

Population Council  
"Norplant® II" Levonorgestrel Implants (Jadelle®)

NDA 20-544  
Supplement 003

JADELLE®

levonorgestrel implants

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

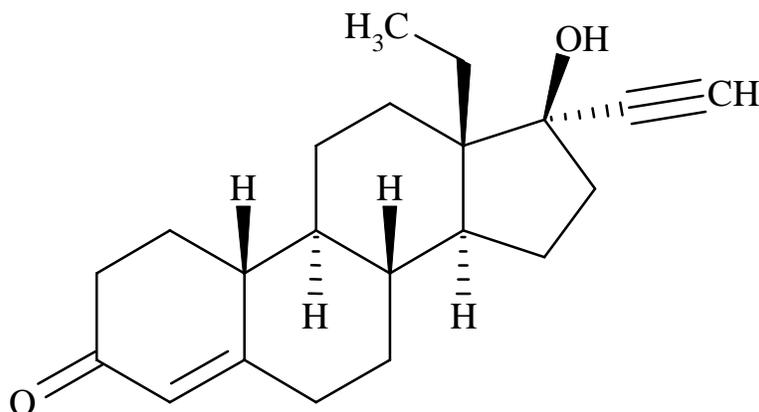
## PRESCRIBING INFORMATION

### DESCRIPTION

Jadelle® is a set of two flexible cylindrical implants, consisting of a dimethylsiloxane/methylvinylsiloxane copolymer core enclosed in thin-walled silicone tubing. Each implant contains 75 mg of the progestin levonorgestrel. The implants are sealed with polydimethylsiloxane adhesive and sterilized. Each implant is approximately 2.5 mm in diameter and 43 mm in length. The implants are inserted in a superficial plane beneath the skin of the upper arm.

The calculated mean daily *in vivo* release rate of levonorgestrel provided by the implants is about 100 µg/day at month 1 followed by a decline to about 40 µg/day at 12 months and to about 30 µg/day at 24 months with a stabilization thereafter at about 30 µg/day.

Jadelle® implants are a progestin-only product and do not contain estrogen. The active ingredient in the implants is levonorgestrel, (-)-13-ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one. It has a molecular weight of 312.45 and the following structural formula:



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## CLINICAL PHARMACOLOGY

Levonorgestrel is a totally synthetic and biologically active progestin that exhibits no significant estrogenic activity and is highly progestational. The absolute configuration conforms to that of D-natural steroids.

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.

## Pharmacokinetics

### *Absorption*

Levonorgestrel is delivered directly into interstitial fluids from the subdermal implants. However, the bioavailability of levonorgestrel after insertion of Jadelle® implants compared with intravenous administration is not known. After placement of Jadelle® implants, maximum levonorgestrel concentrations are reached in about 2 to 3 days, with the mean  $\pm$  standard deviation being  $772 \pm 414$  pg/mL at 2 days. After the initial phase, mean levonorgestrel concentrations slowly decline to approximately  $435 \pm 172$  pg/mL at 1 month,  $357 \pm 155$  pg/mL at 6 months, and  $280 \pm 123$  pg/mL at 3 years. Concentrations at 4 and at 5 years are similar to those at 3 years.

TABLE 1  
Serum Concentrations  
During Jadelle® Use

Time After Placement (months)	Mean $\pm$ SD (pg/mL)	n
1	$435 \pm 172$	181
3	$393 \pm 191$	165
6	$357 \pm 155$	160
12	$340 \pm 159$	148
24	$312 \pm 153$	126
36	$280 \pm 123$	89
48	$271 \pm 126$	67
60	$279 \pm 123$	65

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Serum levonorgestrel concentrations were found to be inversely related to body weight. Serum levonorgestrel concentrations in women weighing more than 70 kg were approximately half as high as in women weighing less than 50 kg.

Because of the range in serum concentrations and variation in individual response, serum concentrations alone are not predictive of the risk of pregnancy in an individual woman. Serum levonorgestrel concentrations in Jadelle® users are substantially below those generally observed in users of oral contraceptives containing the progestins norgestrel or levonorgestrel.

*Distribution*

Levonorgestrel in serum is primarily protein bound. Approximately half is bound to sex hormone binding globulin (SHBG) and half to albumin. SHBG concentrations are depressed by levonorgestrel within a few days of administration, with resultant decreases in circulating levonorgestrel concentrations.

*Metabolism*

Levonorgestrel metabolic pathways have been only partially delineated. 16 $\beta$ -hydroxylation is an identified pathway of metabolism. Concentrations of metabolites in circulation soon exceed those of levonorgestrel, mostly as conjugated sulfates. Metabolic clearance rates may differ among individuals by several fold, which is believed to account in part for the wide variation observed in levonorgestrel serum concentrations among implant users.

*Excretion*

The elimination half-life of levonorgestrel is approximately 13 to 18 hours. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. After removal of the implants, levonorgestrel concentrations decrease below 100 pg/mL by 96 hours and below sensitivity of the assay by 5 days to 2 weeks.

**Special Populations**

*Race*

Studies were conducted among women of different races in Asia, North and South America, Europe and Africa. However, data on race were not collected in the clinical trials with Jadelle® implants.

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*Hepatic Insufficiency*

No formal studies have evaluated the effect of hepatic disease on the disposition of levonorgestrel. However, since levonorgestrel is metabolized in the liver, use in patients with markedly impaired liver function or liver disease is not recommended.

*Renal Insufficiency*

No formal studies have evaluated the effect of renal disease on the disposition of levonorgestrel.

*Drug-Drug Interactions*

See "Drug Interactions" under PRECAUTIONS.

**INDICATIONS AND USAGE**

Jadelle® implants are indicated for the prevention of pregnancy and are a long-term (up to 5 years) reversible method of contraception. Both implants must be removed by the end of the fifth year. New implants may be inserted at that time if continuing contraceptive protection is desired. Following removal, fertility rates return to levels comparable to those in a population of similar women using no method of contraception.

Eight (8) pregnancies occurred within 5 years of Jadelle® placement in multicenter clinical trials involving 1393 women. One of the eight pregnancies was ectopic. The following table shows pregnancy rate as Pearl Indices for each year.

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**Pearl Indices (Pregnancies per 100 woman-years) by Year for Jadelle**

	Year 1	Year 2	Year 3	Year 4	Year 5
Annual Pearl Index	0.08	0.09	0.11	0.00	0.84
95% CI	(0.00,0.43)	(0.00, 0.50)	(0.00, 0.61)	(0.00, 0.50)	(0.27, 1.95)
Cumulative Pearl Index	0.08	0.08	0.09	0.07	0.17
95% CI	(0.00, 0.43)	(0.01, 0.30)	(0.02, 0.26)	(0.01, 0.22)	(0.07, 0.34)

Jadelle is likely to be less effective in obese women. Mean serum levonorgestrel levels decrease as weight increases, and the risk of pregnancy increases as serum levonorgestrel levels decrease (see Pharmacokinetics section).

Typically, pregnancy rates with contraceptive methods are reported only for the first year of use, as shown in Table 2. The efficacy of these contraceptive methods, except for NORPLANT®, the intrauterine device (IUD), and sterilization, depends in part on the reliability of use. The efficacy of Jadelle® implants 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	Typical Use	Perfect Use
Chance	85	85
Spermicides	26	6
Periodic Abstinence	25	
Calendar		9
Ovulation		3
Symptothermal		2
Post-ovulation		1
Cap		
Parous women	40	26
Nulliparous women	20	9
Sponge		
Parous women	40	20
Nulliparous women	20	9
Diaphragm	20	6
Withdrawal	19	4
Condom		
Female (Reality)	21	5
Male	14	3
Pill	5	
Progestin only		0.5
Combined		0.1
IUD		
Progesterone	2.0	1.5
Copper T 380A	0.8	0.6
LNg 20	0.1	0.1
Depo-Provera	0.3	0.3
NORPLANT® and NORPLANT® 2	0.05	0.05
Female sterilization	0.5	0.5
Male sterilization	0.15	0.1

From Hatcher RA et al., *Contraceptive Technology*, 17<sup>th</sup> Revised Edition. New York, NY: Irvington Publishers, 1998. Table 9-2

The gross cumulative rates of discontinuation and continuation in clinical trials of Jadelle® are summarized in Table 3.

