One)	How to Use it	How Well It Works	Benefits	Risks
Male Latex Condoms (with or without spermicide)	Partner must be willing to use each and every time you have sex.	87%[6]	• Protects from STIs and HIV/AIDS	
Cervical Cap (must be used with spermicide)	Place in vagina before you have sex.	78%[6]	• You are in control of its use	• Does not prevent the spread of any STIs or HIV/AIDS
Diaphragm (must be used with spermicide)	Place in vagina before you have sex.	83%[6]	• You are in control of its use	• Does not prevent the spread of any STIs or HIV/AIDS
Vaginal Sponge	Place in vagina before you have sex.	83%[6]	• You are in control of its use	• Does not prevent the spread of any STIs or HIV/AIDS

*Consult your doctor if you are considering choosing 2 primary forms of birth control rather than a primary and secondary form.
†Benefits and Risks are not inclusive. Please review Full Prescribing Information for the products listed.
‡All pictograms from FDA website www.fda.gov/downloads/forconsumers/byaudience/forwomen/freepublications/ucm356451.pdf. Accessed January 20, 2016.

References 1. Werner CA, Papic MJ, Ferris LK, Schwartz EB. Promoting safe use of isotretinoin by increasing contraceptive knowledge. *JAMA Dermatol*. 2015;151(4):389-393. **2.** Skyla® Prescribing Information, Bayer HealthCare Pharmaceuticals Inc., February 2018. **3.** Liletta® Prescribing Information, Actavis Pharma, Inc., August 2017. **4.** PARAGARD® Prescribing Information, Cooper Surgical Inc., January 2018.
5. Trussell, J. Contraception failure in the United States. *Contraception*. 2011;83:397-404. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3638209/. Accessed September 9, 2014. **6**. Bradley SEK, Polis CB, Micks EA, Steiner MJ. Effectiveness, safety, and comparative side effects. In: Cason P, Cwiak C, Edelman A, et al, eds. Contraceptive Technology. 22nd ed. Jones & Bartlett Learning; 2023:130–131

Abstinence

For this REMS, all patients who **can** get pregnant must fully commit to pregnancy prevention. Isotretinoin is not recommended for any patient who **can** get pregnant who cannot or will not follow the pregnancy prevention requirements of the iPLEDGE® REMS.
Abstinence may be appropriate when it is a lifestyle choice, such as religious practice, and not just a social circumstance, such as not having a current partner. If, after counseling, a sexually active patient chooses abstinence, the patient must understand that the patient has committed to not having any sexual contact **(penis-vaginal)** with a partner that could result in pregnancy for 1 month before starting isotretinoin, while on isotretinoin, and for 1 month after stopping isotretinoin.

A patient who switches pregnancy prevention methods during treatment from abstinence to 2 forms of iPLEDGE approved contraception is required to wait for 30 days while consistently using 2 forms of birth control before continuing treatment. The patient will be required to have a negative pregnancy test, completed in a medical setting (e.g., prescriber's office, clinic, laboratory), which starts the 30-day wait period. When the 30-day wait period is over, the patient will need to have a second negative pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory), be confirmed by the prescriber in the iPLEDGE REMS system, and then complete the comprehension questions before continuing treatment.

One of the most common reasons for pregnancy is engaging in sexual contact (penis-vaginal) with a partner that could result in pregnancy when planning to be abstinent.

Unacceptable Forms of Contraception Include:

- Progesterone-only “mini-pills”, this includes the over-the-counter birth control option
- Female condoms
- Natural family planning (rhythm method or fertility awareness)
- Breastfeeding
- Withdrawal
- Cervical shield, a silicone disc with a one-way air valve that creates suction to adhere to the cervix *

*A cervical shield should not be confused with a cervical cap, which is an effective secondary form of contraception.

Patients currently using these unacceptable forms of contraception must switch to the iPLEDGE REMS approved forms of contraception at least 1 month before starting isotretinoin.

Referral For Contraception Counseling

Contraception counseling is an important part of the patient choosing **2** contraceptive forms. The counseling should be done by the prescriber or a healthcare professional with expertise in pregnancy prevention. If you are not comfortable with providing this counseling, you are encouraged to take advantage of the opportunity to refer patients to a qualified counselor.

Before beginning treatment, if you and your patient choose referral to a healthcare professional with expertise in pregnancy prevention, the makers of isotretinoin will reimburse 1 visit for contraception counseling. To facilitate the referral, complete the referral form found in the **Contraception Counseling Guide**, which should be taken to the contraception counselor by the patient or sent in advance. The form instructs the counselor to fill in the appropriate information and return it to the prescriber with the patient’s contraception choices to enter into the iPLEDGE REMS website. The second page of the form has information for the counselor on the reimbursement process. The contraception counselor should access the **Contraception Counseling Guide** to review the pregnancy prevention requirements and the effective forms of contraception of the iPLEDGE REMS.

