What Every Dermatologist Needs to Know About iPLEDGE

With program implementation already underway, prescribers must know the practical requirements of iPLEDGE registration.

By Dina Anderson, MD

The comprehensive iPLEDGE program, approved by the FDA in August and inspired by a similar restrictive program for thalidomide (STEPS), is intended to restrict access to isotretinoin. While the primary focus is preventing birth defects by avoiding fetal exposure to isotretinoin, the program is not exclusively geared to women of childbearing potential. All patients treated with isotretinoin will have to register in iPLEDGE. Full guidelines and physician participation packets are now available. A dermatologist must review these materials and register in iPLEDGE (see Program Overview in Table 1) in order to issue a valid prescription for isotretinoin. The following is a guide to the program and physician responsibilities with some tips on patient management.

What's Changing

Any dermatologist who has ever responsibly prescribed isotretinoin will find the primary objectives of the new program coincide with previous patient screening, counseling, and management efforts. For both male and female patients, the emphasis is on identifying patients who will responsibly adhere to the regimen and comply with necessary screenings. The iPLEDGE "Guide to Best Practice" also addresses the issue of depression possibly associated with isotretinoin therapy; physicians receive educational information about screening patients for depressive symptoms before and during treatment.

While dermatologists agree in theory with the spirit of iPLEDGE, in practice, the program will bring changes that will require a time commitment on the part of the physician and support staff. In addition to the initial physician registration, which is straightforward and not overly taxing for physicians, the biggest change in practice will likely be the overall increased level of documentation and patient monitoring/coordination required—especially for the woman of childbearing potential. Though the iPLEDGE system streamlines coordination of various elements of the program, physicians bear a great deal of responsibility. Among the stated requirements of the program:

- Prescribers or office designee must enter required information (pregnancy test results, two 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—specifically female patients of childbearing potential—meet requirements in the iPLEDGE program.
- The prescriber must also counsel the patient each month about program requirements and confirm via the iPLEDGE system that counseling occurred.

Use of an online or telephone registration and maintenance interface and the coordination of physician, patient, and pharmacy within the program will help streamline patient management. Management of any individual patient may not require significantly more time and effort, though dermatologists managing several patients may find the process daunting.

The registered and activated physician will be responsible for enrollment of every patient—male or female, regardless of age—he or she intends to treat with isotretinoin. Each patient will receive an information/education packet along with a unique ID card and ID number. Then the patient registers online or via telephone in the doctor's office, providing

Table 1. Overview of iPLEDGE*

*Full listing of requirements available at ipledgeprogram.com

- Physicians must register in iPLEDGE.
- Physicians or office designee must counsel patients, register patients, and enter required information in the iPLEDGE system.
- Physicians must document that all patients—and specifically female patients of childbearing potential—meet requirements of the iPLEDGE program.
- Only patients registered by prescribers in iPLEDGE can receive isotretinoin.
- 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.
- Manufacturers will only ship isotretinoin to iPLEDGE-registered pharmacies/wholesalers.

basic registration information. Members of the office staff pre-designated with the iPLEDGE program, rather than the dermatologist, can take patients through this process. Physicians should record the patient's assigned ID numbers in the event patients lose or forget them. All patients must be registered in the program, fully counseled about the program, and sign informed consent prior to receiving/filling a prescription for isotretinoin (which must be filled within seven days from the office visit, which is day one). Additionally, female patients will complete a Patient Information/ Informed Consent About Birth Defects. Female patients of childbearing potential must meet additional criteria (see below).

Women of Childbearing Potential

Which patients are affected by the most stringent requirements of iPLEDGE? A woman of childbearing potential, according to program materials, "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."

These patients require more in-depth counseling about the teratogenic risks associated with isotretinoin therapy and appropriate contraception. In order to fill a prescription, a woman of childbearing potential will have to document in the iPLEDGE system which two forms of contraception she is using (Table 3) as well as accurately respond to questions to demonstrate knowledge about teratogenicity and contraception.

Of note, regulations permit but do not encourage a pledge of committed abstinence as an alternative to contraception. Abstinence must represent a patient conviction rather than a social circumstance. On a personal note, I have accepted abstinence as a form of contraception in patients who demonstrate a commitment to abstinence rather than a circumstance of not having a boyfriend at the time of treatment.

