NORPLANT® SYSTEM
(levonorgestrel implants)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Prescribing Information

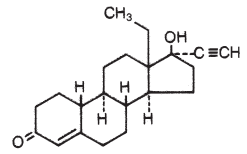
DESCRIPTION

The NORPLANT SYSTEM kit contains levonorgestrel implants, a set of six flexible closed capsules made of silicone rubber tubing (Silastic®, dimethylsiloxane/methylvinylsiloxane copolymer), each containing 36 mg of the progestin levonorgestrel contained in an insertion kit to facilitate implantation. The capsules are sealed with Silastic (polydimethylsiloxane) adhesive and sterilized. Each capsule is 2.4 mm in diameter and 34 mm in length. The capsules are inserted in a superficial plane beneath the skin of the upper arm.

Information contained herewith regarding safety and efficacy was derived from studies which used two slightly different Silastic tubing formulations. The formulation being used in the NORPLANT SYSTEM has slightly higher release rates of levonorgestrel and at least comparable efficacy.

Evidence indicates that the dose of levonorgestrel provided by the NORPLANT SYSTEM is initially about 85 mcg/day followed by a decline to about 50 mcg/day by 9 months and to about 35 mcg/day by 18 months with a further decline thereafter to about 30 mcg/day. The NORPLANT SYSTEM is a progestin-only product and does not contain estrogen.

Levonorgestrel, (d(-)-13-beta-ethyl-17-alpha-ethinyl-17-beta-hydroxygon-4-en-3-one), the active ingredient in the NORPLANT SYSTEM, has a molecular weight of 312.45 and the following structural formula:



Levonorgestrel

CLINICAL PHARMACOLOGY

Levonorgestrel is a totally synthetic and biologically active progestin which exhibits no significant estrogenic activity and is highly progestational. The absolute configuration conforms to that of D-natural steroids. Levonorgestrel is not subjected to a "first-pass" effect and is virtually 100% bioavailable. Plasma concentrations average approximately 0.30 ng/mL over 5 years but are highly variable as a function of individual metabolism and body weight.

Diffusion of levonorgestrel through the wall of each capsule provides a continuous low dose of the progestin. Resulting blood levels are substantially below those generally observed among users of combination oral contraceptives containing the progestins norgestrel or levonorgestrel. Because of the range of variability in blood levels and variation in individual response, blood levels alone are not predictive of the risk of pregnancy in an individual woman.

At least two mechanisms are active in preventing pregnancy: ovulation inhibition and thickening of the cervical mucus. Other mechanisms may add to these contraceptive effects.

Levonorgestrel concentrations among women show considerable variation depending on individual clearance rates, body weight, and possibly other factors. Levonorgestrel concentrations reach a maximum, or near maximum, within 24 hours after placement with mean values of 1600 ± 1100 pg/mL. They decline rapidly over the first month partially due to a circulating protein, SHBG, that binds levonorgestrel and which is depressed by the presence of levonorgestrel. At 3 months, mean levels decline to values of around 400 pg/mL while concentrations normalized to a 60 kg body weight were 327 ± 119 (SD) pg/mL at 12 months with further decline by 1.4 pg/mL/month to reach 258 ± 95 (SD) pg/mL at 60 months. Concentrations decreased with increasing body weight by a mean of 3.3 pg/mL/kg. After capsule removal, mean concentrations drop to below 100 pg/mL by 96 hours and to below assay sensitivity (50 pg/mL) by 5 to 14 days. Fertility rates return to levels comparable to those seen in the general population of women using no method of contraception. Circulating concentrations can be used to forecast the risk of pregnancy only in a general statistical sense. Mean concentrations associated with pregnancy have been 210 ± 60 (SD) pg/mL. However, in clinical studies, 20 percent of women had one or more values below 200 pg/mL but an average annual gross pregnancy rate of less than 1.0 per 100 women through 5 years.

Although lipoprotein levels were altered in several clinical studies with the NORPLANT SYSTEM, the long-term clinical effects of these changes have not been determined. A decrease in total cholesterol levels has been reported in all lipoprotein studies and reached statistical significance in several. Both increases and decreases in high-density lipoprotein (HDL) levels have been reported in clinical trials. No statistically significant increases have been reported in the ratio of total cholesterol to HDL-cholesterol. Low-density lipoprotein (LDL) levels decreased during NORPLANT SYSTEM use. Triglyceride levels also decreased from pretreatment values.

INDICATIONS AND USAGE

The NORPLANT SYSTEM is indicated for the prevention of pregnancy and is a long-term (up to 5 years) reversible contraceptive system. The capsules should be removed by the end of the 5th year. New capsules may be inserted at that time if continuing contraceptive protection is desired.

In multicenter trials with the NORPLANT SYSTEM, involving 2470 women, the relationship between body weight and efficacy was investigated. Tabulated below is the pregnancy experience as a function of body weight. Because NORPLANT SYSTEM is a long-term method of contraception, this is reported over five years of use.

