

Etonogestrel Implant for Contraception

by Susan Kleppin, RPh

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Several contraceptive methods are available to prevent unintended pregnancy in women of child-bearing age. The effectiveness of most methods is significantly dependent upon patient compliance with the contraceptive method selected. Contraceptive implants offer the most effective contraception, with an expected and typical failure rate of 0.035%.² In addition, there are other advantages associated with the use of contraceptive implants as compared to other contraceptive methods including: no need for user compliance; long life-span; minimal requirement for medical follow-up once inserted; low, stable serum hormone levels minimizing metabolic effects; and rapid reversibility upon discontinuation.

Levonorgestrel implant (Norplant) was withdrawn voluntarily by the manufacturer from the United States market in 2002; the company cited a limitation in raw materials. The withdrawal may also have been associated with multiple reports of difficulty in removal of the 6 rod device. Another brand of levonorgestrel, Jadelle, was FDA approved in 2002 but never marketed. Etonogestrel implant (Implanon™) represents the only subdermal contraceptive device available currently in the United States after FDA approval in July 2006.

PHARMACOLOGY/PHARMACOKINETICS

Etonogestrel is a synthetic progestin that inhibits ovulation by altering the hypothalamic-pituitary-ovarian control mechanism. Like other progestins, etonogestrel down-regulates the luteinizing hormone surge that is required to support production, growth, and maturation of ovarian follicles. The drug also impedes conception by preventing implantation of a fertilized egg through inhibition of endometrial proliferation and by increasing the viscosity of cervical mucous which slows sperm migration.^{1,3}

After subdermal insertion of the implant, etonogestrel is released into the circulation and is approximately 100% bioavailable. The initial rate of release is approximately 60-70 mcg/day during the first four weeks after insertion and then subsequently declines to a rate of about 25-30 mcg/day at the end of three years.^{1,3} This rate is sufficient to provide effective contraception for at least three years. The inhibition of ovulation occurs within one day of insertion.³

Etonogestrel is approximately 66% albumin bound in blood. *In vitro* data show that it is metabolized in the liver by the cyto-

Summary

Indications. Etonogestrel implant is indicated for use in women for the prevention of pregnancy.¹

Monitoring Parameters. Patients should be monitored for persistent or recurrent abnormal vaginal bleeding, symptoms of thromboembolic events, severe pain or tenderness of abdomen, and breast lumps.

Dose. A single rod implant containing 68 mg of etonogestrel that is 4 cm in length is inserted subdermally under aseptic conditions in the inner, upper portion of the non-dominant arm. The timing of insertion is dependent upon patient's menstrual history and previous contraceptive use, if any. The implant may be left in place for up to three years.

Pediatrics. No clinical studies have been conducted in women less than 18 years of age. The safety and efficacy of etonogestrel implant have been established in women of reproductive age and are expected to be the same for postpubertal adolescents.

Geriatrics. The medication has not been studied in women over 65 years of age and is not indicated for this patient population.

Pregnancy Category. None assigned. Pregnancy should be ruled out prior to insertion. The etonogestrel implant is not indicated for use during pregnancy. If unplanned pregnancy occurs and will be maintained, the implant should be removed.

Breastfeeding. Based on available data, the etonogestrel implant may be used during lactation after the 4th postpartum week. Small amounts of etonogestrel are excreted in breast milk.

Stability. The implant should be stored at controlled room temperature and protected from light.

Cost. The average wholesale price (AWP) of a single etonogestrel implant is \$708.

chrome P450 3A4 isoenzyme. The biological activity of its metabolites is not known. The elimination half-life of etonogestrel is approximately 25 hours. Excretion is primarily in the urine and to lesser extent in feces. After removal of the implant, etonogestrel levels are undetectable within one week, with return of ovulation in 95% of patients within three weeks.^{1,3}

CLINICAL TRIALS

The package insert for etonogestrel summarizes the results of clinical trials involving a total of 923 subjects; the majority of trials were conducted in foreign countries and remain unpublished in the United States. This monograph summarizes the results of the open-label, prospective clinical trials that have been published in the English language in peer-reviewed journals. No comparative trials with other methods of birth control have been conducted.

