

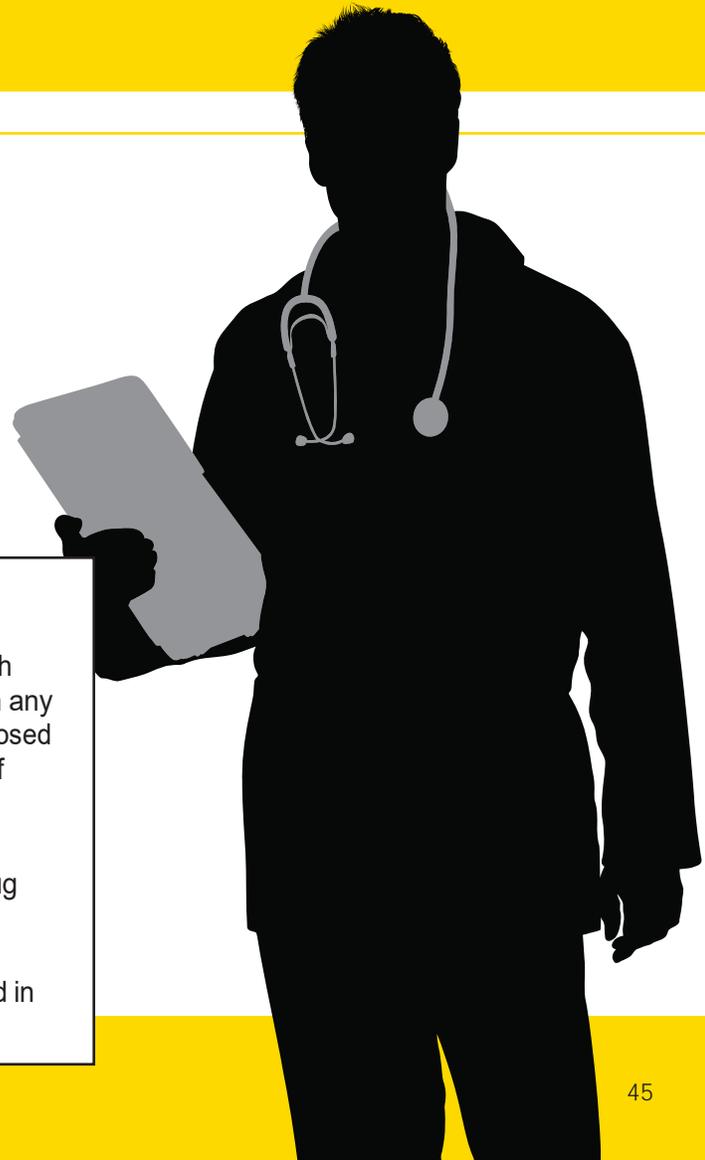


The iPLEDGE Program



Prescriber Contraception Counseling Guide

Helping patients prevent pregnancy



WARNING

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

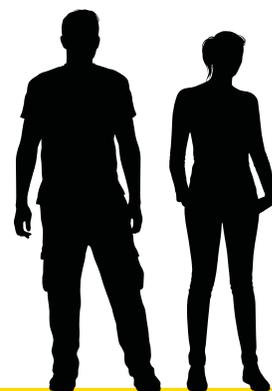
IMPORTANT NOTICE

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

Obtain isotretinoin prescriptions *only* from pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE Program.

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

Introduction

This *Prescriber Contraception Counseling Guide* is intended to aid in counseling a female of reproductive potential who will be taking isotretinoin.

The patient must select and commit to using **2** methods of iPLEDGE Program approved contraception simultaneously, at least 1 of which must be a primary method, unless the patient commits to continuous abstinence (not engaging in sexual activity), or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use **2** methods of iPLEDGE Program approved contraception for at least 1 month prior to initiation of isotretinoin treatment, during isotretinoin treatment, and for 1 month after discontinuing isotretinoin treatment.

It is strongly recommended that a patient use a primary method of contraception and is committed to using a second method as well, even if she says she will be abstinent for the entire required period. Isotretinoin is not recommended for sexually active females of reproductive potential whom you believe will not be able to maintain abstinence or will not use contraception, as the program requires.

The contraceptive that a patient selects can have a dramatic effect on her chance of becoming pregnant. A patient needs to select methods that she and/or her partner will use correctly each time they have intercourse. This *Prescriber Contraception Counseling Guide* will help you enable the patient to select the **2** contraceptive methods that are consistent with the iPLEDGE Program guidelines *and* that she will use correctly and consistently.

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 1 visit for contraception counseling. The *Isotretinoin Educational Kit For Female Patients Who Can Get Pregnant* contains the *Contraception Counseling Guide And Contraception Referral Form*. The referral form is in the guide, which outlines the contraception requirements and the effective methods of contraception of the iPLEDGE Program for the birth control expert.

Contraception counseling is an important part of the patient choosing her **2** contraceptive methods. If practitioners are not comfortable providing this counseling, they are encouraged to take advantage of the opportunity to refer patients to a qualified counselor.

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.

Counseling About Contraception

Please read this *Prescriber Contraception Counseling Guide* completely before you begin your counseling session. The guide reviews the counseling goals and provides an overview of contraception choices from a pregnancy risk management context (necessary for females of reproductive potential taking isotretinoin), information on obtaining a sexual and behavioral history (including additional guidance for interviewing an adolescent), and contraception reference materials.

Patients in the iPLEDGE® Program receive the *Birth Control Workbook*, which contains information on effective primary and secondary methods of contraception. It is not complete information on any of the methods, and the patient is encouraged to ask questions about specific methods or issues.

Counseling Goals

Ensure That The Patient:

- Understands the risk of having a child with significant birth defects from exposure to isotretinoin.
- Understands the need for using 2 methods of contraception together consistently and correctly and knows when to contact her prescriber for emergency contraception (see page 76).
- Chooses the methods of contraception that will work best for her and that she and her partner will actually use. Adherence impacts the failure rate of hormonal combination oral contraceptives more strongly than other primary methods. (Please see “Hormonal Combination Oral Contraceptives as a Primary Method” on page 50.)
- Commits fully to not becoming pregnant and to using 2 methods of contraception simultaneously, consistently, and correctly. If, after counseling, the patient recognizes she will not be able to commit fully, encourage her to not take isotretinoin or do not prescribe.
- Is able and willing to maintain abstinence, if that is her choice after counseling. If a patient who has ever been sexually active chooses abstinence, and you believe that she will not be able to maintain abstinence and will not use contraception, encourage her to not take isotretinoin.



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

Counseling Younger Teens

For younger teens, it is important to stress the following aspects of contraception for the iPLEDGE Program during counseling:

- Effective primary and secondary birth control methods
- Why it is important to use **2** effective methods of birth control simultaneously, consistently, and correctly. Younger teens may need more emphasis on this point to fully understand it and comply.
- The role of emergency contraception. Young teens may need specific direction from you to take immediate action if they had unprotected sex.

