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

WARNING
Isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe 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 registered with and activated in the iPLEDGE Program.
Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. In addition, for female patients of reproductive potential, isotretinoin is indicated only for those female patients who are not pregnant (see boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS sections).

IMPORTANT FACTS ABOUT ISOTRETINOIN

- Isotretinoin is highly teratogenic.
- Treatment with isotretinoin during pregnancy is contraindicated. Female patients should not be pregnant or become pregnant while on isotretinoin therapy and for 1 month thereafter.
- Fetal exposure to isotretinoin may result in life-threatening congenital abnormalities.

THE GUIDE TO BEST PRACTICES FOR THE iPLEDGE® PROGRAM

This guide has been developed to assist you in fulfilling the requirements for isotretinoin pregnancy prevention risk management. Please refer to the CONTRAINDICATIONS AND WARNINGS and the PRECAUTIONS sections of the isotretinoin Package Insert.

CONTRAINDICATIONS AND WARNINGS

Isotretinoin must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

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 female patient who is taking isotretinoin, isotretinoin must be discontinued immediately, and she 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 program is called iPLEDGE®. Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Isotretinoin must only be dispensed by a pharmacy registered and activated with the iPLEDGE Program, and must only be dispensed to patients who are registered and meet all the requirements of the iPLEDGE Program (see PRECAUTIONS).
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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 women. Women 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 her prescriber.

Isotretinoin use is associated with other potentially serious adverse events as well as more frequent, but less serious side effects. More frequent, less serious side effects include cheilitis, dry skin, skin fragility, pruritus, epistaxis, dry nose and dry mouth, and conjunctivitis.

Serious Adverse Event Warnings include psychiatric disorders* (depression, psychosis, and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors). Prescribers should read the brochure Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin. Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of isotretinoin treatment, patients and family members should be asked about any history of psychiatric disorder, and at each visit during treatment patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary.

Other Serious Adverse Events include pseudotumor cerebri; pancreatitis; hyperlipidemia; hearing impairment*; hepatotoxicity; inflammatory bowel disease; skeletal changes† (bone mineral density changes, hyperostosis, premature epiphyseal closure); and visual impairment (corneal opacities, decreased night vision).

Patients should be reminded to read the Medication Guide, distributed by the pharmacist at the time the isotretinoin is dispensed.

*No mechanism of action has been established for these events.
†The use of isotretinoin in patients 12 to 17 should be given careful consideration especially when a known metabolic or structural bone disease exists.
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. 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.

Birth Defects

There is an extremely high risk that a deformed infant will result if pregnancy occurs while female patients 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.

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.
The iPLEDGE® Program

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 program is called the iPLEDGE Program.

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

The goal of the iPLEDGE Program is to:

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

Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Isotretinoin must only be dispensed by a pharmacy registered and activated with the iPLEDGE Program, and must only be dispensed to patients who are registered and meet all the requirements of the iPLEDGE Program.

The Traceable Links of The iPLEDGE Program
Key Features of The iPLEDGE Program

The iPLEDGE Program has specific requirements for prescribers, patients, pharmacies, and wholesalers.

- The iPLEDGE Program system tracks and verifies critical program elements that control access to isotretinoin.
- Only prescribers registered with and activated in the iPLEDGE Program can prescribe isotretinoin.
- Prescribers or their office designee must enter required information (pregnancy test results, 2 methods of contraception used, confirmation of patient counseling) in the iPLEDGE Program system for patients to be qualified to receive a prescription after the patient correctly answers a few comprehension questions.
- Prescribers must document that all patients—and specifically females of reproductive potential—meet the requirements in the iPLEDGE Program.
- Only patients who are registered by prescribers in the iPLEDGE Program can receive isotretinoin.
- Females of reproductive potential must enter required information (2 methods of contraception used, answer questions on program requirements) in the iPLEDGE Program system in order to be qualified to receive a prescription.
- Only pharmacies registered with and activated in the iPLEDGE Program can dispense isotretinoin.
- Pharmacists must receive authorization from the iPLEDGE Program system to fill and dispense every isotretinoin prescription.
- Telephone, fax, and electronic transmission (e.g., e-mail) prescriptions are permitted in the iPLEDGE Program.
- Manufacturers will only ship isotretinoin to iPLEDGE Program registered entities (e.g., direct vendor pharmacies, wholesalers).
- Wholesalers must register annually in the iPLEDGE Program. A registered wholesaler may distribute only FDA-approved isotretinoin product.
- Only wholesalers registered with the iPLEDGE Program can distribute isotretinoin.
- Registered wholesalers can only ship isotretinoin to wholesalers registered in the iPLEDGE Program with prior written consent from the manufacturer or pharmacies licensed in the US and registered and activated in the iPLEDGE Program.
Key Information For Prescribers

The key areas prescribers must understand and follow include:

