

**The iPLEDGE Program**

# **Guide to Best Practices for Isotretinoin**

**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.

# The iPLEDGE Program Guide to Best Practices for Isotretinoin

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Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. In addition, for female patients of childbearing 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 iPLEDGE Program Guide to Best Practices for Isotretinoin**

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 dysmorphism; 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.**

For full prescribing information, including Boxed Warning, Contraindications, Warnings, Precautions, and Adverse Events, please refer to the package insert.

Please see enclosed full prescribing information, including **boxed WARNINGS**.

Please see Important Safety Information on page 5.

**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 iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see **PRECAUTIONS**).**

## 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 within 1 month of discontinuing isotretinoin therapy. 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); 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 posttreatment. Women who become pregnant during this month should be counseled as to the outcome data. In 1989, Dai<sup>1</sup> 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.

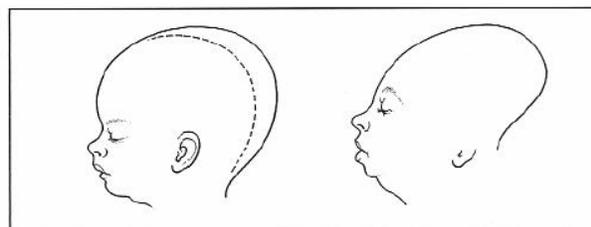
When Isotretinoin is taken during pregnancy, it has been associated with fetal malformations, and there is an increased risk for spontaneous abortions, and premature birth.

The following human fetal abnormalities have been documented:

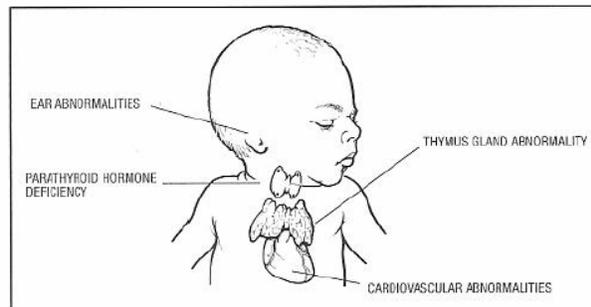
## External Abnormalities

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

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



Line drawing represents the possible abnormalities of 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.

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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.