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TABLE 3  
Discontinuation and Continuation Rates  
(Cumulative Rates per 100 Users, n=1393)

Reasons for discontinuing	Year		
	1	3	5
Pregnancy	0.1±0.1	0.3±0.2	1.1±0.4
Menstrual	4.5±0.6	14.1±1.0	19.3±1.2
Medical	4.7±0.6	14.7±1.0	23.1±1.3
Used other method	0.2±0.1	0.9±0.3	3.7±0.7
Plan pregnancy	1.1±0.3	9.7±0.9	18.6±0.3
Personal (other)	1.6±0.3	7.2±0.8	12.5±0.1
Continuation	88.3±0.9	60.6±1.3	41.5±1.3

**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 components of the implants.

**WARNINGS**

**A. WARNINGS BASED ON EXPERIENCE WITH LEVONORGESTREL-CONTAINING IMPLANTS**

*1. Insertion and Removal Complications*

A surgical incision is required to insert Jadelle® implants. Complications related to insertion such as pain, edema and bruising may occur. Reports of infection (including cellulitis and abscess formation), blistering, ulcerations, sloughing, excessive scarring, phlebitis and hyperpigmentation have been reported at the insertion site for the six NORPLANT® implants and may occur with Jadelle® implants. Arm pain, numbness and tingling may occur following the insertion and removal procedures. With NORPLANT® implants, there have been reports of nerve injury, most commonly associated with deep placement and removal. Expulsion of 1 or more NORPLANT® implants has been reported, more

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frequently when implant placement was shallow or too close to the incision or when infection was present. There have been reports of displacement (i.e. movement) of NORPLANT® implants, most of which involved minor changes in the positioning of the implants, but some have involved significant displacement of up to several inches. Some of these reported displacements 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 in locating implants. Additional incisions and/or office visits may be required. See also "PRECAUTIONS" and "ADVERSE REACTIONS".

*2. Ectopic Pregnancies*

Physicians should be alert to the possibility of an ectopic pregnancy among women using Jadelle® implants who become pregnant or complain of lower abdominal pain. Ectopic pregnancies occurred with Jadelle® implants at a rate less than 0.5 per 1,000 woman-years. This rate is significantly below the rate for US women of reproductive age who do not use contraception, which is 2.7 to 3.0 per 1,000 woman-years. However, any pregnancy that does occur with Jadelle® use is more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

*3. Interaction with Anti-Epileptic and other Drugs*

Jadelle® implants are not recommended for women with epilepsy who use phenytoin, phenobarbital, carbamazepine or oxcarbazepine because Jadelle® implants are likely to be less effective for these women. Although the large clinical trials of NORPLANT® and Jadelle® implants excluded women with epilepsy, there are published studies showing decreased levonorgestrel concentrations in women using these antiepileptic drugs along with levonorgestrel-containing contraceptives.

Women using rifampin have become pregnant during clinical trials of NORPLANT® implants. Rifampin decreases serum levels of progestins. (See also DRUG INTERACTIONS.)

*4. Menstrual changes*

Most women using Jadelle® implants can expect some variation in menstrual bleeding patterns. Irregular menstrual bleeding, prolonged episodes of bleeding and spotting, heavy

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bleeding, intermenstrual spotting and amenorrhea occur in some women. Altered bleeding patterns associated with Jadelle® implants could mask symptoms of cervical or endometrial cancer. See also ADVERSE REACTIONS, *Menstrual Complaints*.

Because some levonorgestrel implant users have 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 implants must be removed.

*5. Weight Gain*

In clinical trials of Jadelle® use, the average weight change over 5 years of use was a gain of about 9 pounds. Approximately 20% of women gained at least 10 pounds in the first year, and 50% gained at least 10 pounds by the end of the fifth year of use.

*6. Ovarian Cysts*

If follicular development occurs with Jadelle® implants, atresia of the follicle may be delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. In the majority of women, enlarged follicles (cysts) will spontaneously disappear and should not require surgery. Rarely, they may twist or rupture, sometimes causing abdominal pain, and surgical intervention may be required.

*7. Foreign-Body Carcinogenesis*

Rarely, cancers have occurred at the site of foreign-body intrusions or old scars. None have been reported in NORPLANT® users or in clinical trials with Jadelle® implants. 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 implants, the risk to users of Jadelle® implants is judged to be minimal.

*8. Thrombosis*

There have been reports of superficial phlebitis in clinical trials of Jadelle® implant and postmarketing reports of thrombophlebitis and superficial phlebitis coincident with NORPLANT® implant use, more commonly in the arm of insertion. Some of these cases have been associated with trauma to that arm. There have also been reports of other thromboembolic disorders and cardiovascular problems (eg, stroke, myocardial infarction,

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pulmonary embolism, and deep-vein thrombosis) coincident with NORPLANT® implant use. See also WARNINGS BASED ON EXPERIENCE WITH COMBINATION (PROGESTIN PLUS ESTROGEN) ORAL CONTRACEPTIVES.

*9. Use Before or During Early Pregnancy*

There were no reports of congenital anomalies for the pregnancies that occurred during use of Jadelle® implants in clinical trials. However, in postmarketing use of the NORPLANT® implants, there have been reports of congenital anomalies in the offspring of women who were using NORPLANT® implants inadvertently during early pregnancy. A cause and effect relationship has not been established. See also WARNINGS BASED ON EXPERIENCE WITH COMBINATION (PROGESTIN PLUS ESTROGEN) ORAL CONTRACEPTIVES.

*10. 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. It has been reported in NORPLANT® implant users; however, a causal relationship is unclear. A cardinal sign of idiopathic intracranial hypertension is papilledema; early symptoms may include headache associated with a change in the frequency, pattern, severity, or persistence. Of particular importance are visual disturbances and headaches that are unremitting in nature. 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. Jadelle® implants should be removed from patients experiencing this disorder.

**B. WARNINGS BASED ON EXPERIENCE WITH COMBINATION (PROGESTIN PLUS ESTROGEN) ORAL CONTRACEPTIVES**

*1. Thromboembolic Disorders and Other Vascular Problems*

**Thromboembolic and Thrombotic Disease:** 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.

**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),

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hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers for both types of strokes, and smoking interacted to increase the risk for hemorrhagic strokes.

**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.

If thromboembolic disorders or cardiovascular problems occur in levonorgestrel implant users, the implants should be removed. Removal should also be considered in women who will be subjected to prolonged immobilization because of surgery or other illnesses. See also **WARNINGS BASED ON EXPERIENCE WITH LEVONORGESTREL-CONTAINING IMPLANTS**.

*2. 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 heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years old who smoke. 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 Jadelle® implants. However, women who use Jadelle® implants should be advised not to smoke.

*3. 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. Physicians should be

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aware of the possibility of elevated blood pressure in individual patients using Jadelle® implants.

*4. Use Before or During Early Pregnancy*

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives before pregnancy. Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. There is no evidence suggesting that the risk associated with levonorgestrel-containing implants is different from that of oral contraceptives. See also WARNINGS BASED ON EXPERIENCE WITH LEVONORGESTREL-CONTAINING IMPLANTS.

*5. Carcinoma*

Numerous epidemiologic studies have been performed to determine the incidence of breast, endometrial, ovarian, and cervical cancer in women using combination oral contraceptives. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However this excess risk appears to decrease over time after discontinuation of combination oral contraceptives, and by 10 years after cessation the increased risk disappears. The risk does not appear to increase with duration of use, and no consistent relationships have been found with dose or type of steroid. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history or her family breast cancer history. Some studies have found a small increase in risk for women who first use combination oral contraceptives before age 20. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in nonusers. Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormone-sensitive tumor.

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

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*6. Hepatic Tumors*

In some studies, hepatic adenomas have been associated with the use of combination oral contraceptives: the estimated incidence is about 3 occurrences per 100,000 users per year, and the risk 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.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the US, and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

*7. Ocular Lesions*

There have been reports of retinal thrombosis associated with the use of oral contraceptives. Although it is believed that this adverse reaction is related to the estrogen component of oral contraceptives, Jadelle® implants 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.

*8. Gallbladder Disease*

Some 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 increased 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 doses of estrogens and progestins.

**PRECAUTIONS**

**General**

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

*1. Physical Examination and Follow-Up*

A complete medical history and physical examination should be undertaken before the implantation or reimplantation of Jadelle implants and at least annually during their use.

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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*

To ensure that the woman is not pregnant at the time of implant 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 abortion. However, Jadelle® implants may be inserted at any other time during the cycle, provided that the possibility of ovulation and conception prior to insertion is considered, pregnancy has been excluded, and a nonhormonal contraceptive method is used for at least 7 days following implant placement. If ovulation and conception have already occurred, pregnancy may be established in the month of insertion.

It is strongly advised that all health-care professionals who insert and remove Jadelle® implants be instructed in the procedures before they attempt them. A proper insertion just under the skin will facilitate removal. Proper insertion and removal should result in minimal scarring. If the implants are placed too deep, they may be more difficult to remove.