- The Non-Compliance Action Policy (NCAP)
- The iPLEDGE® Program educational materials for prescribers and patients
- Activation in the iPLEDGE Program automated system
- Prescriber steps required “Before,” “During,” and “After” treatment with isotretinoin
- Specific program criteria and procedures for females of reproductive potential
- Education for all patients about isotretinoin and the iPLEDGE Program requirements
- Patient registration
- 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, 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 Program. The NCAP sets forth the principles by which Non-Compliance by iPLEDGE Program stakeholders will be evaluated. The NCAP can be found on the iPLEDGE Program web site at www.ipledgeprogram.com.
BEFORE TREATMENT

PLANNING
☐ Verify female patient qualification criteria (see page 27).
☐ Plan for office visits, counseling, pregnancy testing.
☐ Educate about isotretinoin and the contraception requirements of the iPLEDGE Program.
☐ Obtain the Patient Information/Informed Consent (for all patients) form.
☐ Screen with serum or urine pregnancy test, which may be performed in the prescriber’s office: must be negative for patient to enter the iPLEDGE Program system.
☐ Register patient in the iPLEDGE Program system and provide patient with an educational guide, which includes the Patient ID number on perforated, removable cards.

COUNSEL ON CONTRACEPTION
☐ Counsel patient in office or refer to healthcare professional with expertise in contraception. Please see “Referral for Contraception Counseling” section of this guide for information on referring for contraception counseling.
☐ Counsel patient that she must use 2 effective methods of contraception simultaneously for at least 1 month before starting treatment. There is a 30-day mandatory waiting period during which she must be using both chosen methods of birth control before she is eligible to begin treatment with isotretinoin.
☐ Obtain the Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form.
☐ Inform patient about confidential iPLEDGE Program Pregnancy Registry.

PRESCRIBE
☐ Order a pregnancy test using a CLIA-certified laboratory (at least 30 days after registration):
  • During the first 5 days of the menstrual cycle, OR
  • For patients with amenorrhea, irregular cycles, or using a contraceptive method 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 methods of contraception for 1 month.
☐ Confirm patient counseling of program requirements in the iPLEDGE Program system.
☐ Enter pregnancy test results and the patient’s 2 methods of contraception in the iPLEDGE Program system within the 7-day prescription window, counting the date of specimen collection for the pregnancy test as DAY 1. Your patient will not be able to answer her comprehension questions and then obtain her prescription until you have completed this task.
☐ Provide a prescription for up to a maximum 30-day supply of isotretinoin.

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 methods of contraception in the iPLEDGE Program system.
  • 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.

ONE MONTH AFTER THE LAST DOSE
☐ Order a pregnancy test using a CLIA-certified laboratory.
☐ Enter pregnancy test results and the patient’s 2 methods of contraception in the iPLEDGE Program system.
  • 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.

Refer to page 38 for information about reporting pregnancies to the confidential iPLEDGE Program Pregnancy Registry.

Prescribing Checklist tear sheets are available from the iPLEDGE Program. To order see Additional Materials (page 14).
iPLEDGE® Program Checklist
Male Patients And Female Patients Who Cannot Get Pregnant

BEFORE TREATMENT

PLANNING
☐ Plan for monthly office visits.
☐ Educate patients about isotretinoin and the iPLEDGE Program.
☐ Obtain the Patient Information/Informed Consent (for all patients) form.
☐ Register patients in the iPLEDGE Program system and provide patient with an educational guide, which includes the Patient ID number on perforated, removable cards.

PRESCRIBE
☐ Confirm patient counseling of program requirements in the iPLEDGE Program system within the 30-day prescription window, counting the patient’s office visit as DAY 1. The patient will not be able to obtain his/her prescription until you have completed this task.
☐ Provide a prescription for up to a maximum 30-day supply of isotretinoin.

DURING TREATMENT
☐ Counsel patient on program adherence.
☐ Confirm patient counseling of program requirements in the iPLEDGE Program system within the 30-day prescription window, counting the patient’s office visit as DAY 1. The patient will not be able to obtain his/her prescription until you have completed this task.
☐ Provide a prescription for up to a maximum 30-day supply of isotretinoin.

AFTER TREATMENT

AFTER THE LAST DOSE
☐ Counsel patient not to give blood for at least 1 month after the last dose.

Prescribing Checklist tear sheets are available from the iPLEDGE Program. To order see Additional Materials (page 14).
The iPLEDGE Program Web Site And Phone System

The prescriber can access the iPLEDGE Program system via the program web site and automated phone system:

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

The iPLEDGE Program web site and phone system are used to:

- Activate prescriber registration
- Register office staff designees, who are then eligible to complete their activation
- Register patients
- Confirm patient counseling monthly for all patients for each prescription
- Enter monthly pregnancy test results and contraception information for females of reproductive potential. **The patient cannot answer her monthly questions until the prescriber has entered the pregnancy test results in the iPLEDGE Program system.**
- Track the current status of a patient
- Order additional copies of iPLEDGE Program educational materials
- Manage delegates
- Find a participating pharmacy
- Enter and make changes to patient name, address, phone number, and date of birth
- Edit prescriber name, specialty, address, phone and fax numbers, e-mail address, and preferred method of communication (US mail or e-mail)

Logging in to either the web site or phone system requires a username and password, which are supplied upon registration.
**Program Materials**

The iPLEDGE® Program provides educational materials for prescribers, pharmacists, and patients.