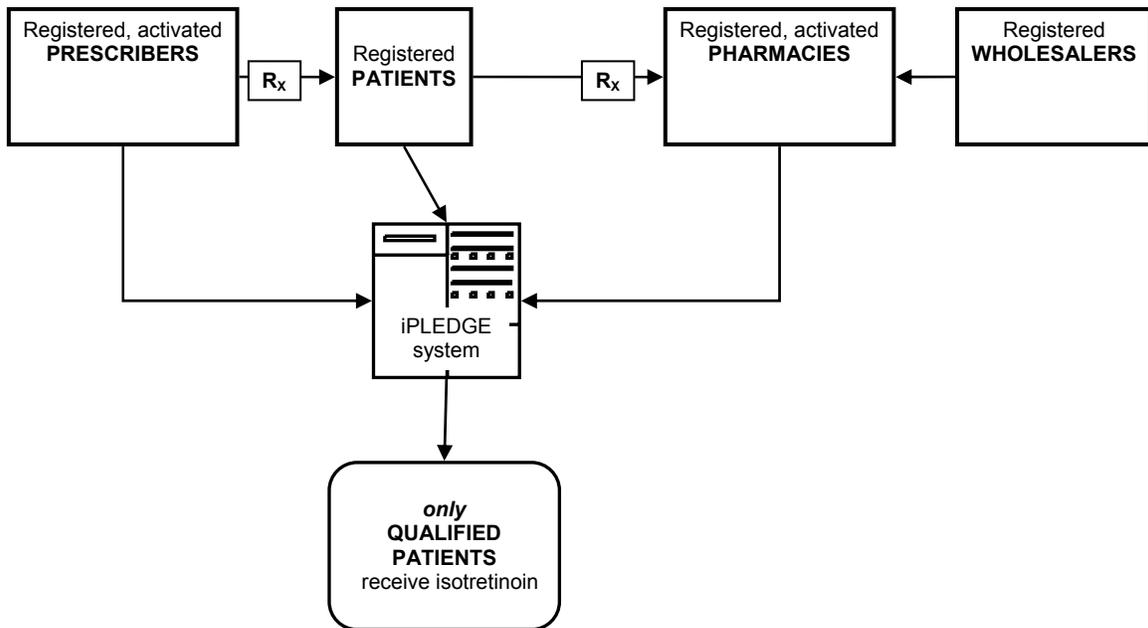
# THE iPLEDGE PROGRAM

**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 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 iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see PRECAUTIONS).

The goal of the iPLEDGE program is to prevent pregnancies in females taking isotretinoin and to prevent pregnant females from taking isotretinoin.

The iPLEDGE program is 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.

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- 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
- Prescribers must document that all patients—and specifically female patients of childbearing potential—meet the requirements in the iPLEDGE program.
- Only patients who are registered by prescribers in the iPLEDGE program can receive isotretinoin.
- Female patients of childbearing potential must enter required information (2 forms of contraception used, answer questions on program requirements) in the iPLEDGE 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 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-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

Prescribers need to follow the key points of the iPLEDGE program. These points are explained in detail in this *iPLEDGE Program Guide to Best Practices for Isotretinoin*. Here is an overview:

- The iPLEDGE program educational materials for prescribers and patients.
- Activation in the iPLEDGE automated system.
- Prescriber steps required “Before,” “During,” and “After” treatment with isotretinoin.
- Specific program criteria and procedures for female patients of childbearing 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.

## THE iPLEDGE WEB SITE AND PHONE SYSTEM

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

- Web site: **[www.ipledgeprogram.com](http://www.ipledgeprogram.com)**
- Phone system: **1-866-495-0654.**

The automated system is used to:

- Activate registration.

- Register patients.
- Confirm patient counseling each month for all patients.
- Enter monthly pregnancy test results and contraception information for female patients of childbearing potential.
- Order additional copies of the *iPLEDGE Program Guide to Best Practices for Isotretinoin* and of patient and professional educational materials.
- Manage delegates and designate office staff.

Logging into either the web site or phone system requires a username and password, which are supplied upon registration.

### **To review and order materials**

On the web site, the prescriber logs on and chooses “Prescriber Information” in the left navigation. In the phone system, the prescriber logs on and presses 7 to “Request Program Information.”

## **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 *iPLEDGE Program Guide to Best Practices for Isotretinoin* 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: A Guide for Prescribers of Isotretinoin*, contains important information about depression, suicide, and psychiatric assessment and referral of your patients.

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Please see enclosed full prescribing information, including **boxed WARNINGS**.

Please see Important Safety Information on page 5.

## Additional materials

Additional resource materials can be viewed on the iPLEDGE web site.

These include:

- Isotretinoin Medication Guide
- Isotretinoin Package Inserts
- Prescribing Checklists

## Patient Materials

The prescriber distributes the *iPLEDGE Program Patient Introductory Brochure* and the patient educational kits, which provide information about the iPLEDGE program requirements.

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

Additionally, the kit for female patients of childbearing 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 DVD

The prescriber educational kit also includes a DVD for patients: **Be Prepared, Be Protected; Be Aware: The Risk of Pregnancy While on Isotretinoin**. This describes the kind of birth defects that may happen if a woman takes any amount of isotretinoin while she is pregnant. It also reviews reasons for contraception failure.

## ACTIVATING REGISTRATION

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

The iPLEDGE 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 "Program Status" on the left navigation.
- In the phone system, logs in and presses 3 to hear "Current Program Status."

The prescriber should review the *iPLEDGE Program Guide to Best Practices for Isotretinoin* 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 system:

- I know how to diagnose and treat the various presentations of acne.
- 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 iPLEDGE Program Guide to Best Practices for Isotretinoin* and *The iPLEDGE Program Prescriber Contraception Counseling Guide*.
- Before beginning treatment of female patients of childbearing potential with isotretinoin and on a monthly basis, the patient will be counseled to avoid pregnancy by using two forms of contraception simultaneously and continuously one month before, during, and one month after isotretinoin therapy, unless the patient commits to continuous abstinence.
- I will not prescribe isotretinoin to any female patient of childbearing 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.

