INTRODUCTION

Consequences related to unintended pregnancies have both social and economic repercussions.1 The Centers for Disease Control and Prevention (CDC) reports that almost 850,000 legal abortions were performed in the U.S. in 2003, or about 241 abortions per 1,000 live births.2 This number does not reflect the procedures that took place in West Virginia, California, and New Hampshire, which did not report any data, or the unplanned pregnancies of mothers who decided to keep their babies.2 Contraceptives, therefore, still represent an area of pharmacotherapy in which improvements are needed.

Several dosage forms of contraception are currently available for women in the U.S.; these include oral, injectable, and transdermal products; vaginal rings; and intrauterine devices (IUDs).3 One of the newest medications in the hormonal contraceptive class is an etonogestrel implant (Implanon, Organon).4 A single rod is placed in the upper arm and is replaced every three years. This implant offers women another option for preventing unplanned pregnancies.4–6

CHEMISTRY AND PHARMACOLOGY

Etonogestrel, a synthetic biologically active metabolite of the synthetic progestin desogestrel,4–6 binds with high affinity to progesterone receptors in the target organs.4–5 Its contraceptive effect is accomplished by several mechanisms.4–6 Primarily, etonogestrel inhibits fertility by inhibiting the release of luteinizing hormone (LH), one of the reproductive hormones important in ovulation.4–5 It also increases the viscosity of cervical mucus, which hinders the passage of spermatozoa and alters the lining of the uterus to prevent implantation of a fertilized egg into the endometrium.4–6

Etonogestrel is a structural analogue of 19-nortestosterone, and its molecular weight is 324.6.4 The chemical formula for etonogestrel is C22H28O2 (Figure 1).

PHARMACOKINETICS

After Implanon is inserted subdermally, etonogestrel is rapidly absorbed into the circulation and becomes almost 100% bioavailable.4,5 During the initial six weeks, the rate of release is 60 to 70 mcg/day, gradually decreasing to a release rate of 35 to 45 mcg/day at the end of the first year.4–5 At the end of the second year, the release rate decreases to 30 to 40 mcg/day. By the end of the third year, the rate falls to about 25 to 30 mcg/day.4–5

Etonogestrel is highly protein bound to serum proteins, predominantly albumin and, to a lesser extent, sex hormone-binding globulin.4–5 It undergoes extensive liver metabolism by cytochrome P450 3A4 (CYP 3A4) isoenzymes.3–5 For the most part, etonogestrel and its metabolites are excreted renally.4,5 The elimination half-life of etonogestrel is 25 hours; therefore, the contraceptive effects are reversible after the subdermal implant is removed.4,5

All clinical trials that were conducted in the U.S. enrolled women who were between 80% and 130% of their ideal body weight.4,7,8 Therefore, the implant’s pharmacokinetics in women above 130% of their ideal body weight has not been established.4–6 Theoretically, the implant might be less effective in overweight women, because body weight and serum concentrations are inversely related.4,5

CLINICAL TRIALS

Croxatto et al.7

An open-label, multicenter study was conducted to assess Implanon’s efficacy, safety, and ability to restore fertility. A total of 635 healthy women were followed for two to three years between 1991 and 1997 at 21 sites in nine countries. Of the initial patients, 147 from the largest two sites consented to the extended study of three years.

To be included in the trial, patients had to be 18 to 40 years old and sexually active. They also had to satisfy recommendations for progestin-only contraceptives and have normal menstrual cycles. Subjects were excluded if they were

**Figure 1** Chemical structure of etonogestrel. (Data from Implanon package insert, 2006.)
pregnant or lactating, if their weight was outside 80% to 130% of the ideal, or if they were using any liver enzyme inducers (e.g., anticonvulsants). Before insertion of the implant, the investigators obtained a baseline medical and gynecological history, conducted a pelvic examination, and obtained a Papanicolaou (Pap) smear. Weight, blood pressure, implant site, and adverse effects were assessed every three months over the entire study period. Medical physical examinations and Pap smears were performed yearly.

The primary efficacy endpoint was pregnancy. No pregnancies were recorded in any of the study participants over the three-year period. Upon removal of the implant, normal menses resumed within 90 days for approximately 91% of subjects. Fertility returned quickly, with 20 pregnancies reported within three months of implant removal.

**Funk et al.**

In another open-label, multicenter study, the investigators observed women for up to two years between 1993 and 1996. The study included 330 sexually active women 18 to 40 years of age who resided in the U.S. These participants also had normal menses and a body weight between 80% and 130% of ideal.

Subjects were excluded from the study if they had any condition that contraindicated implantation, such as liver function abnormalities, or hypertension; if they had used hormonal contraception or had been pregnant within the previous month; or if any of the women 35 years of age and older had a history of smoking.