TABLE 1
Annual and Five-Year Cumulative Pregnancy Rates
Per 100 Users by Weight Class

Weight class	year 1	year 2	year 3	year 4	year 5	Cumulative
<50 kg (<110 lbs)	0.2	0	0	0	0	0.2
50-59 kg (110-130 lbs)	0.2	0.5	0.4	2.0	0.4	3.4
60-69 kg (131-153 lbs)	0.4	0.5	1.6	1.7	0.8	5.0
≥70 kg (≥154 lbs)	0	1.1	5.1	2.5	0	8.5
All	0.2	0.5	1.2	1.6	0.4	3.9

Typically, pregnancy rates with contraceptive methods are reported for only the first year of use as shown below. The efficacy of these contraceptive methods, except the IUD and sterilization, depends in part on the reliability of use. The efficacy of the NORPLANT SYSTEM does not depend on patient compliance. However, no contraceptive method is 100% effective.

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TABLE 2
Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Use of a Contraceptive Method

Method	Perfect Use	Typical Use
NORPLANT SYSTEM (6 capsules)	0.05	0.05
Male sterilization	0.1	0.15
Female sterilization	0.5	0.5
Depo-Provera® (injectable progestogen)	0.3	0.3
Oral contraceptives		5
Combined	0.1	NA
Progestin only	0.5	NA
IUD		
Progesterone	1.5	2.0
Copper T 380A	0.6	0.8
Condom (male) without spermicide	3	14
(female) without spermicide	5	21
Cervical cap		
Nulliparous women	9	20
Parous women	26	40
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	6	26
Periodic abstinence (all methods)	1-9*	25
Withdrawal	4	19
No contraception (planned pregnancy)	85	85

NA - not available

*Depending on method (calendar, ovulation, symptothermal, post-ovulation)

Adapted from Hatcher RA et al., *Contraceptive Technology, 17th Revised Edition.* New York, NY: Ardent Media, Inc., 1998.

NORPLANT SYSTEM (levonorgestrel implants) gross annual discontinuation and continuation rates are summarized in Table 3.

TABLE 3
Annual and Five-Year Cumulative Rates
per 100 Users

	year 1	year 2	year 3	year 4	year 5	Cumulative
Pregnancy	0.2	0.5	1.2	1.6	0.4	3.9
Bleeding Irregularities	9.1	7.9	4.9	3.3	2.9	25.1
Medical (excl. bleeding irreg.)	6.0	5.6	4.1	4.0	5.1	22.4
Personal	4.6	7.7	11.7	10.7	11.7	38.7
Continuation	81.0	77.4	79.2	76.7	77.6	29.5

CONTRAINDICATIONS

1. Active thrombophlebitis or thromboembolic disorders. There is insufficient information regarding women who have had previous thromboembolic disease.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected pregnancy.
4. Acute liver disease; benign or malignant liver tumors.
5. Known or suspected carcinoma of the breast.
6. History of idiopathic intracranial hypertension.
7. Hypersensitivity to levonorgestrel or any of the other components of the NORPLANT SYSTEM.

WARNINGS

A. Warnings Based on Experience with the NORPLANT SYSTEM

1. Insertion and Removal Complications

A surgical incision is required to insert NORPLANT SYSTEM capsules. Complications related to insertion such as pain, edema, and bruising may occur. There also have been reports of infection (including cellulitis and abscess formation), blistering, ulcerations, sloughing, excessive scarring, phlebitis, and hyperpigmentation at the insertion site. There have been reports of arm pain, numbness, and tingling following the insertion and removal procedures. There also have been reports of nerve injury, most commonly associated with deep placement and removal. Expulsion of capsules has been reported more frequently when placement of the capsules was shallow or too close to the incision or when infection was present. There have been reports of capsule displacement (i.e., movement), most of which involved minor changes in the positioning of the capsules. However, infrequent reports (< 1%) of significant displacement (a few to several inches) have been received. Some of these reports have been associated with pain and difficult removal. Removal is also a surgical procedure and may take longer, be more difficult, and/or cause more pain than insertion and may be associated with difficulty locating capsules. These complications may lead to the need for additional incisions and/or office visits. See also "**PRECAUTIONS**" and "**ADVERSE REACTIONS**."

2. Bleeding Irregularities

Most women can expect some variation in menstrual bleeding patterns. Irregular menstrual bleeding, intermenstrual spotting, prolonged episodes of bleeding and spotting, and amenorrhea occur in some women. Irregular bleeding patterns associated with the NORPLANT SYSTEM could mask symptoms of cervical or endometrial cancer. Overall, these irregularities diminish with continuing use. Since some NORPLANT SYSTEM users experience periods of amenorrhea, missed menstrual periods cannot serve as the only means of identifying early pregnancy. Pregnancy tests should be performed whenever a pregnancy is suspected. Six (6) weeks or more of amenorrhea after a pattern of regular menses may signal pregnancy. If pregnancy occurs, the capsules must be removed.

Although bleeding irregularities have occurred in clinical trials, proportionately more women had increases rather than decreases in hemoglobin concentrations, a difference that was highly statistically significant. This finding generally indicates that reduced menstrual blood loss is associated with the use of the NORPLANT SYSTEM. In rare instances, patients experienced heavy bleeding that resulted in hemoglobin values consistent with anemia.