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## Procedures for Activating in the iPLEDGE System

The prescriber can access the iPLEDGE system to activate registration via the web site, [www.ipledgeprogram.com](http://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 the system requires the username (DEA number or program-generated username) and password received with the registration materials.

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 system, or if a password is lost.

### 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, selects "**Activate**" from the "**Activate My Registration**" section of the page. The system will provide prompts to complete the activation process.

### 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. Presses 4 to select "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 female patients of childbearing 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 once a month, and then only 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. They must also enter this information after the first appointment.

There are different program requirements for male patients and female patients who are not of childbearing potential and for female patients of childbearing potential. The prescriber must determine if a patient is a female patient of childbearing 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 patient of childbearing potential must also answer questions in the iPLEDGE system about the program requirements and pregnancy prevention. She must also enter the two forms of birth control she is using. In addition to the monthly counseling information, the prescriber must also enter into the system the patient's 2 forms of contraception and the results of the monthly pregnancy test.

This information is the criteria the system uses to authorize a pharmacy to fill a prescription.

The *iPLEDGE Program Guide to Best Practices for Isotretinoin* includes a checklist of steps to follow before, during, and after patient treatment. (See page 16.) Here are the main requirements for patients and pharmacists.

## Requirements for 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 fill the prescription within 7 days of 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 30 day supply of isotretinoin per prescription. Each month, continuation of therapy requires the patient to satisfy the iPLEDGE program requirements to obtain a new prescription. The prescriber must also counsel the patient each month about the iPLEDGE program requirements and then confirm via the iPLEDGE system that this counseling occurred.

### Female patients of childbearing 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.

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- Have a second pregnancy test, performed in a CLIA-certified laboratory, after being on two effective forms of contraception for 1 month and before starting isotretinoin therapy.\*
- Fulfill monthly requirements:
  - Have a serum or urine pregnancy test performed in a CLIA-certified laboratory.\*
  - Access the system to answer questions about the iPLEDGE requirements and pregnancy prevention in the iPLEDGE system.
  - Enter into the iPLEDGE 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

Female patients of childbearing potential must answer questions each month about the iPLEDGE program and pregnancy prevention. They 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.

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 system will direct her to review her material and try again at a later time. If she fails on a second try, she will be directed to contact her doctor.

## 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 a prescription** for a maximum 30-day supply of isotretinoin.
- **Upon authorization, the iPLEDGE system** provides a Risk Management Authorization (RMA) number to the dispensing pharmacist. The pharmacist should record the RMA number directly on the prescription.
- **Upon authorization, the iPLEDGE system** provides a **“Do Not Dispense to Patient After”** date (7 days from office visit date) to the dispensing pharmacist. The pharmacist should record this date on the prescription bag sticker.

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\* For timing information about monthly pregnancy tests, see number 4 on page 19 under “Qualification criteria for female patients of childbearing potential.”

- **The iPLEDGE system** only authorizes filling and dispensing prescriptions when patients have met the qualification criteria in the system each month.
- **Prescriptions** that are more than 7 days beyond the date of the office visit will not be authorized by the iPLEDGE system.
- **Prescriptions must be picked up by the patient no later than the “Do Not Dispense to Patient After” date, and if not picked up, then the prescription is to be returned to stock.**
- **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.

## Pharmacy Information

Patients can only fill isotretinoin prescriptions at pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE program.

The web site, [www.ipledgeprogram.com](http://www.ipledgeprogram.com), provides a database of registered pharmacies. Patients can access this information by logging in and choosing “Find a Participating Pharmacy” on the patient home page.

Patients can also get pharmacy information on the automated phone line, **1-866-495-0654**, by pressing 6 for “More Choices,” and then pressing 5 to find a participating pharmacy.