Croxatto et al conducted an open-label, multicenter clinical trial to assess the efficacy, safety, and acceptability of etonogestrel implant.⁴ The study was conducted in 21 centers in nine countries. The study was designed to last for two years but was later extended to three years in two study centers. The study included healthy women who were sexually active and of childbearing potential, who were requesting contraception. All were between the ages of 18 and 40 years. They were included if they had a

menstrual cycle of 24-35 days with a maximum intra-individual variation of \pm three days. Women were excluded if they were pregnant, breastfeeding, or had a body weight that was less than 80% of ideal or greater than 130% of ideal. Liver enzyme-inducing medications were not allowed during the study.

The implant was inserted in the inner aspect of the non-dominant upper arm. The women had to be on or between the first and fifth day of a spontaneous menses. Six hundred and thirty-five women were enrolled in the study and had the implant inserted. It was later discovered that not all women fulfilled the inclusion/exclusion criteria for the study. Protocol violations included undiagnosed pregnancy, age >40 years, weight >130% of ideal and irregular menstrual cycles. Despite the violations, the data on these women were included in the published results except for one woman who had the implant removed 30 days after it was placed secondary to pregnancy.

A medical and gynecological history was taken at baseline and a physical and pelvic examination was conducted. Body weight and blood pressure were recorded at baseline and then repeated every three months. The implant site was examined every three months and the patient diary recording vaginal bleeding was reviewed to see whether a pregnancy test was indicated in case of amenorrhea. Study subjects were also questioned about unwanted effects at each quarterly visit.

The total exposure to the etonogestrel implant was 1200 woman-years or 15,653 28-day cycles. No pregnancies occurred during treatment, resulting in a Pearl index of 0 (95% confidence interval 0 – 0.2). The Pearl index is the most common technique used to measure effectiveness of contraceptive methods in clinical trials. It is determined by the number of unintended pregnancies related to 100 woman-years.

Four hundred and thirty-six women completed two years of treatment. A total of 147 women opted to continue the study for a third year but only 137 of these actually completed. Ten percent (n=64) discontinued treatment after six months and another 62 women discontinued treatment at 12 months. After 24 months, the total number of women who had discontinued treatment was 186 (31%). The majority of women who discontinued treatment in the first two years (17.2%) did so secondary to an unacceptable menstrual bleeding pattern. Other reasons for discontinuation included the desire to become pregnant, no need for contraception, and those who were moving away from the study center.

Safety was monitored with recording of adverse events other than vaginal bleeding. Serious adverse events were defined as any experience that was either fatal or life-threatening, permanently disabling, required hospitalization, or resulted in a congenital anomaly, cancer, or an overdose. Fifty serious adverse events were reported, with six judged by investigators to be possibly related to treatment with etonogestrel including development of a uterine fibroid, development of an ovarian cyst, intraductal papilloma with fibrocystic mastopathy, headache, transient ischemic attack and increased heart rate. The most commonly reported adverse events included acne, breast pain, vaginitis, headache and abdominal pain. At the start of the study, 36% of the study subjects had a history of dysmenorrhea which improved in 87% of women after the implant was inserted. Acne had been assessed

at study enrollment during the medical history. At the end of the study, 12.8% of women reported their acne had improved while 12.6% indicated that their acne had worsened or was a new condition.

