Most Recent Modification: July 2016

The iPLEDGE Program

The Guide To Best Practices For the iPLEDGE Program

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

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.

iPLEDGE™

Committed to Pregnancy Prevention

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The Guide To Best Practices For the iPLEDGE Program

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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**).

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

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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. Therapy 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 therapy 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 therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary.

Other Serious Adverse Event Warnings 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.

Pregnancy After Isotretinoin Therapy

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. 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.[1] 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.

* No mechanism of action has been established for these events.

† The use of isotretinoin in patients ages 12 to 17 should be given careful consideration especially when a known metabolic or structural bone disease exists.

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

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.**

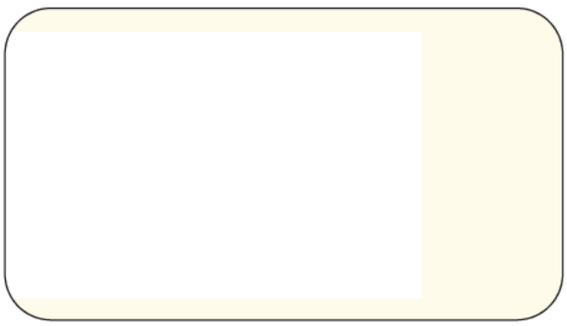
External abnormalities

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.

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.



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

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

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THE iPLEDGE PROGRAM

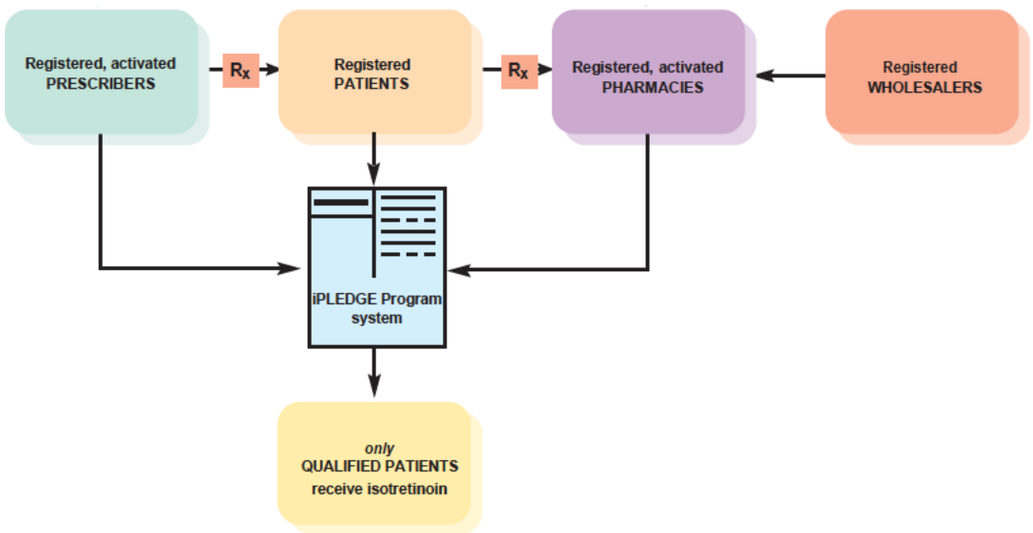
Because of isotretinoin's teratogenicity and to minimize fetal exposure, isotretinoin is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE. The iPLEDGE Program is a single, shared Risk Evaluation and Mitigation Strategy (REMS) program for prescribing and dispensing all isotretinoin products (brand and generic products) and includes a pregnancy registry.

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).

The goals of the iPLEDGE Program are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions.

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

The trackable links of the iPLEDGE Program



Key Features Of The iPLEDGE Program

The iPLEDGE Program has specific requirements for prescribers, patients, pharmacists, and wholesalers. Here is an overview:

- The iPLEDGE 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 forms of contraception used, confirmation of patient counseling) in the iPLEDGE 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.

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- Only patients who are registered by prescribers in the iPLEDGE Program can receive isotretinoin.
- Females of reproductive potential must enter required information (2 forms 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 access the iPLEDGE Program system to receive authorization 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.

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 website at www.ipledgeprogram.com

KEY INFORMATION FOR PRESCRIBERS

Prescribers need to follow the key points of the iPLEDGE Program. These points are explained in detail in *The Guide To Best Practices For the iPLEDGE Program*. The key areas the prescriber must understand 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

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS .**

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THE iPLEDGE 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 automated system is used to:

- Activate registration
- 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 *The Guide To Best Practices For the iPLEDGE Program* and of patient and professional educational materials
- Manage delegates and designate office staff
- 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.

To review and order 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 two 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.

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PROGRAM MATERIALS

The iPLEDGE Program provides educational materials for prescribers and patients. There is also a guide for pharmacists.

