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iPLEDGE®
Committed to Pregnancy Prevention

The iPLEDGE REMS

Prescriber Guide

The resource to help your patients prepare, plan treatments, and prevent pregnancies during the course of isotretinoin treatment

INDICATION

Isotretinoin is indicated 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 5mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition,[1] means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, isotretinoin should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, isotretinoin is indicated only for those patients who are not pregnant, because isotretinoin can cause severe birth defects (see Boxed CONTRAINDICATIONS AND WARNINGS).

CONTRAINDICATIONS AND WARNINGS

Isotretinoin must not be used by patients who are or may become 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 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.

Birth defects which have been documented following isotretinoin exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

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

If pregnancy does occur during treatment of a patient who is taking isotretinoin, isotretinoin must be discontinued immediately, and the patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.

SPECIAL PRESCRIBING REQUIREMENTS

Because of isotretinoin's teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This REMS is called iPLEDGE®. 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 (see **PRECAUTIONS**).

Reference: 1. Pochi PE, Shalita AR, Strauss JS, Webster SB. Report of the consensus conference on acne classification. J Am Acad Dermatol 24:495-500, 1991.

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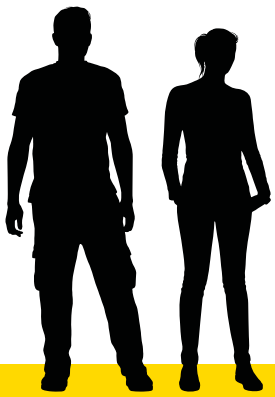


About Isotretinoin

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.

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

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 become pregnant for 1 month post treatment. Women who become 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 postmarketing 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.

†

Reference: 2. Dai WS, Hsu M-A, Itri LM. Safety of pregnancy after discontinuation of isotretinoin. Arch Dermatol. 1989;125:362-355.

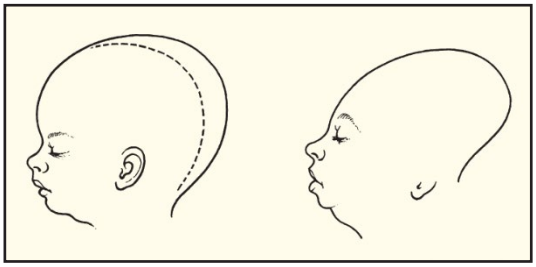
Birth Defects

There is an extremely high risk that a deformed infant will result if pregnancy occurs while patients who **can** become 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

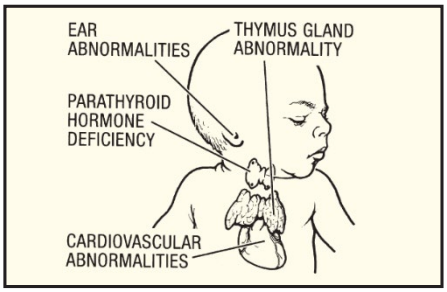
Skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate.



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.

The iPLEDGE® REMS

Because of isotretinoin's teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This REMS is called the iPLEDGE REMS.

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

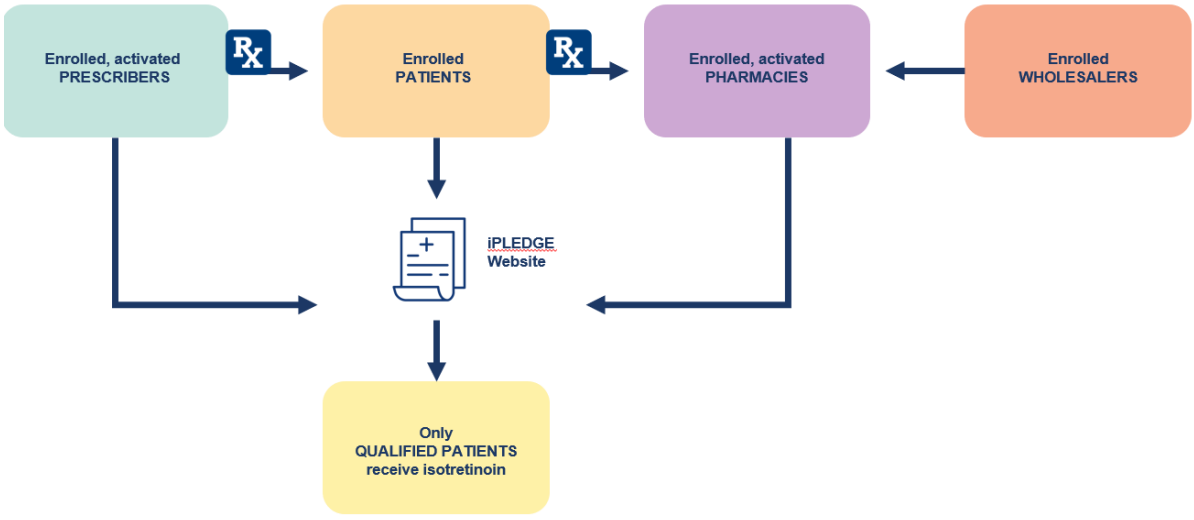
The iPLEDGE REMS is a, shared (includes multiple manufacturers) Risk Evaluation and Mitigation Strategy (REMS) with requirements for prescribers, pharmacies, patients, and wholesalers. The iPLEDGE REMS also includes a pregnancy registry for patients who get pregnant.