Contraception Requirements

Using 2 Methods of Contraception Provides More Protection

Use of 2 iPLEDGE Program approved methods of contraception (at least 1 of which is a primary method) simultaneously substantially reduces the risk that a female will become pregnant.

In the US, the pregnancy rate for females between the ages of 15-44 who were **trying not** to get pregnant was 51/1000 and 48% of those females were using birth control in the month they got pregnant.*

In addition, it is not known if hormonal contraceptives are less effective when used with isotretinoin.¹ Because of this possibility and the fact that all contraceptive methods are less than 100% effective, the iPLEDGE Program requires the additional protection of a second method of contraception.

*Finer LB and Henshaw SK. *Perspectives on Sexual and Reproductive Health*. Vol. 38 (No. 2): June 2006.

Selecting an Effective Primary Method of Contraception

Table 1 lists, by typical use failure rate, the primary methods of contraception acceptable in the iPLEDGE® Program. The single most important decision in contraception for the iPLEDGE Program is selecting a primary method that the patient can and will use as correctly as possible. Other important factors to consider in counseling the patient on selecting a primary method include side effects, contraindications, and the patient’s ability to use it correctly. All of these factors influence compliance with the iPLEDGE Program requirements to prevent pregnancy.

Table 1: Primary Methods of Contraception by Typical Use Failure Rate		
Method	Percentage of Females Experiencing an Unintended Pregnancy Within the First Year of Use ^a	
	Perfect Use	Typical Use
Implantable Hormones	0.05%	0.05%
Male Vasectomy	0.10%	0.15%
Hormonal IUD (LNg 20)	0.20%	0.20%
Tubal Sterilization	0.50%	0.50%
Non-hormonal IUD (Copper T380A) ^b	0.60%	0.80%
Hormonal Injectable (single)	0.20%	6.00%
Hormonal Transdermal Patch	0.30%	9.00%
Hormonal Vaginal Ring	0.30%	9.00%
Hormonal Combination Oral Contraceptives ^b	0.30%	9.00%

a. Adapted from Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83:397–404.

Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3638209/>. Accessed September 9, 2014.

b. The IUD Progesterone T and progestin-only “mini-pills” are not acceptable for the iPLEDGE® Program. (See “Unacceptable Methods Of Contraception” on page 52).

Hormonal Combination Oral Contraceptives as a Primary Method

If the patient is currently taking or planning to take oral contraceptives, review that section in the *Birth Control Workbook* with her.

For a patient who has indicated she has difficulty taking oral contraceptives correctly, other contraception not requiring daily dosing may be a better choice. It is critical that such a patient choose a method other than daily oral contraceptive agents.



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



Selecting an Effective Secondary Method of Contraception

Table 2 lists the acceptable secondary methods of contraception in the iPLEDGE Program. There are 2 methods of secondary contraception: barrier and other. Barrier methods include the diaphragm and cervical cap (both of which must be used with a spermicide) and the male latex condom (which can be used with or without a spermicide). The other method is the vaginal sponge, which contains a spermicide. The most important issue for a secondary method is that it be used correctly each time the patient has intercourse and that it be in place should the primary method fail.

Help the patient select a secondary method that she and/or her partner can fully commit to using correctly each time they have intercourse.

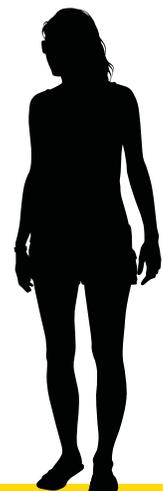
Table 2: Secondary Methods of Contraception Listed by Typical Use Failure		
	Percentage of Females Experiencing an Unintended Pregnancy Within the First Year of Use ^a	
Method	Perfect Use	Typical Use
Barrier Methods		
Male Latex Condom ^b	2%	18%
Diaphragm [*]	6%	12%
Cervical Cap ^{*,a}	9%	20%
Other Methods		
Vaginal Sponge ^c	9%	12%

a. Adapted from Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83:397–404. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3638209/>. Accessed September 9, 2014.

b. Male latex condom failure rates are for use without spermicide. Female condoms are not acceptable for the iPLEDGE[®] Program (See “Unacceptable Methods Of Contraception” on page 52.)

c. Failure rate for nulliparous women. The rate is approximately double for parous women.

*Failure rates for diaphragm and cervical cap are for methods including the use of spermicide.



Unacceptable Methods of Contraception

The following methods of contraception are not acceptable for the iPLEDGE® Program:

- Progesterone-only “mini-pills”
- Female condoms
- Natural family planning (rhythm method or fertility awareness)
- Breastfeeding
- Withdrawal
- Cervical shield*

Patients currently using these unacceptable methods of contraception must switch to iPLEDGE Program approved methods of contraception.

Emergency Contraception

Review this section in the *Birth Control Workbook* with the patient. She should know when to call her prescriber for possible emergency contraception. She should also realize that emergency contraception should not be used on a regular basis as a replacement for the other contraceptive methods she selected.

Abstinence

For this program, all females of reproductive potential must fully commit to pregnancy prevention.

Isotretinoin is not recommended for any female of reproductive potential who cannot or will not follow the contraceptive requirements of the iPLEDGE Program. Abstinence may be appropriate when it is a lifestyle choice, such as religious practice, and not just a social circumstance, such as not having a current partner. If, after counseling, a sexually active patient chooses abstinence, she must understand that she has committed to not engaging in sexual activity for 1 month before she starts taking isotretinoin, while she is on isotretinoin and for 1 month after she stops taking isotretinoin.

One of the most common reasons that women get pregnant is that they engage in sexual activity when they planned to be abstinent.



*A cervical shield should not be confused with a cervical cap, which is an effective secondary method of contraception.

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

Referring to a Gynecologist

You may want to refer your 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

You should also ask for gynecologic consultation under the following circumstances:

- Your 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
- Your patient has irregular menses, possibly related to pregnancy; an eating disorder; or endometriosis. It is important to weigh your patient. 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 infection.

Obtaining a Sexual And Behavioral History

There are several reasons to take a sexual and behavioral history. You need to know about sexual promiscuity, risk-taking behavior, reactions to previous contraceptive medication, and current contraceptive practices to assess whether your patient is appropriate for the iPLEDGE Program. This information may help you eliminate unsuitable patients or refer those whose contraceptive needs require gynecologic referral.

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

General Interview Information

Preparation

Ensure that your patient feels safe and comfortable.

- This is important for an effective counseling session.
- Allow time for taking the history, answering questions, and decision-making.
- A private office is more conducive to counseling than an examination room is. This may permit a more open and personal exchange.
- Interruptions by other staff members and telephone calls should be discouraged.

Use open-ended questions to encourage discussion.

- Your patient may be reluctant or embarrassed to answer questions about her sexual history.
- It may help to start asking about less sensitive material.

Being objective and non-judgmental is important in building rapport. Make sure your patient understands your questions and the information you are giving her. Listen to her use of language and tailor your language to be sure she understands.

