Isotretinoin is teratogenic and must not be used by pregnant women. 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.

The goal of the iPLEDGE program is to prevent pregnancies in females taking isotretinoin and to prevent pregnant females from taking isotretinoin, through a special restricted distribution program approved by the Food and Drug Administration. With the program goal in mind, iPLEDGE data is routinely analyzed by risk management experts to identify inconsistencies in iPLEDGE program requirements.

Based upon an analysis of data since the launch and implementation of iPLEDGE in 2006, the following topics have been identified as areas requiring increased awareness and enhanced education. The following is important information for prescribers and office staff designees to review in order to comply with the specific iPLEDGE program requirements, and be able to educate patients on the requirements.

- Know and identify the criteria to qualify a female patient as a female of non-childbearing potential (FNCBP) in iPLEDGE
- Understand abstinence as an approved birth control method
- Encourage patients to take a more active role in their prescription authorization by the pharmacy in the iPLEDGE program
- Actively discuss with female patients of childbearing potential (FCBP) the importance of contraception and assist the female of childbearing potential to choose two forms of approved and appropriate contraception specifically for that patient. Accurately record this information in iPLEDGE
- Understand the requirement for the timing of pregnancy tests in iPLEDGE and to document the test results in the iPLEDGE system
- Understand post-therapy testing and the 30-day pregnancy test requirements

Each bullet is discussed further below.

**Know and identify the criteria to qualify a female patient as a female of non-childbearing potential (FNCBP) in iPLEDGE**

Every patient registered in iPLEDGE must be registered as one of three patient risk categories (male, female of non-childbearing potential or female of childbearing potential).

According to the isotretinoin FDA-approved label, the definition of a female of non-childbearing potential is a patient that has undergone a hysterectomy or bilateral oophorectomy, has medically confirmed ovarian failure or has been medically confirmed to be post-menopausal. If a female patient does not satisfy at least one of the above criteria, she **must** be registered in iPLEDGE as a female of childbearing potential.
<table>
<thead>
<tr>
<th>Criteria That Qualify a Patient as an FNCBP</th>
<th>Criteria That DO NOT Qualify a Patient as an FNCBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has had a hysterectomy</td>
<td>Has had a tubal ligation</td>
</tr>
<tr>
<td>Has had a bilateral oopherectomy</td>
<td>Is abstinent</td>
</tr>
<tr>
<td>Has medically documented ovarian failure</td>
<td>Has a partner who has had a vasectomy</td>
</tr>
<tr>
<td>Is medically confirmed post-menopausal</td>
<td>Is menopausal</td>
</tr>
</tbody>
</table>

**Understand abstinence as an approved birth control method**

Abstinence means that the female patient will not have sex or sexual contact with any male 24 hours a day, 7 days a week for the month prior to therapy, during treatment, or for 30 days after the last dose of isotretinoin.

Abstinence 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 contraceptive counseling, a 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. One of the most common causes of unplanned pregnancy is failing to remain abstinent.

When entering abstinence as the patient’s choice of contraception, both the prescriber and the patient should select Abstinence and None as the two forms of contraception.

**Encourage patients to take a more active role in their prescription authorization by the pharmacy in the iPLEDGE program**

Every isotretinoin prescription filled is required to be authorized by the pharmacist in the iPLEDGE program. A Risk Management Authorization (RMA) number is generated and recorded when a pharmacy authorizes a prescription in iPLEDGE. Filling a prescription without an RMA number may cause an interruption in an FCBP patient’s therapy.

Without a recorded RMA number, it appears that the FCBP patient has missed her prescription window. It also may mean the pharmacy has not checked to see if the patient has been qualified to receive her prescription. If this is her first window or if none of her previous prescriptions have an RMA number, the patient will be locked out of the iPLEDGE system for 19 days (to satisfy the requirement that an FCBP patient’s first prescription must be preceded by two negative pregnancy tests that are at least 19 days apart).

It is important that the patient inquire of the pharmacy when receiving a prescription if it was authorized in iPLEDGE because every prescription requires this step. Prescribers are encouraged to remind their patients of this.