The goal of the iPLEDGE REMS is to:

- prevent pregnancies in patients taking isotretinoin
  and to
- prevent pregnant patients from taking isotretinoin

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



Key Information For Prescribers

The key areas prescribers must understand and follow include:

- The Non-Compliance Action Policy (NCAP)
- The iPLEDGE® REMS educational materials for prescribers and patients
- Activation in the iPLEDGE REMS automated system
- Prescriber steps required "Before," "During," and "After" treatment with isotretinoin
- Specific program criteria and procedures for patients who **can** become pregnant
- Education for all patients about isotretinoin and the iPLEDGE REMS requirements
- Patient enrollment
- The initial and monthly procedures for prescribing isotretinoin and information on the requirements for pharmacists
- Information on what to do in the event of a pregnancy
- Prescriber delegates and office staff designees

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**.

Activating Prescriber Enrollment

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

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

- On the website, log in and choose “My Program Status” on the left navigation
- In the phone system, log in and select the option to hear “Program Status”

You should review the iPLEDGE REMS Prescriber Guide to understand the program requirements. Activation requires you to attest to the following statements in the iPLEDGE REMS website:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy.
- I have the expertise to provide the patient with detailed pregnancy prevention counseling, or I will refer the patient to an expert for such counseling, reimbursed by the manufacturer.
- I will comply with the iPLEDGE Program requirements described in the booklet entitled *iPLEDGE REMS Prescriber Guide*.
- Before beginning treatment of patients who **can** become pregnant with isotretinoin, and on a monthly basis, the patient will be counseled to avoid pregnancy by using 2 forms of contraception simultaneously and continuously for at least one month prior to initiation of isotretinoin treatment, during isotretinoin treatment and for one month after discontinuing isotretinoin treatment, unless the patient commits to continuous abstinence, not having any sexual contact with a partner that could result in pregnancy.
- I will not prescribe isotretinoin to any patient who **can** become pregnant until verifying a negative screening pregnancy test and monthly negative CLIA-certified (Clinical Laboratory Improvement Amendment) pregnancy tests. Patients should have a pregnancy test at the completion of the entire course of isotretinoin and another pregnancy test one month later.
- I will report any pregnancy case that I become aware of while the patient who **can** become pregnant is on isotretinoin or one month after the last dose to the pregnancy registry.

***NOTE: Each prescriber’s office location that conducts pregnancy tests must be CLIA certified.**

iPLEDGE® REMS Checklist

Patients Who Can Become Pregnant

iPLEDGE®
Committed to Pregnancy Prevention

BEFORE TREATMENT

PLANNING

☐ **Verify** patient who **can** become pregnant qualification criteria (see page 10).

☐ **Plan** for office visits, counseling, pregnancy testing.

☐ **Educate** about isotretinoin and the contraception requirements of the iPLEDGE REMS.

☐ **Screen** with serum or urine pregnancy test, which may be performed in the prescriber's office: must be negative for the patient to enter the iPLEDGE REMS website.

☐ **Enroll** patient in the iPLEDGE REMS website, ensure the patient can access their Patient ID number and educational materials.

☐ **Obtain** the Patient informed consent using the Enrollment Form for Patients Who Can Become Pregnant

COUNSEL ON CONTRACEPTION

☐ **Counsel** patient in the office or refer to healthcare professional with expertise in contraception. Please see the "Referral for Contraception Counseling" section for information on referring for contraception counseling.