### **Only FDA-approved isotretinoin products can be prescribed, dispensed, and used.**

#### **Product**

Accutane<sup>®</sup> (isotretinoin capsules)  
 Amnesteem<sup>®</sup> (isotretinoin capsules)  
 Claravis<sup>™</sup> (isotretinoin capsules)  
 Sotret<sup>®</sup> (isotretinoin capsules)

#### **Company**

Roche Laboratories, Inc  
 Mylan Pharmaceuticals Inc  
 Barr Laboratories, Inc  
 Ranbaxy Laboratories, Ltd.

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# iPLEDGE PROGRAM PRESCRIBING CHECKLISTS

## Female Patients of Childbearing 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 system.
- **Obtain** the Patient Information/Informed Consent (for all patients) form.
- **Register patient** in iPLEDGE system and provide patient ID number and card.

### COUNSEL ON CONTRACEPTION

- **Counsel** patient in office or refer to healthcare professional with expertise in contraception. Please see page 24 for information on referring for contraception counseling.
- **Counsel** patient that she must use 2 effective forms of contraception simultaneously for at least one month before starting therapy.
- **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 or irregular cycles please refer to the section on Qualification Criteria for Female Patients of Childbearing Potential 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 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 system within 7 days of the patient's office visit.

### 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 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 system within 7 days of the patient's office visit.

**Refer to page 27 for information about reporting pregnancies to the confidential iPLEDGE Program Pregnancy Registry.**

## 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 system within 7 days of the patient's office visit.

### 1 MONTH AFTER THE LAST DOSE

- **Order** a pregnancy test using a CLIA-certified laboratory.
- **Enter** pregnancy test results in the iPLEDGE system.

## 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 system and provide patient ID number and card.

#### PRESCRIBE

- **Confirm** patient counseling about program requirements in the iPLEDGE system within 7 days of the patient's office visit.
- **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 system within 7 days of the patient's office visit.
- **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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Please see enclosed full prescribing information, including **boxed WARNINGS**.

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# DETERMINE CHILDBEARING POTENTIAL OF FEMALE PATIENTS

## Qualification Criteria

The prescriber must determine if a female patient is of childbearing potential before enrolling her in the iPLEDGE program. The definition of a female patient of childbearing 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 patient of childbearing 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 you are 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 female patients of childbearing potential**

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

1. Female patients of childbearing potential must have had two 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 two 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 and within 7 days following the office visit, 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 within 7 days following the office visit, immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.
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.
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.

### **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. The iPLEDGE program also requires monthly counseling about contraception and behaviors associated with an increased risk of pregnancy.

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In addition to their required doctor appointments, female patients of childbearing potential each month must also enter their 2 effective forms of contraception in the iPLEDGE 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:

<p>Primary forms</p> <ul style="list-style-type: none"><li>• tubal sterilization</li><li>• partner's vasectomy</li><li>• intrauterine device</li><li>• hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)</li></ul>	<p>Secondary forms</p> <p><i>Barrier forms (always used with spermicide):</i></p> <ul style="list-style-type: none"><li>• male latex condom</li><li>• diaphragm</li><li>• cervical cap</li></ul> <p><i>Others:</i></p> <ul style="list-style-type: none"><li>• vaginal sponge (contains spermicide)</li></ul>
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## Unacceptable Forms of Contraception Include:

- Progesterone-only “mini pills,” e.g.:
  - **Ortho Micronor Tablets**<sup>®</sup> (Ortho-McNeil)
  - **Ovrette Tablets**<sup>®</sup> (Wyeth)
- IUD Progesterone T
- Female condoms
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

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## **Abstinence**

For this program, all female patients of childbearing 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 patient of childbearing potential who cannot or will not follow the contraceptive requirements of the iPLEDGE program. All female patients of childbearing 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 female patients of childbearing 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.<sup>2</sup> 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.

## 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 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 if:

- 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 symptoms of sexually transmitted disease.

## 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

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## 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 System**

Patients may be registered in the iPLEDGE system either via the web site or phone system after obtaining the Patient Information/Informed Consent (for all patients) 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 presses 2 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 patient of childbearing potential (Yes or No)
- Screening pregnancy test date and results

### **ID Number and ID Card**

The ID number and ID card are provided with the patient education materials. It is important that patients do not lose the card. Keep a record of the patient’s number.