Dermatologists unfamiliar with or uncomfortable with counseling on contraception or prescribing contraceptives should refer the patient to an appropriate specialist. The manufacturers will pay for a consult for patients to receive contraception counseling. Dermatologists are responsible to repeat counseling about contraception and behaviors associated with an increased risk of pregnancy on a monthly basis. Confidential birth control information is available 24 hours a day at (866) 495-0654.

In a change from previous practices, female patients will have two negative pregnancy tests before initiation of isotretinoin therapy. The screening test will occur when the decision is made to pursue therapy and the patient initially enrolls in iPLEDGE. The confirmation test will take place 19 days or more after the first test. Guidelines state:

- For patients with regular menstrual cycles, the second pregnancy test must be done during the first five days of the menstrual period and within seven days following the office visit, immediately preceding the beginning of isotretinoin therapy, after the patient has used two forms of contraception for one month.
- For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done within seven days following the office visit, immediately preceding the beginning of isotretinoin therapy and after the patient has used two forms of contraception for one month.

The confirmation and all subsequent tests must be completed by a CLIA-certified lab. A monthly serum or urine test must be conducted and registered before another 30-day prescription is written. Patients will undergo and register results of a pregnancy test at the end of therapy

Table 2. Patient Requirements*

*From Guide to Best Practices for Isotretinoin

To receive isotretinoin ALL patients must:

1. Be registered with iPLEDGE by prescriber
2. Understand that severe birth defects can occur with use of isotretinoin by females
3. Be reliable in understanding and carrying out instructions
4. Sign a Patient Information/Informed Consent form that contains warnings about potential risks associated with isotretinoin
5. Fill the prescription within 7 days
6. Not donate blood while on Isotretinoin and for one month after treatment ends
7. Not share isotretinoin with anyone, even someone who has similar symptoms

Refills are not allowed. Patients can only receive a maximum 30 day supply per prescription. Each month, continuation of therapy requires the patient to satisfy iPLEDGE program requirements.

Female patients of childbearing potential must:

1. Have an initial pregnancy test which may be performed in the prescriber's office.
2. Be counseled on contraception.
3. Use 2 forms of contraception together for 1 month before, during, and for 1 month after treatment with isotretinoin.
4. Have a second pregnancy test, performed in a CLIA-certified laboratory, after being on two effective forms of contraception for 1 month before starting isotretinoin therapy.
5. Fulfill monthly requirements:

- Serum or urine pregnancy test (CLIA-certified)
- Access system to answer questions about requirements and pregnancy prevention.
- Enter into the iPLEDGE system the 2 forms of contraception being used.
- Have a pregnancy test after last dose, (CLIA-certified); Continue using 2 forms of contraception 1 month after last dose; Have a pregnancy test 1 month after last dose.

Table 3. Acceptable and Unacceptable Forms of Contraception

Effective Forms of Contraception

Primary forms

- tubal sterilization
- partner's vasectomy
- IUD
- hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)

Secondary forms

Barrier forms (always used with spermicide):

- male latex condom
- diaphragm
- cervical cap

Others:

- vaginal sponge (contains spermicide)

Unacceptable Forms of Contraception Include:

- Progesterone-only "mini pills," e.g.: Ortho Micronor Tablets (Ortho-McNeil), Ovrette Tablets (Wyeth)
- IUD Progesterone T
- Female condoms
- Fertility awareness
- Withdrawal
- Cervical shield
- Natural family planning (rhythm method) or breastfeeding

and one month after discontinuation of isotretinoin. Gone are the days of testing patients with home pregnancy kits in the office.

Physicians must pledge to enforce testing and documentation requirements prior to issuing a prescription. Additionally, registered physicians must report to the pregnancy registry any pregnancy in a female patient on isotretinoin or during the first month after the last dose. Importantly, the guidelines specifically state, "The patient should understand that ultimately, it is her responsibility to avoid exposing an unborn baby to isotretinoin."

Physician Responsibility

Clearly, dermatologists play a key role in patient screening, education, and monitoring. This is nothing new. However, with the implementation of the central iPLEDGE registry, dermatologists will find themselves updating some of their approaches and spending more time overseeing the various elements of patient screening and compliance. While the telecommunications system will streamline the process, there will still be an increased burden on dermatologists. This is especially true of the physician and staff registration process and in the monthly assessment of female patients of childbearing potential. These time and resource requirements should not limit our use of a potentially beneficial treatment in appropriate patients, but we must have realistic expectations of the requirements of program compliance and be prepared to deal with them.