Ten women had significant changes in blood pressure readings over the course of the study. A systolic blood pressure measurement of >140 mm Hg and that increased >20 mm Hg from baseline at two or more assessments or at the last assessment was considered clinically significant. A diastolic blood pressure measurement of >90 mm Hg and an increase of >10 mm Hg from baseline at two or more assessments or at the last assessment were also considered clinically significant. Five women (0.8%) had a clinically significant systolic blood pressure reading and seven (1.1%) had a clinical significant diastolic blood pressure reading during or at the end of the study. Mean systolic and diastolic blood pressure readings showed a small decrease over time. The body mass index (BMI) of study subjects showed an increase of >10% over baseline in 20.2% of women. The mean percent increase in BMI was 3.5%. Fifteen women discontinued treatment because of weight gain. Problems at the implant site were rarely reported. In total, 96.2% of patients had no problems reported.

After removal of the implant, women were followed for three months. Of those who used no contraception or a non-hormonal method of contraception post implant removal, menses returned to normal in 90.9% within three months and was not related to the length of time that the implant was in place.

The study results show that etonogestrel implant was very efficacious. The results of the study did confirm that use of progestin-only contraceptive methods is associated with irregular bleeding patterns in a high proportion of users and is often associated with discontinuation secondary to patient dissatisfaction.

Investigators at four study centers in China conducted a similar non-comparative, open-label study to evaluate the efficacy, cycle control, and acceptability of the etonogestrel implant.⁵ A total of 200 healthy women between the ages of 20 and 35 years who were sexually active, had childbearing potential, and who did not have contraindications to contraceptive steroids were enrolled. The women had normal menstrual cycles between 24 and 35 days in length. Women who were pregnant or breastfeeding were excluded from the study as well as anyone who had been treated with an injectable or implanted hormonal contraceptive in the six months prior to study enrollment or with oral contraceptives in the menstrual cycle just prior to enrollment. The implant was inserted in upper arm of each subject on or between the first and fifth day of menstruation or eight weeks postpartum and remained in place for two to four years prior to removal. The time required for the removal of the implant was recorded.

A medical and gynecological history was taken at baseline and a physical and pelvic examination was conducted. Laboratory assessment of hemoglobin and urine glucose, and a pregnancy test were performed prior to implant insertion. Body weight, blood pressure, and hemoglobin concentrations were measured at regular intervals. The implant site was also examined. A pregnancy test was repeated if there was any suspicion of pregnancy. Women noted vaginal bleeding patterns in a diary, using standard World Health Organization definitions of bleeding patterns.

Total exposure to etonogestrel implant was 644.6 woman-

years and average use per subject was 38.7 woman-months. No pregnancies occurred during treatment. A Pearl index was not calculated since the study was too small.

During the first two years of the study, 26 patients discontinued treatment – eight secondary to adverse events, 13 due to irregular vaginal bleeding, three due to amenorrhea, and two patients had no further need for contraception. In the third and fourth year of the study, 23 more patients discontinued treatment, mostly for personal reasons.

A reference period of 90 days was used for assessment of bleeding. In the first reference period, irregular bleeding and spotting occurred with more frequency than in subsequent periods. During the next 15 reference periods, the median number of bleeding-spotting days was between 18 and 21 for all but the second reference period. In the third and fourth years of implant use, the median number of episodes was three per reference period. The mean overall incidence of prolonged bleeding fell significantly during the study, from 69% in the first reference period to 44% in the fourth reference period, 31% in the eighth reference period and to 26% in the 16th reference period. The highest incidence of amenorrhea occurred in reference periods two through eight.

The implants were generally well tolerated. The most common adverse event was related to bleeding pattern, and in 25 patients, led to discontinuation of treatment. The cumulative discontinuation rates secondary to irregular bleeding patterns were 8% at two years, 12% at three years, and 13% at four years. Hemoglobin levels remained stable. Both small decreases and increases in mean systolic blood pressure and diastolic blood pressure were observed with no trends noted. Individual values remained within normal limits for all subjects.

Insertion of the implant was well tolerated in all but one woman who complained of pain at the insertion site at a single visit post insertion. Implants were removed in an average of 2.9 minutes and removal was accomplished without complications in all but one patient. In this individual, the implant had migrated from the insertion site. Mean body weight increased by 2.9 kg in women who completed four years of the study.

