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iPLEDGE®
Committed to Pregnancy Prevention
The iPLEDGE REMS

Pharmacist Guide

The resource to help you understand and comply with the iPLEDGE REMS for 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 5 mm 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 that 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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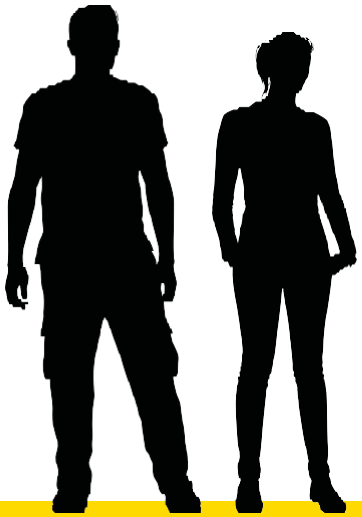


About Isotretinoin

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 by pregnant patients. 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 one 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. Patients 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 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.

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.

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

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.

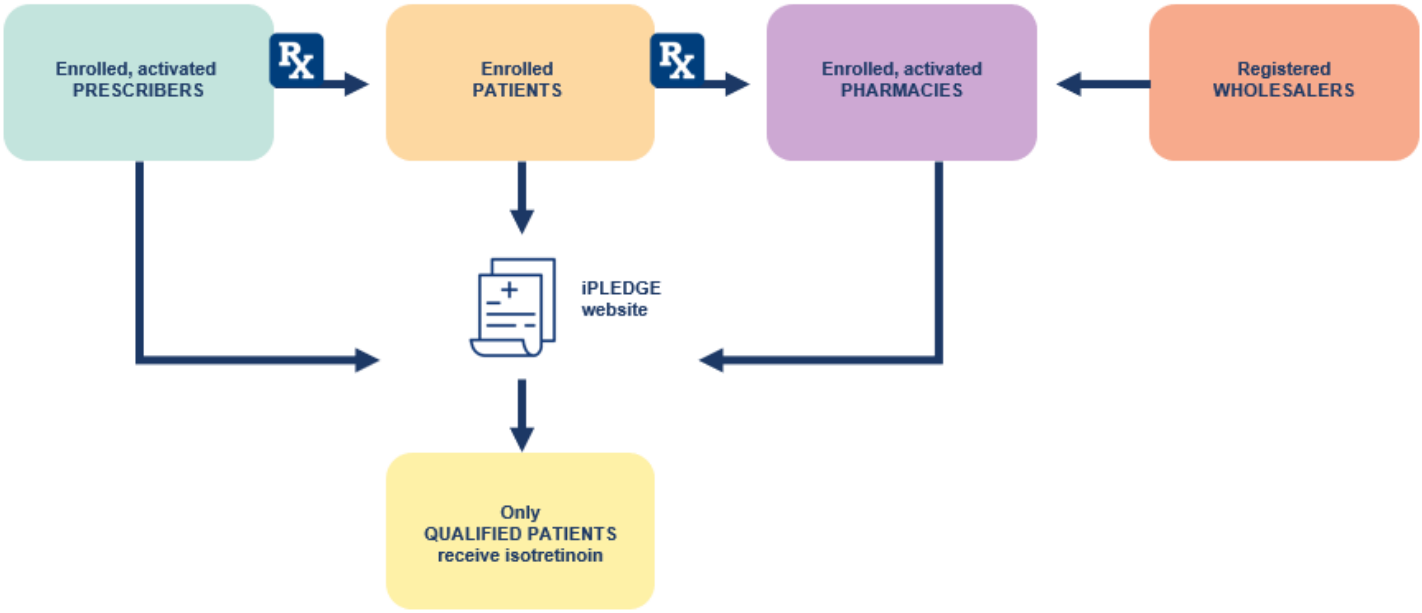
The iPLEDGE REMS is a shared Risk Evaluation and Mitigation Strategy (REMS) program with requirements for prescribers, pharmacies, patients, and wholesalers. The iPLEDGE REMS also includes a pregnancy registry for patients who become pregnant.

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 who are enrolled by their prescriber/doctor and meet all the requirements of the iPLEDGE REMS (see the PRECAUTIONS section of the isotretinoin Package Insert).