Sexual History Questions

1. Does she menstruate? Does she menstruate regularly?
 - Most females (95%) have their menstrual period every 21 to 35 days and usually in a recurrent and regular pattern. A female whose menses vary by a week or more from month to month or vary in length or quantity of flow would qualify as irregular.
2. Has she had a hysterectomy or oophorectomy?
3. Is she still menstruating?
4. Is she postmenopausal?
5. Is she sexually active?
 - If not, is there any possibility of a sexual relationship developing?
6. If she is sexually active, are her partners men, women, or both?
7. Has she ever used contraception? Does she currently use contraception?
 - If yes, which method(s) and for how long?
 - Specifically question the use of unacceptable methods such as the progesterone-only mini-pills or female condom.



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

8. If she uses oral contraceptives, does she take them exactly as prescribed?
If so, which brands?
9. Does she use a secondary method of contraception every time she has sex?
If so, which method?
10. How many sexual partners has she had in the past 6 months? How many sexual partners does she currently have?
11. How long has she been with her current partner(s)? Is she monogamous?
12. Has she ever had a sexually transmitted infection? Has she ever been sexually abused?
13. Has she ever been pregnant? Does she have children?
14. Has she ever had an unintended pregnancy? What was the outcome?

Behavioral History Questions

1. Does she engage in risk-taking behavior, such as using drugs or alcohol?
2. How is she doing in school/at work?
3. How is her relationship with her parents? With her siblings?
4. What is her cohabitational status? Is she married? Living with a partner?
5. Is she currently using any prescription or non-prescription medications, herbal supplements, or vitamins?

Additional Guidance For Interviewing an Adolescent*

This section offers guidance on how to approach an adolescent to obtain a sexual and behavioral history, taking into consideration concerns adolescents have about independence, parental oversight, and privacy.

Discuss Confidentiality First

- Inform the patient that she has a private and privileged relationship with you.
- Identify restrictions for which you may need to breach confidentiality, such as reporting physical or sexual abuse to health authorities.
- Tell her that you will not talk with her parent or parents about something she has said without discussing it with her first.

*Adapted from: Sexual History Taking. American College of Obstetrics and Gynecology, Committee on Adolescent Health Care, ACOG Committee Opinion No. 300. October 2004:p3.

Additional Guidance For Interviewing an Adolescent (Cont.)

Start Gently When Asking About Personal History

- Start with non-threatening topics and gradually move to more sensitive issues.
- Explain that you ask all of your patients about sexual activity and tell her why this information is important.
- Consider using 1 of the following questions to initiate the discussion about the patient's sexual history.
 - Are you dating anyone?
 - Are you intimate with anyone?
 - Are you physically close with anyone?

Identify Risk Behaviors

- Leave room for discussing casual sex partners (who, for example, may not be perceived as “boyfriends”).
 - Did you choose to have sex?
 - Has anyone forced you to have sex?
- Establish the sex of partner or partners first. Do not assume heterosexual behavior.
- Ask about oral and anal sex, and describe what you mean by this, if necessary.
 - Anal intercourse may be used by some teenagers to preserve virginity and protect against pregnancy, so they may not be using their secondary methods.
- Ask about the number of partners, STIs (sexually transmitted infections), and pregnancy prevention methods used.
 - Specifically, ask which methods the patient is using.
 - Find out if they are using unacceptable methods of contraception such as the progesterone-only mini-pill, female condom, or withdrawal.

Keep The Lines of Communication Open

- Encourage adolescents to discuss these issues with their parents. You can assist the adolescent in telling her parents about her sexual activity and her need to use **2** methods of contraception for the iPLEDGE® Program.
- Congratulate the patient for showing ability to think about her sexual health and be responsible.



Contraception Reference Material

The following sections contain some pertinent details, advantages, and disadvantages of the **primary** and **secondary** methods of effective contraception. This is not complete product information. Please refer to individual product labeling for contraindications, warnings and precautions, instructions for use, adverse events, and other product-specific information.

The percentages that follow for perfect use and typical use of a contraceptive are percentages of females having an unintended pregnancy during the first year of use, expressed as “1 female in X years.”² Perfect use is defined as the use of the method correctly and consistently covering every act of intercourse. Typical use reflects the practices of the average user.

Primary Methods of Contraception

The effective primary methods of birth control fall into 3 categories:

- Single Hormonal Contraceptives
- Combination Hormonal Contraceptives
- Non-Hormonal Contraceptives

None of the primary methods protect against STIs or HIV/AIDS.

Single Hormone Contraceptives (Progestin-only)

Oral contraceptives containing no estrogen (progestin-only “mini-pills” see page 52) are not an acceptable method of contraception during isotretinoin treatment.

Single hormone methods contain a progestin that can suppress ovulation, thicken cervical mucus, and produce endometrial atrophy. Accepted methods include single hormone injection, the hormonal IUD, and implantable hormones.



Single Hormone Injections³

Mechanism of action: Inhibition of follicular maturation and ovulation

Rate of Unintended Pregnancies

Perfect Use: 0.2% (1 female in approximately 500 will become pregnant)

Typical Use: 6.00% (1 female in approximately 17 will become pregnant)

Contraindications

Pregnancy, unexplained abnormal vaginal bleeding, breast cancer, or significant liver problems

Instructions For Use

Single hormonal injection of a progestin every 3 months

Advantages

Some Advantages May Include:

- It works for 3 months at a time
- The patient does not need to remember to take a pill each day
- It is good for female patients who cannot take estrogen

Disadvantages

Some Disadvantages May Include:

Black Box Warning: Prolonged use of this [drug] may result in significant loss of bone density, and loss is greater the longer the drug is administered. Bone density loss may not be completely reversible after discontinuation of the drug. A female should only use this [drug] as a long-term birth control method (for example, longer than 2 years) if other birth control methods are inadequate for her.

- Does not protect against STIs or HIV/AIDS
- It can cause irregular bleeding
- It requires a healthcare professional visit for injection every 3 months
- If patient is planning to get pregnant *after* she finishes isotretinoin treatment, it may take up to 18 months for return of ovulation
- Isotretinoin may make single hormonal methods less effective



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



Hormonal Intrauterine Device (IUD)^{3,4}

The hormonal IUD is indicated for contraception in female patients who have had at least 1 child, are in a monogamous relationship, and are at low risk for STIs.

Mechanism of action: Thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium

Rate of Unintended Pregnancies

Perfect Use: 0.2% (1 female in 500 will become pregnant)

Typical Use: 0.2% (1 female in 500 will become pregnant)

Contraindications

- Pregnancy or suspicion of pregnancy
- Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity
- Acute pelvic inflammatory disease (PID) or history of PID without subsequent intrauterine pregnancy
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia or unresolved, abnormal Pap smear
- Carcinoma of the breast
- Genital bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis, lower genital tract infections
- Acute liver disease or liver tumor (benign or malignant)
- Female patient or her partner has multiple sexual partners
- Conditions associated with increased susceptibility to infections with microorganisms
- Genital actinomycosis
- Previously inserted IUD that has not been removed
- History of ectopic pregnancy or condition that would predispose to ectopic pregnancy

Instructions For Use

The IUD is inserted by a healthcare professional. The patient should check for IUD strings often in the first few months after insertion and after each period. If the patient cannot find the strings, the strings feel shorter or longer, she can feel the IUD itself, there are any signs of symptoms of PID, or she misses a period, instruct her to call her prescriber.