Bruising may occur at the implant site during insertion or removal. There have also been reports of arm pain, numbness, and tingling following these procedures. In some women, hyperpigmentation occurs over the implantation site but it is usually reversible following removal. During postmarketing use of NORPLANT® implants, other cutaneous reactions that have been reported include blistering, ulcerations, and sloughing. See the detailed "Instructions for Insertion and Removal" section below.

*3. Infections*

Infection at the implant site, including cellulitis, has been uncommon. During clinical trials with the Jadelle® implants, infection at the insertion site occurred in 0.4% of women. Attention to aseptic technique and proper insertion and removal of Jadelle® implants reduces the possibility of infection. If infection occurs, suitable treatment should be instituted. If infection persists, the implants should be removed.

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*4. Expulsions and Displacement*

Expulsion of one or both implants is uncommon. It is more likely to occur when placement of the implants is extremely shallow, too close to the incision, or when infection is present. An expelled implant must be replaced with a new sterile implant. If infection is present, it should be resolved before another implant is inserted. Protection against pregnancy is likely to be inadequate with fewer than two implants.

There have been reports of implant displacement (i.e., movement) with NORPLANT® implants, most of which involve minor changes in the position of the implants. However, infrequent reports of significant displacement (up to several inches) have been received. Some instances of displacement have been associated with pain or discomfort. When implant displacement occurs, the removal technique may have to be modified, for example, by an additional incision or visit.

*5. Removal*

Women should be advised that Jadelle® implants can be removed for any reason whenever the woman wishes and must be removed by the end of five years. The removal should be done by personnel familiar with the removal techniques.

Before initiation of the removal procedure, the two Jadelle® implants should be located by palpation. If both implants cannot be located by palpation, they may be localized by ultrasound (7 MHz), X-ray, or compression mammography. If both implants cannot be removed at the first attempt, removal should be attempted later when the site has healed.

Upon removal, Jadelle® implants should be disposed of in accordance with the Centers for Disease Control and Prevention guidelines for the handling of biohazardous waste.

*6. Lipid and Carbohydrate Metabolism*

Serum lipoprotein levels were altered in three clinical studies involving 544 women using Jadelle implants. Although these changes were statistically significant, all mean values remained within the normal ranges. The long-term clinical effects of these changes have not been determined.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use Jadelle® implants.

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Changes in carbohydrate tolerance and insulin sensitivity following oral glucose loads have been reported in some studies among users of NORPLANT® implants and of Jadelle® implants. These changes include modest elevations of serum insulin concentrations as well as increases in serum glucose levels. These changes were not associated with development of clinical or laboratory evidence of diabetes mellitus. While the clinical significance of these findings is unknown, diabetic patients should be carefully observed while using Jadelle® implants.

*7. Liver Function*

If jaundice develops in any woman using Jadelle® implants, consideration should be given to removing the implants. Steroid hormones may be poorly metabolized in patients with impaired liver function.

*8. 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 that cause or might be aggravated by fluid retention.

*9. Emotional Disorders*

Consideration should be given to removing Jadelle® implants in women who become significantly depressed, because depression may be drug related. Women with a history of depression should be carefully observed, and removal considered if depression recurs to a serious degree.

*10. Contact Lenses*

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

*11. 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® implant users; however, the rate of reporting is significantly lower than the expected incidences 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

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autoimmune diseases among NORPLANT® implant users is coincidental, health-care providers should be alert to the earliest manifestations of autoimmune disease in users of Jadelle® implants.

*12. Drug Interactions*

Jadelle® implants are not recommended for women who require chronic use of phenytoin, phenobarbital, carbamazepine or oxcarbazepine because Jadelle® is likely to be less effective for these women. Although the large clinical trials of NORPLANT® and of Jadelle® implants excluded women with epilepsy, there are published studies showing decreased levonorgestrel concentrations in women taking these antiepileptic drugs along with levonorgestrel-containing contraceptives. These drugs may increase the metabolism of levonorgestrel through induction of microsomal liver enzymes. For women receiving long-term therapy with hepatic enzyme inducers, a different method of contraception should be considered. Women on short-term therapy with hepatic enzyme inducers should consider using a back-up method of contraception (such as condoms or spermicides) for the duration of therapy.

Rifampicin is known to decrease the effectiveness of combination oral contraceptives; its effect on levonorgestrel concentrations has not been established. Data from clinical trials of NORPLANT® implants, however, indicate low serum concentrations and subsequent pregnancy in one woman using rifampicin.

Herbal products containing St. John's Wort (*hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and may reduce the effectiveness of contraceptive steroids.

*13. Laboratory Test Interactions*

Certain endocrine tests may be affected by Jadelle® use:

1. SHBG concentrations are decreased.
2. Thyroxine concentrations may be slightly decreased and triiodothyronine uptake increased.

*14. Carcinogenesis*

See "Warnings" section.

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*15. Pregnancy*

See "Warnings" section.

*16. Nursing Mothers*

Hormonal contraceptives are not considered the contraceptives of first choice for breast-feeding women. Levonorgestrel has been identified in breast milk. When breast-feeding mothers used NORPLANT® implants beginning during the 5<sup>th</sup> to 7<sup>th</sup> week postpartum, no significant effects were observed on the growth or development of their infants who were followed up to 12 months of age.

*17. Pediatric Use*

Safety and efficacy of Jadelle® implants have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

*18. Geriatric Use*

This product has not been studied in women over 65 years of age and is not indicated in this population.

*19. Information for the Patient*

See "Patient Labeling."

Two copies of the Patient Labeling are included. 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 Jadelle® implants compared to 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**

Jadelle® implants were used by 1393 subjects during clinical trials. The adverse medical events reported by subjects during these trials are given below.

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*Menstrual Complaints*

Various menstrual complaints reported by more than 1.0% of subjects during the first year of Jadelle® use are listed below.

Menstrual Condition	Year 1	Years 1-5
	%	%
Menorrhagia (increased duration)	13.4	25.9
Amenorrhea	9.8	13.9
Menometrorrhagia	9.6	20.5
Oligomenorrhea	9.5	12.8
Long spotting duration or length unclear	8.9	15.1
Dysmenorrhea	3.5a	8.0a
Polymenorrhea	2.7	5.0
Premenstrual syndrome	1.8a	5.8a
Menorrhagia (increased amount)	1.6	4.5
Hypomenorrhea	1.5	2.9

a Excludes women with condition reported at admission, prior to initiation of Jadelle® implants.

Dysmenorrhea and premenstrual syndrome were reported at admission into the studies by 7.8% and 4.9% of the subjects, respectively.

*Insertion and Removal Difficulties*

Removal complications or difficulties, including damage to the implants, were reported in 7.5% of the more than 1,100 Jadelle® removals. Complications of insertion or removal included deep placement, multiple or long incisions, bruising, displacement, pain, prolonged removal, incomplete removal requiring an additional visit or visits, broken implants, and fibrous pericapsular tissue. See also WARNINGS BASED ON EXPERIENCE WITH LEVONORGESTREL-CONTAINING IMPLANTS.

*Other Adverse Events*

Adverse reactions that were reported by 10% or more of the subjects during 5 years of Jadelle® use in clinical trials are listed below.

- |                                       |                                   |
|---------------------------------------|-----------------------------------|
| Application site reaction, pain, etc. | Nausea                            |
| Dizziness                             | Pelvic pain                       |
| Headache                              | Urinary tract symptoms, infection |
| Leukorrhea                            | Vaginitis <sup>a</sup>            |
| Mastalgia                             | Weight increase                   |

a) includes also genital pruritus, infections and vaginal problems not elsewhere classified.

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Adverse reactions that were reported by 1.0-9.9% of the subjects during 5 years of Jadelle® use in clinical trials are listed below.

Abdominal pain	Flu-like symptoms
Abnormal vision	Folliculitis
Acne	Hypertension
Alopecia	Hypertrichosis
Anorexia	Hypoesthesia
Anxiety	Insomnia
Appetite increase	Injury
Asthenia	Libido decreased
Asthma	Migraine
Back Pain	Nervousness
Benign breast neoplasm	Nonpuerperal lactation
Breast fibroadenosis	Ovarian cyst, follicle enlargement
Bronchitis	Pain
Cervical lesion	Palpitation
Cervical cytology, grade 3 or 4	Perineal pain
Cervicitis	Pruritus
Constipation, flatulence, or dyspepsia	Purpura
Chest pain	Rash
Contact dermatitis	Somnolence
Depression	Syncope
Dermatitis	Upper respiratory infection <sup>a</sup>
Dyspnea	Uterine enlargement
Dyspareunia	Varicose veins
Emotional liability	Vomiting
Fatigue	Vulvar disorder <sup>b</sup>
	Weight decrease

a) includes rhinitis, pharyngitis and sinusitis as well as undefined upper respiratory infection

b) includes genital ulceration, herpes simplex and papilloma virus and other vulvar disorders

## **OVERDOSAGE**

All Jadelle® implants should be removed before inserting a new set of implants or initiating use of any other hormonal contraceptive. If more than 2 Jadelle® implants are *in situ*, or if any Jadelle® implants are *in situ* while another hormonal contraceptive is used, uterine bleeding patterns may be altered.