Prescriber Materials

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

1. *The Guide To Best Practices For the iPLEDGE Program* describes the requirements of the iPLEDGE Program for prescribers and for male and female patients.
2. *The iPLEDGE Program Prescriber Contraception Counseling Guide* is an overview of the effective forms of contraception and is a companion to the patient *iPLEDGE Program 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
- FAQ's (Frequently Asked Questions)

Patient Materials

The prescriber distributes *The iPLEDGE Program 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 kits include:

- The appropriate patient guide—*The iPLEDGE Program Guide To Isotretinoin For Male Patients And Female Patients Who Cannot Get Pregnant or The iPLEDGE Program Guide To Isotretinoin For Female Patients Who Can Get Pregnant*

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.**

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- The Patient Information/Informed Consent (for all patients) form
- The patient ID card and number

Additionally, the kit for females of reproductive potential includes:

- *The iPLEDGE Program Birth Control Workbook*. This provides in-depth information about effective forms of contraception with iPLEDGE and their optimal use.
- *The iPLEDGE Program Contraception Referral Form And Contraception Counseling Guide*. 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.

Educational Video

The prescriber educational kit also includes educational materials for patients with two videos: ***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.

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 iPLEDGE Program Prescriber Contraception Counseling Guide* to understand the program. 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 *The Guide To Best Practices For the iPLEDGE Program* and *The iPLEDGE Program Prescriber Contraception Counseling Guide*.

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- 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 forms of contraception simultaneously and continuously 1 month before, during, and 1 month after isotretinoin therapy, 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 1 month later.
- I will report any pregnancy case that I become aware of while the female patient is on isotretinoin or 1 month after the last dose to the pregnancy registry.

Procedures For Activating In The iPLEDGE System

The prescriber can access the iPLEDGE Program system to activate registration via the web site, **www.ipledgeprogram.com**, or the automated phone system, **1-866-495-0654.** The web site is the faster and easier way to access the system. Identification in either system requires the username (DEA number or program-generated user-name) and password received with the registration materials. For information on the internet browsers compatible with the iPLEDGE Program web system, consult the FAQ's on the home page of the site, www.ipledgeprogram.com.

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

After initial activation, a prescriber must re-activate at least annually to remain active in the iPLEDGE Program. The iPLEDGE Program system 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 on the left-hand navigation menu on all pages.

Using the web site

The prescriber:

1. Logs in by entering username (DEA number or program-generated username) and password.
   - The system will provide prompts to change the prescriber's password and set the prescriber's Date of Personal Significance.
2. On the Prescriber home page, select "Activate My Registration". **The system will provide prompts to complete the activation process.** If your current activation is nearing expiration, the Prescriber home page will prominently display a direct link to re-activate.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

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Using the phone system

The prescriber:

1. Logs in and follows the prompts.
   - The system will provide prompts to change the prescriber's password and set the prescriber's Date of Personal Significance.
2. Selects the option to "Activate Your Registration." The system will provide prompts to complete the activation process.

OVERVIEW: PROGRAM REQUIREMENTS

The iPLEDGE Program has specific requirements for prescribers, patients, and pharmacists. One of the prescriber's main responsibilities is knowing and educating patients about these requirements.

Prescribers are responsible for registering every patient, who meets the program requirements, in the iPLEDGE Program via the automated system. They are responsible for educating patients about the side effects of isotretinoin and the high risk of birth defects for females of reproductive potential while taking the drug. As part of this process, they are also responsible for counseling patients about the monthly steps they must follow to receive isotretinoin.

Prescribers can only write a patient's prescription for isotretinoin for up to a maximum of a 30-day supply. Patients must plan for monthly appointments to receive their prescriptions. At each of these appointments, the prescriber must counsel the patient about the iPLEDGE Program requirements and then confirm via the iPLEDGE automated system that this counseling occurred.

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:

Female patients who can get pregnant…	Male patients and female patients who cannot get 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 being 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 patient can no longer fill and pick up their prescription, and must start the process over to get a new prescription window*

*There are generally no restrictions regarding the timing of office visits. One notable exception is that females of reproductive potential who do not obtain their first month of therapy prescription in their first 7-day prescription window, must wait at least 19 days from their most recent pregnancy test until getting their next pregnancy test. This is based on the requirement that the most recent pregnancy test prior to beginning therapy must be conducted in the first 5 days of her menstrual cycle.

There are different program requirements for male patients and females of non-reproductive potential and for females of reproductive potential..

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The prescriber must determine if a patient is a female of reproductive potential (see page 18) and document that she meets the specific requirements of the program. These include taking pregnancy tests and using 2 forms of birth control consistently. Both of these requirements must be followed before, during, and after treatment.

To receive monthly prescriptions, a female of reproductive potential must also answer questions in the iPLEDGE Program system 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 reliance on abstinence) into the system.** In addition to answering the questions, the patient must also enter the 2 forms of birth control she is using (or indicate that she 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 will begin with the date that the specimen draw was performed.**

These are the criteria the system uses to authorize a pharmacy to fill and dispense a prescription.

The Guide To Best Practices For the iPLEDGE Program includes a checklist of steps to follow before, during, and after patient treatment. *(see page 15)*

Below are the main requirements for patients and pharmacists.