The study results show that etonogestrel implant was highly

effective. The number of bleeding-spotting days reported is similar to natural cycles of women in the same age group.

One open-label clinical trial assessing the safety and efficacy of etonogestrel implant has been conducted in the United States.⁶ Healthy, sexually active women between the ages of 18 and 40 years were eligible to participate in the study if they were within 80% to 130% of their ideal body weight and had normal menstrual cycles. Exclusion criteria included use of an injectable hormonal contraceptive within the six months preceding study enrollment; use of other hormonal contraceptives within the preceding month; removal of an implantable contraceptive within the two months preceding study enrollment; abortion or miscarriage within 1 month prior to study enrollment; history of smoking in patients age 35 or older; pregnancy; current breastfeeding; history of ectopic pregnancies; presence or history of major gynecologic disorders; liver function abnormalities; hyperlipoproteinemia; hypertension; or abnormal Pap smear at screening. Women were told not to use sex steroids, hydantoins, barbiturates, primidone, carbamazepine, rifampin, or griseofulvin during the study.

The implant was inserted subdermally in the upper non-dominant arm after a screening assessment was completed and inclusion and exclusion criteria were reviewed. The assessment included a medical, gynecologic and drug history as well as physical examination and laboratory assessments. Each study subject was asked to complete diary cards, recording vaginal bleeding or spotting on a daily basis. Subjects were evaluated every three months for review of the diaries, medication history, and an assessment of adverse effects. If the patient had recorded no bleeding or only spotting in the previous 45 days, a serum pregnancy test was performed. Vital signs, weight, and routine blood and urine laboratory tests were performed every six months. The time required for implant insertion and removal were recorded. A subgroup of patients had ophthalmologic evaluations at study enrollment and every 12 months.

A total of 3330 subjects used the implant for a total of 474 woman-years, equivalent to 6186 cycles. The mean exposure was 530 days. Two hundred twenty-six women (68%) were treated for at least one year and 169 (51%) completed both years of the study. No pregnancies occurred during treatment.

TABLE 1. CYP3A INHIBITORS AND INDUCERS

POTENT INHIBITORS	MODERATE INHIBITORS	INDUCERS
amiodarone	amprenavir	carbamazepine
atazanavir	aprepitant	efavirenz
cisapride	ciprofloxacin	nevirapine
clarithromycin	diltiazem	phenytoin
indinavir	erythromycin	phenobarbital
itraconazole	fluconazole	rifabutin
ketoconazole	fluvoxamine	rifampin
nefazodone	fosamprenavir	St. John's Wort
nelfinavir	grapefruit juice	
ritonavir	norfloxacin	
telithromycin	verapamil	
troleandomycin		
voriconazole		

A total of 49% of subjects did not complete the entire two-year study. The most common reasons for treatment discontinuation were bleeding pattern changes (13%) and other types of adverse events (23%). Other withdrawals were secondary to illness, protocol violations, or patient decision not to continue.

The mean time required for insertion of the implant was 0.5 min and the mean time for removal was 3.5 min. No insertion site complications were reported in relation to insertion or removal.

Uterine bleeding patterns were assessed using 90 day reference periods. The number of subjects who discontinued treatment secondary to irregular bleeding was highest in the first eight months of the study and decreased thereafter. The mean number of days with bleeding or spotting, the number of bleeding-spotting episodes and the length of the episodes decreased consistently over time.

Two hundred and eighty-two subjects (86%) reported one or more adverse events during the two-year study. Most commonly reported adverse events felt by investigators to be related to the study medication included headache, vaginitis, acne, dysmenorrhea, emotional lability, weight increase, and depression. Some subjects reported decreases in acne and dysmenorrhea. No significant changes in lab parameters were noted. The only notable change in lab test results noted was a decrease in triglycerides and total cholesterol (noted at least one during the study) observed in 33% and 21% of study subjects, respectively. No clinically significant changes in blood pressure, BMI, or ophthalmologic exam were noted.