Referring to a Gynecologist

You may want to specifically refer your patient to a gynecologist for an exam prior to starting oral contraceptive agents or a hormonal transdermal patch, insertion of an IUD or hormonal vaginal ring, fitting a diaphragm or a cervical cap, or for a more detailed explanation of contraception options. You may wish to ask for gynecologic consultation if:

- The patient’s history is suggestive of polycystic ovary syndrome (Stein-Leventhal syndrome). In addition to acne, there are conditions such as excessive facial hair growth, obesity, amenorrhea (no menstrual period) or irregular, heavy bleeding or anovulation.
- The patient has irregular menses, possibly related to pregnancy; an eating disorder; or endometriosis.
- There are indications of sexual abuse found during the physical examination or counseling session.
- There is a history or symptoms of sexually transmitted infection (STI).

What Steps Are Required if a Patient Wants to Switch Pregnancy Prevention Methods During Treatment?

If a patient chooses to change one or both of the 2 forms of iPLEDGE REMS-approved contraception that they have been using during treatment, prescribers can make the change on the iPLEDGE REMS website by navigating to the Patient Details page for the patient and clicking on the Patient Contraception tab.

A patient who switches from abstinence to 2 forms of iPLEDGE approved contraception is required to wait for 30 days while consistently using 2 forms of birth control before continuing treatment. The patient will be required to have a negative pregnancy test (screening), completed in a medical setting (e.g., prescriber's office, clinic, laboratory), which starts the 30-day wait period. When the 30-day wait period is over, the patient will need to have a second negative pregnancy test (confirmatory) completed in a medical setting (e.g., prescriber's office, clinic, laboratory), be confirmed by the prescriber in the iPLEDGE REMS system, and then complete the comprehension questions before continuing treatment.

What Should a Patient Know if Their Contraception Fails or if They Have Unprotected Sex?

Emergency Contraception

Emergency birth control is meant only for emergencies. It does NOT take the place of the patient's usual 2 forms of birth control, and it will not protect against sexually transmitted infections (STIs). Emergency birth control is not to be used instead of regular birth control and it does not work if the patient is already pregnant.

Emergency birth control is also called "after sex" or "morning after" birth control. It can prevent pregnancy after sex (penis-vaginal) without adequate protection. Emergency birth control prevents release of the egg, joining of the sperm and the egg, or implanting of the egg in the uterus. Emergency birth control is only for a patient who is sure they are not already pregnant.[1]

Emergency Contraceptive Pills (ECPs)—some must be used within 3 days; others must be used within 5 days of having sex penis-vaginal) without adequate protection. The sooner the patient takes ECPs, the more likely they are to work. It is best if ECPs are started within 12 hours after having sex without adequate protection.[1] Advise the patient that ECPs may cause severe nausea and advise the patient on appropriate treatment.

ECPs do not take the place of the patient's usual birth control, nor do they continue to prevent pregnancy during the rest of the menstrual cycle.

1: Emergency Contraception Review: Evidence-based Recommendations for Clinicians: Cleland K, Raymond E, Westley E, Trussel J. Clin Obstet Gynecol. 2014 Dec;57(4):741–750

When Would a Patient Need Emergency Birth Control?

A patient may need emergency birth control if they have had sex (penis-vaginal) without adequate protection, such as:

- Forgetting to take 2 or more birth control pills and having sex
- Having sex without using a second form of birth control
- Being late for their birth control hormonal shot and having sex
- Their partner's condom broke or slipped off
- Their diaphragm or cervical cap slipped out of place or ripped during sex

Where Can a Patient Get Emergency Birth Control?

A patient can get emergency birth control from:

- Private doctors or nurse practitioners
- Planned Parenthood
- Women's health centers
- Many hospital emergency rooms (unless they are owned by organizations opposing birth control)
- Available over the counter at pharmacies

The patient should also realize that emergency contraception should not be used on a regular basis as a replacement for the other contraceptive forms selected.

Pregnancy Test Requirements for Patients Who Can Get Pregnant

- **At patient enrollment**:
  - Assess the patient's pregnancy status by reviewing a screening pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a negative pregnancy test result.
  - **For a patient who can get pregnant with regular menstrual cycles:**
    - During the first 5 days of the patient's menstrual period, immediately before starting isotretinoin treatment and after the patient has used their chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) for 1 month:
      - Assess the patient's pregnancy status by reviewing a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a second negative result. Document and submit the result to the REMS.
    - The screening pregnancy test and confirmatory pregnancy test must be completed at least 30 days apart

- **For a patient who can get pregnant with amenorrhea, irregular cycles, or using a contraceptive form that precludes withdrawal bleeding**:
  - Immediately before starting isotretinoin treatment and after the patient has used their chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) for 1 month:
    - Assess the patient's pregnancy status by reviewing a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a second negative result. Document and submit the result to the REMS.
  - The screening pregnancy test and confirmatory pregnancy test must be completed at least 30 days apart.
- For patients who can get pregnant who miss the 7-day prescription window and have not started isotretinoin:
  - Assess the patient's pregnancy status by repeating a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a negative result. Document and submit the result to the REMS.