3. Ovarian Cysts (Delayed Follicular Atresia)

If follicular development occurs with the NORPLANT SYSTEM, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. These enlarged follicles cannot be distinguished clinically from ovarian cysts. In the majority of women, enlarged follicles will spontaneously disappear and should not require surgery. Rarely, they may twist or rupture, sometimes causing abdominal pain, and surgical intervention may be required.

4. Ectopic Pregnancies

Ectopic pregnancies have occurred among NORPLANT SYSTEM users, although clinical studies have shown no increase in the rate of ectopic pregnancies per year among NORPLANT SYSTEM users as compared with users of no method or of IUDs. The incidence among NORPLANT SYSTEM users was 1.3 per 1000 woman-years, a rate significantly below the rate that has been estimated for noncontraceptive users in the United States (2.7 to 3.0 per 1000 woman-years). The risk of ectopic pregnancy may increase with the duration of NORPLANT SYSTEM use and possibly with increased weight of the user. Physicians should be alert to the possibility of an ectopic pregnancy among women using the NORPLANT SYSTEM (levonorgestrel implants) who become pregnant or complain of lower-abdominal pain. Any patient who presents with lower-abdominal pain must be evaluated to rule out ectopic pregnancy.

5. Foreign-body Carcinogenesis

Rarely, cancers have occurred at the site of foreign-body intrusions or old scars. None has been reported in NORPLANT SYSTEM clinical trials. In rodents, which are highly susceptible to such cancers, the incidence decreases with decreasing size of the foreign body. Because of the resistance of human beings to these cancers and because of the small size of the capsules, the risk to users of the NORPLANT SYSTEM is judged to be minimal.

6. Thromboembolic Disorders and Other Vascular Problems

An increased risk of thromboembolic and thrombotic disease (pulmonary embolism, superficial venous thrombosis, and deep-vein thrombosis) has been found to be associated with the use of combination oral contraceptives. The relative risk has been estimated to be 4- to 11-fold higher for users than for nonusers. There have also been post-marketing reports of these events coincident with NORPLANT SYSTEM use. The reports of thrombophlebitis and superficial phlebitis have more commonly occurred in the arm of insertion. Some of these cases have been associated with trauma to that arm.

Cerebrovascular Disorders: Combination oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years) hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes. There have been post-marketing reports of stroke coincident with NORPLANT SYSTEM (levonorgestrel implants) use.

Myocardial Infarction: An increased risk of myocardial infarction has been attributed to combination oral-contraceptive use. This is thought to be primarily thrombotic in origin and is related to the estrogen component of combination oral contraceptives. This increased risk occurs primarily in smokers or in women with other underlying risk factors for coronary-artery disease, such as family history of coronary-artery disease, hypertension, hypercholesterolemia, morbid obesity, and diabetes. The current relative risk of heart attack for combination oral-contraceptive users has been estimated as 2 to 6 times the risk for nonusers. The absolute risk is very low for women under 30 years of age.

Studies indicate a significant trend toward higher rates of myocardial infarctions and strokes with increasing doses of progestin in combination oral contraceptives. However, a recent study showed no increased risk of myocardial infarction associated with the past use of levonorgestrel-containing combination oral contraceptives. There have been post-marketing reports of myocardial infarction coincident with NORPLANT SYSTEM use.

Patients who develop active thrombophlebitis or thromboembolic disease should have the NORPLANT SYSTEM capsules removed. Removal should also be considered in women who will be subjected to prolonged immobilization due to surgery or other illnesses.

7. Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. There is no evidence suggesting that the risk associated with NORPLANT SYSTEM use is different.

There have been rare reports of congenital anomalies in offspring of women who were using the NORPLANT SYSTEM inadvertently during early pregnancy. A cause and effect relationship is not believed to exist.

8. Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (pseudotumor cerebri, benign intracranial hypertension) is a disorder of unknown etiology which is seen most commonly in obese females of reproductive age. There have been reports of idiopathic intracranial hypertension in NORPLANT SYSTEM users. A cardinal sign of idiopathic intracranial hypertension is papilledema; early symptoms may include headache (associated with a change in frequency, pattern, severity, or persistence; of particular importance are those headaches that are unremitting in nature) and visual disturbances. Patients with these symptoms, particularly obese patients or those with recent weight gain, should be screened for papilledema and, if present, the patient should be referred to a neurologist for further diagnosis and care. NORPLANT SYSTEM should be removed from patients experiencing this disorder.

B. Warnings Based on Experience with Combination (Progestin plus Estrogen) Oral Contraceptives

1. Cigarette Smoking

Cigarette smoking increases the risk of serious cardiovascular side effects from the use of combination oral contraceptives. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years old. While this is believed to be an estrogen-related effect, it is not known whether a similar risk exists with progestin-only methods such as the NORPLANT SYSTEM; however, women who use the NORPLANT SYSTEM should be advised not to smoke.