Requirements For All Patients

To receive isotretinoin, all patients must meet all of the following conditions:

1. ***Must*** be registered with the iPLEDGE Program by the prescriber
2. ***Must*** understand that severe birth defects can occur with the use of isotretinoin by female patients
3. ***Must*** be reliable in understanding and carrying out instructions
4. ***Must*** sign a Patient Information/Informed Consent (for all patients) form that contains warnings about the potential risks associated with isotretinoin
5. ***Must*** obtain the prescription within the prescription window defined as follows:
   - Male patients and female patients who cannot get pregnant must obtain their prescription within the 30-day prescription window, counting the office visit as DAY 1.
   - Female patients who can get pregnant must obtain their prescription within 7 days of their pregnancy test, which is determined by the date of the blood draw or urine sample used in the test. The pregnancy test can be obtained before, during or after the office visit.

6. ***Must*** not donate blood while on isotretinoin and for 1 month after treatment has ended

7. ***Must*** not share isotretinoin with anyone, even someone who has similar symptoms

All patients should understand that refills are not allowed. Patients can only receive a maximum of a 30-day supply of isotretinoin per prescription. For each prescription, continuation of therapy requires the patient to satisfy the iPLEDGE Program requirements to obtain a new prescription. The prescriber must also counsel the patient monthly about the iPLEDGE Program requirements and then confirm via the iPLEDGE Program system that this counseling occurred.

Females of reproductive potential must:

- Have an initial pregnancy test, which may be performed in the prescriber's office
- Be counseled on contraception requirements
- Use 2 forms of contraception together for sexual intercourse for 1 month before, during, and for 1 month after treatment with isotretinoin
- There is a 30-day mandatory waiting period during which females of reproductive potential must be using both chosen forms of birth control simultaneously before they are eligible to begin treatment with isotretinoin.
- Have a second pregnancy test within the first 5 days of the menstrual cycle, performed in a CLIA-certified laboratory, after being on 2 effective forms of contraception for 1 month and before starting isotretinoin therapy.* This second pregnancy test must be at least 19 days after the initial pregnancy test.
- Fulfill monthly requirements before receiving each prescription:
  - Have a serum or urine pregnancy test performed in a CLIA-certified laboratory*
  - Access the system to answer questions about the iPLEDGE Program requirements and pregnancy prevention
  - Enter into the iPLEDGE Program system the 2 forms of contraception being used
- Have a pregnancy test after their last dose, performed in a CLIA-certified laboratory
- Continue using 2 forms of contraception for 1 month after their last dose
- Have a pregnancy test 1 month after their last dose

About the patient questions

Prior to being able to obtain a prescription, females of reproductive potential ***must*** answer questions about the iPLEDGE Program and pregnancy prevention. **These questions must be answered after their prescriber has confirmed counseling, entered pregnancy test results and 2 contraceptive methods (or reliance upon abstinence) into the iPLEDGE Program system, but before the 7-day prescription window for their prescription expires.** Patients answer these questions via the web site or phone system. (Access information is provided in the patient guide.) The patient may use her patient guide and *The iPLEDGE Program Birth Control Workbook* to help with the answers.

* For timing information about monthly pregnancy tests, see number 1 on page 19 under "Qualification criteria for females of reproductive potential"

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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 Program system will direct her to review her materials and try again at a later time. She may also contact her prescriber so that her program education and counseling can be reinforced. The patient should also review her educational materials and then answer the question again.

Requirements For Pharmacists

- Isotretinoin can only be obtained from pharmacies registered with and activated in the iPLEDGE Program.
- Registered and activated pharmacies can obtain isotretinoin only from wholesalers registered with the iPLEDGE Program.
- **The dispensing pharmacist must obtain authorization and a Risk Management Authorization (RMA) number** before filling and dispensing prescriptions.
- **Upon receiving authorization, the dispensing pharmacist can fill and dispense a prescription** for a maximum 30-day supply of isotretinoin.
- **Upon authorization, the iPLEDGE Program system** provides the RMA number to the dispensing pharmacist. The pharmacist should document the RMA number.
- **Upon authorization, the iPLEDGE Program system** provides a "**Do Not Dispense To Patient After**" date to the dispensing pharmacist. This date is calculated as 30 days from the office visit for male patients and females of non-reproductive potential, or 7 days from the pregnancy test date for females of reproductive potential. The pharmacist should record this date on the prescription bag sticker.
- **The iPLEDGE Program system** 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 male patients and females of non-reproductive potential) or more than 7 days beyond the pregnancy test date (for females of reproductive potential), will not be authorized by the iPLEDGE Program system.
- 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 Program system and the product returned to inventory.
- **No automatic refills** are permitted.
- **Isotretinoin** comes in blister packs of 10 capsules. The pharmacist cannot break a blister pack.
- An isotretinoin Medication Guide must be given to the patient each time isotretinoin is dispensed, as required by law.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.**

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Pharmacy Information

Patients can only obtain isotretinoin prescriptions from pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE Program.

The web site, **www.ipledgeprogram.com**, provides a database of registered pharmacies. Patients and prescribers can access this information by logging in and choosing the "Find a Participating Pharmacy" button on their home page.