- **During treatment, before each prescription:**
  - Within 7 days before each prescription:
    - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.
  - For patients who can get pregnant who miss the 7-day prescription window :
    - Assess the patient's pregnancy status by repeating a pregnancy test and confirming a negative result. Document and submit the result to the REMS.

- **During treatment, on the date of the last dose:**
  - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.

- **After treatment discontinuation, 30 days after the date of the last dose:**
  - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.

Requirements and Additional Considerations for Prescribers Who Allow Patients to Complete Pregnancy Tests Outside of a Medical Setting (at-home pregnancy testing)

- Patients who can get pregnant can complete pregnancy tests using an over the counter pregnancy test for pregnancy tests during treatment and after treatment.
    - This is an option at discretion of prescriber and appropriate patient selection is important. Prescribers should be confident the patient can perform the test accurately and make sure it's not expired and stored correctly
- Prescribers that choose to allow 1 or more of their patients to complete pregnancy tests outside of a medical setting should be aware of the potential for patient misinterpretation of pregnancy test results when reporting to their prescriber, along with the potential for patient intentional falsification of pregnancy test results when reporting to their prescriber.
    - Patient misinterpretation or falsification of pregnancy test results submitted to their prescriber may increase the risk of embryo-fetal toxicity associated with isotretinoin.
    - It is the prescriber's responsibility to establish and follow processes and procedures to obtain results from patients and to minimize misinterpretation and falsification. Prescribers should develop a process that works for their workflow and this process should be documented and available for review by the REMS as needed.
        - Patient misinterpretation, falsification, and approaches to prescriber processes and procedures for mitigating the risk of misinterpretation and falsification have been described in scientific literature, described below.
            - Due to the COVID-19 Public Health Emergency and published guidance from the FDA[1], the iPLEDGE REMS allowed prescribers and patients who can get pregnant to use at-home pregnancy tests to determine the patient's pregnancy status. Patients were required to report the results and dates of these pregnancy tests to their prescriber, who were also required to report the results and dates to the iPLEDGE REMS.
                - During the period that the Public Health Emergency was in effect, one health institution reported that 15.7% of isotretinoin patients using home pregnancy tests during this timeframe intentionally falsified at-home pregnancy test results when reporting the results to their prescriber (N=89).[2]
                    - The institution reported that some patients that falsified pregnancy test results did so via submission of images of pregnancy tests found on the internet, reuse of previously submitted pregnancy test result images, and modification of previously submitted pregnancy test result images.[2]
                    - Similar methods of falsification were identified in a subsequent publication by a different institution.[3]

        - During the timeframe, clinicians surveyed about the use of at-home pregnancy tests for their isotretinoin patients expressed concern about the accuracy of at-home pregnancy tests (27%), concern about patient ability to interpret pregnancy tests appropriately (26%), and concern about patient deception (56%).[4]
    - Additionally, consumer interpretation of different at-home pregnancy test products have been reported to be unreliable.[5]
- Prescribers that choose to allow 1 or more of their patients to complete pregnancy tests outside of a medical setting should also be aware of reported institutional practices that were described as approaches to help mitigate against the risk of misinterpretation or intentional falsification of pregnancy tests results, including but not limited to:
    - Requiring that a patient submit images of their at-home pregnancy test result to their prescriber and that the submitted image include a hand-written date and patient initials/name.[3,4]
        - One institution requires the hand-written date and patient name be written with a dark marker.[4]
    - Requiring that patients submit images of both their home pregnancy test result and the test's interpretation instructions.[3]

1: Coronavirus (COVID-19) update: FDA provides update on patient access to certain REMS drugs during COVID-19 public health emergency. US Food and Drug Administration. **2**: Measuring the rate of patients' deliberate circumvention of iPledge pregnancy testing; Smith, Gideon P. et al., Journal of the American Academy of Dermatology, Volume 87, Issue 5, 1129 – 1130 **3:**Falsification of at-home isotretinoin pregnancy testing during the COVID-19 pandemic: A case series and proposal of mitigation strategies, Hadley Johnson, Alison Ranum, Matthew Mansh, Ronda S. Farah, David R. Pearson, JAAD Case Reports, Volume 28, Pages 49-53, ISSN 2352-5126, https://doi.org/10.1016/j.jdcr.2022.07.045. **4**: Commentary on intentional falsification of at-home pregnancy tests, Lalor, Leah et al., JAAD Case Reports, Volume 29, 167 – 168 **5**: Johnson S, Cushion M, Bond S, Godbert S, Pike J. Comparison of analytical sensitivity and women's interpretation of home pregnancy tests. Clin Chem Lab Med. 2015;53(3):391-402

What Are the Steps Needed for a Patient Who Can Get Pregnant to Become Eligible to Get Their Isotretinoin Prescription?

Before treatment initiation (first dose):

- Counsel the patient on the risks of isotretinoin and REMS requirements using the **Guide for Patients Who Can Get Pregnant**. Document using the **Patient Enrollment Form for Patients Who Can Get Pregnant**.
- Counsel the patient on the pregnancy prevention requirements using the **Guide for Patients Who Can Get Pregnant** or provide the **Contraception Counseling Guide** and refer the patient for expert counseling. Document using the **Patient Enrollment Form for Patients Who Can Get Pregnant**.
- Assess the patient's pregnancy status by reviewing a screening pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and

confirming a negative pregnancy test result. Document and submit the result to the REMS using the **Patient Enrollment Form for Patients Who Can Get Pregnant**.