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## **DOSAGE AND ADMINISTRATION**

Jadelle® implants are a set of two flexible cylindrical implants, each containing 75 mg of the progestin levonorgestrel. The total administered (implanted) dose is 150 mg. Insertion of the two implants should be performed during the first 7 days following the onset of menses by a health-care professional familiar with the levonorgestrel implant insertion technique. It is strongly recommended that all health-care providers receive instruction in the proper insertion and removal procedures. Insertion is subdermal in the midportion of the inner surface of the upper arm about 8 to 10 cm above the medial epicondyle. The two implants should be placed in a “V” shape about 30 degrees apart. Proper insertion will facilitate removal. (See “Instructions for Insertion and Removal.”)

## **HOW SUPPLIED**

Jadelle® implants are supplied in a sterile package containing a set of two levonorgestrel-containing implants.

**Store at room temperature, 15-30° C (59-86°F)**

References available upon request.

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## **INSTRUCTIONS FOR INSERTION AND REMOVAL**

Jadelle® implants are a set of two cylindrical levonorgestrel-releasing implants that are inserted subdermally in the medial aspect of the upper arm.

Jadelle® implants provide up to 5 years of effective contraceptive protection.

The basis for successful use and subsequent removal of Jadelle® implants is a correct and carefully performed subdermal insertion of the two implants. It is recommended that health-care professionals performing insertions or removals of Jadelle® implants be instructed and supervised in proper techniques prior to attempting these procedures independently. During insertion, special attention should be given to the following:

- aseptic technique
- correct subdermal placement of the implants
- careful technique to minimize tissue trauma.

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

## **INSERTION PROCEDURE**

Insertion should be performed within 7 days from the onset of menses. However, Jadelle® implants may be inserted at any time during the cycle provided that the possibility of ovulation and conception has been considered, pregnancy has been excluded, and a nonhormonal contraceptive method is used for at least 7 days. If ovulation and conception have already occurred, pregnancy may be established in the month of insertion. It is recommended that a complete history and physical examination, including a gynecologic examination, be performed before the insertion of Jadelle® implants. Determine if the subject has any allergies to the antiseptic or anesthetic to be used or any contraindications to the use of levonorgestrel or any of the components of the implants. If none are found, the implants are inserted using the procedure outlined below.

One Jadelle® unit consists of two levonorgestrel implants in a sterile pouch. The insertion is performed under aseptic conditions using a trocar to place the implants under the skin.

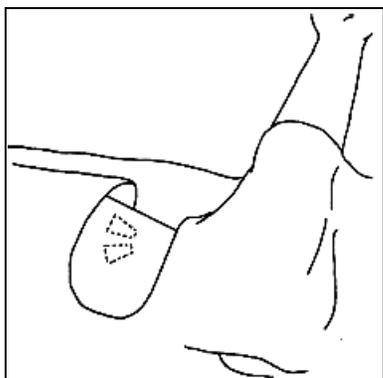


**Figure 1:** The following equipment is recommended for the insertion:

- 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.



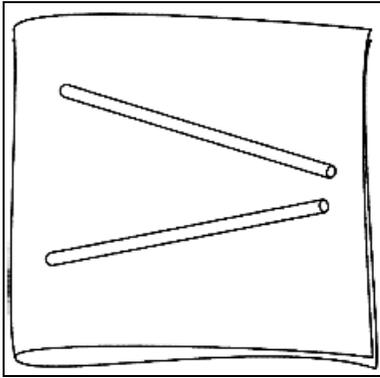
**Figure 2:** Have the patient lie on her back on the examination table with her nondominant arm flexed at the elbow and externally rotated so that her hand is lying by her head. The implants will be inserted subdermally and positioned in a "V" shape. The optimal insertion area is in the inner surface of the upper arm about 8 to 10 cm above the medial epicondyle.



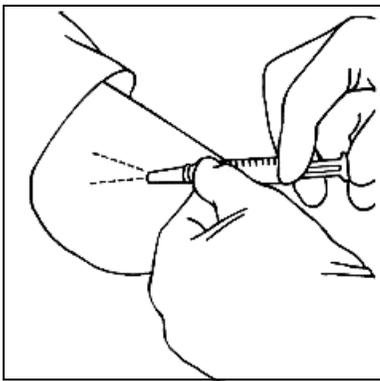
**Figure 3:** Clean the patient's upper arm with antiseptic solution and then frame the insertion area with a fenestrated drape.

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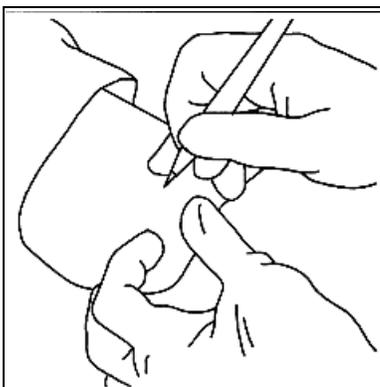
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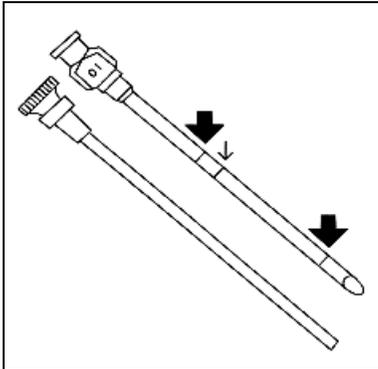
**Figure 4:** Open the Jadelle® package carefully by pulling apart the sheets of the pouch, allowing the two implants to fall onto a sterile drape.



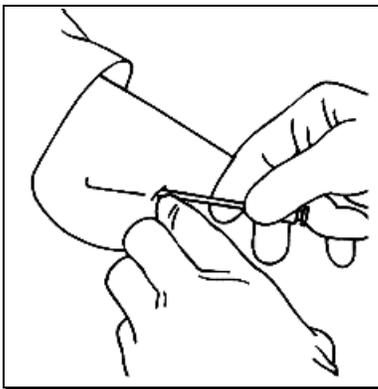
**Figure 5:** After determining the absence of known allergies to the anesthetic agent or related drugs, fill a 5-mL syringe with the local anesthetic. Since blood loss is minimal with this procedure, use of epinephrine-containing anesthetics is not considered necessary. Anesthetize the insertion area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



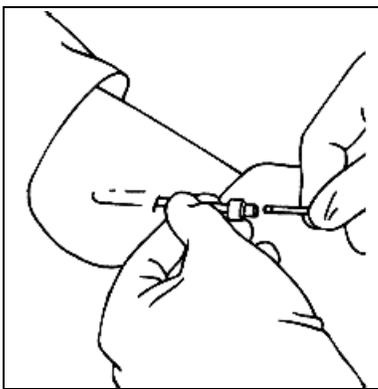
**Figure 6:** Use the scalpel to make a small incision (about 2 mm) just through the dermis of the skin. Alternatively, the trocar may be inserted directly through the skin without making an incision with the scalpel. The bevel of the trocar should always face up during the insertion.



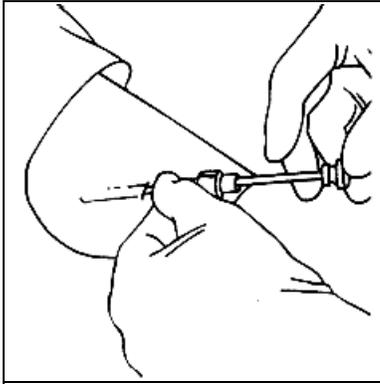
**Figure 7:** The trocar has three marks on it. The mark closest to the hub indicates how far the trocar should be introduced under the skin to place the Jadelle® implants. The middle mark (indicated by the small arrow) is **not** used with Jadelle® insertions and should be ignored. The mark closest to the tip indicates how much of the trocar should remain under the skin following placement of the first implant.