A complete list of FDA-approved isotretinoin products that may be prescribed and dispensed may be found by calling 1-866-495-0654 or via www.ipledgeprogram.com.

iPLEDGE PROGRAM PRESCRIBING CHECKLISTS

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:

Female patients who can get pregnant…	Male patients and female patients who cannot get 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 being 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 patient can no longer fill and pick up their prescription, and must start the process over to get a new prescription window*

*There are generally no restrictions regarding the timing of office visits. One notable exception is that females of reproductive potential who do not obtain their first month of therapy prescription in their first 7-day prescription window, must wait at least 19 days from their most recent pregnancy test until getting their next pregnancy test. This is based on the requirement that the most recent pregnancy test prior to beginning therapy must be conducted in the first 5 days of her menstrual cycle.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.** 6/4/12 1 29 PM

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Females Of Reproductive Potential

Before

PLANNING

- ❑ **Plan** for office visits, counseling, pregnancy testing.
- ❑ **Educate** about isotretinoin and the contraception requirements of the iPLEDGE Program.
- ❑ **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.
- ❑ **Obtain** the Patient Information/Informed Consent (for all patients) form.
- ❑ **Register** patient in the iPLEDGE Program system and provide patient with an educational kit, 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 page 22 for information on referring for contraception counseling.
- ❑ **Counsel** patient that she must use 2 effective forms of contraception simultaneously for at least 1 month before starting therapy. There is a 30-day mandatory waiting period during which she must be using both chosen forms of birth control before she is eligible to begin treatment with isotretinoin.
- ❑ **Inform** patient about confidential iPLEDGE Program Pregnancy Registry.

PRESCRIBE

- ❑ Verify female patient qualification criteria.
- ❑ **Order** a pregnancy test using a CLIA-certified laboratory:
  - 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 therapy and after the patient has used 2 forms of contraception for 1 month. Please refer to the section on. "Qualification criteria for females of reproductive potential" (*see page 19*) for details on the timing of this test.
- ❑ **Obtain** the Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form.
- ❑ **Confirm** patient counseling of program requirements in the iPLEDGE Program system.
- ❑ **Provide** a prescription for up to a maximum 30-day supply of isotretinoin.
- ❑ **Enter** pregnancy test results and the patient's 2 forms 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.

During
(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 Program system.
- ❑ **Provide** a prescription for up to a maximum 30-day supply of isotretinoin.
- ❑ **Enter** pregnancy test results and the patient's 2 forms 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.

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After

AFTER THE LAST DOSE

- ❑ **Counsel** patient on contraception adherence for 30 more days.
- ❑ **Counsel** patient not to give blood for at least 1 month 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 Program system.
  - If you do not enter the results of the pregnancy test at the conclusion of therapy, the patient will be classified as Lost to Follow Up, and both you and the patient may be contacted for additional information.

1 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 Program system.
  - If you do not enter the results of the pregnancy test 1 month after the conclusion of therapy, 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 27 for information about reporting pregnancies to the confidential iPLEDGE Program Pregnancy Registry.

Male Patients And Female Patients Who Cannot Get Pregnant

Before

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 kit, which includes the Patient ID number on perforated, removable cards.

PRESCRIBE

- ❑ **Confirm** patient counseling about 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
(at each monthly visit)

- ❑ **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

AFTER THE LAST DOSE

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

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DETERMINE REPRODUCTIVE POTENTIAL OF FEMALE PATIENTS

Qualification Criteria

The prescriber must determine if a female is of reproductive potential before enrolling her in the iPLEDGE Program. The definition of a female of reproductive potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

- A woman who has had a tubal sterilization is considered a female of reproductive potential in the iPLEDGE Program.

Definition of menopause

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.

Screen patients

Data support that there are key issues in identifying female patients for treatment with isotretinoin.

The prescriber should:

1. Identify patients whose acne could be effectively managed without isotretinoin and avoid prescribing it for such patients
2. Identify those who are already pregnant when considering isotretinoin
3. Identify those who may not be reliable in avoiding pregnancy for the required period before, during, and after therapy

The patient should understand that, ultimately, it is her responsibility to avoid exposing an unborn baby to isotretinoin. The patient must understand the critical responsibility she assumes in electing to undertake therapy with isotretinoin and that any method of birth control, apart from complete abstinence, can fail.

The prescriber must verify that each individual patient receives adequate counseling about all her pregnancy prevention options (including abstinence) and that she knows how to select and use 2 separate, effective contraceptive methods.

Qualification criteria for females of reproductive potential

Once the prescriber decides to pursue qualification of the patient, a female of reproductive potential must follow these steps.

1. Before the patient can begin isotretinoin therapy, there is a 30-day wait period where the patient must be on two forms of birth control simultaneously. Additionally, she will need to have 2 negative pregnancy tests. Femalesof reproductive potential must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the 2 tests must be at least 19 days.
    - For patients with regular menstrual cycles, the second pregnancy test must be done during the first 5 days of the menstrual period, immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.
    - 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 therapy and after the patient has used 2 forms of contraception for 1 month.
    - The patient must be using her two forms of contraception for at least 30 days prior to beginning therapy on isotretinoin, and her second pregnancy test must occur after this 30-day period is complete.
2. The patient must sign a Patient Information/Informed Consent (for all patients) form and a Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form.