☐ **Counsel** patient on the mandatory use of **2** effective forms of contraception simultaneously for at least 1 month before starting treatment. There is a 30-day mandatory waiting period during which the patient must be using both chosen forms of birth control before being eligible to begin treatment with isotretinoin.

☐ **Obtain** the patient's informed consent using the Patient Enrollment Form for Patients Who Can Become Pregnant

☐ **Inform** patient about confidential iPLEDGE REMS Pregnancy Registry

PRESCRIBE

☐ **Order** a pregnancy test using a CLIA-certified laboratory (at least30 days after registration):

- 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 **2** forms of contraception for 1 month.

☐ **Confirm** patient counseling of program requirements in the iPLEDGE REMS website.

☐ **Enter** pregnancy test results and the patient's **2** forms of contraception 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 contraception adherence.

☐ **Order** a pregnancy test using a CLIA-certified laboratory.

☐ **Confirm** patient counseling of program requirements in the iPLEDGE REMS website.

☐ **Enter** pregnancy test results and the patient's 2 forms of contraception 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 using a CLIA-certified laboratory after the last dose.

☐ **Enter** pregnancy test results and the patient's 2 forms of contraception 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 contraception 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 using a CLIA-certified laboratory.

☐ **Enter** pregnancy test results and the patient's 2 forms of contraception 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' below for information about reporting pregnancies to the confidential iPLEDGE REMS Pregnancy Registry.

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Determine Reproductive Potential of Patients Who Can Become Pregnant

Qualification Criteria

Before enrolling your patient in the iPLEDGE REMS, you must determine if this is a patient who **can** become pregnant. In the iPLEDGE REMS, the definition of a patient who **can** become pregnant is:

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

iPLEDGE REMS Definition of Patient Categories

Patients Who Can Become Pregnant	Patients Who Can NOT 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 bilateral oophorectomy (surgical removal of both ovaries) • Cisgender females and transgender males who are post-menopausal according to the iPLEDGE Program definition* • Transgender female (born male and transitioned to female)

*Menopause can be assumed to have occurred in a woman when there is either:**1)** Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed), OR **2)** Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of **hormonal deficiency** by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years).

Hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:

1. If age >54 years and with the absence of normal menses: Serum FSH (Follicle Stimulating Hormone) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;
2. If age <54 years and with the absence of normal menses: Negative serum or urine -HCG with concurrently elevated serum FSH (Follicle Stimulating Hormone) level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

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 the prescriber is not comfortable with providing this counseling, they are encouraged to take advantage of the opportunity to refer patients to a qualified counselor.

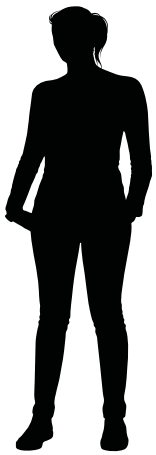
Before beginning treatment, if you and the patient choose referral to a healthcare professional with expertise in pregnancy prevention, the makers of isotretinoin will reimburse 1 visit for contraception counseling. To facilitate the referral, complete the referral form, which should be taken to the 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 contraception requirements and the effective forms of contraception of the iPLEDGE REMS.

Referring to a Gynecologist

You may want to specifically refer a 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).



Requirements for Patients Who Can Become Pregnant

The requirements include the patient taking pregnancy tests and using 2 forms of birth control consistently for at least 1 month prior to initiation of isotretinoin treatment, during isotretinoin treatment, and for 1 month after discontinuing isotretinoin treatment. To receive monthly prescriptions, a patient who can become pregnant must also answer questions in the iPLEDGE® REMS website about the program requirements and pregnancy prevention. **Answering these questions can only take place after the prescriber has confirmed counseling and entered the pregnancy test result and the patient's 2 forms of contraception (or committing to abstinence, not having any sexual contact with a partner that could result in pregnancy) into the system.** 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).

The pregnancy test can be obtained prior to, at the time of, or after the office visit. **However, the 7-day prescription window (allowable timeframe) will begin on the date that the specimen collection was performed**.

MORE EFFECTIVE

MORE EFFECTIVE

About The Patient Comprehension Questions

Prior to being able to obtain a prescription, patients who **can** become pregnant must answer questions about the iPLEDGE REMS and pregnancy prevention.