2. Elevated Blood Pressure

Increased blood pressure has been reported in users of combination oral contraceptives. The prevalence of elevated blood pressure increases with long exposure. Although there were no statistically significant trends among NORPLANT SYSTEM users in clinical trials, physicians should be aware of the possibility of elevated blood pressure with the NORPLANT SYSTEM.

3. Carcinoma

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using combination oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combination oral contraceptive use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in combination oral contraceptive users, the biological effects of combination oral contraceptives, or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combination oral contraceptive users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. Although the results were broadly similar for progestin-only oral contraceptives, the data are based on much smaller numbers of progestin-only oral contraceptive users and therefore are less conclusive than for combination oral contraceptives. This information should be considered when prescribing the NORPLANT SYSTEM.

Some studies suggest that combination oral-contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In spite of many studies of the relationship between combination oral-contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

Evidence indicates that combination oral contraceptives may decrease the risk of ovarian and endometrial cancer. Irregular bleeding patterns associated with the NORPLANT SYSTEM could mask symptoms of cervical or endometrial cancer.

4. Hepatic Tumors

Hepatic adenomas have been found to be associated with the use of combination oral contraceptives with an estimated incidence of about 3 occurrences per 100,000 users per year, a risk that increases after 4 or more years of use. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal hemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

5. Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. Although it is believed that this adverse reaction is related to the estrogen component of oral contraceptives, the NORPLANT SYSTEM capsules should be removed if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral-contraceptive formulations containing lower hormonal doses of estrogens and progestins. The association of this risk with the use of the NORPLANT SYSTEM progestin-only method is not known.

PRECAUTIONS

General

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. Physical Examination and Follow-Up

A complete medical history and physical examination should be taken prior to the implantation or reimplantation of NORPLANT SYSTEM capsules and at least annually during its use. These physical examinations should include special reference to the implant site, blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. Insertion and Removal

To be sure that the woman is not pregnant at the time of capsule placement and to assure contraceptive effectiveness during the first cycle of use, it is advisable that insertion be done during the first 7 days of the menstrual cycle or immediately following an abortion. However, NORPLANT SYSTEM capsules may be inserted at any time during the cycle provided pregnancy has been excluded and a nonhormonal contraceptive method is used for at least 7 days following insertion. Insertion is not recommended before 6 weeks postpartum in breast-feeding women.

Insertion and removal instructions must be followed closely. It is strongly advised that all health-care professionals who insert and remove NORPLANT SYSTEM capsules be instructed in the procedures before they attempt them. Proper insertion just under the skin will facilitate removal.

If infection develops after insertion, suitable treatment should be instituted. If infection persists, capsules should be removed.

In the case of capsule expulsion, the expelled capsule must be replaced using a new sterile capsule, as contraceptive efficacy may be inadequate with fewer than 6 capsules. If infection is present, it should be treated and cured before capsule replacement.

Removal should be done upon patient request, for medical indications, or at the end of 5 years of use, by personnel instructed in the removal technique. If the capsules were placed deeply, they may be harder to remove. The use of general anesthesia during removal should generally be avoided.

Before initiating the removal procedure, all NORPLANT SYSTEM capsules should be located via palpation. If all 6 capsules cannot be located by palpation, they may be localized by ultrasound (7 MHz), X-ray, or compression mammography. If all capsules cannot be removed at the first attempt, removal should be attempted later when the site has healed.

Upon removal, NORPLANT SYSTEM capsules should be disposed of in accordance with the Center for Disease Control and Prevention guidelines for the handling of biohazardous waste.

See also "**WARNINGS**," "**ADVERSE REACTIONS**" and "**INSTRUCTIONS FOR INSERTION AND REMOVAL—Removal Procedure**."

3. Carbohydrate and Lipid Metabolism

An altered glucose tolerance characterized by decreased insulin sensitivity following glucose loading has been found in some users of combination and progestin-only oral contraceptives. The effects of the NORPLANT SYSTEM on carbohydrate metabolism appear to be minimal. In a study in which pretreatment serum-glucose levels were compared with levels after 1 and 2 years of NORPLANT SYSTEM use, no statistically significant differences in mean serum-glucose levels were evident 2 hours after glucose loading. The clinical significance of these findings is unknown, but diabetic patients should be carefully observed while using the NORPLANT SYSTEM.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use the NORPLANT SYSTEM. Some progestins may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See "**WARNINGS**," A. 6.)

4. Liver Function

If jaundice develops in any women while using the NORPLANT SYSTEM, consideration should be given to removing the capsules. Steroid hormones may be poorly metabolized in patients with impaired liver function.

5. Fluid Retention

Steroid contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

6. Emotional Disorders

Consideration should be given to removing NORPLANT SYSTEM capsules in women who become significantly depressed since the symptom may be drug-related. Women with a history of depression should be carefully observed and removal considered if depression recurs to a serious degree.

7. Contact Lenses

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

8. Autoimmune Disease

Autoimmune diseases such as scleroderma, systemic lupus erythematosus and rheumatoid arthritis occur in the general population and more frequently among women of childbearing age. There have been rare reports of various autoimmune diseases, including the above, in NORPLANT SYSTEM users; however, the rate of reporting is significantly less than the expected incidence for these diseases. Studies have raised the possibility of developing antibodies against silicone-containing devices; however, the specificity and clinical relevance of these antibodies are unknown. While it is believed that the occurrence of autoimmune disease among NORPLANT SYSTEM users is coincidental, health-care providers should be alert to the earliest manifestations.