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3. The patient must select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless the patient commits to continuous abstinence from heterosexual contact, or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of isotretinoin therapy, during isotretinoin therapy, and for 1 month after discontinuing isotretinoin therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis prior to issuing each prescription.

Monthly requirements

Each month of therapy, patients must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month, in a CLIA-certified laboratory, prior to the female patient receiving each prescription. A pregnancy test must also be ordered at the end of therapy (after the last dose), and 1 month after the last dose. If the results of the pregnancy tests at the conclusion of therapy, and the pregnancy test 1 month after the conclusion of therapy, are not entered into the iPLEDGE system, the patient will be classified as Lost to Follow Up, and both the prescriber and the patient will be contacted for additional information. The iPLEDGE Program also requires monthly counseling about contraception and behaviors associated with an increased risk of pregnancy.

In addition to their required doctor appointments, females of reproductive potential each month must also enter their 2 effective forms of contraception in the iPLEDGE Program system and answer questions about the iPLEDGE Program and pregnancy prevention.

Effective Forms Of Contraception

Effective forms of contraception include both primary and secondary forms of contraception.

Primary forms	Secondary forms
• Tubal sterilization • Partner's vasectomy • Intrauterine device • Hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)	*Barrier forms (always used with spermicide)* • Diaphragm • Cervical cap *Barrier forms (used with or without permicide)* • Male latex condom *Others:* • Vaginal sponge (contains spermicide)

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.**

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Unacceptable Forms Of Contraception Include:

- Progesterone-only "mini-pills,"
- Female condoms
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield‡

Abstinence

For this program, all females of reproductive potential must fully commit to pregnancy prevention. Abstinence without appropriate contraception is not recommended for patients in the iPLEDGE Program who are or have been sexually active. Abstinence may be appropriate when it is a lifestyle choice (e.g., religious practice) and not just a social circumstance (e.g., not having a current partner). If, after counseling, a sexually active patient chooses abstinence without contraception, she must understand that isotretinoin is not recommended for any female of reproductive potential who cannot or will not follow the contraceptive requirements of the iPLEDGE Program. All females of reproductive potential must receive contraception counseling.

Contraception Counseling

The prescriber must ensure that each individual patient receives adequate counseling about all her pregnancy prevention options (including abstinence) and that she knows how to select and use 2 separate, iPLEDGE Program-effective forms of contraception that will give her the lowest failure rate.

The patient must understand the critical responsibility she assumes in electing to undertake therapy with isotretinoin and that any form of birth control, apart from complete abstinence, can fail. All females of reproductive potential must read the patient *iPLEDGE Program Birth Control Workbook*.

Reinforce the message

Counseling about contraception must be repeated on a monthly basis. Approximately 30% of female patients said they did not use 2 forms of contraception, even when knowing the risks and having consented.[2] Active counseling is one of the best tools toward getting patient compliance.

When counseling patients on contraception, the prescriber should refer to *The iPLEDGE Program Prescriber Contraception Counseling Guide*, which contains an overview of issues in contraception and the effective forms of contraception in the iPLEDGE Program. It is a companion to the patient *iPLEDGE Program Birth Control Workbook*.

It is especially important to assess the patient's ability to understand her responsibilities and instructions, and to reinforce these instructions at every clinical visit. It is very important to be able to make a careful assessment of a female patient's reproductive history, contraceptive knowledge, and previous use of contraception forms. This assessment and contraceptive education should continue throughout isotretinoin treatment.

*Ortho Micronor is a registered trademark of Ortho-McNeil Pharmaceutical, Inc.

‡ A cervical shield should not be confused with a cervical cap, which is an effective secondary form of contraception. See page 20.

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Referral for contraception counseling

Before beginning treatment, the prescriber or patient may choose referral to a healthcare professional with expertise in pregnancy prevention. The makers of isotretinoin will reimburse one visit for contraception counseling. The patient educational kit contains *The iPLEDGE Program Contraception Referral Form And Contraception Counseling Guide*. The form is in the booklet; the guide outlines the contraception requirements and the effective forms of contraception of the iPLEDGE Program for the birth control expert.

The referral form 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 Program system. The reverse side of the form has information for the counselor on the reimbursement process.

Referring to a gynecologist

The prescriber may want to specifically refer a patient to a gynecologist for:

- An examination 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
- More detailed explanation of contraception options

The prescriber should also ask for gynecologic consultation under the following circumstances:

- The patient's history is suggestive of polycystic ovary syndrome (Stein-Leventhal syndrome). In addition to acne she may have:
  - Excessive facial hair growth (common when acne is present)
  - Obesity
  - Amenorrhea (no menstrual period) or irregular, heavy bleeding
  - Anovulation
- The patient has irregular menses, possibly related to pregnancy; an eating disorder; or endometriosis. It is important that the prescriber weighs the patient if there is suspicion of a potential eating disorder. Patients with eating disorders may:
  - Not admit to the problem
  - Be very underweight
- There are indications of sexual abuse found during the physical examination or counseling session.
- There is history or are symptoms of sexually transmitted infection.