- 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 Informed Consent to the patient.
- For a patient who can get pregnant with regular menstrual cycles:
  - During the first 5 days of the patient's menstrual period, immediately before starting isotretinoin treatment and after the patient has used their chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) for 1 month:
    - Assess the patient's pregnancy status by reviewing a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a second negative result. Document and submit the result to the REMS.
  - The screening pregnancy test and confirmatory pregnancy test must be completed at least 30 days apart
- For a patient who can get pregnant with amenorrhea, irregular cycles, or using a contraceptive form that precludes withdrawal bleeding:
  - Immediately before starting isotretinoin treatment and after the patient has used their chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) for 1 month:
    - Assess the patient's pregnancy status by reviewing a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a second negative result. Document and submit the result to the REMS.
  - The screening pregnancy test and confirmatory pregnancy test must be completed at least 30 days apart.
- For patients who can get pregnant who miss the 7-day prescription window and have not started isotretinoin:
  - Assess the patient's pregnancy status by repeating a confirmatory pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) and confirming a negative result. Document and submit the result to the REMS.

During treatment, before each prescription

- Assess the patient's current reproductive status.
- For patients who can get pregnant:
  - Counsel the patient on the risks of isotretinoin and REMS requirements using the **Guide for Patients Who Can Get Pregnant.** Document and submit confirmation of counseling to the REMS.
  - Document and submit the patient's chosen pregnancy prevention methods (i.e., 2 forms of contraception or abstinence [not having any sexual contact with a partner that could result in pregnancy]) to the REMS.
  - Within 7 days before each prescription:
    - Assess the patient's pregnancy status by reviewing a pregnancy test and confirming a negative result. Document and submit the result to the REMS.

- For patients who can get pregnant who miss the 7-day prescription window:
  - Assess the patient's pregnancy status by repeating a pregnancy test and confirming a negative pregnancy test result. Document and submit the result to the REMS.

Patient Prescription Window

Patients Who Can Get Pregnant have a specific period of time in which they can obtain their prescription. This is called the "prescription window".

The prescription window is 7 days and starts on the date that the urine or blood sample is taken for a pregnancy test ("Day of the pregnancy test"). This date is counted as DAY 1.

To determine the end date of their 7-day prescription window, these patients should add 6 days to the date that the blood or urine sample is taken. **For example:**

Day 1 Day of the pregnancy test	Day 2 – Day 6	Day 7 – Last day to obtain prescription
(Friday, March 1)	(Saturday, March 2 thru Wednesday, March 6)	(Thursday, March 7)

The 7-day timeframe to obtain the prescription expires at 11:59 p.m. Eastern Time on Day 7.

After 11:59 p.m. Eastern Time on the last day of the prescription window, the prescription can no longer be obtained, and the patient must start the process over to get a new prescription window.

Patient Comprehension Questions and Documentation of Pregnancy Prevention Methods

Prior to being able to obtain a prescription, patients who **can** get pregnant must answer questions about the iPLEDGE REMS and pregnancy prevention. In addition to answering the questions, the patient must also enter the 2 forms of birth control that the patient is using (or indicate that the patient is relying on abstinence).

- These questions must be answered after you have confirmed counseling, entered pregnancy test results and **2** contraceptive forms (or commitment to abstinence) into the iPLEDGE REMS website, but before the 7-day prescription window (allowable timeframe) for their prescription expires.
- Patients answer these questions via the website or phone system. (Access information is provided in the patient guide.) The patient may use their patient guide to help with the answers.
- The system provides questions in several specific categories and correct answers for those questions, with references to the appropriate patient education material.

- A replacement question in the same category is provided for an incorrectly answered question. If a patient misses a replacement question, the iPLEDGE REMS website will direct them to review the materials and try again at a later time. Patients may also contact you so that REMS education and counseling can be reinforced. The patient should also review educational materials and then answer the questions again.

What Happens If My Patient Misses the Prescription Window and Does Not Get Their Isotretinoin Prescription?

Missing the First Window (before treatment initiation)

- A repeat confirmatory pregnancy test must be completed in a medical setting. This test may be repeated as soon as the window is missed without a waiting period.
- You must confirm the patient counseling and enter the 2 contraceptive forms (or commitment to abstinence) again, and the patient must enter the 2 contraceptive forms (or commitment to abstinence) and complete the comprehension questions again.

Missing Subsequent Windows (during treatment)

- A repeat pregnancy test must be completed in a medical setting or may be completed by the patient outside a medical setting. This test may be repeated as soon as the window is missed without a waiting period.
- You must confirm the patient counseling and enter the 2 contraceptive forms (or commitment to abstinence) again, and the patient must enter the 2 contraceptive forms (or commitment to abstinence) and complete the comprehension questions again.