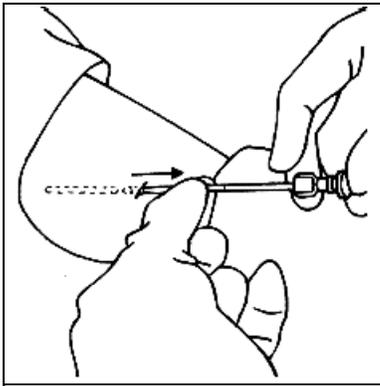
**Figure 8:** Insert the tip of the trocar beneath the skin at a shallow angle. Throughout the insertion procedure, the trocar should be oriented with the bevel up. It is important to keep the trocar subdermal by tenting the skin with the trocar, as failure to do so may result in deep placement of the implants and could make removal more difficult. Advance the trocar gently under the skin to the mark *nearest* the hub of the trocar; be careful to use the appropriate mark. Do not force the trocar, and if resistance is encountered, try another direction.



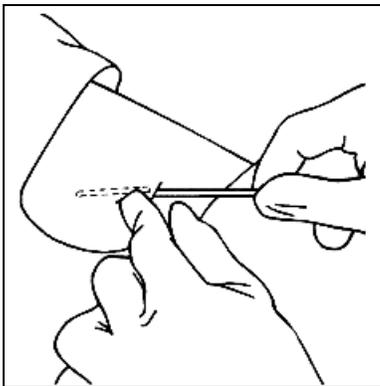
**Figure 9:** When the trocar has been inserted the appropriate distance, remove the obturator and load the first implant into the trocar using the thumb and forefinger.



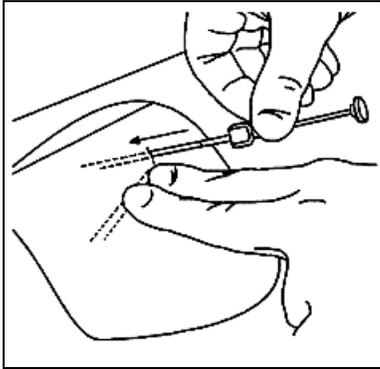
**Figure 10:** Gently advance the implant with the obturator towards the tip of the trocar until you feel resistance. Never force the obturator.



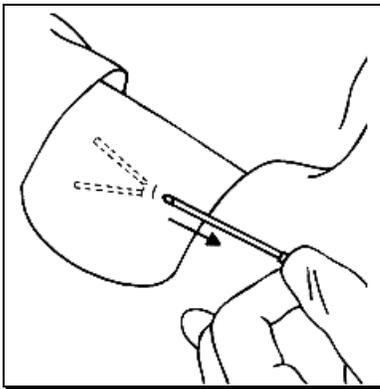
**Figure 11:** Then holding the obturator stationary, *withdraw the trocar* to the mark closest to the trocar tip. It is important to keep the obturator stationary and not to push the implant into the tissue. Do not completely remove the trocar until both implants have been placed. The trocar is withdrawn only to the mark closest to its tip.



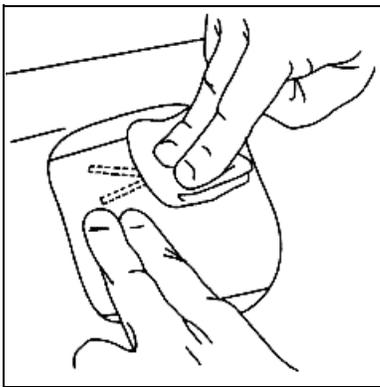
**Figure 12:** The implant should have been released under the skin when the mark closest to the tip of the trocar is visible at the insertion point. Release of the implant can be checked by palpation.



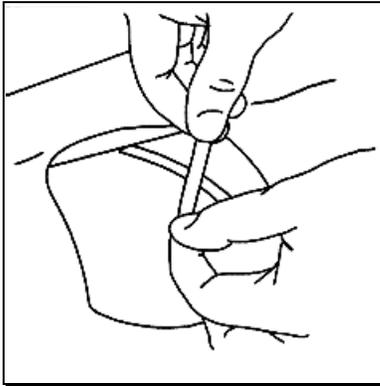
**Figure 13a:** To place the second implant, align the trocar so that the second implant will be positioned at about a 30-degree angle relative to the first. Fix the position of the previous implant with the forefinger and middle finger of the free hand, and advance the trocar along the tips of the fingers. This will ensure a suitable distance of about 30 degrees between implants and keep the trocar from puncturing the previously inserted implant.



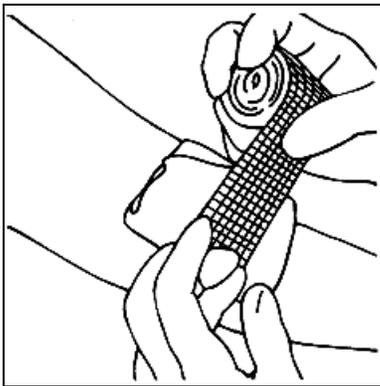
**Figure 13b:** Leave a distance of about 5 mm between the incision and the tips of the implants. This will help avoid spontaneous expulsions.



**Figure 14:** After placement of the second implant, a sterile gauze may be used to apply pressure briefly to the insertion site and ensure hemostasis. Palpate the distal ends of the implants to make sure that both 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 placement area with a dry compress, and wrap gauze snugly around the arm to ensure hemostasis.

Observe the patient for a few minutes for signs of syncope or bleeding from the insertion site 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 skin closure as soon as the insertion area has healed, ie, typically in 3 days.

### **REMOVAL PROCEDURE**

Described below is a removal procedure which was used during the clinical trials for NORPLANT® implants and for Jadelle® 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 advantage over another.

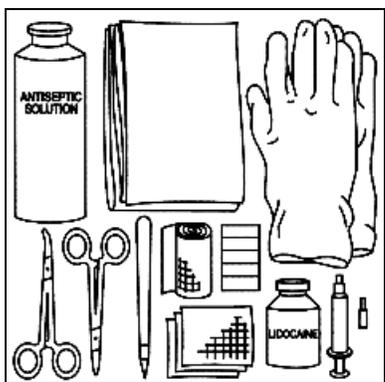
It is recommended that removals be scheduled so that preparations for carrying out the procedure can be facilitated.

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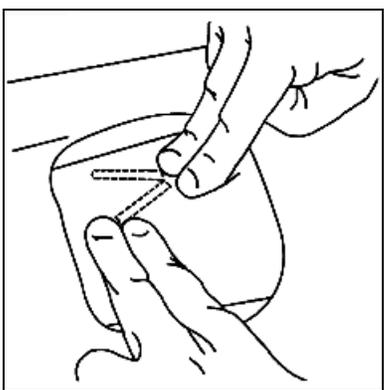
Removal of the implants should be performed very gently and will take more time than insertion. Implants are sometimes nicked, cut, or broken during removal. The overall incidence of removal difficulties in the clinical trials, including damage to the implants, was 7.5%. If removal of the implant(s) proves difficult, close the incision and bandage the wound, and have the patient return for another visit. The remaining implant(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 implant removal prove difficult. A nonhormonal method of contraception should be used until both implants are completely removed.

The position of the patient and the need for aseptic technique are the same as for insertion.



**Figure 17:** The following equipment is needed for the removal:

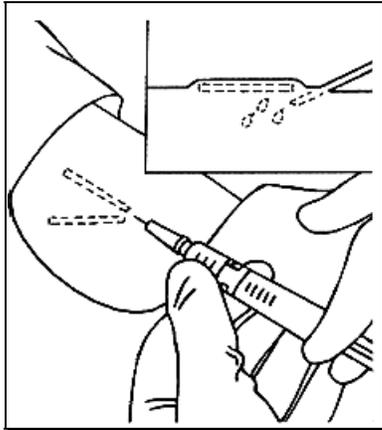
- an examining table for the patient to lie on.
- sterile surgical drapes, sterile gloves (free of talc), antiseptic solution.
- local anesthetic, needles, and syringe.
- #11 scalpel, forceps (straight and curved mosquito).
- skin closure, sterile gauze, and compresses.



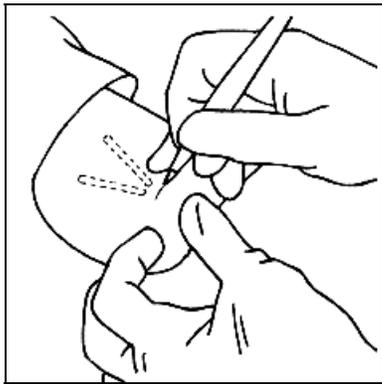
**Figure 18:** Palpate the area to locate both implants. If the implants cannot be palpated, they may be located by ultrasound (7 MHz) or X-ray (soft tissue). Once both implants are located, clean the patient's upper arm with antiseptic solution and then frame the area with a fenestrated drape. You may mark the position of the Jadelle® implants with a sterile marker.