A recently published Cochrane review identified eight clinical trials that compared Implanon™ to Norplant. An analysis of the data from these trials revealed that the mean time for Implanon™ removal was 2.6 minutes (SD 2; range 0.2 to 20 minutes) and for Norplant removal was 10.2 minutes (SD 8.2; range 1.3 to 50 minutes). Norplant users were significantly more likely to experience problems at removal than Implanon™ users (0.2% vs 4.8%, $p < 0.001$).⁷

MEDICATION SAFETY

The manufacturer is requiring that all health care professionals (physicians and nurse practitioners) complete training on insertion and removal of the implant. The manufacturer does not allow purchase of the drug unless the training has been completed.

The manufacturer has developed a patient information leaflet about the use of etonogestrel implant, a user card that records the insertion and removal dates, and a patient consent form that health care providers are asked to use. The use of the leaflet has not been mandated by the FDA.

ADVERSE EFFECTS

The most common adverse effect reported in clinical trials was irregular bleeding, which occurred in 11% of all patients enrolled. Other adverse events that lead to discontinuation of treatment in clinical trials include emotional lability, weight gain, headache, acne, and depression.¹ A pregnancy that occurs in a patient using an etonogestrel implant may be more likely to be ectopic than a pregnancy occurring in a patient using no contraception.¹

Pain is the most frequent implant site complication. Hematoma, redness, and swelling have also been reported.^{1,3}

There have been postmarketing reports of serious thromboembolic events, including pulmonary embolism and stroke, in patients using etonogestrel implant for contraception.¹ The manufacturer recommends that consideration be given to implant removal if a patient will be immobilized long-term due to surgery or illness.

Etonogestrel implant is contraindicated in pregnancy, in smokers, or in women with active liver disease or with a history of breast cancer or thrombosis. This is based on experience with combination (progestin + estrogen) oral contraceptives.

DRUG INTERACTIONS

No drug interactions have been studied. Medications that induce hepatic enzymes may increase the metabolism of progestins such as etonogestrel and result in decreased efficacy and pregnancy. Inhibition of CYP3A may increase serum etonogestrel concentrations and increase the risk of toxicity.^{1,3} Concurrent therapy with CYP3A inhibitors and inducers listed in Table 1 should be avoided.

COST, DOSE AND HOW SUPPLIED

Each implantable rod contains 68 mg of etonogestrel and measures 4 cm x 2 mm. The rod is not biodegradable or radio-opaque. It should be inserted subdermally using the accompanying preloaded sterile applicator in the inside of the upper arm. It must be removed after a period of no more than three years.

Timing of insertion is dependent upon the patient's recent history:¹

1. No preceding hormonal contraceptive use in last month – insert between days one through five of menses
2. Switching from combination hormonal contraceptive – insert anytime within seven days of last active oral contraceptive tablet OR insert anytime during the seven day ring-free period of NuvaRing use OR anytime during seven days patch free period of a transdermal contraceptive system
3. Switching from a progestin-only method – insert any day of the month when switching from a progestin only pill (no days skipped) OR on the same day as contraceptive implant

TABLE 2. AVERAGE COST FOR LONG-ACTING PROGESTIN ONLY CONTRACEPTIVES

DRUG	AWP PER UNIT	DURATION OF USE	AWP FOR ONE YEAR OF TREATMENT
Etonogestrel (Implanon™)	\$708	3 years	\$236
Medroxyprogesterone acetate injection (generic)	\$58.23	3 months	\$232.92
Levonorgestrel intrauterine system (Mirena)	\$585.89	5 years	\$117.18

removal OR on the same day as removal of a progestin-containing intrauterine device OR on the day when the next contraceptive injection would be due

4. Following first trimester abortion or miscarriage – insert immediately following a complete first trimester abortion or miscarriage. If not inserted within five days, it should be inserted between days one through five of menses
5. Following delivery or a second trimester abortion – insert between 21-28 days postpartum if not exclusively breastfeeding or following second trimester abortion. If more than 4 weeks have elapsed, pregnancy should be excluded and the patient should use non-hormonal method of birth control during first seven days after insertion.