Confidential birth control information

The iPLEDGE Program has automated confidential birth control information that patients can use 24 hours a day, 7 days a week. Patients can call the program's toll-free number **1-866-495-0654** and obtain information on a variety of subjects, including:

1. Isotretinoin and Birth Defects
2. Sex, Pregnancy, and Birth Control
3. Different Methods of Birth Control
4. Emergency Contraception
5. Pregnancy and Pregnancy Testing

This is also a good option for patients who are vision impaired. Patients are always referred to their prescribers for additional information and clarification.

iPLEDGE PROGRAM PRESCRIBING INFORMATION

Register Patients In The iPLEDGE Program System

Patients may be registered in the iPLEDGE Program system either via the web site or phone system after obtaining the Patient Information/Informed Consent (for all patients) form and providing the patient with an ID number and ID card. The process is faster and easier using the web site.

On the web site, the prescriber logs in and chooses "Register New Patient." In the phone system, the prescriber logs in and selects the option to "Register a New Patient."

The system will request this specific patient information:

- Patient ID number
- Patient first and last name and middle initial
- Home address
- Phone number
- Date of birth
- Gender
- Last four digits of the Social Security number
- Female of reproductive potential (Yes or No)
- Screening pregnancy test date and results

ID number and ID card

The ID number and perforated ID cards are provided with the patient education materials. It is important that patients do not lose the cards. Prescribers should keep a record of the patient's number.

- All patients need the ID number and ID card to obtain their prescriptions, and to access the web site or automated phone line.
- Females of reproductive potential will need their ID number to access the iPLEDGE Program system to answer questions about the iPLEDGE Program and preventing pregnancy.

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Informed consents

Patients will need to sign the following consent forms to be in the iPLEDGE Program.

- Patient Information/Informed Consent (for all patients)
- Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)

For females of reproductive potential, signing the Patient Information/ Informed Consent About Birth Defects (for female patients who can get pregnant) form means the following.

- They understand the teratogenic risks of isotretinoin.
- They agree to follow the contraception requirements of the iPLEDGE Program before, during, and for 1 month after their treatment with isotretinoin.

Prescriptions: System Requirements

Before a patient can obtain a prescription for isotretinoin at a registered pharmacy, the iPLEDGE Program system requires that the information below be entered into the system and the timing criteria for filling and dispensing a prescription be met. This is the information that the system will use to authorize filling a prescription and to provide the Risk Management Authorization (RMA) number and the **"Do Not Dispense To Patient After"** date.

All patients

Prescriber confirms that:

- The patient is registered with the iPLEDGE Program
- The patient was counseled on the iPLEDGE Program requirements

Females of reproductive potential

Prior to the patient obtaining each prescription, the prescriber must access the iPLEDGE Program system to:

- Confirm that the patient was counseled about isotretinoin and the iPLEDGE Program contraception requirements
- Enter the 2 forms of contraception that the patient is using
- Enter pregnancy result into the iPLEDGE Program system, within the 7-day prescription window, counting the date of blood draw or urine sample as DAY 1
- **The patient cannot answer her monthly questions and get a prescription filled until after these activities are completed by the prescriber.**

A positive pregnancy test prevents the prescription from being filled.

Patient must access the iPLEDGE Program system after the prescriber has entered the pregnancy test results to:

- Correctly answer the questions about the iPLEDGE Program and pregnancy prevention
- Enter the 2 forms of contraception she is using

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

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.**

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Timing criteria for the prescription to be obtained from the Pharmacy

- All patients must obtain their prescriptions as follows:
  - For male and female patients who cannot get pregnant, prescriptions must be obtained within the 30-day prescription window, counting the office visit as DAY 1
  - For female patients who can get pregnant, prescriptions must be obtained within the 7-day prescription window counting the day of the blood draw or urine sample as DAY 1
- Patients will not be able to obtain prescriptions after their prescription window has expired.

The iPLEDGE Program system will automatically provide the pharmacist with a "Do Not Dispense To Patient After" date, which is the end of the prescription window. The pharmacist cannot fill or dispense the patient's prescription after that date.

After The Last Dose

All patients should be reminded not to give blood for at least 1 month after their last dose.

Females of reproductive potential must have pregnancy tests:

- After their last dose, and
- 1 month after their last dose
- If this information is not entered, the patient will be classified as Lost to Follow Up, and both the prescriber and the patient will be contacted for more information.

It is important to stress the need for continued contraception during the 1 month after the last dose. Patients also should be reminded to enter their 2 forms of contraception.

Post Treatment iPLEDGE Program Requirements

When a patient will no longer be taking isotretinoin, action is required by the prescriber to record specifics of the end of therapy. Specifically the following information is required by the iPLEDGE Program:

- If known when issuing the prescription, the prescriber will indicate that a prescription will be the last one for this patient. This will remind the prescriber of the patient requirements for post-treatment activity
- The prescriber **must** discontinue the patient within the iPLEDGE Program in one of the following ways:
  - On the website, select "Manage Patients", select the patient being discontinued, and choose the button for "Discontinue Patient".
  - On the phone system, select the option to "Manage Active Patients", and then select the option to "Complete or Discontinue Patient Treatment".