**Prescriber Materials**

It is important that the prescriber reviews the materials in the educational kit.

1. *Guide to Best Practices For The iPLEDGE Program* describes the requirements of the iPLEDGE Program for prescribers and for male and female patients.

2. *Prescriber Contraception Counseling Guide* is an overview of the effective methods of contraception and is a companion to the patient *Birth Control Workbook*.

3. The brochure *Recognizing Psychiatric Disorders in Adolescents And Young Adults* contains important information about depression, suicide, and psychiatric assessment and referral of your patients.

**Additional Materials**

Additional resource materials can be viewed on the iPLEDGE Program web site. These include:

- Isotretinoin Medication Guide
- Isotretinoin Package Inserts
- Prescribing Checklists
- Isotretinoin Contraception Referral Form
- Prescriber Activation Instructions
- Instructions for Registering and Managing Office Staff Designees
- Patient and Prescriber Flowcharts
- FAQs (Frequently Asked Questions)
Patient Materials

The prescriber distributes the *Patient Introductory Brochure* to patients considering taking isotretinoin. A patient educational kit, which provides information about the iPLEDGE Program requirements, should be given to the patient when they are registered in the iPLEDGE Program.

All materials include:

- The appropriate patient guide—the *Guide to Isotretinoin For Male Patients And Female Patients Who Cannot Get Pregnant* or the *Guide to Isotretinoin For Female Patients Who Can Get Pregnant*
- The *Patient Information/Informed Consent* (for all patients) form
- *Safety Information About Isotretinoin*
- The patient ID card and number

Additionally, the kit for females of reproductive potential includes:

- The *Contraception Counseling Guide And Contraception Referral Form*. This includes the form to refer your patient to a contraception expert for counseling and a guide for the counselor about the requirements of the iPLEDGE Program.
- The *Patient Information/Informed Consent About Birth Defects* (for female patients who can get pregnant) form
- The *Birth Control Information Sheet*—a 1-page guide to iPLEDGE Program approved contraception
- The *Birth Control Workbook*. This provides in-depth information about effective methods of contraception with iPLEDGE and their optimal use.

Educational Video

*Be Prepared, Be Protected and Be Aware: The Risk of Pregnancy While on Isotretinoin.* These describe the kind of birth defects that may happen if a woman takes any amount of isotretinoin while she is pregnant and also review reasons for contraception failure.
Patient Materials (Cont.)

Additional Educational Materials

You can order additional program materials using either the web site or the phone system as follows:

1. After logging on to the web site, there are 2 ways to order materials:
   a. Using the navigation menu on the left side of the page, select the “Order Materials” button.

   OR

   b. Using the navigation menu on the left side of the page, choose “Prescriber Information.” In the “View Information Online” section, select “To Order Educational Materials, please click here.”

2. In the phone system, log in and select the option to “Request Program Information.”

Materials will be shipped via ground delivery, and should arrive in 5 to 7 business days. The prescriber address in the iPLEDGE® Program at the time of the order will be used for the shipping destination. This address can be changed by the user as needed to direct shipments to specific desired locations.

Web site: www.ipledgeprogram.com
Phone system: 1-866-495-0654
Activating Registration

iPLEDGE registration must be activated in the iPLEDGE Program system before a prescriber can prescribe isotretinoin. Activation must occur annually.

The iPLEDGE Program system will report the expiration date of the prescriber’s activation. To retrieve this information, the prescriber:

- On the web site, logs in and chooses “My Program Status” on the left navigation
- In the phone system, logs in and selects the option to hear “Program Status”

The prescriber should review the Guide To Best Practices for the iPLEDGE Program and the Prescriber Contraception Counseling Guide to understand the program requirements. Activation requires the prescriber to attest to the following statements in the iPLEDGE Program system:

- 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 her to an expert for such counseling, reimbursed by the manufacturer.
- I will comply with the iPLEDGE Program requirements described in the booklets entitled Guide To Best Practices for the iPLEDGE Program and Prescriber Contraception Counseling Guide.
- Before beginning treatment of females of reproductive potential with isotretinoin, and on a monthly basis, the patient will be counseled to avoid pregnancy by using 2 methods 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.
- I will not prescribe isotretinoin to any female of reproductive potential until verifying she has 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 female patient is on isotretinoin or one month after the last dose to the pregnancy registry.