After insertion of the implant, participants visited the clinic every three months. Physical and gynecological examinations were performed at 12 and 24 months.

Efficacy and safety assessments were based on pregnancy rates, medical examinations, and vital signs. The investigators also assessed the return of the menstrual cycle and fertility upon removal of the implant. None of the women became pregnant while the implant was in place.

After removal of the implant, normal menstrual cycles resumed in 88% of patients within three months. After treatment, 11 pregnancies were documented between 7 and 131 days after implant removal.

**Zheng et al.**

An open-label, comparative, randomized, multicenter study was performed to compare the efficacy, tolerability, and bleeding patterns in Implanon versus Norplant (Wyeth), which contains levonorgestrel, a progestin. During the course of the study, from 1991 to 1996, 200 women were observed for two years with an optional extension to four years.

To be eligible for inclusion in the study, the women had to be healthy, 20 to 25 years of age, and sexually active with proven fertility and with menstrual cycles of 24 to 35 days’ duration. Patients were excluded if they were pregnant, were breast-feeding, or had taken oral or hormonal contraceptives within a specified period before the start of the study. Before the study began, each patient underwent a pregnancy test, a urinalysis, and a gynecological examination. The implant site, blood pressure, body weight, and hemoglobin levels were assessed every 90 days. A physical examination and a Pap smear were performed at the end of the study.

The effectiveness of the contraceptives was based on the number of pregnancies reported during the study. No pregnancies were reported in either treatment group, and no statistically significant difference existed between the groups in terms of the contraceptive’s efficacy or tolerability. However, it took slightly less time to insert and remove Implanon than Norplant.

**ADVERSE DRUG EVENTS**

Etonogestrel was generally well tolerated in clinical trials. The most frequent adverse drug events (ADEs) reported in the trials were acne, headache, weight gain, emotional lability, depression, and bleeding irregularities (Table 1). Most of the ADEs were mild to moderate.

**Dermatological problems.** Acne is a side effect that is associated with the androgenic effects of progestins. In clinical trials, the incidence of new-onset acne was reported in 13.5% of patients, with 1.3% of patients reporting treatment-emergent acne. Similar reports of acne were reported by Funk et al., with an incidence of new-onset acne of 14.5%; 16% of patients reported a decrease, and 70% reported no change. A higher incidence of acne, occurring in 18.5% of patients, was reported in Brache’s three-year comparative trial of etonogestrel and levonorgestrel implants.

**Headache.** Headache was the most frequently reported ADE among women using implantable contraceptives. In the Flores study, headache was reported in 25% of the patients receiving etonogestrel implants. Similarly, other clinical trials reported an incidence of headache in 24.9% of patients who received the etonogestrel implant.

Headaches were also reported in more than 5% of women in clinical trials of injectable Depo-Provera (medroxyprogesterone acetate, Pfizer), the NuvaRing vaginal ring (etonogestrel/ethinyl estradiol, Organon), Ortho Evra patch (norelgestromin/ethinyl estradiol, Ortho-McNeil), and the Mirena IUD (levonorgestrel, Bayer). A causative association between headaches and the use of oral contraceptives has not been confirmed, but the incidence is higher in women taking progestin-only formulations.

**Weight gain.** Most long-term contraceptive use leads to some degree of weight gain. In clinical trials, increased weight was reported in 13.7% of women receiving the etonogestrel implant, with 2.3% of patients reporting weight gain as the reason for implant removal.

In a three-year comparative trial con-

### Table 1 Common Treatment-Emergent Adverse Drug Events in 1% or More Subjects in Clinical Trials of Etonogestrel (Implanon)

<table>
<thead>
<tr>
<th>Adverse Drug Event</th>
<th>All Studies (N = 942)</th>
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<tbody>
<tr>
<td>Bleeding irregularities</td>
<td>11.0%</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>2.3%</td>
</tr>
<tr>
<td>Prolonged bleeding</td>
<td>11.0%</td>
</tr>
<tr>
<td>Frequent bleeding</td>
<td>2.3%</td>
</tr>
<tr>
<td>Infrequent bleeding</td>
<td>2.3%</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>2.3%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>24.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>1.3%</td>
</tr>
<tr>
<td>Acne</td>
<td>1.0%</td>
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</table>

Data from Implanon package insert, 2006.
ducted by Brache et al., weight gain occurred in 6.5% of patients using etonogestrel implants and in 7% of patients using levonorgestrel implants. A significant number of women in clinical trials also reported weight gain with the use of Depo-Provera, NuvaRing, Mirena, and oral contraceptives.