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.**

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- When discontinuing a patient through either the website or the phone system, the prescriber must enter the Date of Last Dose, and the reason why this patient will no longer be taking isotretinoin. This reason will be selected from a list presented by the iPLEDGE Program system, including Completed Therapy, Pregnancy, or Other. On the website, explanatory comments can also be provided, and may be required by the iPLEDGE Program system.
  - If the reason for discontinuation is related to an Adverse Event, please be as specific as possible in the comments entered in the iPLEDGE Program system.
- For females of reproductive potential, **a final pregnancy test is required at the date of last dose, and 30 days after date of last dose**.

If this information is not provided, and a patient has no activity in the iPLEDGE Program system for specific periods of time, the patient will be classified as Lost to Follow Up. If this occurs, prescribers and patients will be contacted by the iPLEDGE Program.

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 Program Pregnancy Registry

The iPLEDGE Program Pregnancy Registry collects data on pregnancies that occur in female 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 Program. The data are also used to evaluate further ways to reduce fetal exposure. Information gathered in the iPLEDGE Program Pregnancy Registry will be used for statistical purposes only and will be held in the strictest confidence.

The prescriber must report to the iPLEDGE Program Pregnancy Registry any pregnancy case that he/she becomes aware of while the female 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 female patients taking isotretinoin

1. Positive pregnancy test results should be entered in the iPLEDGE Program system. A Safety Surveillance Associate will call the prescriber.
2. A prescriber should call the iPLEDGE Program Call Center if he or she does not have a pregnancy test result but thinks the patient is pregnant.

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

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In partners of males being treated with isotretinoin

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

Males And Birth Defects

Unlike in female patients, there is no pattern of birth defects in babies whose fathers were taking isotretinoin. Approximately 3 to 5 babies in 100 (3% to 5%) are born with some kind of birth defect from other causes, not from isotretinoin.[3]

Isotretinoin also has not been shown to affect a male's ability to father children. Studies did not show effects on sperm count, how sperm look, or how well they swim and move. (For more information, see page 3.)

DELEGATES AND OFFICE STAFF

The iPLEDGE Program allows the prescriber to delegate patient management to other prescribers registered with the iPLEDGE Program (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 must first add the name and required information for delegates into the iPLEDGE Program system. This function also allows the prescriber to define time frames for delegation and add or delete delegates.

To delegate to another prescriber

The prescriber:

1. Logs in to the web site, **www.ipledgeprogram.com**
2. Chooses "Manage Delegates/Designees" from the Prescriber home page
3. Chooses "Manage Delegates" from the Manage Delegates and Designees page
4. Enters the desired Delegate's iPLEDGE user ID, and the date, if any, when the delegate's role is to expire.
5. Chooses "Add" new delegate for first-time entry

Office Designees

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

- Register patients and maintain the patient's information in the iPLEDGE Program
- Enter patient pregnancy results
- Confirm patient counseling
- Discontinue patients
- Manage delegates
- Check patient's program status

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The following functions are available only to a prescriber:

- Prescriber registration
- Prescriber activation—initial and renewal
- Serious Medical Reasons Exemption process

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

- They need to register only once, regardless of the number of prescribers with whom they are associated.
- They may support all the registered prescribers in a multi-physician practice.
- 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 Program system, neither the prescriber nor the designated office staff can register a patient.

Designated office staff may access the automated system but must provide their own user ID and date of personal significance as identifiers.

The registered and activated prescriber is responsible for all information entered and activities performed in the iPLEDGE Program system by the office staff designee.

To designate office staff

The prescriber:

1. Logs in to the web site, **www.ipledgeprogram.com**
2. Chooses "Manage Delegates/Designees" from the Prescriber home page
3. Chooses "Register New Designee" from the Manage Delegates and Designees page
4. Fills in the required information on the registration online form
5. Selects "Save and Print" to save the new information and print the registration form

The office staff designee:

1. Signs and dates the completed form
2. Faxes or mails the completed form to the number or address provided

A username and password will be mailed 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 password and choose a Date of Personal Significance as a system identifier

REFERENCES

1 Dai WS, Hsu MA, Itri LM Safety of pregnancy after discontinuation of isotretinoin *Arch Dermatol.* 1989;125:362-355

2 Mitchell, Allen A MD Isotretinoin Survey Allen A Mitchell, MD and Carla M Van Bennekom RN, MPH Slone Epidemiology Center at Boston University For presentation at FDA Advisory Committee Meeting: February 26-27, 2004

3 Centers for Disease Control and Prevention Birth defects: frequently asked questions Available at: http //www.cdc.gov/ncbddd/bd/faq1.htm#Whatisabirthdefect Accessed August 8, 2005

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

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ACTIVATING DESIGNEE REGISTRATION

iPLEDGE registration must be activated in the iPLEDGE Program system before a designee can interact with the iPLEDGE Program. Activation must occur annually.