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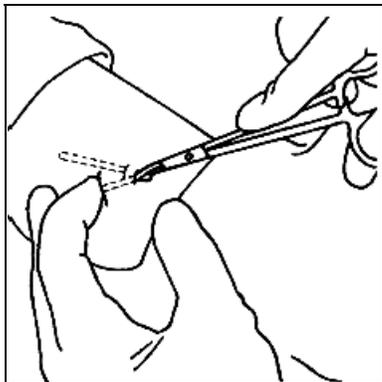
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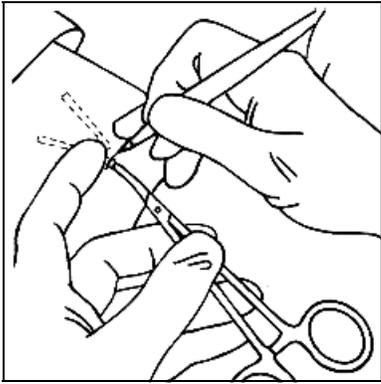
**Figure 19:** Once both implants are located, apply a small amount of local anesthetic at the skin and *under* the ends of the implants nearest the original incision site. This will serve to raise the ends of the implants. Anesthetic injected over the implants will obscure them and make removal more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



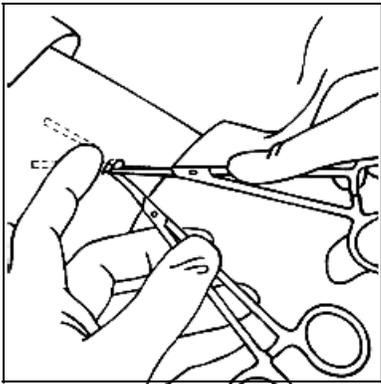
**Figure 20:** Make a 4-mm incision with the scalpel close to the proximal ends of the implants (below the bottom of the "V"). Do not make a large incision.



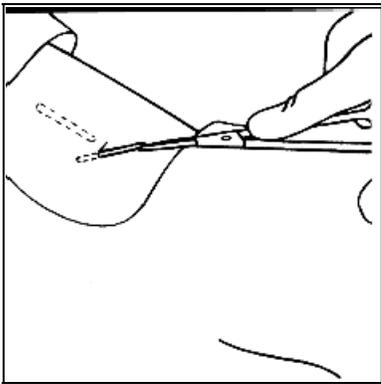
**Figure 21:** Push each implant gently towards the incision with the fingers. When the tip is visible or near to the incision, grasp it with a mosquito forceps.



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

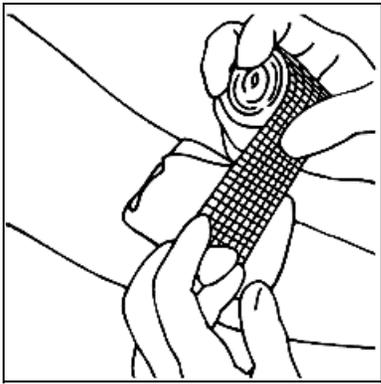
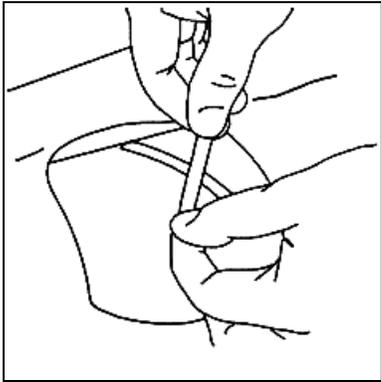


**Figures 23 and 24:** Grasp the proximal end of the implant with the second forceps and gently remove it. Repeat the procedure for the second implant.



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**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, the contraceptive effects reverse quickly and a woman can become pregnant at a rate similar to women who have not used the method. If the patient wishes to continue using the method, a new set of Jadelle® implants can be inserted through the same incision in the same or opposite direction.

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## **HINTS**

### **Insertion**

- Counselling of the patient on the benefits and side effects of the method and the insertion and removal procedures before insertion will greatly increase patient satisfaction.
- Correct subdermal placement of the implants 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 should be held with the bevel up and should be supported by the index finger to raise the skin visibly at all times during insertion.
- To avoid damaging the first implant, stabilize it with your forefinger and middle finger and then advance the trocar alongside the fingertips at an angle of about 30 degrees.
- After insertion, make a drawing for the patient's file showing the location of the 2 implants and describe any variations in placement. This will greatly aid removal.
- Jadelle® packaging contains stick-on labels identifying the lot number for both the provider's and the patient's records. Both the provider and the patient should retain these stick-on labels in case a need arises to determine which lot is being used by the woman. The stick-on label for the patient may be affixed to her copy of the patient information materials. Please also be sure to inform the patient on the patient package insert that she is to retain the stick-on label identifying the lot number in case of future problems with the lot.

### **Removal**

- The removal of the implants will take more time than the insertion.
- Before initiating removal, the two implants should be located by palpation. If both implants cannot be palpated, they may be located by ultrasound (7 MHz) or X-ray (soft tissue).
- Before removal, apply the anesthetic *under* the ends of the implants nearest the original insertion site.
- If removal of the implants proves difficult, interrupt the procedure, close the incision and bandage the wound, and have the patient return for another visit. The remaining implant(s) will be easier to remove after the area is healed. It may be appropriate to seek

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consultation or provide referral for patients in whom initial attempts at implant removal prove difficult.

*References provided on request.*

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## JADELLE® IMPLANTS

### PATIENT LABELING

**This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) or other sexually transmitted diseases.**

### WHAT YOU SHOULD KNOW ABOUT JADELLE® IMPLANTS BEFORE YOU DECIDE TO USE THEM

You need to read and understand this brochure *before* you decide to use Jadelle® implants. It tells you about the risks and benefits of Jadelle® implants. Discuss it with your health care provider. Ask him/her to explain anything you do not understand.

There is a more technical brochure about Jadelle® implants that was written for health care providers. If you would like to read that brochure too, ask your health care provider for a copy. You may need help to understand some of the information.

*Before* you decide to use Jadelle® implants or any other birth control method, compare it to other birth control methods. If you want to learn more about other methods, ask your health care provider. Another method may be better for you than Jadelle® implants.

Jadelle® implants differ from most other methods of birth control. Each of the two small, flexible silicone Jadelle implants contains a hormone. These implants must be inserted in your arm by a minor surgical procedure performed by a health care provider in the office. You should know that some health care providers have more experience than others in inserting Jadelle® implants. Be sure to ask your health care provider whether he/she has received instruction in how to insert Jadelle® implants and remove them.

You can decide to have Jadelle® implants removed at any time. You should know that removing Jadelle® implants may be more difficult than inserting them. It may take longer and involve more pain. It may leave scars. This risk does not exist with most other birth control methods.

Some women should not use Jadelle® implants. To find out whether you are one of these women, talk to health care provider and read this brochure carefully, especially the

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sections entitled “WHO SHOULD NOT USE JADELLE® IMPLANTS” and “OTHER CONSIDERATIONS BEFORE CHOOSING JADELLE® IMPLANTS.”

Some women who use Jadelle® implants will have side effects. You should know the danger signs described in this brochure.

## **INTRODUCTION**

Each woman who considers using Jadelle® implants should understand the benefits and risks of this form of birth control as compared with other contraceptive methods. This leaflet will give you much of the information you will need to make a decision on whether to use Jadelle®, but it is not a replacement for a careful discussion with your health-care provider. You should discuss the information provided in this leaflet with him or her, both when choosing whether to use Jadelle® and during revisits. You should also follow your health-care provider's advice with regard to regular checkups while using Jadelle® implants.

Jadelle® implants are two thin flexible implants that are inserted just under the skin on the inner surface of your upper arm in a minor, outpatient surgical procedure. The implants contain the synthetic hormone levonorgestrel (a progestin). A similar product, NORPLANT® implants, consists of six capsules that are inserted under the skin and also contain levonorgestrel as the active ingredient. Levonorgestrel is also used in many birth control pills.

Immediately after insertion of Jadelle® implants, a low continuous dose of the hormone is released into your body. Pregnancy is prevented by stopping ovulation (so eggs will not be produced regularly); and thickening the cervical mucus (making it more difficult for the sperm to reach the egg). There may also be other effects that contribute to pregnancy prevention. Following removal, the effects reverse quickly and a woman can become pregnant as easily as if she had never used Jadelle® implants.