Drug Interactions

Reduced efficacy (pregnancy) has been reported for NORPLANT SYSTEM users taking phenytoin and carbamazepine. These drugs may increase the metabolism of levonorgestrel through induction of microsomal liver enzymes. NORPLANT SYSTEM users should be warned of the possibility of decreased efficacy with the use of drugs exhibiting enzyme-inducing activity such as those noted above and rifampin. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

Drug/Laboratory Test Interactions

Certain endocrine tests may be affected by NORPLANT SYSTEM use:
1. Sex-hormone-binding globulin concentrations are decreased.
2. Thyroxine concentrations may be slightly decreased and triiodothyronine uptake increased.

Carcinogenesis

See "**WARNINGS**" section.

Pregnancy

Pregnancy Category X. See "**WARNINGS**" section.

Nursing Mothers

Steroids are not considered the contraceptives of first choice for breast-feeding women. Levonorgestrel has been identified in the breast milk. The health of breast-fed infants whose mothers began using the NORPLANT SYSTEM during the 5th to 7th week postpartum was evaluated; no significant effects were observed on the growth or development of infants who were followed to 12 months of age. No data are available on use in breast-feeding mothers earlier than this after parturition.

Pediatric Use

Safety and efficacy of the NORPLANT SYSTEM (levonorgestrel implants) have been established in women of reproductive age. Safety and efficacy are expected to be similar for postpubertal adolescents under 16 and users 16 and older. Use of this product before menarche is not indicated.

Information for the Patient

See Patient Labeling.

Two copies of the Patient Labeling are included to help describe the characteristics of the NORPLANT SYSTEM to the patient. One copy should be provided to the patient. Patients should also be advised that the Prescribing Information is available to them at their request. It is recommended that prospective users be fully informed about the risks and benefits associated with the use of the NORPLANT SYSTEM, with other forms of contraception, and with no contraception at all. It is also recommended that prospective users be fully informed about the insertion and removal procedures. Health-care providers may wish to obtain informed consent from all patients in light of the techniques involved with insertion and removal.

ADVERSE REACTIONS

The following adverse reactions have been associated with the NORPLANT SYSTEM during the first year of use. They include:

Many bleeding days or prolonged bleeding	27.6%
Spotting	17.1%
Amenorrhea	9.4%
Irregular (onsets of) bleeding	7.6%
Frequent bleeding onsets	7.0%
Scanty bleeding	5.2%
Pain or itching near implant site (usually transient)	3.7%
Infection at implant site	0.7%

In addition, removal difficulties affecting subjects (including multiple incisions, capsule fragments remaining, pain, multiple visits, deep placement, lengthy removal procedure, or other) have been reported with a frequency of 6.2%, which is based on 849 removals occurring through 5 years of use. See "**WARNINGS**" and "**PRECAUTIONS**."

Clinical studies comparing NORPLANT® SYSTEM users with other contraceptive method users suggest that the following adverse reactions occurring during the first year are probably associated with NORPLANT SYSTEM use. These adverse reactions have also been reported post-marketing:

Headache	Acne
Nervousness/Anxiety	Change of appetite
Nausea/Vomiting	Mastalgia
Dizziness	Weight gain
Adnexal enlargement	Hirsutism, hypertrichosis,
Dermatitis/Rash	and scalp-hair loss

In addition, the following adverse reactions have been reported with a frequency of 5% or greater during the first year and are possibly related to NORPLANT SYSTEM use:

Breast discharge	Abdominal discomfort
Cervicitis	Leukorrhea
Musculoskeletal pain	Vaginitis

The following adverse reactions have been reported post-marketing with an incidence of less than 1% and are possibly related to NORPLANT SYSTEM use:

Emotional lability	Dysmenorrhea
Idiopathic intracranial hypertension (IIH, pseudotumor cerebri, benign intracranial hypertension)	Migraine
	Arm pain
	Numbness
	Tingling
	Depression
Induration	Excessive scarring
Bruising	Hyperpigmentation
Abscess, cellulitis	Nerve injury

The following adverse reactions have been reported post-marketing with an incidence of less than 1%. These events occurred under circumstances where a causal relationship to the NORPLANT SYSTEM is unknown. These reactions are listed as information for physicians:

Breast cancer	Thrombotic thrombocytopenic purpura (TTP)
Congenital anomalies	
Pulmonary embolism	Stroke
Superficial venous thrombosis	Pruritus
	Urticaria
Deep-vein thrombosis	Asthenia (fatigue/weakness)
Myocardial infarction	Phlebitis
Blistering, ulcerations, and sloughing	

OVERDOSAGE

Overdosage can result if more than six capsules of the NORPLANT SYSTEM are in situ. All implanted NORPLANT SYSTEM capsules should be removed before inserting a new set of NORPLANT SYSTEM capsules. Overdosage may cause fluid retention with its associated effects and uterine bleeding irregularities.