- The designee should review *The Guide To Best Practices For the iPLEDGE Program* and *The iPLEDGE Program Prescriber Contraception Counseling Guide* to understand the program. Activation requires the designee to attest to the following statements in the iPLEDGE Program system:
  - **Isotretinoin is teratogenic and must not be used by pregnant women.** The goals of the iPLEDGE program 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 is routinely analyzed to identify actions of non-compliance.

Information entered into the iPLEDGE system 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 Program requirements can result in removal from the iPLEDGE Program.

Prescribers are responsible for all iPLEDGE activities performed by their Office Staff Designees. If an Office Staff Designee is found to be non-compliant with the iPLEDGE Program, resulting actions, including possible removal from the iPLEDGE Program, can include both the designee and the prescriber.

- **Verified Non-Compliance may be reported to the FDA.**

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For More Information About Isotretinoin

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

Please see accompanying complete product information, including boxed **CONTRAINDICATIONS AND WARNINGS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS.**

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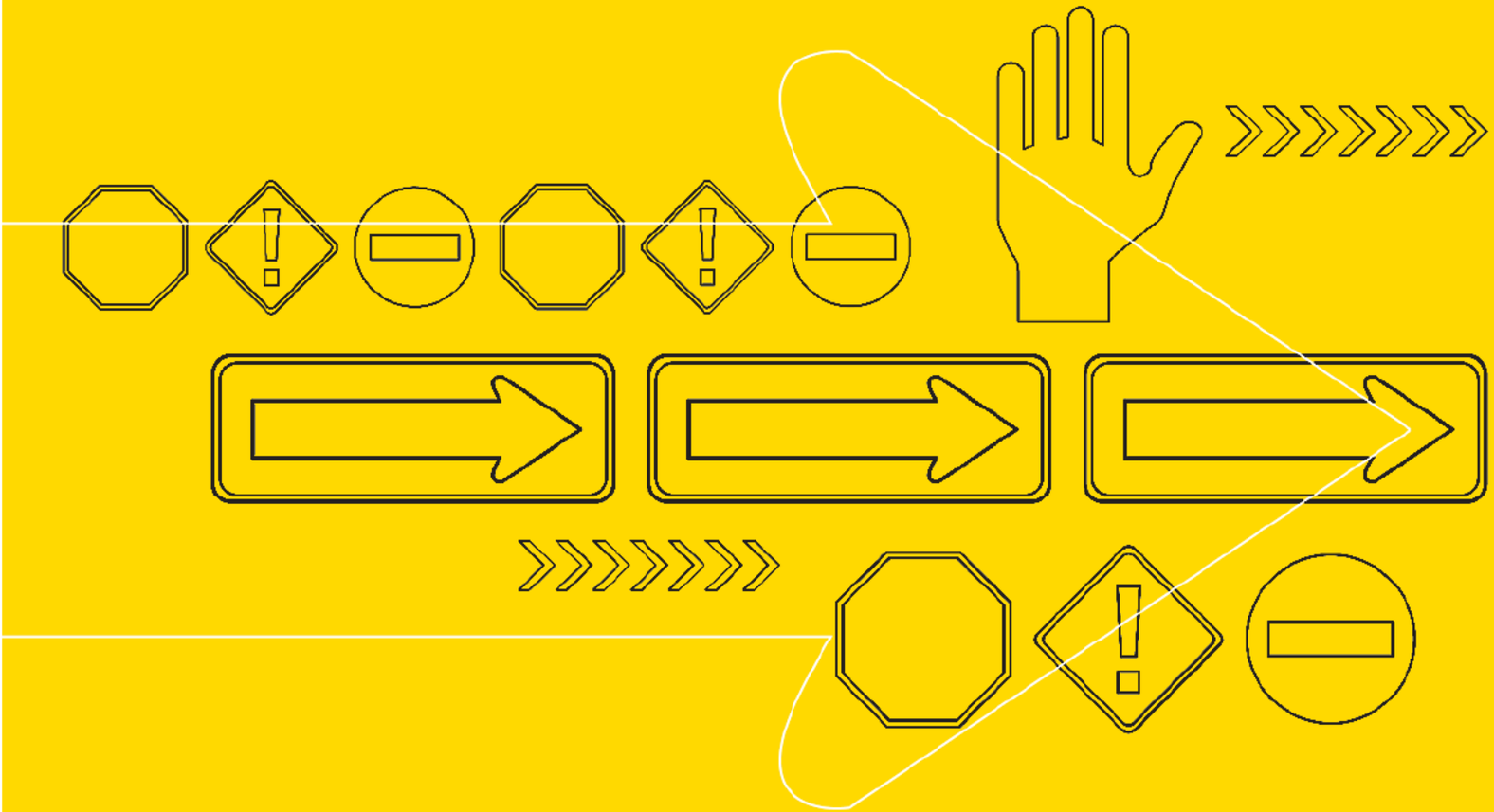

www.ipledgeprogram.com 1-866-495-0654

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.

iPLEDGE™
Committed to Pregnancy Prevention

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