The prescriber may see that a prescription was authorized by looking at the “Prescriptions Filled” section of the new Patient Status screen. This can be done by selecting the patient on the “Manage Patient” screen and then selecting the “Check Patient Status” button. The date of all authorized fills for this patient will be listed in this section.
If a prescriber sees that a prescription was not filled with an authorization, the prescriber is encouraged to discuss this with the patient.

**Actively discuss with female patients of childbearing potential (FCBP) the importance of contraception and assist the female of childbearing potential to choose two forms of approved and appropriate contraception specifically for that patient. Accurately record this information in iPLEDGE.**

It is important that every month the prescriber and FCBP patient discuss and agree upon the patient’s two forms of contraception to ensure proper use and compliance. After confirming the contraceptive choices with the patient, both the prescriber and patient can accurately enter this information in iPLEDGE.

Incorrect entries may cause a delay or interruption to the patient’s therapy and may indicate that the patient has not been compliant with the contraception choice that month. A mismatch between the prescriber’s entry and the patient’s entry for the primary form of contraception will prevent the patient from answering her monthly comprehension questions correctly.

Changing the patient from abstinence to a primary form of contraception during therapy will create a 30 day lockout and require that the patient meet all requirements of an FCBP.

**Understand the requirement for the timing of pregnancy tests in iPLEDGE and to document the test results in the iPLEDGE system.**

In iPLEDGE, a female patient of childbearing potential must have 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. This test may be conducted by the prescriber in the office.

The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the 2 tests should be at least 19 days.

- For patients with regular menstrual cycles, the second pregnancy test should 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.

Every monthly pregnancy test must be a CLIA-certified lab test and must be documented in the iPLEDGE system.
Understand post-therapy testing and the 30-day pregnancy test requirements
In iPLEDGE, a female patient of childbearing potential must have a pregnancy test performed in a CLIA-certified lab after her last dose and one month after her last dose.

The results of both pregnancy tests must be entered into the iPLEDGE system by the prescriber.

It is important for a prescriber to remember to discontinue a patient in the iPLEDGE system upon the patient’s completion of therapy. This can be done by selecting the “Discontinue Patient” button on the “Manage Patients” screen. This is a program requirement and is being monitored by the iPLEDGE risk management team.

In summary, the iPLEDGE program is committed to preventing pregnancies in females taking isotretinoin and preventing pregnant females from taking isotretinoin. As part of this commitment, data entered in iPLEDGE will be continually monitored and analyzed to identify inconsistencies in the data and non-compliant stakeholders. Non-compliant stakeholders will be reported to the FDA and depending on the infraction, may be removed from the program.

Please refer to the enclosed isotretinoin package inserts for full prescribing and dispensing instructions.

SAFETY NOTICE
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. Because of this toxicity, isotretinoin can only be marketed under a special restricted distribution program. This program is called iPLEDGE™. Under this program, prescribers must be registered and activated with the iPLEDGE program and can prescribe isotretinoin only to registered patients who meet all the requirements of iPLEDGE. Isotretinoin can be dispensed only by a pharmacy registered and activated with iPLEDGE. Registered and activated pharmacies can only receive isotretinoin from wholesalers registered with iPLEDGE.

Patients on isotretinoin have been known to become depressed or to develop other serious mental health problems. Some people have had thoughts of hurting themselves or putting an end to their own lives. Some people tried to end their own lives and some have ended their own lives. There have been reports that people on isotretinoin were aggressive or violent. No one knows if isotretinoin caused these problems or behaviors or if they would have happened even if the person did not take isotretinoin.

Isotretinoin use has been associated with pseudotumor cerebri, a condition caused by increased pressure on the brain. This condition may occur more often in patients also taking tetracycline. Patients should be aware of other serious side effects, including problems with the pancreas, liver, stomach, bones, muscles, hearing, vision, lipids, allergic reactions, blood sugar, or red and white blood cells. The most common, less serious adverse events include dry skin, chapped lips, dry eyes, and dry nose that may lead to nosebleeds. Patients should be advised about these adverse events and routinely monitored by a doctor during treatment with isotretinoin.