Hormonal Intrauterine Device (Cont.)

Advantages

Some Advantages May Include:

- It can be used for long-term contraception (5 years) and is relatively quickly reversible (i.e., return to fertility)

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- It requires insertion and removal by a healthcare professional
- Common adverse events include menstrual changes, lower abdominal pain and cramping, acne or other skin problems, back pain, breast tenderness, headache, mood changes, nausea
- Enlarged ovarian follicles have been diagnosed in about 12% of hormonal IUD users; most disappear spontaneously during 2 to 3 months of observation
- All types of IUDs may increase the risk of pelvic inflammatory disease (PID); side effects of all types of IUDs may include cramps and heavier and longer periods in the first few months after it is placed
- IUD may be expelled, often during menses
- Isotretinoin, antibiotics, St. John's Wort, and certain anticonvulsants may make hormonal methods less effective
- IUDs may cause menstrual changes or amenorrhea
- If a pregnancy occurs, it is more likely to result in an ectopic pregnancy



Implantable Hormones³

Implantable hormones (etonogestrel implant) are a long acting (up to 3 years), reversible method of progestin-only contraception. This method of contraception involves a sterile rod(s), the size of a matchstick, for subdermal insertion under the skin on the inner side of the upper arm during a minor in-office surgical procedure.

Mechanism of Action: Inhibition of ovulation, increased viscosity of the cervical mucus, and alteration in the endometrium

Rate of Unintended Pregnancies

Perfect Use: 0.05% (1 female in 2000 will become pregnant)

Typical Use: 0.05% (1 female in 2000 will become pregnant)

Contraindications

- Known or suspected pregnancy
- Current or past history of thrombosis or thrombotic disorders



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



- Hepatic tumors (benign or malignant), active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected carcinoma of the breast or personal history of breast cancer
- Hypersensitivity to any of the components of the implant

Advantages

Some Advantages May Include:

- Effective birth control for up to 3 years
- The patient does not need to remember to take a pill each day
- Fertility may return quickly when implant is removed
- Can be used in patients who cannot take estrogen

Disadvantages

Some Disadvantages May Include:

- Implant does not protect against STIs or HIV/AIDS
- May cause irregular and unpredictable bleeding or amenorrhea
- Other side effects can include headache, acne, dysmenorrhea, and emotional lability
- Associated with an increased risk of myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gall bladder disease
- Complications of insertion can include: swelling, redness, pain, bruising, scarring, infection, paresthesias, bleeding, and hematoma
- Complications of removal include: a broken rod, scar tissue making removal more difficult
- Rarely, it can be difficult or impossible to remove which may result in a surgical procedure
- If pregnancy occurs, there is a higher chance of an ectopic pregnancy
- Ovarian cysts that usually disappear spontaneously
- Studies were not done in women who weighed more than 130% of their ideal body weight or patients who are chronically taking medication that induces liver enzymes, and it is possible that the implant may be less effective in women who are overweight
- Isotretinoin, antibiotics, and St. John's Wort may make hormonal methods less effective

If you use an implant, always verify its presence in the patient's arm immediately after insertion by palpation. Until you confirm proper insertion, your patient must use a non-hormonal contraceptive method and is not eligible to start isotretinoin.



Combination Hormonal Contraceptives

Combination hormonal contraceptives include combination oral contraceptives, the transdermal patch, the vaginal ring, and hormonal implants. They use estrogen and a progestin in combination to suppress ovulation. In general, these methods have similar contraindications and adverse event profiles.



Mechanism of Action: Inhibition of ovulation



Contraindications



- Thrombophlebitis disorders, history of deep vein thrombosis (DVT), or thromboembolic disorder
- Cerebral vascular or coronary artery disease
- Migraine with focal aura
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Acute or chronic hepatocellular disease with abnormal liver function
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to product
- Smoking and over the age of 35



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



Hormonal Combination Oral Contraceptives³

With perfect use, the failure rate for combination oral contraceptives is equal to that of the best currently available contraceptive measure. **With typical use, oral contraceptives have the highest failure rate of the effective primary methods (Table 1).** Do not prescribe combination oral contraceptives for patients whom you do not think will take them exactly as prescribed. Other primary methods that do not require daily action by the patients, such as an IUD, may be a better choice for reducing the likelihood of pregnancy.

Note: Progesterone-only contraceptives (mini-pill) are not acceptable for the iPLEDGE Program because they are not an effective method of birth control. If your patient is using them, she will have to choose another effective primary method of birth control.

Rate of Unintended Pregnancies

Perfect Use: 0.3% (1 female in approximately 333 will become pregnant)

Typical Use: 9.00% (1 female in approximately 11 will become pregnant)

Additional Warnings

- Female patients with significant hypertension should not be started on oral contraceptives.
- Female patients who have had major surgery with immobilization or any leg surgery should not be started on oral contraception.
- Cigarette smoking increases the risk of serious cardiovascular adverse events with oral contraceptives. Female patients who use oral contraceptives should be strongly advised not to smoke. The risk increases with age and with the number of cigarettes smoked.
- Increased risk of venous thromboembolism and stroke

Instructions For Use

- Once daily for hormone pills for a specified time period, often followed by placebos for a specified number of days. The patient should take oral contraceptives exactly as prescribed.

Missed pill(s):

- Missed more than 2 pills: instruct the patient to call as soon as she realizes that she has missed 2 or more pills; she should be evaluated for possible emergency contraception, depending on her sexual activity. The patient should be counseled not to have intercourse for the rest of the cycle.

Hormonal Combination Oral Contraceptives (Cont.)

Advantages

Some Advantages May Include:

- May decrease the risk of the following:
 - endometrial and ovarian cancer
 - functional ovarian cysts
 - pelvic inflammatory disease
 - benign breast disease
 - ectopic pregnancy
- May decrease the incidence of dysmenorrhea and acne
- Some patients have more regular, lighter, and shorter periods

Disadvantages

Some Disadvantages May Include:

- Combination oral contraceptives do not protect against STIs or HIV/AIDS
- Common adverse events include breakthrough bleeding, nausea and vomiting, and headaches
- Associated with an increased risk of myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease
- Less effective with medications affecting hepatic metabolism such as anticonvulsants; may be less effective with the antibiotics rifampin and griseofulvin*; possible interaction with St. John's Wort
- Isotretinoin may make hormonal methods less effective
- If pills are skipped or missed, the risk of pregnancy is very high



*ACOG Practice Bulletin, Number 18, July 2000.