## **EFFECTIVENESS OF JADELLE® IMPLANTS**

Jadelle® implants are one of the most effective reversible birth control methods. No method is 100% effective. The average annual pregnancy rate over a 5-year period for Jadelle® implants is less than 1%. That is less than one pregnancy for every 100 women during each year of use. Jadelle may be less effective in obese women. Over the five year period, the

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cumulative or total pregnancy rate is about 1%. In comparison, pregnancy rates during the first year of using other birth control methods are as follows:

Typical Failure Rates (%) During the First Year of Use of a Contraceptive Method	
Method	Typical Use
NORPLANT® SYSTEM	0.1
Male sterilization	0.15
Female sterilization	0.5
Depo-Provera® (injectable progestogen)	0.3
Oral contraceptives	5.0
IUD	
Progesterone	2.0
Copper T 380A	0.8
Condom (male) without spermicide	14
(female) without spermicide	21
Cervical cap	
Nulliparous women	20
Parous women	40
Sponge	
Nulliparous	20
Parous	40
Diaphragm with spermicidal cream or jelly	20
Spermicides alone (foam, creams, jellies, and vaginal suppositories)	26
Periodic abstinence (all methods)	25
Withdrawal	19
No contraception (planned pregnancy)	85

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

Except for Jadelle® implants, NORPLANT® implants, sterilization, and the IUD, the effectiveness of contraceptive methods depends in part on how reliably they are used.

Jadelle® implants provide 5 years of protection against pregnancy but can be removed at any time. At the end of the fifth year, the implants will be less effective and must be removed; a new set may be inserted at the time of removal for continued protection if desired.

**WHO SHOULD NOT USE JADELLE® IMPLANTS**

Some women should not use Jadelle® implants. You should not have the implants inserted if you have:

- Any chance that you may be pregnant.

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- Liver disease, or liver tumors (either benign or cancerous)
- Unexplained bleeding between your periods.
- Breast cancer.
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes.  
Women who have had previous blood clots should consult with their health-care provider on whether to use Jadelle® implants.
- History of idiopathic intracranial hypertension.
- Hypersensitivity or allergy to levonorgestrel or silicone.
- A need for certain medications for seizures (epilepsy) or tuberculosis (TB) that could make Jadelle® less effective (see Drug Interactions)

**OTHER CONSIDERATIONS BEFORE CHOOSING JADELLE®IMPLANTS**

Tell your health-care provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram
- Diabetes
- Elevated cholesterol or triglycerides
- High blood pressure
- Gallbladder, heart, or kidney disease
- History of blood clots, heart attack, or stroke
- Clinical depression
- Migraine headaches
- History of scanty or irregular menstrual periods

Women with the above conditions may need to be checked more often by their health-care provider if they choose to use Jadelle® implants.

Be sure to inform your health-care provider if you smoke or are on any medications.

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## RISKS OF USING JADELLE® IMPLANTS

### A. Risks Based on Experience with the NORPLANT® SYSTEM and Jadelle® implants.

#### 1. *Insertion and Removal Complications*

Jadelle® implants are inserted and removed by a minor surgical procedure in your healthcare provider's office. You may experience pain, swelling, or bruising. Arm pain, itching, numbness and tingling may also occur following insertion or removal. Some women using NORPLANT® implants experienced infection, abscess, blisters, ulcers, peeling, scarring, or darkening of the skin at the insertion site, inflammation of blood vessels, or nerve injury. NORPLANT® implants occasionally come out of the skin or move to a slightly different position. These events could also occur with Jadelle® implants.

Removal may take longer than insertion and may be more difficult and/or cause more pain, especially if the implants are difficult to locate. Occasionally, additional incisions and/or office visits are required.

#### 2. *Changes In Menstrual Bleeding Patterns*

Most women experience some change in their usual monthly bleeding pattern. These menstrual changes vary from woman to woman and include:

- Prolonged bleeding or spotting (more days than you would usually experience)
- Bleeding or spotting between periods
- Heavy bleeding
- No bleeding at all for several months
- A combination of these patterns.

It cannot be predicted what kind of change you may experience. Contact your health-care provider if you experience heavy bleeding. Persistent heavy bleeding could lead to anemia. If you have regular periods and then miss a period, you should have a pregnancy test. If you are pregnant, Jadelle® implants must be removed.

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4. *Ovarian Cysts*

If follicles (eggs and their surrounding cells) in the ovary develop while using Jadelle® implants, disappearance of the follicles is sometimes delayed, and the follicles may continue to grow beyond their normal size. These enlarged follicles (cysts) may produce abdominal pain in some women, although most women would not be aware of them unless they were found by chance on a physical exam. In most women, these cysts will disappear on their own and should not require surgery. Rarely, they may twist or rupture, and surgery is required.

5. *Ectopic Pregnancies*

The risk of having an ectopic pregnancy (a pregnancy that develops outside of the uterus) during Jadelle® use is less than the risk of ectopic pregnancy in women using no birth control method; however, if you become pregnant while using Jadelle®, that pregnancy is more likely to be ectopic than if you become pregnant using no birth control. Symptoms of an ectopic pregnancy include spotting and cramping pain. Contact your health-care provider if you suspect that you may be pregnant or if you experience abdominal pain.

6. *Blood Vessel Complications*

Inflammation of blood vessels can occur with use of Jadelle® implants or NORPLANT® implants, usually in the same arm as the implants. This may occur with injury to that arm. There have also been reports of blood clots and cardiovascular problems (stroke, heart attack, blood clots in the lung, and deep-vein blood clots) with NORPLANT® implants use. (See also Risks Based on Experience With Combination Oral Contraceptives below.)

**B. Risks Based on Experience With Combination Oral Contraceptives**

Combination oral contraceptives contain a progestin such as levonorgestrel and an estrogen, another type of hormone. Some rare but serious side effects have been associated with use of combination oral contraceptives. It is unknown whether the risks associated with combination oral contraceptive-use may also be risks with a progestin-only birth control method like Jadelle® implants.

1. *Risk of Developing Blood Clots*

Blood clots and blockage of blood vessels can be serious. In particular, a clot in the veins of the legs can cause inflammation and risk of further clots. A clot that travels to the lungs can

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cause a sudden blocking of the vessel carrying blood to the lungs, resulting in respiratory collapse and even death. Rarely, clots occur in the blood vessels of the eye and may cause double vision, impaired vision, or even blindness. Any of these conditions can cause serious disability or death. Patients who develop blood clots in the legs, arms, lungs, or eyes should have the Jadelle® implants removed. In addition, patients restricted to bed rest or who have limited movement for a prolonged period due to surgery or other illness may be at increased risk of developing blood clots. Jadelle® implants may need to be removed in such patients.

2. *Risk of Heart Attacks and Strokes*

The combination pill may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain), angina pectoris, or heart attacks (blockage of blood vessels to the heart). Any of these conditions can cause death or serious disability. Smoking greatly increases the probability of suffering heart attacks and strokes. Use of combination oral contraceptives together with cigarette smoking greatly increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age who smoke. It is not known whether a similar interaction occurs with Jadelle® implants. Therefore, women who use Jadelle® implants should not smoke.

2. *High Blood Pressure*

An increase in blood pressure has been reported in combination oral contraceptive users. Elevated blood pressure occurs more often with long-term oral contraceptive exposure. A similar finding has been reported for women using NORPLANT® implants.

3. *Gallbladder Disease*

Combination pill users probably have a greater risk of gallbladder disease than nonusers. A similar finding has been reported for women using NORPLANT® implants.

4. *Liver Tumors*

In rare cases, the combination pill can cause dangerous liver tumors that can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers. However, liver cancers are very rare. It is not known whether Jadelle can cause liver tumors.

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5. *Cancer of the Reproductive Organs and Breasts*

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase the chance of having breast cancer diagnosed, particularly after use at a young age. After stopping hormonal contraceptive use, the chances of getting breast cancer begin to go back down.

You should have regular breast examinations by a health care provider and examine your own breasts monthly. Tell your health care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram.

Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

**WARNING SIGNALS**

If any of these adverse effects occur following insertion of Jadelle® implants call your health-care provider immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf or arm (indicating a possible clot in the leg or arm)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe or persistent headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke or other neurologic problem)
- Persistent headaches, particularly if you are obese or have had recent weight gain (indicating possible idiopathic intracranial hypertension)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your health-care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area or lower abdominal area (possibly indicating an ectopic pregnancy, a ruptured or twisted ovarian cyst, or a ruptured liver tumor)

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- Sleep disorders, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression)
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems)
- Heavy vaginal bleeding
- Delayed menstrual cycles after a long interval of regular cycles
- Arm pain
- Pus or bleeding at implant site
- Expulsion of an implant.