- 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 program education and counseling can be reinforced. The patient should also review educational materials and then answer the questions again.

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]	MORE EFFECTIVE	>99%[1]	• Nothing to do or remember • Light or no periods • May decrease acne • No increased risk of clots	• Irregular periods
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
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
Tubal Sterilization 	A surgical procedure to close the tubes between the uterus and the ovaries.		>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
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
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
Vaginal Ring 	You place it in the vagina. Replace per prescriber's instructions.		92%[1]	• Lighter periods • May decrease acne	• Blood clots
Hormonal Patch 	You place it on the skin. Replace weekly.		92%[1]	• Lighter periods • May decrease acne	• Blood clots
Birth Control Pill (Combination Type) 	Swallow at the same time daily.		92%[1]	• Lighter periods • May decrease acne	• Blood clots

Secondary Form of Birth Control (Choose One)	How to Use it	Benefits	Risks
Male Latex Condoms (with or without spermicide)	Partner must be willing to use each and every time you have sex.	• Protects from STIs and HIV/AIDS	• Allergic reactions
Cervical Cap, Diaphragm (must be used with spermicide). **Vaginal Sponge**	Place in the vagina before you have sex.	• You are in control of its use	• Allergic reactions

*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.

Abstinence

For this program, all patients who **can** become pregnant must fully commit to pregnancy prevention. Isotretinoin is not recommended for any patient who **can** become pregnant who cannot or will not follow the contraceptive 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 taking isotretinoin, while on isotretinoin and for 1 month after stopping isotretinoin.

A patient who switches contraception choices during treatment from abstinence to two 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, which starts the 30-day wait period. When the 30-day wait period is over, the patient will need to have negative pregnancy test, complete the comprehension questions and be confirmed by the prescriber 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”
- Female condoms
- Natural family planning (rhythm method or fertility awareness)
- Breastfeeding
- Withdrawal
- Cervical shield*

Contraception Counseling

The prescriber 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.

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

The Importance of the Patient Prescription Window

All patients have a specific period of time in which they can obtain their prescription. This is called the "prescription window", and its start and end dates depend on the type of patient, as follows:

Patients Who Can Become Pregnant	Patients Who Cannot Become Pregnant
The prescription window is 7 days and starts on the date that the urine or blood sample is taken for a 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 of the blood or urine sample is taken.	The prescription window is 30 days and starts on the date the prescriber enters as the date of the office visit. This date is counted as DAY 1. To determine the end date of their 30-day prescription window, these patients should add 29 days to the date of their office visit.

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.*

*One notable exception is that patients who **can** become pregnant who do not obtain their first month of treatment prescription in their first 7-day prescription window must wait at least 19 days from their most recent pregnancy test until getting their new pregnancy test. This is based on the requirement that the most recent pregnancy test prior to beginning treatment must be conducted in the first 5 days of the menstrual cycle.

There are different program requirements for patients who **cannot** become pregnant and for patients who **can** become pregnant. .

NOTE: The iPLEDGE REMS Sponsors monitor and investigates 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 program 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** become pregnant.

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

In the Event of Pregnancy

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 become pregnant while taking isotretinoin or 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 Pregnancy Registry any pregnancy case that you become aware of while the patient is on isotretinoin or 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 Safety Surveillance Associate 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 throughout the pregnancy and up to one year following birth, as applicable. 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.

*The information in this section refers to partners of cis-male or transgender females who retain male reproductive organs.

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.

Program Materials

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

Prescriber Materials	Patient Materials
iPLEDGE REMS Prescriber Guide	*iPLEDGE REMS Factsheet*
Recognizing Psychiatric Disorders in Adolescents And Young Adults	*iPLEDGE REMS Guide for Patients Who Can Get Pregnant*
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*

Determine the Reproductive Potential of Patients

You must determine if your patient can become pregnant before enrollment in the iPLEDGE® REMS.

In the iPLEDGE REMS, the definition of a patient who cannot become pregnant is:

- A patient who has had a hysterectomy and/or bilateral oophorectomy
- A patient who is post-menopausal
- A patient who was born with male reproductive organs

iPLEDGE® REMS Checklist
Patients Who Cannot Become Pregnant

BEFORE TREATMENT

PLANNING

☐ **Plan** for monthly office visits.

☐ **Educate** patients about isotretinoin.