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



Hormonal Transdermal Patch⁵

Rate of Unintended Pregnancies

Perfect Use: 0.3% (1 female in approximately 333 will become pregnant)

Typical Use: 9.00% (1 female in approximately 11 will become pregnant)

Instructions For Use

The hormonal skin patch is a thin, plastic patch the female patient puts on her skin which releases birth control hormones.

One patch is used per week for 3 consecutive weeks. The patch is replaced on the same day of the week. The fourth week is patch-free. Menses occurs at this time.

If the female patient is starting the patch for the first time, she should wait until the day she begins her menstrual period.

Slipped or missed patches:

- If the patch falls off or is partially detached for less than 24 hours, the patient can reapply in the same place. Otherwise, replace with a new patch immediately. Change patches on the original schedule.
- If the patch is detached for more than 1 day or the patient is not sure how long the patch was detached, she should start a new cycle with a new change day by applying a new patch. It will not be effective for contraception for the first week.
- The patient should be instructed not to have intercourse during this first week.

Advantages

Some Advantages May Include:

- The patient does not need to remember to take a pill each day
- Some female patients have more regular, lighter, and shorter periods
- Fertility returns quickly when the patch is stopped

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- Less effective in female patients over 198 pounds
- Not effective if it becomes loose or falls off for more than 24 hours or if the same patch is left on the skin for more than 1 week
- Has the same labeling for contraindications, warnings, and precautions as oral contraceptives
- Common side effects include breakthrough bleeding, nausea, headaches, and breast tenderness
- Isotretinoin, antibiotics, St. John's Wort, and certain anticonvulsants may make hormonal methods less effective
- Possible increased risk of blood clots



Hormonal Vaginal Ring^{6,7}

Rate of Unintended Pregnancies

Perfect Use: 0.3% (1 female in approximately 333 will become pregnant)

Typical Use: 9.00% (1 female in approximately 11 will become pregnant)

Instructions For Use

The hormonal vaginal ring is a small flexible ring containing birth control hormones which is placed into the vagina and changed once a month.

Patient inserts ring in the vagina, where it should remain for 3 weeks. She removes ring for 1 week to bring on menses. A new ring is used each month for continuous contraception.

Advantages

Some Advantages May Include:

- The patient does not need to remember to take a pill each day
- It does not need to be fitted by a clinician
- Some female patients have more regular, lighter, and shorter periods
- Fertility returns quickly when the ring is stopped

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- The ring cannot be used with a diaphragm or cervical cap
- Some female patients may have trouble inserting the ring
- It has the same labeling for contraindications, warnings, and precautions as oral contraceptives
- Efficacy of the ring is lessened if:
 - The unopened package containing the ring is put into direct sunlight or exposed to very high temperatures
 - It slips out of the vagina and is not replaced in 3 hours
 - It does not stay in the vagina for 3 weeks
 - It is left in the vagina for more than 3 weeks
- Common side effects include breakthrough bleeding, nausea and vomiting, and headaches
- Isotretinoin, antibiotics, and St. John's Wort may make hormonal methods less effective



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



Non-hormonal Contraceptives^{3,8}

Accepted non-hormonal methods of contraception include the copper IUD, tubal sterilization, and partner's vasectomy. These non-hormonal methods do not protect against STIs or HIV/AIDS.



Copper IUD

The copper IUD is made of polyethylene covered with copper.

Mechanism of Action: Prevents fertilization by altering tubal and uterine transport of sperm

Rate of Unintended Pregnancies

Perfect Use: 0.6% (1 female in approximately 166 will become pregnant)

Typical Use: 0.8% (1 female in 125 will become pregnant)

Contraindications

- Pregnancy or suspicion of pregnancy
- Abnormalities of the uterus resulting in distortion of the uterine cavity
- Acute pelvic inflammatory disease (PID) or a history of PID
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical malignancy, including unresolved, abnormal Pap smear
- Genital bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis, including bacterial vaginosis, until infection is controlled
- Diagnosed Wilson's disease
- Known allergy to copper
- Female patient or her partner has multiple sexual partners
- Genital actinomycosis
- A previously inserted IUD that has not been removed

Instructions For Use

Patient should check for IUD strings often in first few months after insertion and after each period. If patient cannot find the strings, the strings feel shorter or longer, she can feel the IUD itself, there are any signs of symptoms of PID, or she misses a period, she should call her prescriber.

Copper IUD (Cont.)

Advantages

Some Advantages May Include:

- Female patients who cannot take hormones can use it
- It can be used for long-term contraception (10 years) and is relatively quickly reversible (i.e., return to fertility)

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- It requires insertion and removal by a healthcare professional
- It should be used in female patients who are not at risk for STIs
- All types of IUDs may increase the risk of pelvic inflammatory disease (PID)
- Side effects of all types of IUDs may include cramps, and heavy, longer periods
- The IUD may be expelled, often during menses



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



Tubal Sterilization

Tubal sterilization may be accomplished using a variety of techniques. They are all considered to be very effective, virtually permanent methods of pregnancy prevention and, with the exception of hysteroscopic tubal sterilization, are immediately effective. For purposes of the iPLEDGE Program, a patient should not be permitted to consider her hysteroscopic tubal sterilization as an accepted method of contraception unless she has had a confirmatory hysterosalpingogram (HSG) or other confirmation.

Mechanism of Action: Tubal sterilization is the closing off of the fallopian tubes to prevent the egg from moving down the fallopian tube to the uterus and to prevent the sperm from reaching the egg.

Rate of Unintended Pregnancies

Perfect Use: 0.5% (1 female in 200 will become pregnant)

Typical Use: 0.5% (1 female in 200 will become pregnant)

Advantages

Some Advantages May Include:

- Very effective, virtually permanent means of contraception

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- Difficult to reverse
- Requires surgery
- If a pregnancy does occur, there is an increased risk of an ectopic pregnancy



Male Vasectomy

A male's vasectomy which involves the mechanical blocking of the vasa deferentia in males is an effective primary method of contraception. Males should have semen analysis after 15 to 20 ejaculations to be sure semen is free from sperm. If the patient has more than 1 partner, each partner must be sterilized for male sterilization to be effective as the patient's only primary method. If the patient uses male sterilization as a primary method, she should be encouraged to choose another primary method as a second method.

Mechanism of Action: This procedure blocks the vasa deferentia to prevent semen from entering the seminal fluid.