If these recommendations for insertion are not followed, a backup non-hormonal method of birth control should be used for seven days after insertion.

The implant should be stored at controlled room temperature and protected from light.

The AWP of each implant is \$708. Cost comparisons with other available long-acting progestin only contraceptives are outlined in Table 2.

CONCLUSION

Etonogestrel implant is a long-acting progestin-only contraceptive that is very efficacious and may be particularly useful in patients who may have compliance issues with other contraceptive methods, are unable to tolerate or have contraindications to estrogen-containing products, or who might prefer a subdermal device.

Pharmacists should be cognizant of the potential for drug interactions with etonogestrel implant, particularly those involving CYP3A inducers as these could result in contraceptive failure and unplanned pregnancy. When completing medication reconciliation activities with female patients, pharmacists should specifically question the patient about contraceptive implant, injection, or intrauterine device use. Patients may not consider these prescription medications as they do not self-administer them. This scrutiny will ensure that adequate drug-drug interaction counseling is provided. ●

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First DataBank/Medi-Span AWP Settlement

by Mark E. Kinney, RPh

The New England Carpenter's Health and Benefits Fund and the local AFSCME chapter sued First DataBank in 2005 for allegedly inflating the published average wholesale price (AWP) of certain brand name drugs. The plaintiffs identified the price manipulation as occurring between 2001 and 2002. The parties subsequently agreed to a settlement that significantly expanded the number of brand name drugs to 8,467 national drug codes (NDCs) representing nearly 95% of the brand name drugs sold in the country today. Medi-Span, which also reports AWP, was included as a party to the settlement in 2007. The proposed final settlement would have required First DataBank and Medi-Span to:

- Reduce published AWP from WAC plus 25% to WAC plus 20% for 8,467 brand name drug NDCs.
- Stop reporting the Blue Book AWP two years after the settlement was final.
- Set up a "data room" to give payers access to information for future litigation.
- Pay the PAL legal fees.
- Assist in a mediation process, monitored by the court, to establish a benchmark for pharmaceutical reimbursement.
- Not pay restitution for damages caused by their actions.

According to the affidavit of expert witness Raymond Harman, PhD, the projected first-year savings of the AWP roll-back would be \$4.23 billion.

Settlement Update

Subsequent to the failed Jan. 22, 2008 final fairness hearing, the parties to the settlement have provided the court with a new proposal. A status hearing held on March 19, 2008 provided the court with an outline of the new agreement. Once again the settlement calls for the elimination of published AWP prices in two years. Judge Saris reminded the parties, "I am unlikely to require as part of a settlement that all AWP's from now until the end of time be eliminated." The judge also had to reiterate her objection to the inclusion of a "data room" for payers to access for future AWP lawsuits. The "data room" exclusion is important, as state Medicaid programs and patients paying "usual & customary" prices for prescription medications are not part of the settlement "class."

The concern for community pharmacy at the March hearing was the indication from Judge Saris that she would closely consider a 5% decrease on 1400 NDCs (reported to be the drugs actually impacted by the alleged inflation scheme from 2002). Judge Saris said, "I like the idea there's some money in the pot for people from the past. I like the idea you only rolled back for drugs that were specifically at issue here."

Based on preliminary data the decrease from 8000 NDCs to 1400 NDCs may still represent more than 50% of brand name drug sales. A 5% roll-back would likely be a billion dollar loss for community pharmacy until new contracts could be negotiated – if they could be renegotiated at all. Further economic analysis of the proposed settlement relating to its impact on community pharmacy will be provided to the court prior to a yet-to-be scheduled final hearing. Objectors to the settlement included IPC, NCPA, NACDS and PCMA. ●

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