- All patients need the ID number and ID card for their monthly appointments, to fill their prescriptions, and to access the web site or automated phone line.
- Female patients of childbearing potential will need their ID number to access the iPLEDGE system to answer questions about the iPLEDGE program and preventing pregnancy.
- If the patient does need a new card, he or she can ask for one on the web site or through the automated phone line.

## **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 female patients of childbearing potential, signing the Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form means that:

- 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.
- They agree to be contacted by the iPLEDGE program Pregnancy Registry if they become pregnant at any time during or within the 1 month after the end of therapy. (See page 27.)

## **Prescriptions: System Requirements**

Before a patient can fill a prescription for isotretinoin at a registered pharmacy, the iPLEDGE 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 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.

### **Female patients of childbearing potential**

Prescriber should access the iPLEDGE system within 7 days of the patient’s office visit date 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.

A positive pregnancy test prevents the prescription from being filled.

Patient should access the iPLEDGE system within 7 days of the office visit date 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.

### **Timing criteria**

- All patients must fill their prescriptions within 7 days of the date of the office visit, counting the office visit as DAY 1.

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- Patients will not be able to pick up prescriptions after this time period.

**The iPLEDGE system will automatically provide the pharmacist with a “Do Not Dispense To Patient After” date. 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.

### **Female patients of childbearing potential must have pregnancy tests:**

- After their last dose, and
- 1 month after their last dose

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 two forms of contraception.

## **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**. Press 3 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 enter in the iPLEDGE system. A Safety Surveillance Associate will call the prescriber.
2. A prescriber should call the iPLEDGE call center if they do not have a pregnancy test result but thinks the patient is pregnant.

#### **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 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.<sup>8</sup>

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 5.)

## DELEGATES AND OFFICE STAFF

The iPLEDGE program allows the prescriber to delegate patient management to other prescribers registered with the iPLEDGE program and to designate office staff to assist with data entry.

### Delegating to Another Prescriber

The prescriber must first add the name and required information for delegates into the iPLEDGE 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 into the web site, [www.ipledgeprogram.com](http://www.ipledgeprogram.com).
2. Chooses "Manage Delegates" from the Prescriber home page.
3. Chooses "Add" new delegate for first-time entry.
4. Enters the requested information:
  - Delegated prescriber DEA number or iPLEDGE program ID number
  - Expiration date for delegation

### Designating Office Staff

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
- Enter patient pregnancy results
- Confirm patient counseling
- Discontinue patients
- Manage delegates
- Check patient's program status

The following functions are available only to a prescriber:

- Prescriber registration

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- Prescriber activation—initial and renewal

A prescriber may have one or more designated office staff. Designated office staff 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.
- May support all the registered prescribers in a multi-physician practice.
- Have rights for any patient delegated to a delegated prescriber.

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

- If a prescriber is not activated in the iPLEDGE 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 system by the office staff designee.**

### **To designate office staff**

The prescriber:

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

The office staff designee:

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

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

- To log into the automated system.
- On the first log in, to reset password and choose a Date of Personal Significance as a system identifier.

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## NOTES:

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Please see enclosed full prescribing information, including **boxed WARNINGS**.

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**NOTES:**

## For More Information About Isotretinoin

To get information about specific brands of isotretinoin, call the individual manufacturers at the numbers below.

Product	Company	Phone number
Accutane® (isotretinoin capsules)	Roche Laboratories, Inc.	1-800-526-6367
Amnesteem® (isotretinoin capsules)	Mylan Pharmaceuticals Inc.	1-800-796-9526
Claravis™ (isotretinoin capsules)	Barr Laboratories, Inc.	1-800-227-7522
Sotret® (isotretinoin capsules)	Ranbaxy Laboratories, Inc.	1-800-406-7984

### IMPORTANT NOTICE

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

Fill your isotretinoin prescriptions *only* at pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE program.

[www.ipledgeprogram.com](http://www.ipledgeprogram.com) 1-866-495-0654

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