Rate of Unintended Pregnancies

Perfect Use: 0.1% (1 female in 1000 will become pregnant)

Typical Use: 0.15% (1 female in approximately 666 will become pregnant)

Advantages

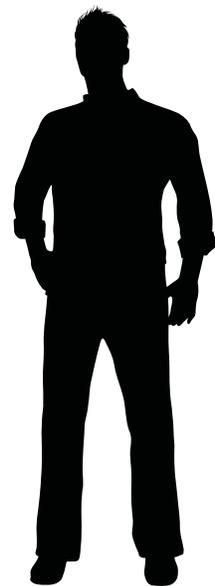
Some Advantages May Include:

- Very effective, virtually permanent means of contraception

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- Low success rate in reversing
- Requires surgery
- Not effective right away





Secondary Methods of Contraception

Most of the secondary methods are barrier contraceptives that prevent sperm from entering the vagina (condom) or cervix (diaphragm and cervical cap). Barrier methods include the diaphragm and the cervical cap, both of which must be used with spermicide. The male latex condom can be used with or without spermicide. The vaginal sponge is a delivery system for spermicide and has spermicide embedded in it. Female condoms are not acceptable for the iPLEDGE[®] Program.

Diaphragms and cervical caps are barrier contraceptives that are considered moderately effective when used in combination with a spermicide. The male latex condom is a barrier contraceptive that is considered moderately effective when used with or without spermicide. The vaginal sponge is also considered moderately effective. The most important issue is whether the secondary method will be used each time the patient has intercourse. If the patient selects a secondary method as the second method of contraception, she must understand how it is used and be fully committed to using it each time she has intercourse.

Female patients under 30 and female patients who have intercourse 3 or more times per week may have a higher failure rate with vaginal secondary methods.

Note: The female condom, a thin, flexible plastic tube that covers the cervical os, is not an acceptable secondary method for the iPLEDGE Program.

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



Male Latex Condom Used With or Without Spermicide³

If the patient does not feel she can convince her partner(s) to use a latex condom (with or without spermicide) each time they have intercourse, she would need to select another secondary method where she has the control or select a second primary method.

Rate of Unintended Pregnancies

Perfect Use: 2% when used without spermicide (1 female in 50 will become pregnant)

Typical Use: 18% when used without spermicide (1 female in 6 will become pregnant)

Male condom (latex) may be used with or without spermicide.

Instructions For Use

Unrolled onto erect penis before there is any contact with female genitals; use only water-based lubricants with latex condoms.

Advantages

Some Advantages May Include:

- Protects against STIs and HIV/AIDS
- Easy to buy, no doctor/prescriber appointment needed, no pelvic exam needed
- Easy to tell when it breaks or slips, important for seeking emergency contraception
- May lower risk of cervical dysplasia and cancer⁹

Disadvantages

Some Disadvantages May Include:

- Condoms can break or slip during sex
- May decrease sensitivity and spontaneity, may have trouble maintaining erection
- Must remember to use every time



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



Diaphragm Used With Spermicide^{3,10}

Rate of Unintended Pregnancies

Perfect Use: 6% when used with spermicide (1 female in approximately 17 will become pregnant)

Typical Use: 12% when used with spermicide (1 female in approximately 8 will become pregnant)

Description

Dome-shaped rubber cap with a flexible rim available in many sizes (50-95 mm diameter) and different styles

Additional Warnings

- There is an association between Toxic Shock Syndrome (TSS) and diaphragm use.
- A diaphragm must be removed after 6 to 8 hours to decrease the risk of TSS.
- There may be increased risk of urinary tract infections, candidiasis, or bacterial vaginosis.
- A diaphragm may cause allergic reactions in females sensitive to latex or rubber.

Advantages

Some Advantages May Include:

- Female patients can easily carry a diaphragm with them and have control of its use
- Immediately effective
- No hormones
- No interruption of sex play; can be inserted any time before intercourse and must stay in place for at least 6 to 8 hours after intercourse; a diaphragm should not be worn for more than 24 hours
- May lower risk of cervical dysplasia and cancer
- Can be used during a menstrual period

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- Requires a prescription, pelvic examination, and periodic refitting; lasts about 1 to 2 years
- Some female patients find it hard to insert
- Spermicide must be inserted in the vagina if there is repeated intercourse
- Can get pushed out of place during sex
- Must be checked for holes after sex and cleaned after use



Cervical Cap Used With Spermicide^{3,11}

Rate of Unintended Pregnancies in Nulliparous Females

Perfect Use: 9% when used with spermicide (1 female in approximately 11 will become pregnant)

Typical Use: 20% when used with spermicide (1 female in 5 will become pregnant)

The failure rate is double in parous females.

Description

Deep rubber cap with firm rim and a groove inside the rim that fits snugly around the cervix

Advantages

Some Advantages May Include:

- Same as diaphragm
- No need to add more spermicide if female patient has repeated intercourse
- Continuous protection for 48 hours

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- Some female patients find it harder to insert than a diaphragm
- It cannot be used during a menstrual period
- Patient needs a prescription and a pelvic examination to fit a cervical cap; a cap lasts about 1 year
- Must be checked for holes and tears after sex and cleaned after use
- Less effective with multiparous females



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



Vaginal Sponge (Contains Spermicide)^{3,12}

Rate of Unintended Pregnancies in Nulliparous Females

Perfect Use: 9% (product contains spermicide) (1 female in approximately 11 will become pregnant)

Typical Use: 12% (product contains spermicide) (1 female in approximately 8 will become pregnant)

The failure rate is double in parous females.

Description

Soft, disposable, non-abrasive polyurethane foam that is a delivery system for 1 gram of the spermicide nonoxynol-9

Advantages

Some Advantages May Include:

- Female patients can easily carry a vaginal sponge with them and have control of its use
- Immediately effective
- No hormones
- No interruption of sex play; can be inserted any time before intercourse and is effective for up to 24 hours
- No need to put in more spermicide with repeated intercourse
- No special fitting, available over the counter
- Not associated with TSS

Disadvantages

Some Disadvantages May Include:

- Does not protect against STIs or HIV/AIDS
- Less effective with multiparous females

Emergency Contraception³

Emergency contraception is indicated after sex without adequate protection:

- No contraception is used
- A secondary method slips or breaks
- Missed pill or injection
- Rape

Hormonal Emergency Contraception Pills (ECPs)

Emergency contraception is available without a prescription regardless of age. Patients must understand that the sooner ECPs are started, the more likely they are to be effective. Common side effects include nausea and vomiting. Consider prescribing medication to reduce these side effects.

Always consult complete Prescribing Information for any medications prescribed or currently being taken by your patient.

Reporting a 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 30 days 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.



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



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Mirena[®] is a registered trademark of the Bayer Oy Corporation.

NuvaRing[®] is a registered trademark of Merck Sharp & Dohme B.V.

OrthoEvra[®] is a registered trademark of Ortho-McNeil Pharmaceutical, Inc.

Today[®] Sponge is a registered trademark of Alvogen Group, Inc.

Isotretinoin Products

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**.

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



iPLEDGE®

Committed to Pregnancy Prevention



Web site: www.ipledgeprogram.com

Phone system: 1-866-495-0654

WARNING

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

IMPORTANT NOTICE

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

Obtain isotretinoin prescriptions *only* from pharmacies that are licensed in the United States and are registered with and activated in the iPLEDGE Program.