DOSAGE AND ADMINISTRATION

The NORPLANT SYSTEM consists of six Silastic® capsules, each containing 36 mg of the progestin, levonorgestrel. The total administered (implanted) dose is 216 mg. Implantation of all six capsules should be performed during the first 7 days of the onset of menses by a health-care professional instructed in the NORPLANT SYSTEM insertion technique. Insertion is subdermal in the midportion of the upper arm about 8 to 10 cm above the elbow crease. Distribution should be in a fanlike pattern, about 15 degrees apart, for a total of 75 degrees. Proper insertion will facilitate later removal. (See section on Insertion/Removal.)

HOW SUPPLIED

The NORPLANT SYSTEM Kit includes the following items:

1 NORPLANT SYSTEM (levonorgestrel implants), a set of six implants (capsules)

1 NORPLANT SYSTEM trocar	1 Package of skin closures
1 Scalpel	3 Packages of gauze sponges
1 Forceps	1 Stretch bandage
1 Syringe	1 Surgical drape (fenestrated)
2 Syringe needles	2 Surgical drapes

Store at room temperature away from excess heat and moisture.

NDC 0008-2564-01

References available upon request.

INSTRUCTIONS FOR INSERTION AND REMOVAL

The NORPLANT SYSTEM consists of six levonorgestrel-releasing capsules that are inserted subdermally in the medial aspect of the upper arm.

The NORPLANT SYSTEM provides up to 5 years of effective contraceptive protection.

The basis for successful use and subsequent removal of NORPLANT SYSTEM capsules is a correct and carefully performed subdermal insertion of the six capsules. It is recommended that health-care professionals performing insertions or removals of NORPLANT SYSTEM capsules avail themselves of instruction and supervision in the proper technique prior to attempting these procedures. During insertion, special attention should be given to the following:

— asepsis.
— correct subdermal placement of the capsules.
— careful technique to minimize tissue trauma.

This will help to avoid infections and excessive scarring at the insertion area and will help keep the capsules from being inserted deeply in the tissue. If the capsules are placed deeply, they will be more difficult to remove than correctly placed subdermal capsules.

Insertion Procedure

Insertion should be performed within seven days from the onset of menses. However, NORPLANT SYSTEM capsules may be inserted at any time during the cycle provided pregnancy has been excluded and a nonhormonal contraceptive method is used for at least 7 days following insertion. It is recommended that a complete history and physical examination, including a gynecologic examination, be performed before the insertion of NORPLANT SYSTEM capsules. Determine if the subject has any allergies to the antiseptic or anesthetic to be used or contraindications to progestin-only contraception. If none are found, the capsules are inserted using the procedure outlined below.

One NORPLANT SYSTEM set consists of six capsules in a sterile pouch. The insertion is performed under aseptic conditions using a trocar to place the capsules under the skin.

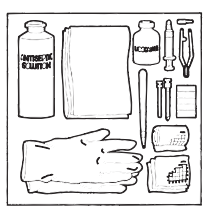


Figure 1: The following equipment is recommended for the insertion:
— an examining table for the patient to lie on.
— sterile surgical drapes, sterile gloves (free of talc), antiseptic solution.
— local anesthetic, needles, and syringe.
— #11 scalpel, #10 trocar, forceps.
— skin closure, sterile gauze, and compresses.

The plastic cover and tray are NOT STERILE.

Figure 2: Have the patient lie on her back on the examination table with her left arm (if the patient is left-handed, the right arm) flexed at the elbow and externally rotated so that her hand is lying by her head. The capsules will be inserted subdermally through a small 2-mm incision and positioned in a fanlike manner with the fan opening towards the shoulder.

Figure 3: Prep the patient's upper arm with antiseptic solution; cover the arm above and below the insertion area with a sterile cloth. The optimal insertion area is in the inside of the upper arm about 8 to 10 cm above the elbow crease.

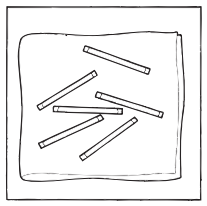


Figure 4: Open the sterile NORPLANT SYSTEM (levenonorgestrel implants) package carefully by pulling apart the sheets of the pouch, allowing the capsules to fall onto a sterile drape. Count the six capsules.

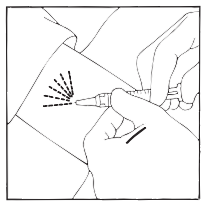


Figure 5: After determining the absence of known allergies to the anesthetic agent or related drugs, fill a 5-mL syringe with the local anesthetic. Since blood loss is minimal with this procedure, use of epinephrine-containing anesthetics is not considered necessary. Anesthetize the insertion area by first inserting the needle under the skin and injecting a small amount of anesthetic. Then anesthetize six areas about 4 to 4.5 cm long, to mimic the fanlike position of the implanted capsules.