What Happens If Your Patient Gets Pregnant?

Counseling a Pregnant Patient

If a pregnancy does occur during isotretinoin treatment, isotretinoin must be discontinued immediately. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Reporting Pregnancy

The iPLEDGE® REMS Pregnancy Registry

The iPLEDGE REMS Pregnancy Registry collects data on pregnancies that occur in patients who get pregnant while taking isotretinoin and within 1 month of their last dose. 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. Information gathered in the iPLEDGE REMS Pregnancy Registry will be used for statistical purposes only and will be held in the strictest confidence.

You **must** report to the iPLEDGE REMS any pregnancy case that you become aware of while the patient is on isotretinoin and 1 month after the last dose. Report a pregnancy by calling **1-866-495-0654.** Select the option "To Report a Pregnancy." All pregnancies should also be reported to the FDA via the MedWatch number: **1-800-FDA-1088**.

In Patients Taking Isotretinoin

1. Positive pregnancy test results should be entered in the iPLEDGE REMS website. A Pregnancy Registry representative will call you.
2. You should call the iPLEDGE REMS Contact Center if you do not have a pregnancy test result but think that the patient is pregnant.

   After a healthcare provider or designee enters a positive pregnancy test or pregnant diagnosis into the iPLEDGE REMS website, the office will be contacted by a Pregnancy Registry representative. The prescriber or designee is strongly encouraged to provide all requested pregnancy-related details for the initial report and updates. Your contribution to this collaborative program will enable the Sponsors of the iPLEDGE REMS to make continuous evaluations and improvements and may help prevent pregnancies in the future.

In Partners of Patients Being Treated With Isotretinoin

If the prescriber becomes aware of a pregnancy in the partner of a patient taking isotretinoin, the prescriber should report this pregnancy to the iPLEDGE REMS Pregnancy Registry. The information will be forwarded to the manufacturer of the specific isotretinoin product for follow-up.

iPLEDGE® REMS Checklist

Patients Who Can Get Pregnant

BEFORE TREATMENT

PLANNING

- ☐ Verify patient who can get pregnant based on the patient category definitions.
- ☐ **Plan** for office visits, counseling, pregnancy testing.
- ☐ **Educate** patient about isotretinoin and the pregnancy prevention requirements of the iPLEDGE REMS.
- ☐ **Screen for pregnancy** with serum or urine pregnancy test, which must be completed in a medical setting (e.g., prescriber's office, clinic, laboratory). The pregnancy test must be negative for the patient to be enrolled in the iPLEDGE REMS.
- ☐ **Enroll** patient in the iPLEDGE REMS, ensure the patient can access their Patient ID number and educational materials.
- ☐ **Obtain** the Patient informed consent using the downloadable Informed Consent (for all patients) Form or the online Enrollment Form for Patients Who Can Get Pregnant

COUNSEL ON PREGNANCY PREVENTION METHODS

- ☐ **Counsel** patient or refer to a healthcare professional with expertise in contraception. Please see the "Referral for Contraception Counseling" section for information on referring for contraception counseling.
- ☐ **Counsel** patient on pregnancy prevention options, including the mandatory use of 2 effective forms of contraception simultaneously, or **commitment to** abstinence, for at least 1 month before starting treatment. There is a 30-day mandatory waiting period during which the patient must be using their chosen option.
- ☐ **Obtain** the patient's informed consent using the downloadable Informed Consent About Birth Defects Form or the online Patient Enrollment Form for Patients Who Can Become Pregnant.
- ☐ **Inform** patient about confidential iPLEDGE REMS Pregnancy Registry.

PRESCRIBE

- ☐ **Order** a confirmatory pregnancy test (at least 30 days after enrollment):
  - **Completed** in a medical setting (e.g., prescriber's office, clinic, laboratory)
  - During the first 5 days of the menstrual cycle, OR
  - For patients with amenorrhea, irregular cycles, or using a contraceptive form that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of isotretinoin treatment and after the patient has used chosen pregnancy prevention methods for 1 month.
- ☐ **Confirm** patient counseling of REMS requirements in the iPLEDGE REMS website.
- ☐ **Enter** pregnancy test results and the patient's 2 forms of contraception or commitment abstinence in the iPLEDGE REMS website within the 7-day prescription window (allowable timeframe), counting the date of specimen collection for the pregnancy test as DAY 1. Your patient will not be able to answer the comprehension questions and then obtain the prescription until you have completed this task.
- ☐ **Provide** a prescription for no more than a 30-day supply

DURING TREATMENT (at each monthly visit)

- ☐ **Counsel** patient on chosen pregnancy prevention methods adherence.
- ☐ **Order** a pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) or using a home pregnancy test.
- ☐ **Confirm** patient counseling of REMS requirements in the iPLEDGE REMS website.
- ☐ **Enter** pregnancy test results and the patient's 2 forms of contraception or commitment to abstinence in the iPLEDGE REMS website within the 7-day prescription window (allowable timeframe), counting the date of specimen collection for the pregnancy test as DAY 1. Your patient will not be able to answer the comprehension questions and then obtain the prescription until you have completed this task.
- ☐ **Provide** a prescription for no more than a 30-day supply.