☐ **Enroll** patients in the program

☐ **Obtain** the Patient's informed consent on the Patient Enrollment Form for Patients who cannot get pregnant

PRESCRIBE

☐ **Confirm** patient counseling of program requirements in the iPLEDGE REMS system within the 30-day prescription window, counting the patient's office visit as DAY 1. The patient will not be able to obtain their prescription until you have completed this task.

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

DURING TREATMENT

☐ **Counsel** patient on program adherence.

☐ **Confirm** patient counseling of program requirements in the iPLEDGE REMS website within the 30-day prescription window, counting the patient's office visit as DAY 1. The patient will not be able to obtain their prescription until you have completed this task.

☐ **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

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
- Enter patient pregnancy results
- Confirm patient counseling
- Discontinue patients
- Manage delegates
- Check patient's program 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
- 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 physicians.
- They have rights for any patient delegated to an assigned prescriber.

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

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

Office Designees(Cont.)

Designees should not access the iPLEDGE REMS website using an ID other than their own under any circumstances. Designated office staff may access the automated system but must provide their own user ID and Date of Personal Significance as identifiers.

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 Delegates/Designees" from the Prescriber home page
3. Chooses "Add New Designee" from the Manage Delegates and 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

Managing Office Staff Designees Go to www.ipledgeprogram.com and log in by entering your username (DEA number or program-generated username) and password. You will be presented with the Prescriber home page. Select the "Manage Delegates/Designees" button. The Manage Delegates and Designees page will be presented. Select the "Manage Designees" button to display the Manage Designees page. On the Manage Designees page, enter the Office Staff Designee's iPLEDGE username and select "Add."

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 program. 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 goals of the iPLEDGE REMS are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions. With these program goals 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 website 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 "Activate" button on the Prescriber home page when the activation for a prescriber is nearing expiration. However, a prescriber can re-activate at any time using the "Prescriber Activation" button.

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

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Prescriber Flowchart

A flowchart to assist the prescriber with the iPLEDGE® REMS requirements

ENROLLED AND ACTIVATED PRESCRIBER

Patients Who Can Become Pregnant

BEFORE TREATMENT

- ☐ **Educate** the patient about isotretinoin and contraception requirements of the iPLEDGE® REMS
- ☐ **Screen** by obtaining a negative pregnancy test
- ☐ **Enroll** patient in the program
- ☐ **Obtain** a signed Patient informed consent using the 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 for at least 1 month before starting treatment
- ☐ **Order** a pregnancy test using a CLIA-certified lab 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)
- ☐ **Access*** the website to confirm patient counseling of program and contraception requirements, and to enter the pregnancy test result and the patient's forms of contraception
- ☐ **Provide** a prescription for no more than a 30-day supply

EACH MONTH DURING TREATMENT

- ☐ **Counsel** patient on program and contraception requirements
- ☐ **Order** a pregnancy test using a CLIA-certified lab
- ☐ **Access*** the system to confirm patient counseling of program and contraception requirements and to enter pregnancy test result and the patient's forms of contraception
- ☐ **Provide** a prescription for no more than a 30-day supply

AFTER TREATMENT

- ☐ **Order** a pregnancy test using a CLIA-certified lab immediately after the last dose
- ☐ **Counsel** the patient to continue to use **2** effective forms of contraception simultaneously and 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
- ☐ **Access*** the system to enter pregnancy test results after every pregnancy test
- ☐ **Counsel** the patient not to use leftover medication and
- ☐ **Counsel** the patient to properly dispose of unused medication to avoid unintended exposed pregnancies

Patients Who Cannot Become Pregnant

BEFORE TREATMENT

- ☐ **Educate** the patient about isotretinoin
- ☐ **Enroll** patient in the program
- ☐ **Obtain** a signed Patient informed consent using the Enrollment Form for Patients who cannot get Pregnant
- ☐ **Access*** the website to confirm patient counseling of program requirements
- ☐ **Provide** a prescription for no more than a 30-day supply

EACH MONTH DURING TREATMENT

- ☐ **Counsel** patient on program requirements
- ☐ **Access*** the system to confirm patient counseling of program requirements
- ☐ **Provide** a prescription for no more than a 30-day supply

AFTER TREATMENT

- ☐ **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

For iPLEDGE® REMS Information

www.ipledgeprogram.com
1-866-495-0654

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WARNING

Isotretinoin must not be used by patients who are or may become 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 Program.