The traceable links of the iPLEDGE REMS



Pharmacies And The iPLEDGE® REMS

Key Information For Pharmacists

The key areas pharmacists must understand and follow include:

- The Non-Compliance Action Policy (NCAP)
- **The Responsible Site Pharmacist (RSP) must enroll and activate the pharmacy** in the iPLEDGE REMS website and must reactivate annually.
    - **Visit www.ipledgeprogram.com, and select the Pharmacy Enrollment icon.**
- Prior to obtaining authorization for the pharmacy to dispense a prescription, the prescriber and patient must enter the required information into the iPLEDGE REMS website.
- **The dispensing pharmacist must receive a Risk Management Authorization (RMA)** before filling and dispensing prescriptions. This authorization can be obtained in one of the following ways:
    - Obtain an RMA via the iPLEDGE REMS website to ensure that all requirements have been met for the patient to receive isotretinoin.
    - Obtain an RMA via the iPLEDGE REMS automated phone system to ensure that all requirements have been met for the patient to receive isotretinoin.
    - Pharmacies that elect to utilize QR codes may use the QR code presented by the patient at the time of the patient's visit to the pharmacy. The QR code is part of the patient's electronic profile and integrated into the iPLEDGE REMS website. This QR code will provide a direct path the iPLEDGE REMS website and verify REMS requirements for the patient are met. If requirements are met, the pharmacist will enter the prescription information needed to generate the RMA per current process.
- If all of the iPLEDGE REMS requirements have been met, this will also generate an RMA number, **which the pharmacist should ensure is documented prior to dispensing no more than a 30-day supply.**
- **Upon authorization, the iPLEDGE REMS website provides a "Do Not Dispense To Patient After" date for Patients who can become pregnant.** This date is calculated as 30 days from the office visit for patients who **cannot** become pregnant or 7 days from the specimen collection date for patients who **can** become pregnant. It is recommended that the pharmacist documents this date on the prescription bag.
- Patients who present a prescription beyond this date will not be authorized in the iPLEDGE REMS website to receive isotretinoin. The pharmacist must not dispense the prescription after this date.

- **Prescriptions must be obtained no later than the "Do Not Dispense To Patient After" date, for patients who can become pregnant, and if not obtained, then the RMA must be reversed in the iPLEDGE® REMS website, and the product returned to inventory.**
- **The iPLEDGE REMS website** only authorizes filling and dispensing prescriptions when patients have met the qualification criteria in the system.
- Prescriptions that are more than 30 days beyond the date of the office visit (for patients who **cannot** become pregnant) or more than 7 days beyond the pregnancy test date (for patients who **can** become pregnant) will not be authorized by the iPLEDGE REMS website.
- **No automatic refills** are permitted.
- Telephone, fax, and electronic transmission (e.g., e-mail) prescriptions are permitted in the iPLEDGE REMS.
- Isotretinoin comes in blister packs of 10 capsules. The pharmacist cannot break a blister pack.

Non-Compliance Action Policy (NCAP)

The Non-Compliance Action Policy was implemented to monitor compliance, address deviations, and institute appropriate corrective actions to improve minimization of drug exposure during pregnancy and compliance with elements to assure safe use under the iPLEDGE REMS. 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.

To Find a Registered Wholesaler

On the website, log in and choose "Find Wholesaler" in the left navigation. A list of registered wholesalers and distributors will be presented.

Counseling a Potentially Pregnant Patient

If a patient expresses concern that they may be pregnant, tell the patient to stop taking isotretinoin immediately and call the prescriber.

The Responsible Site Pharmacist

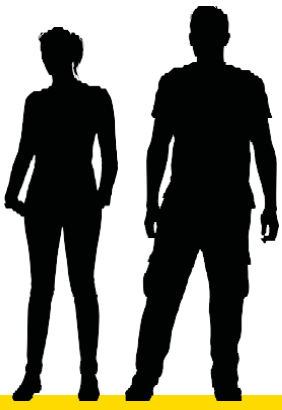
Each pharmacy in the iPLEDGE® REMS must designate a pharmacist as the Responsible Site Pharmacist. The Responsible Site Pharmacist is the point of contact for the pharmacy and the iPLEDGE REMS. The Responsible Site Pharmacist performs the following tasks:

- Enrolls the pharmacy with the iPLEDGE REMS. NCPDP is the user name for that specific pharmacy
    - Visit www.ipledgeprogram.com, and select the Pharmacy Enrollment icon.
- Activates the pharmacy registration initially and annually; attests to program requirements
- Trains all pharmacists and pharmacy staff who participate in the filling and dispensing of isotretinoin prescriptions and keeps a log or record of the staff who have been trained
- Ensures that all pharmacy staff using the iPLEDGE REMS are aware of the pharmacy's username, password, and Date of Personal Significance for the iPLEDGE REMS website

Activation

Before a pharmacist can fill and dispense prescriptions for isotretinoin, the Responsible Site Pharmacist must activate the pharmacy's enrollment in the iPLEDGE REMS website. The program activation expires annually. The Responsible Site Pharmacist, representing the pharmacy, must activate annually to continue ordering, filling, and dispensing isotretinoin. Upon logging in, the iPLEDGE REMS website will automatically prompt the pharmacy that their activation will soon expire. If your pharmacy's activation expires, and you do not intend to reactivate, you must return all unused isotretinoin immediately to the manufacturer or delegate.