AFTER TREATMENT

AFTER THE LAST DOSE

- ☐ **Order** a pregnancy, test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) or using a home pregnancy test
- ☐ **Enter** pregnancy test results in the iPLEDGE REMS website.
  - If you do not enter the results of the pregnancy test at the conclusion of treatment, the patient will be classified as Lost to Follow-Up, and both you and the patient may be contacted for additional information.
- ☐ **Counsel** patient on chosen pregnancy prevention methods adherence for 30 more days.
- ☐ **Counsel** patient not to give blood for at least 1 month after the last dose.
- ☐ **Counsel** the patient not to use leftover medication
- ☐ **Counsel** the patient to properly dispose of unused medication to avoid unintended exposed pregnancies

ONE MONTH AFTER THE LAST DOSE

- ☐ **Order** a pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) or using a home pregnancy test.
- ☐ **Enter** pregnancy test results in the iPLEDGE REMS website.
  - If you do not enter the results of the pregnancy test at the conclusion of treatment, the patient will be classified as Lost to Follow-Up, and both you and the patient may be contacted for additional information.
- ☐ **Counsel** the patient not to use leftover medication
- ☐ **Counsel** the patient to properly dispose of unused medication to avoid unintended exposed pregnancies; refer to the section 'In the Event of Pregnancy' above for information about reporting pregnancies to the confidential iPLEDGE REMS Pregnancy Registry.

Prescriber Requirements for Patients Who Cannot Get Pregnant

- Before initiating treatment with isotretinoin, I must
  - Assess the patient's reproductive status. Document using the **Patient Enrollment Form for Patients Who Cannot Get Pregnant.**
  - Counsel the patient on the risks of isotretinoin, not to share isotretinoin, not to donate blood while on treatment and for 30 days after stopping treatment, and the REMS requirements using the **Guide for Patients Who Cannot Get Pregnant**. Document using the **Patient Enrollment Form for Patients Who Cannot Get Pregnant** on the iPLEDGE website**.**
  - Enroll the patient by completing and submitting the **Patient Enrollment Form for Patients Who Cannot Get Pregnant** on the iPLEDGE website. Provide a copy of the Informed Consent to the patient.
- During isotretinoin treatment, I must
  - Assess the patient's current reproductive status.
- At all times, I must
  - Prescribe no more than a 30-day supply
  - Not prescribe refills

Counseling for Patients Who Cannot Get Pregnant

Counseling is required at enrollment using the **Guide for Patients Who Cannot Get Pregnant.**
It is important patients understand the following:

- Risks of isotretinoin
- Not to share isotretinoin
- Not to donate blood during therapy and for 30 days after the last dose
- REMS Requirements

You must document counseling at enrollment using the enrollment form.

Reinforcement of counseling is recommended throughout the treatment course.

iPLEDGE® REMS Checklist
Patients Who Cannot Get Pregnant

BEFORE TREATMENT

PLANNING

☐ **Plan** for monthly appointments.

☐ **Educate** patients about isotretinoin, not to share isotretinoin, and not to donate blood during treatment and for 30 days after the last dose.

☐ **Enroll** patients in the REMS

☐ **Obtain** the Patient's informed consent on the **Patient Enrollment Form for Patients Who Cannot Get Pregnant.**

PRESCRIBE

☐ **Confirm** patient counseling of REMS requirements in the iPLEDGE REMS system. The patient will not be able to obtain their first prescription until you have completed this task.

☐ **Provide** a prescription for no more than a 30-day supply.

DURING TREATMENT

☐ Reinforce **counseling**

☐ **Provide** a prescription for no more than a 30-day supply.

AFTER TREATMENT

☐ **Counsel** patient not to give blood for at least 1 month after the last dose.

☐ **Counsel** the patient to not share any leftover isotretinoin with anyone.

☐ **Counsel** the patient not to use leftover medication

☐ **Counsel** the patient to properly dispose of unused medication to avoid unintended exposed pregnancies

Noncompliance Action Policy

Non-Compliance Action Policy (NCAP)



The Non-Compliance Action Policy was implemented to monitor compliance with the iPLEDGE REMS requirements, address deviations, and institute appropriate corrective actions. The NCAP sets forth the principles by which Non-Compliance by iPLEDGE REMS stakeholders will be evaluated. The NCAP can be found on the iPLEDGE REMS website at **www.ipledgeprogram.com/#Main/Resources**.

Delegates And Office Staff

The iPLEDGE REMS allows the prescriber to delegate patient management to other prescribers enrolled with the iPLEDGE REMS (these are known as delegates) and to designate office staff to assist with data entry (these are known as designees).

Delegating to Another Prescriber

The prescriber can manage delegates by going to the prescriber home page at www.ipledgeprogram.com. The **prescriber** must first add the name and required information for delegates into the iPLEDGE REMS website. This function also allows the prescriber to define time frames for delegation and add or delete delegates.