**Psychiatric effects.** In clinical trials, psychiatric ADEs, including depression, emotional lability, and anxiety, were reported in 3% to 14% of patients. Emotional lability was the most common ADE with etonogestrel therapy. These psychiatric ADEs have also been reported in women using Depo-Provera, NuvaRing, Ortho Evra, Mirena, and oral contraceptives. Emotional lability led to discontinuation of the medication in 1% to 2.5% of women enrolled in clinical trials for NuvaRing and Ortho Evra.

**Bleeding irregularities.** Irregular bleeding was the most frequently reported ADE and the most common reason for discontinuing treatment of the etonogestrel implant in clinical trials. In a study by Bitzer et al., the most common treatment-emergent ADEs that led to premature removal of the etonogestrel implant were bleeding abnormalities, including amenorrhea, dysmenorrhea, and frequent, prolonged, or infrequent bleeding. No patterns were associated with the incidence of bleeding (any type of bleeding irregularity can occur spontaneously).

Discontinuation of therapy generally occurred within the first two years of etonogestrel use. The incidence of bleeding irregularities with Implanon was reported in 45% of patients, and 14% of women discontinued therapy prematurely. Croxatto et al. reported a higher percentage of patients discontinuing therapy (17.2%) because of bleeding irregularities during the first two years of Implanon use.

**DRUG INTERACTIONS**

Etonogestrel, a progestin, is a substrate of the CYP 3A4 oxidase system. CYP 3A4 is involved in the metabolism of the largest quantity of substrates and comprises the largest quantity of all the cytochrome substrates in the liver. Many medications are inducers of CYP 3A4 and increase the metabolism of etonogestrel. Anticonvulsants, barbiturates, St. John’s wort, nevirapine (Viramune, Boehringer Ingelheim), and rifampin act as CYP 3A4 inducers to increase hepatic metabolism of this contraceptive. The reverse is also true for CYP 3A4 inhibitors, including azole antifungals. CYP 3A4 inhibitors decrease the clearance of etonogestrel and increase plasma concentrations, thus raising the likelihood of progestin-related side effects (Table 2).

Retinoids, such as Roche’s acitretin (Soriatane) and isotretinoin (Accutane), interfere with the contraceptive action of oral progestin regimens. Thus, two forms of reliable birth control are recommended with the use of a progestin-only contraceptive and retinoids, given the confirmed incidence of birth defects with these products.

Other medications have been linked to a decline in the effectiveness of progesterone contraception by an alternate mechanism. Protease inhibitors, modafinil (Provigil, Cephalon), and mycophenolate mofetil (CellCept, Roche) resulted in a significant decline in the area-under-the-concentration-time curve (AUC) and, consequently, in the etonogestrel plasma concentration (Table 3).

**PREGNANCY AND LACTATION**

Studies have been performed in both rats and rabbits with etonogestrel doses of up to 790 times the human dose with...
risk for fetal harm or defects with use of oral contraception reveal no increased risk for fetal harm or defects with use before or in early pregnancy. Thus far, there is no evidence to show that the risk would differ for etonogestrel. If Implanon is not inserted within the appropriate time frame, an alternative method of contraception is not necessary. If Implanon is not inserted within the appropriate time frame, nonhormonal contraceptive may be used for continued protection.

The patient's medical history should be evaluated to determine the appropriateness of therapy and to determine whether there are any contraindications to the use of Implanon. These contraindications include:

- a known or suspected pregnancy.
- a current or a past history of thrombosis or thromboembolic disorders.
- hepatic tumors (benign or malignant) or active liver disease.
- undiagnosed abnormal genital bleeding.
- known or suspected carcinoma of the breast or a personal history of breast cancer.
- hypersensitivity to any of the components of Implanon.

PATIENT COUNSELING

Patients should be informed that the etonogestrel implant is a hormonal contraceptive that protects against pregnancy but not human immunodeficiency virus (HIV) infection or other sexually transmitted diseases. The implant must be placed properly by a trained physician, and patients must undergo a minor surgical procedure in the medical office. The patient should be able to feel the implant by placing her fingertips over the area.

Complications with inserting or removing the implant are rare, but they can occur. There may be pain, irritation, swelling, scarring, or infection at the insertion site. Patients should be advised that the implant must be replaced every three years, although it can be removed at any time. Another implant can be placed immediately after removal of the expired device for continued protection. Because fertility returns quickly after implant removal, patients should immediately initiate another form of contraception to prevent pregnancy.

Clinicians should emphasize to their patients that they should not use the implant if they have a history of blood clots, unexplained vaginal bleeding, liver disease, or breast cancer. Patients should also be informed of the most common side effects, which include irregular bleeding, mood swings, weight gain, headache, acne, and depression.

Because of the tendency for drug interactions with etonogestrel, patients are advised to tell their physicians of any prescription or over-the-counter medications they are taking.