Recognizing Psychiatric Disorders in Adolescents And Young Adults

A guide to recognizing psychiatric disorders in
adolescents and young adults for prescribers
of isotretinoin

Recognizing Psychiatric Disorders in Adolescents And Young Adults

A Guide For Prescribers of Isotretinoin

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.

Recognizing Psychiatric Disorders in Adolescents And Young Adults

A Guide For Prescribers of Isotretinoin

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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.

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).

WARNINGS

Psychiatric Disorders: Isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric). 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. Signs and symptoms of depression, as described in the brochure *Recognizing Psychiatric Disorders In Adolescents And Young Adults*, include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop isotretinoin and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of isotretinoin therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether isotretinoin therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of isotretinoin therapy.

Pseudotumor Cerebri: Isotretinoin use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue isotretinoin immediately and be referred to a neurologist for further diagnosis and care (see ADVERSE REACTIONS: Neurological).

ADVERSE REACTIONS

Neurological: pseudotumor cerebri (see WARNINGS: Pseudotumor Cerebri), dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesia, seizure, stroke, syncope, weakness
Psychiatric: suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression, violent behaviors (see WARNINGS: Psychiatric Disorders), emotional instability

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstatement of therapy.

REPORTING ADVERSE EVENTS

Specific information about adverse events that may occur during isotretinoin therapy may be reported to the individual makers of isotretinoin and/or to the Food and Drug Administration MedWatch Program at 1-800-FDA-1088 or via www.fda.gov/medwatch/report.htm.

The contact information for specific brands of isotretinoin can be obtained by calling 1-866-495-0654 or via www.ipledeprogram.com.

ISOTRETINOIN

Isotretinoin is a retinoid related to vitamin A. Patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.

Introduction

Mental health problems are underdiagnosed and undertreated.¹ Dermatologists and other isotretinoin prescribers often see patients who are otherwise healthy, and they may be among the only professionals who have opportunities to evaluate patients' mental health. Healthcare providers who recognize the signs and symptoms of psychiatric illness and respond appropriately can improve, and perhaps even save, their patients' lives.

Isotretinoin may cause depression, psychosis, and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. Although causality has not been established for these reports, awareness of signs and symptoms may save your patient's life. This brochure provides an overview of depression. The goal of this brochure is to help you identify when a psychiatric consult is advisable.

You and your staff may feel uncomfortable evaluating your patients' mental health status. It is often difficult to distinguish clinical depression from other responses. It may also be difficult to decide whether erratic behavior may warrant psychiatric evaluation, especially if that behavior seems to be age-appropriate in a teenager. However, as with any specialized problem, you may identify patients who seem to need more than dermatologic care, and you may need to refer them to a specialist. Knowing when to make a referral for a patient who may be at psychiatric risk can make a major difference in the patient's life. In extreme cases, it can mean the difference between life and death.

Depression

Depression and suicidal tendencies are 2 important psychiatric conditions that may be observed in dermatology and family practice settings. This brochure provides an overview of depression because depression is the most commonly reported psychiatric adverse event in patients taking isotretinoin and is also a well-established risk factor for suicidal behavior.

Depression is characterized by symptoms that include intense, persistent sadness; anxiety; loss of pleasure from usual activities; and loss of energy.² These feelings can be normal responses to a negative life event, but clinical depression is either not triggered by such an event or is disproportionate to the trigger.³

Depression can be episodic. According to the National Comorbidity Survey, 16.2% (between 32.6 and 35.1 million) of Americans will experience depression at some point during their lives, and 6.6% (between 13.1 and 14.2 million) are depressed in any given month.^{4,5} Several epidemiological studies reported that up to 8.3% of adolescents in the United States suffer from depression.⁶ Older adolescents experience more depressive symptoms than adults and comparable symptom persistence, suggesting that these adolescents may be at the highest risk for depression.⁷

Depression (Cont.)

Depression can take several forms: 3 of the most common are dysthymia, major depression, and bipolar disorder.² These 3 disorders are characterized by various combinations of the symptoms listed in Table 1. Not every patient exhibits all depressive symptoms. Some patients, especially adolescents, may display irritability instead of sadness.

TABLE 1. Symptoms of Depression

- Persistent sad, anxious, or “empty” mood
- Feelings of hopelessness, pessimism
- Feelings of guilt, worthlessness, helplessness
- Loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex
- Decreased energy, fatigue, being “slowed down”
- Difficulty concentrating, remembering, making decisions
- Insomnia, early-morning awakening, or oversleeping
- Appetite and/or weight loss or overeating and weight gain
- Thoughts of death or suicide; suicide attempts
- Restlessness, irritability
- Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain
- Start acting on dangerous impulses
- Start seeing or hearing things that are not real

Table 1 modified from National Institute of Health. “Depression.” Available at: <http://www.nimh.nih.gov/publicat/depression.cfm#ptdep1>. Accessed February 23, 2005.

Dysthymia has characteristics similar to those of major depression but is not as disabling. People with dysthymia often function adequately but not at previous wellness levels, and are at risk for episodes of major depression. In major depression, a combination of symptoms prevents the patient from working, studying, and/or engaging in normal activities.

In bipolar disorder, the patient alternates between periods of depression (severe lows) and episodes of mania (severe highs).²

Symptoms of Mania²

- Abnormal or excessive elation
- Unusual irritability
- Decreased need for sleep
- Grandiose notions
- Increased talking
- Racing thoughts
- Increased sexual desire
- Markedly increased energy
- Poor judgment
- Inappropriate social behavior

Cause of Depression

The causes of depression are often multifactorial and may include:

- Genetic predisposition²
- Stress at home, work, or school²
- Loss of a parent or loved one⁸
- Alcohol or substance abuse⁹
- Breakup of a romantic relationship¹⁰
- Medications¹¹

Suicide

Suicide accounts for more than 30,000 American deaths each year. It is the third leading cause of death (after accidents and homicide) among people aged 15 to 24, which makes it responsible for more deaths in this age group than any physical illness.¹²⁻¹⁴ Of the total number of suicides among people ages 15 to 24 in 2001, 86% were male and 14% were female.^{15, 16} Healthcare providers often miss the warning signs because patients may hide suicidal intent very successfully. In fact, 60% of people who commit suicide had seen a physician within 1 month of their deaths.⁹ Suicidal tendencies rarely arise spontaneously; 93% of people who commit suicide suffer from depression, schizophrenia, and/or substance abuse.¹⁷

Suicide (Cont.)

Up to 60% of adolescents and young adults think about suicide at some point,¹² but fortunately these thoughts usually pass. Few people who have suicidal thoughts make the attempt, and most attempts at suicide are unsuccessful.¹³ The following are some elements of a suicide risk assessment that can be used to determine the individual's risk level for suicide¹⁸:

- Ideation (thoughts of death or suicide)
- Suicidal intent
- Plan (specific time, place, and method)
- Means (e.g., a firearm in the house or a supply of drugs)

Women are twice as likely as men to attempt suicide, but men are 4 times more likely to be successful. Women usually use means from which they may be rescued, such as a drug overdose,¹⁹ whereas men tend to use firearms or automobiles. Firearms are used in 55% of all completed suicides.¹³

Despite a patient's attempt to hide suicidal thoughts, he or she may send deliberate warning signals, some of which can be explicit.² Every mention or discussion of "killing myself" should be treated with utmost seriousness.