Office Designees

You may assign a member of your staff as your Office Staff Designee once the registration process has been completed. An activated and designated Office Staff Designee may perform most patient activities for you in the iPLEDGE REMS website. **An activated designated Office Staff Designee may NOT confirm the serious medical reason(s) exemption process in the iPLEDGE website on your behalf, as the confirmation requires the digital signature of an enrolled prescriber**.

The iPLEDGE REMS provides a unique username and password to identified office staff to allow them to perform the following activities for the prescriber:

- Initiate Enrollment and maintain the patient's information in the iPLEDGE REMS
- Confirm patient counseling
- Enter patient pregnancy test results
- Enter patient pregnancy prevention methods
- Discontinue patients
- Manage delegates
- Check patient's REMS status

Only the prescriber may access the following functions:

- Prescriber Enrollment
- Prescriber Activation—initial and renewal
- Finalize Patient Enrollment or Re-enrollment by attesting that the patient category and patient information is correct and providing electronic signature
- Change a patient's category
- Serious Medical Reasons Exemption process

A prescriber may have 1 or more office staff designees. Designees may be associated with 1 or more prescribers.

- They need to register, and upon their initial activation, they can work with multiple prescribers who assign them as designees. However, the designee must attest and activate annually.
- They may support all the enrolled prescribers in multiple prescriber practices.
- They have rights for any patient delegated to an assigned prescriber.

Rights to perform the functions depend on the prescriber's rights and REMS status.

- If a prescriber is not activated in the iPLEDGE REMS website, neither the prescriber nor the designated office staff can enroll a patient.

Designees should not access the iPLEDGE REMS website using an ID other than their own under any circumstances. Designated office staff may access the iPLEDGE REMS system, but must provide their own user ID and password for the iPLEDGE REMS website or the Date of Personal Significance when accessing the iPLEDGE REMS IVRS (interactive voice response system).



Please note: The enrolled and activated prescriber is responsible for all information entered and activities performed in the iPLEDGE REMS website by the office staff designee.

To Designate Office Staff

The prescriber:

1. Logs in to the website, **www.ipledgeprogram.com**
2. Chooses "Manage Designees" from the Prescriber home page
3. Chooses "Add Designee" from the Manage Designees page
4. Fills in the required information on the registration online form and submits

The office staff designee:

1. Signs and dates the completed form online.

A username and password will be emailed to the designee upon completion of the registration process. The designee uses them:

- To log in to the automated system
- On the first log-in, to reset the password and choose a Date of Personal Significance as a system identifier and to attest to the iPLEDGE REMS requirements

Managing Office Staff Designees

Go to www.ipledgeprogram.com and log in by entering your username and password. You will be presented with the Prescriber home page. Select the “Manage Designees” option. The Manage Designees page will be presented. From here you may add new designees or edit and remove existing designees.

It is important to note the following:

- Your Office Staff Designee’s access to activities in the iPLEDGE REMS website is dependent on your access to the system. Specifically, if you have not been activated in the system or if your activation has expired, your Office Staff Designee will not be able to perform activities in the iPLEDGE REMS website.
- Although several prescribers may utilize the same Office Staff Designee, the Office Staff Designee only needs to register in the iPLEDGE REMS once.

Activating Designee Registration

iPLEDGE REMS registration must be activated in the iPLEDGE REMS website before a designee can interact with the iPLEDGE REMS.

The designee should review the *iPLEDGE REMS Prescriber Guide* to understand the REMS. Activation requires the designee to acknowledge the following statements in the iPLEDGE REMS website annually:

- **Isotretinoin is teratogenic and must not be used by patients who are pregnant.** The goal of the iPLEDGE REMS is to mitigate the risk of embryo-fetal toxicity. With this REMS goal in mind, iPLEDGE data are routinely analyzed to identify actions of Non-Compliance.
- **Information entered into the iPLEDGE REMS website is considered part of the patient’s medical record and can be used to investigate suspected Non-Compliance.** Verified Non-Compliance with regard to the iPLEDGE REMS requirements can result in Permanent Deactivation from the iPLEDGE REMS.
- **Prescribers are responsible for all iPLEDGE REMS activities performed by their office staff designees.** If an office staff designee is found to be non-compliant with the iPLEDGE REMS, resulting actions, including possible Permanent Deactivation from the iPLEDGE REMS, can include both the designee and the prescriber.
- **Verified Non-Compliance may be reported to the FDA.**

Date of Personal Significance

The system requires setting your Date of Personal Significance. This is a date that you will be able to easily remember. It will be used to verify your identity if needed by the iPLEDGE REMS IVRS or if a password is lost.

After initial activation, you must re-activate at least annually to remain active in the iPLEDGE REMS. The iPLEDGE REMS website will display the “Activation Expiring Soon” on the Prescriber Portal My Profile page when the activation for a prescriber is nearing expiration. However, a prescriber can re-activate at any time on the Prescriber Portal My Profile page.