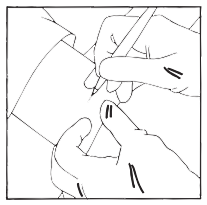


Figure 6: Use the scalpel to make a small incision (about 2 mm) just through the dermis of the skin. Alternatively, the trocar may be inserted directly through the skin without making an incision with the scalpel. The bevel of the trocar should always face up during the insertion.

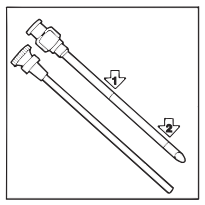


Figure 7: The trocar has two marks on it. The first mark is closer to the hub and indicates how far the trocar should be introduced under the skin before the loading of each capsule. The second mark is close to the tip and indicates how much of the trocar should remain under the skin following the insertion of each implant.

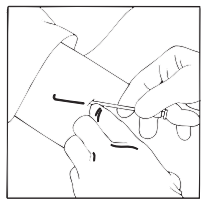


Figure 8: Insert the tip of the trocar through the incision beneath the skin at a shallow angle. Once the trocar is inserted, it should be oriented with the bevel up toward the skin to keep the capsules in a superficial plane. It is important to keep the trocar subdermal by tenting the skin with the trocar, as failure to do so may result in deep placement of the capsules and could make removal more difficult.

Advance the trocar gently under the skin to the first mark near the hub of the trocar. The tip of the trocar is now at a distance of about 4 to 4.5 cm from the incision.

Do not force the trocar, and if resistance is felt, try another direction.

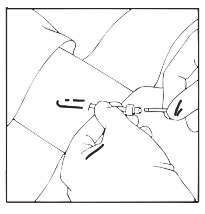


Figure 9: When the trocar has been inserted the appropriate distance, remove the obturator and load the first capsule into the trocar using the thumb and forefinger.

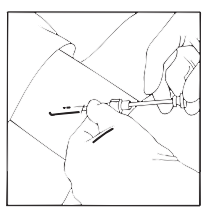


Figure 10: Gently advance the capsule with the obturator towards the tip of the trocar until you feel resistance. Never force the obturator.

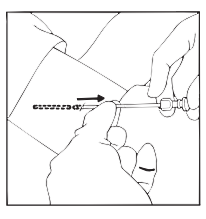


Figure 11: Hold the obturator steady, and bring the trocar back until it touches the handle of the obturator.

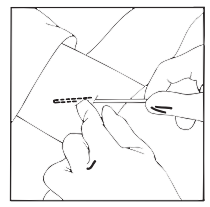


Figure 12: The capsule should have been released under the skin when the mark close to the tip of the trocar is visible in the incision. Release of the capsule can be checked by palpation. It is important to keep the obturator steady and not to push the capsule into the tissue.

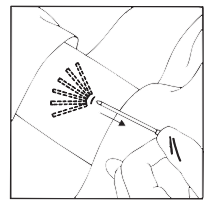


Figure 13: Do not remove the trocar from the incision until all capsules have been inserted. The trocar is withdrawn only to the mark close to its tip. Each succeeding capsule is always inserted next to the previous one, to form a fanlike shape. Fix the position of the previous capsule with the forefinger and middle finger of the free hand, and advance the trocar along the tips of the fingers. This will ensure a suitable distance of about 15 degrees between capsules and keep the trocar from puncturing any of the previously inserted capsules.

Leave a distance of about 5 mm between the incision and the tips of the capsules. This will help avoid spontaneous expulsions. The correct position of the capsules can be ensured by feeling them with the fingers after the insertion has been completed.

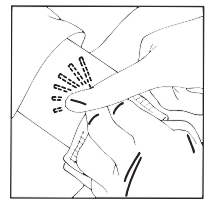


Figure 14: After placement of the sixth capsule, a sterile gauze may be used to apply pressure briefly to the insertion site to ensure hemostasis. Palpate the distal ends of the capsules to make sure that all six have been properly placed.

Figure 15: Press the edges of the incision together, and close the incision with a skin closure. Suturing the incision should not be necessary.

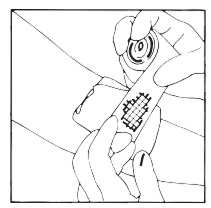


Figure 16: Cover the insertion area with a dry compress, and wrap gauze around the arm to ensure hemostasis.

Observe the patient for a few minutes for signs of syncope or bleeding from the incision before she is discharged.

Advise the patient to keep the insertion area dry and avoid heavy lifting for 2 to 3 days. The gauze may be removed after 1 day, and the butterfly bandage as soon as the incision has healed, i.e., normally in 3 days.

Removal Procedure

Described below is a removal procedure which was developed and used during the clinical trials for the NORPLANT SYSTEM (levenonorgestrel implants). As with many surgical procedures, variations of the technique have appeared and some have been published. No one particular procedure routinely appears to have any advantage over another.

It is recommended that removals be prescheduled so that preparations for carrying out the procedure can be facilitated.