Evaluating And Referring Patients For Psychiatric Disorders

Although only 5% of the population is depressed at any given time,²⁰ the incidence has been found to be closer to 15% to 20% in primary care settings.²¹ Given that 1 in 5 patients who come to your office may have some degree of depression, a few questions can identify patients who may be at risk.

It is important to find out whether a patient is under care or has ever been under care for an emotional problem or psychiatric disorder, particularly depression. Knowing a patient's current medications, for example, if he or she is taking antidepressants, can further identify those patients who may be at even greater risk than the general population.

Talking About Depression

Although it can be awkward to explain to a patient that he or she may have signs of depression (or any mental illness), the awkwardness can be minimized by reminding the patient that:

- Depression is very common
- It matches some of the symptoms the patient described
- It is treatable

Assessments: Depression

While taking a history, the prescriber should suspect the likelihood of depression if the patient has symptoms such as⁶:

- Persistent sad or irritable mood
- Loss of interest in activities once enjoyed
- Significant change in appetite or body weight
- Difficulty sleeping or oversleeping
- Psychomotor agitation or retardation
- Loss of energy
- Feelings of worthlessness or inappropriate guilt
- Difficulty concentrating
- Recurrent thoughts of death or suicide

In children and young adolescents, other signs to look for include⁶:

- Frequent, vague, non-specific physical complaints such as headaches, muscle aches, stomach aches, or tiredness
- Frequent absences from school or poor performance in school
- Talk of or efforts to run away from home
- Outbursts of shouting, complaining, unexplained irritability, or crying
- Being bored
- Lack of interest in playing with friends
- Alcohol or substance abuse
- Social isolation, poor communication
- Fear of death
- Extreme sensitivity to rejection or failure
- Increased irritability, anger, or hostility
- Reckless behavior
- Difficulty with relationships

The prescriber should also discuss with the patient:

- Alcohol or substance abuse
- Chronic pain
- Real or perceived disfigurement

Studies indicate that acne is associated with symptoms such as social embarrassment, low self-esteem, and anxiety, but an association of acne with frank depressive disorders has not been established, nor has treatment of acne by itself been shown to ameliorate frank depressive disorders.²²⁻²⁴

Evaluating And Referring Patients For Psychiatric Disorders (Cont.)

Assessments: Suicide

Psychiatric specialists have identified several factors for suicide risk. These include¹⁹:

- Presence or history of depression, bipolar disorder, or other psychiatric disorder
- Access to firearms in the home
- Family history of suicide or violence, including abuse
- Poor physical health, chronic illness, or chronic pain
- Alcohol or substance abuse
- Previous suicide attempt

It is important to note that depression itself is a major risk factor for suicidal behavior.¹⁹ Thus, special attention is needed when prescribing drugs that may cause depression. An association with isotretinoin should be considered in patients with signs and symptoms of depression, even in the presence of other life stressors. Discontinuation of isotretinoin may be insufficient intervention and a formal psychiatric evaluation should be conducted. It is also important to note that signs and symptoms of depression are not included in all reported cases of suicidal behavior. It is not known if this means the signs were masked by the patient, unrecognized by observers, or if the suicidal tendency arose impulsively. It is important that patients taking isotretinoin be made aware of this so that they might recognize any such signs and symptoms. Patients (and parents, if the patient is a minor) should be instructed to stop isotretinoin and seek immediate medical help.

Talking with patients about suicide does not encourage or remind them that suicide is an option.¹⁹

Knowing When to Refer

You should refer the patient to a psychiatric specialist for further evaluation if any of the following apply:

- Risk factor(s) for suicide is (are) present
- The patient has, or may have, clinical depression or bipolar disorder, or if the prescriber believes that there may be a problem but cannot classify it
- The patient has expressed interest in, or spontaneously mentioned, suicide
- There is any question about the patient's safety

Summary

Prescribers who are alert to the warning signs of psychiatric disorders can guide patients to receive the help they need. Observing patients for signs of depression and suicidal ideation, and referring appropriate patients to a psychiatric specialist, need not be complicated. The benefits to patients can be immense, even life saving.

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

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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.



Prescriber Flowchart

A flowchart to assist the prescriber with the iPLEDGE[®] Program requirements



REGISTERED AND ACTIVATED PRESCRIBER

Females of reproductive potential (FRP)

Male patients/Females of non-reproductive potential (FNRP)

BEFORE TREATMENT

- Educate** the patient about isotretinoin and contraception requirements of the iPLEDGE[®] Program
- Screen** by obtaining a negative pregnancy test
- Obtain** a signed Patient Information/Informed Consent (for all patients) form
- Obtain** a signed second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)
- Register** patient in the program and provide patient ID card
- Counsel** patient, or refer to an expert, that she must use 2 effective methods of contraception simultaneously and correctly for at least 1 month before starting treatment
- Order** a pregnancy test using a CLIA-certified lab during the first 5 days of the menstrual cycle, at least 30 days after registration (patients with amenorrhea/irregular cycle, please refer to the PI)
- Access*** the system to confirm patient counseling of program and contraception requirements, and to enter pregnancy test result and the patient's methods of contraception
- Provide** a prescription for a maximum 30-day supply

- Educate** the patient about isotretinoin
- Obtain** a signed Patient Information/Informed Consent (for all patients) form for treatment
- Register** patient in the program and provide patient ID card
- Access*** the system to confirm patient counseling of program requirements
- Provide** a prescription for a maximum 30-day supply

EACH MONTH DURING TREATMENT

- Counsel** patient on program and contraception requirements
- Order** a pregnancy test using a CLIA-certified lab
- Access*** the system to confirm patient counseling of program and contraception requirements and to enter pregnancy test result and the patient's methods of contraception
- Provide** a prescription for a maximum 30-day supply

- Counsel** patient on program requirements
- Access*** the system to confirm patient counseling of program requirements
- Provide** a prescription for a maximum 30-day supply

AFTER TREATMENT

- Order** a pregnancy test using a CLIA-certified lab immediately after the last dose
- Counsel** the patient to continue to use 2 effective methods of contraception simultaneously and correctly for at least 1 month after last dose
- Counsel** the patient not to share any leftover isotretinoin with anyone
- Counsel** the patient not to donate blood for 1 month after last dose
- Order** a pregnancy test 1 month after the last dose
- Access*** the system to enter pregnancy test results after every pregnancy test

- Counsel** the patient not to share any leftover isotretinoin with anyone
- Counsel** the patient not to donate blood for 1 month after last dose

*You can access the system via the web site, www.ipledgeprogram.com, or the telephone, 1-866-495-0654.