If a patient becomes pregnant, the implant should be removed immediately. It is unlikely that there would be fetal harm if the implant is removed just before or in the beginning of the pregnancy. The implant may be used in

<table>
<thead>
<tr>
<th>Table 4 Recommended Times for Etonogestrel (Implanon) Insertion</th>
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<tbody>
<tr>
<td><strong>No preceding hormonal contraceptive use in the past month</strong></td>
</tr>
<tr>
<td>• Counting the first day of menstruation as “day 1,” Implanon must be inserted between day one and day five, even if bleeding is still occurring.</td>
</tr>
<tr>
<td><strong>Switching from a combination hormonal contraceptive</strong></td>
</tr>
<tr>
<td>• Any time within seven days after the last active (estrogen plus progestin) oral contraceptive tablet.</td>
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<tr>
<td>• Any time during the seven-day ring-free period of NuvaRing (an etonogestrel/ethinyl estradiol vaginal ring)</td>
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<tr>
<td>• Any time during the seven-day patch-free period of a transdermal contraceptive system</td>
</tr>
<tr>
<td><strong>Switching from a progestin-only method</strong></td>
</tr>
<tr>
<td>• Any day of the month when switching from a progestin-only tablet, do not skip any days between the last tablet and insertion of Implanon.</td>
</tr>
<tr>
<td>• On the same day as contraceptive implant removal.</td>
</tr>
<tr>
<td>• On the same day as removal of a progestin-containing intrauterine device.</td>
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<tr>
<td>• On the day when the next contraceptive injection would be due.</td>
</tr>
<tr>
<td><strong>Following first-trimester abortion or miscarriage</strong></td>
</tr>
<tr>
<td>• Implanon may be inserted immediately following a complete first-trimester abortion.</td>
</tr>
<tr>
<td><strong>Following delivery or a second-trimester abortion</strong></td>
</tr>
<tr>
<td>• Implanon may be inserted between 21 and 28 days after delivery if the patient is not exclusively breast-feeding or between 21 and 28 days following a second-trimester abortion.</td>
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Data from Implanon package insert, 2006.
breast-feeding patients if the delivery was more than four weeks earlier.1–6

COST ANALYSIS

Pregnancy and childbirth have a significant impact on the cost of health care. Contraception adds to the cost of medications, but it saves money for health plans if it prevents an unintended pregnancy. Considering the major contraceptive dosage forms, the etonogestrel implant has been associated with a low number of pregnancies.1

An analysis was performed to determine the direct costs to health care plans for hormonal contraceptive products during a three-year interval for 1,000 women.15 The analysis included annual pharmacy and medical costs, pregnancies resulting from contraceptive failure, and patients’ discontinuation of therapy.15 For etonogestrel, total costs after the first year were greater as a result of the high number of patients who discontinued use during the first year.15 These patients drove the overall cost upward, because the costs associated with inserting and removing the implant occurred within the same year, with an appointment required to complete the procedure in both cases.15

The costs of the second and third year were approximately half those of the first year,15 thereby illustrating the importance of using this form of contraception for women seeking long-term protection. Even with the high cost of the first year, etonogestrel ranked second-lowest in cost.15

Other dosage forms evaluated were oral tablets, injections, the vaginal ring, transdermal delivery systems, and IUDs.15 After a three-year period, extended-cycle oral contraceptives cost the most and IUD dosage forms cost the least.15

The long-acting, reversible form of contraception offered by etonogestrel is not only reliable; it also removes the dependence on the patient’s compliance and correct usage, which are required with other dosage forms.1 Cost effectiveness is also determined by the patient’s quality of life, acceptability of the device, stage of life, and past medical history.4 Regardless of the circumstances, any form of contraception must meet these requirements satisfactorily to provide true savings in health care.15

CONCLUSION

The current trend in smaller family size throughout the world is resulting in an increased demand for contraceptive methods over an extended period of time.15 Some advantages of long-term contraceptives include the lack of the patient’s need to pay attention to them, their reliability without the need for strict patient compliance, their high efficacy, and their reversible effects after removal.15 Disadvantages of long-term contraception include dependence on properly trained health care personnel to initiate and end therapy, the requirement of minor surgery for insertion and removal of the implant, a high prevalence of bleeding irregularities, and the initial high cost.15

Implanon is a long-acting contraceptive method indicated for the prevention of pregnancy.4,15 In clinical trials, Implanon was safe, effective, and rapidly reversible.4 Because the most common reason for discontinuing therapy was related to abnormal bleeding, patient counseling with an emphasis on bleeding irregularities is essential.4,7,15 Informing patients extensively about all of the advantages and disadvantages of long-acting contraception before implant insertion is important and optimizes success.8,15

REFERENCES