Prescriber Flowchart

iPLEDGE®
Committed to Pregnancy Prevention

ENROLLED AND ACTIVATED PRESCRIBER

BEFORE TREATMENT

Patients Who Can Get Pregnant

- ☐ **Educate** the patient about isotretinoin and pregnancy prevention requirements of the iPLEDGE® REMS
- ☐ **Screen** by obtaining a negative pregnancy test, completed in a medical setting (e.g., prescriber's office, clinic, laboratory).
- ☐ **Enroll** patient in the REMS
- ☐ **Obtain** a signed Patient Informed Consent using the **Patient Enrollment Form for Patients Who Can Get Pregnant**
- ☐ **Counsel** patient, or refer to an expert, that the patient must use **2** effective forms of contraception simultaneously and correctly or commit to abstinence for at least 1 month before starting treatment
- ☐ **Order** a confirmatory pregnancy test during the first 5 days of the menstrual cycle, at least 30 days after enrollment (patients with amenorrhea/irregular cycle, please refer to the PI). This pregnancy test must be completed in a medical setting (e.g., prescriber's office, clinic, laboratory).
- ☐ **Access*** the website to confirm patient counseling of REMS and pregnancy prevention requirements, and to enter the pregnancy test result and the patient's pregnancy prevention methods
- ☐ **Provide** a prescription for no more than a 30-day supply

Patients Who Cannot Get Pregnant

- ☐ **Educate** the patient about isotretinoin
- ☐ **Enroll** patient in the REMS
- ☐ **Obtain** a signed Patient Informed Consent using the **Patient Enrollment Form for Patients Who Cannot Get Pregnant**
- ☐ **Access*** the website to confirm patient counseling of REMS requirements
- ☐ **Provide** a prescription for no more than a 30-day supply

EACH MONTH DURING TREATMENT

- ☐ **Counsel** patient on REMS and pregnancy prevention requirements
- ☐ **Order** a pregnancy test completed in a medical setting (e.g., prescriber's office, clinic, laboratory) or using a home pregnancy test
- ☐ **Access*** the system to confirm patient counseling of REMS and pregnancy prevention requirements and to enter pregnancy test result and the patient's pregnancy prevention methods
- ☐ **Provide** a prescription for no more than a 30-day supply

- ☐ **Provide** a prescription for no more than a 30-day supply

AFTER TREATMENT

- ☐ **Order** a pregnancy test immediately after the last dose, completed in a medical setting (e.g., prescriber's office, clinic, laboratory) or using a home pregnancy test
- ☐ **Counsel** the patient to continue to use **chosen pregnancy prevention methods** correctly for at least 1 month after the last dose
- ☐ **Counsel** the patient not to share any leftover isotretinoin with anyone
- ☐ **Counsel** the patient not to donate blood for 1 month after last dose
- ☐ **Order** a pregnancy test 1 month after the last dose, completed in a medical setting (e.g., prescriber's office, clinic, laboratory) or using a home pregnancy test
- ☐ **Access*** the system to enter pregnancy test results after every pregnancy test
- ☐ **Counsel** the patient not to use leftover medication
- ☐ **Counsel** the patient to properly dispose of unused medication to avoid unintended exposed pregnancies

- ☐ **Counsel** the patient not to share any leftover isotretinoin with anyone
- ☐ **Counsel** the patient not to donate blood for 1 month after the last dose
- ☐ **Counsel** the patient not to use leftover medication
- ☐ **Counsel** the patient to properly dispose of unused medication to avoid unintended exposed pregnancies

*You can access the system via the website, **www.ipledgeprogram.com**, or the telephone, **1-866-495-0654**

iPLEDGE®
Committed to Pregnancy Prevention

Isotretinoin Products

To get information about specific brands of isotretinoin, the contact information for individual manufacturers can be obtained by calling **1-866-495-0654** or via www.ipledgeprogram.com.

REMS Materials

The iPLEDGE REMS materials can be accessed, downloaded or ordered from the iPLEDGE REMS website.

Prescriber Materials	Patient Materials
Prescriber Guide	*Guide for Patients Who Can Get Pregnant (also available in Spanish)*
Recognizing Psychiatric Disorders in Adolescents And Young Adults	*Guide for Patients Who Cannot Get Pregnant (also available in Spanish)*
Contraception Counseling Guide	*Patient Enrollment Form for Patients who can get Pregnant*
Non-Compliance Action Policy	*Patient Enrollment Form for Patients who cannot get Pregnant*
Pregnancy Registry Healthcare Provider Guide	*Informed Consent (For all Patients) (also available in Spanish)*
	Informed Consent About Birth Defects (For Patients who can get Pregnant) (also available in Spanish)
	Pregnancy Registry Patient Guide (also available in Spanish)

For iPLEDGE® REMS Information

www.ipledgeprogram.com
Phone system: **1-866-495-0654**



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WARNING

Isotretinoin must not be used by patients who are or may get pregnant. There is an extremely high risk of life-threatening birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for a short period 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.

IMPORTANT NOTICE

Use only isotretinoin products approved by the US Food and Drug Administration.

Obtain isotretinoin prescriptions *only* from pharmacies that are licensed in the United States and are enrolled with and activated in the iPLEDGE REMS.