The iPLEDGE REMS website will report the expiration date of a pharmacy's enrollment. 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 "Current Program Status."



Activation requires attesting to the following statements in the iPLEDGE® REMS system:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I will train all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions on the iPLEDGE REMS requirements.
- I will comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE REMS requirements described in the booklet entitled *iPLEDGE REMS Pharmacist Guide*, specifically the "Key Information for Pharmacists" section including the following dispensing information:
    - Prescriptions must be obtained no later than the **"Do Not Dispense To Patient After"** date, and if not obtained, then the RMA must be reversed in the iPLEDGE REMS website, and the product returned to inventory.
- I will obtain isotretinoin from only iPLEDGE® registered wholesalers.
- I will not sell, buy, borrow, loan, or otherwise transfer isotretinoin in any manner to or from another pharmacy.
- I will return to the manufacturer (or delegate) any unused product if the pharmacy is deactivated by the iPLEDGE REMS or if the pharmacy chooses to not reactivate annually.
- I will not fill isotretinoin for any party other than a qualified patient.
- I will comply with the audits by the iPLEDGE Sponsors or third party acting on behalf of the iPLEDGE Sponsors to ensure that all processes and procedures are in place and being followed for the iPLEDGE REMS.

Training Pharmacy Staff

The Responsible Site Pharmacist is responsible for the training, and the documentation of training, of all pharmacists and staff in an enrolled pharmacy.

The training for all pharmacists and staff must include:

- Knowing about isotretinoin teratogenicity and the contraception and program requirements of the iPLEDGE REMS
- Being able to access the iPLEDGE REMS website and obtain authorization to fill and dispense a prescription
- Correctly using the RMA number and "Do Not Dispense To Patient After" date
- Familiarity with the Non-Compliance Action Policy and the sanctions that can occur for pharmacy Non-Compliance activities

Training begins by providing the *iPLEDGE REMS Pharmacist Guide* to all pharmacists. Additional copies can be requested through the iPLEDGE REMS website and the iPLEDGE REMS phone system.

Changing The Responsible Site Pharmacist

The pharmacy can change its designated Responsible Site Pharmacist at any time. To make the change, the new Responsible Site Pharmacist or the former Responsible Site Pharmacist must call the iPLEDGE® REMS at **1-866-495-0654** and select #0 to transfer to the Contact Center. The new Responsible Site Pharmacist must re-activate the pharmacy in the iPLEDGE REMS (for activation information, **see page 8**). If the pharmacy activation expires and you do not intend to reactivate, you must return all unused isotretinoin immediately to the manufacturer or their delegate.

Patient Criteria For Authorization To Fill And Dispense

This is the information that must be entered by prescribers and patients into the iPLEDGE REMS website for all patients and, specifically, for patients who **can** become pregnant. This is the information the system uses to authorize filling a prescription and to provide the RMA number and the "Do Not Dispense To Patient After" date.

All patients

Prescriber confirms that:

- The patient is enrolled with the iPLEDGE REMS
- The patient was counseled about the iPLEDGE REMS requirements

Patients who can become pregnant

Prescriber:

- Confirms that the patient was counseled about the iPLEDGE REMS contraception requirements
- Enters the **2** forms of contraception that the patient is using
- Enters pregnancy test results to start the 7-day prescription window, counting the date of the specimen collection as DAY 1

Patient:

- Correctly answers the questions about pregnancy prevention and the iPLEDGE REMS
- Enters the **2** forms of contraception the patient is using

The primary form of contraception reported by both the prescriber and the patient must match.

Note: The system will automatically provide the pharmacist with the "Do Not Dispense To Patient After" date. The pharmacist must not dispense the prescription after this date.

iPLEDGE® Program Approved Forms of Contraception

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Choose 1 Primary + 1 Secondary Birth Control Form

MORE EFFECTIVE

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
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%[2]	• 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%[2]	• 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

MORE EFFECTIVE

MORE EFFECTIVE

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 the 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 the 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.

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

IMPORTANT NOTE: Per the Non-Compliance Action Policy (NCAP), any pharmacy that receives a denial to fill the prescription in the iPLEDGE REMS website, but dispenses the prescription without an RMA will be subject to a 90-day Temporary Deactivation.