Removal of the capsules should be performed very gently and will usually take more time and may be more difficult and/or more painful than insertion. Capsules are sometimes nicked, cut, or broken during removal, or may be difficult to locate. The incidence of overall removal difficulties, including those that did not result in patient complaints (e.g., damage to the capsules), was 13.2%. Less than half of these removal difficulties have caused inconvenience to the patient. If the removal of some of the capsules proves difficult, have the patient return for another visit. The remaining capsule(s) will be easier to remove after the area is healed. It may be appropriate to seek consultation or provide referral for patients in whom initial attempts at capsule removal prove difficult. If contraception is still desired, a barrier method should be advised until all capsules are removed.

The position of the patient and the asepsis are the same as for insertion.

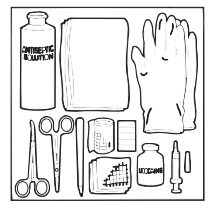


Figure 17: The following equipment is needed for the removal:
— an examining table for the patient to lie on.
— sterile surgical drapes, sterile gloves (free of talc), antiseptic solution.
— local anesthetic, needles, and syringe.
— #11 scalpel, forceps (straight and curved mosquito).
— skin closure, sterile gauze, and compresses.

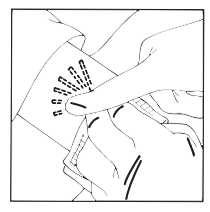


Figure 18: Palpate the capsules to make sure that all six capsules have been located, marking their position with a sterile marker. If all six capsules cannot be located by palpation, they may be localized by ultrasound (7 MHz), X-ray, or compression mammography.

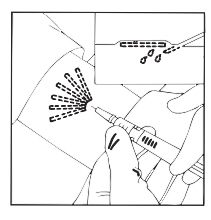


Figure 19: Once all six capsules are located, apply a small amount of local anesthetic *under* the capsule ends nearest the original incision site. This will serve to raise the ends of the capsules. Anesthetic injected over the capsules will obscure them and make removal more difficult. Additional small amounts of the anesthetic can be used for the removal of each of the capsules, if required.

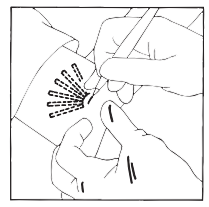


Figure 20: Make a 4-mm incision with the scalpel close to the ends of the capsules. Do not make a large incision.

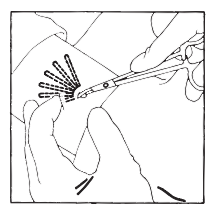


Figure 21: Push each capsule gently towards the incision with the fingers. When the tip is visible or near to the incision, grasp it with a mosquito forceps.

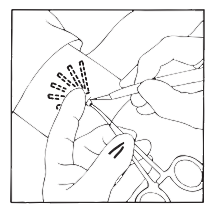
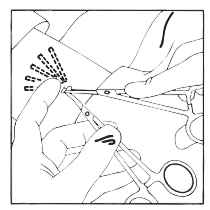
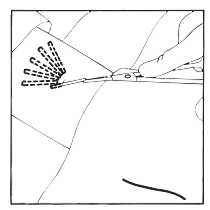


Figure 22: Use the scalpel, forceps, or gauze to very gently open the tissue sheath that has formed around the capsule.

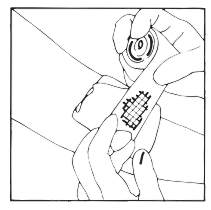


Figures 23 and 24: Remove the capsule from the incision with the second forceps.



Figures 25 and 26: After the procedure is completed, the incision is closed and bandaged as with insertion. The upper arm should be kept dry for a few days.

Following removal, fertility rates return to levels comparable to those seen in the general population of women using no method of contraception, and a pregnancy may occur at any time. If the patient wishes to continue using the method, a new set of NORPLANT SYSTEM (levenonorgestrel implants) capsules can be inserted through the same incision in the same or opposite direction.



HINTS

Insertion

— Counseling of the patient on the benefits and side effects of the method prior to insertion will greatly increase patient satisfaction.
— Correct subdermal placement of the capsules will facilitate removal.
— Before insertion, apply the anesthetic just beneath the skin so as to raise the dermis above the underlying tissue.
— Never force the trocar.
— To ensure subdermal placement, the trocar with bevel up should be supported by the index finger and should visibly raise the skin at all times during insertion.
— To avoid damaging the previous implanted capsule, stabilize the capsule with your forefinger and middle finger and advance the trocar alongside the finger tips at an angle of 15 degrees.
— After insertion, make a drawing for the patient's file showing the location of the 6 capsules and describe any variations in placement. This will greatly aid removal.

REMOVAL

— Alternate removal techniques have been developed.
— The removal of the implants will usually take more time and may be more difficult and/or more painful than the insertion. Capsules are sometimes nicked, cut, or broken during removal, or may be difficult to locate.
— Before initiating removal, all capsules should be located by palpation. If all six capsules cannot be located by palpation, they may be localized by ultrasound (7 MHz), X-ray, or compression mammography.
— Before removal, apply the anesthetic *under* the capsule ends nearest the original incision site.
— If the removal of some of the capsules proves difficult, interrupt the procedure and have the patient return for another visit. The remaining capsule(s) will be easier to remove after the area is healed.
— It may be appropriate to seek consultation or provide referral for patients in whom initial attempts at capsule removal prove difficult.

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