**PRECAUTIONS**

**GENERAL**

1. *Physical Examination and Follow-Up* — Prior to insertion of Jadelle® implants, your health-care provider will inquire about your medical history and perform a physical exam, including a gynecologic exam. Be sure to have periodic checkups as advised by your health-care provider while the implants are in place.
2. *Carbohydrate and Lipid Metabolism* — Blood sugar levels may be increased by progestin-only contraceptives such as Jadelle® implants. Diabetic patients should be observed carefully while using Jadelle® implants. Some progestins may increase lipid (eg, cholesterol, triglyceride) levels. Patients being treated for increased lipid levels should be followed closely while using Jadelle® implants.
3. *Liver Function* — Jadelle® implants may need to be removed if yellowing of the skin or whites of the eyes occurs. Hormones may be poorly metabolized in patients with liver diseases.
4. *Fluid Retention* — If you experience fluid retention (with swelling of the fingers or ankles, and possibly increased blood pressure) while using Jadelle® implants, contact your health-care provider.
5. *Emotional Disorders* — Jadelle® implants may need to be removed if you become severely depressed.
6. *Contact Lenses* — If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your health-care provider.

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7. *Idiopathic Intracranial Hypertension (pseudotumor cerebri, benign intracranial hypertension)* — An increase in intracranial pressure has been reported in rare cases in NORPLANT® implant users. Symptoms may include headache (associated with a change in the frequency, pattern, severity, or persistence. Of particular importance are visual disturbances and headaches that do not stop. Contact your health-care provider if you experience these symptoms, particularly if you are obese or have had recent weight gain. While it is unclear if this condition is caused by the implants, your health-care provider may recommend that Jadelle® implants be removed.
8. *Use in Early Pregnancy*—Birth defects have not been reported with Jadelle® use. There have been reports of birth defects when NORPLANT® implants were used unintentionally during early pregnancy, but a cause and effect relationship has not been established. You should check with your health-care provider about the risks of any medication taken during pregnancy. Do not have implants placed if you are pregnant or believe you may be pregnant.
9. *While Breast-Feeding* — Women who are breast-feeding or intend to breast-feed should discuss this with their health-care provider when considering the use of Jadelle® implants. Studies have shown no significant effects on the growth or health of infants whose mothers used NORPLANT® implants beginning 5 to 7 weeks after childbirth.
10. *Infections* — Infection at the implant site is uncommon. If infection does occur, contact your health-care provider for treatment. The implants may need to be removed if the infection continues.
11. *Expulsion and Displacement (Movement)* — Expulsion of an implant (i.e., when an implant comes out of the insertion site/skin) may occur. If an implant is expelled, your health-care provider should replace it with a new sterile implant. If infection is present, it should be resolved before any implant is replaced. To avoid pregnancy when only one implant is in place, a back-up nonhormonal contraceptive method (such as condoms or spermicides) should be used.
12. After Jadelle® implants are inserted, they may move from the original position. Rarely, movement up to several inches has been reported with NORPLANT® implants. With NORPLANT® implants, movement accompanied by pain and discomfort has been reported. If movement of one or both Jadelle® implants occurs,

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particularly if accompanied by pain and/or discomfort, notify your health-care provider.

**Drug Interactions**

Certain drugs may interact with the hormone delivered by Jadelle® implants to make them less effective in preventing pregnancy. Such drugs include drugs used for epilepsy, such as phenytoin (Dilantin® is one brand), carbamazepine (Tegretol® is one brand), oxcarbazepine (Trileptal is one brand), and phenobarbital . Certain other drugs, such as rifampicin, may also make Jadelle® implants less effective. You may need to use a different birth control method if you require drugs that can make Jadelle® implants less effective. Discuss this with your health-care provider.

**Laboratory Tests Interactions**

If you are scheduled for any laboratory tests, tell your health-care provider that you are using Jadelle® implants. Certain blood tests are affected by synthetic hormones.

**SIDE EFFECTS OF JADELLE® IMPLANTS.**

The most frequently reported side effects are menstrual cycle changes. SEE RISKS OF USING JADELLE® IMPLANTS.

Women using Jadelle® implants have also experienced the following conditions.

- Acne
- Appetite changes
- Breast pain
- Contact dermatitis
- Dizziness
- Hair loss
- Headache
- Lesions or inflammation of the cervix
- Leukorrhea (whitish discharge from the vagina)
- Libido decrease (less interest in sex)
- Nausea

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- Nervousness
- Pain, discoloration, or other skin reaction at implant site
- Pelvic pain
- Vaginal infection (due to yeast, trichomonas, bacteria), urinary tract symptoms, or genital pruritus (itching)
- Weight change, usually an increase

A woman who already has acne or excess hair on her face or body could experience worsening of these problems

The following additional complaints have been reported by NORPLANT® implant users.

- Migraine
- Mood swings
- Muscle and skeletal pain
- Pruritus (itching)
- Skin rashes
- Thrombotic thrombocytopenic purpura (TTP)
- Urticaria (hives)

## **INSERTION AND REMOVAL OF JADELLE® IMPLANTS**

### **A. Insertion**

Insertion and removal of Jadelle® implants should be performed by a health-care provider knowledgeable of the procedures.

Prior to insertion of Jadelle® implants, your health-care provider will ask about your medical history and perform a physical examination, including a pelvic exam. To make sure you are not already pregnant, Jadelle® implants should be inserted within 7 days after the onset of menstrual bleeding or immediately following termination of pregnancy. If Jadelle® implants are inserted at any other time during the cycle, pregnancy must be excluded, and a nonhormonal contraceptive method (such as condoms, spermicides, or diaphragms) must be used for at least 7 days following insertion. If ovulation and conception have already occurred before Jadelle® is inserted, pregnancy could occur during the month of insertion.

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Jadelle® implants are inserted under the skin on the inner surface of your upper arm during a minor, outpatient surgical procedure under sterile conditions. A local anesthetic is used to numb a small V-shaped area in the upper arm, after which a small incision, less than 1/8 inch long, is made in the same area. The two implants are placed one at a time with a special instrument. The incision is covered with a small adhesive bandage and protective gauze. Because a local anesthetic is used, there should be little or no discomfort during insertion.

When the anesthetic wears off, there may be some tenderness in the area of the implants for a day or two. Some discoloration, bruising, and swelling may also be present for a few days after the procedure.

Following insertion, you can resume work and other activities. Be careful, however, not to bump the site or get the incision wet for at least 3 days. Also avoid heavy lifting for 2 to 3 days. The protective gauze should remain in place for 24 hours and a small adhesive bandage for 3 days.

Be sure to have periodic checkups as advised by your health-care provider while Jadelle® implants are in place.

**B. Removal**

The implants must be removed at the end of 5 years because they become less effective. They can be removed at any time before then, however, if you want to stop using the method for any reason. Removal will take longer than insertion.

Just as for insertion, your health-care provider will numb the area with a local anesthetic. Under sterile conditions, a small (1/8 inch) incision will be made through which the implants should be removed. The removal process takes more time than the insertion procedure. If the implants are too deep, they can be more difficult to remove. If both implants cannot be removed, additional visits and incisions may be required. A nonhormonal method of contraception (such as condoms, spermicides, or diaphragms) should be used until both implants are completely removed.

Avoid bumping the incision site for a few days. The area should be kept clean, dry, and bandaged until healed (3 to 5 days) to avoid infection. Bruising may occur at the implant site following removal.

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If you want to continue using Jadelle® implants, a new set can be inserted at the same time the old set is removed. The second set can be placed in the same arm, and frequently through the incision from which the earlier set was removed, or in the other arm.

If you do not want to continue with Jadelle® implants and do not want to become pregnant, ask your health-care provider to recommend another birth control method.

Once the implants are removed, the effects reverse quickly and a woman can become pregnant as easily as if she had not used the method.

**ADDITIONAL INFORMATION**

If you would like more information about Jadelle® implants, a copy of the Prescribing Information can be obtained from your health-care provider.

**WHAT I KNOW ABOUT JADELLE® IMPLANTS**

I have read this brochure and have discussed it with my health care provider. He/she has answered all my questions. I understand that there are risks as well as benefits from using Jadelle® implants. I understand that there are other forms of contraception that do not have the risks of Jadelle® implants, but may have different risks.

I also understand that this form is important. It demonstrates that I am making an informed and carefully considered decision to use Jadelle® implants. I have checked below those statements that I agree with:

\_\_\_\_\_ I have been told how Jadelle® implants work to keep women from getting pregnant.

\_\_\_\_\_ I have been told that the risk of getting pregnant while using Jadelle® implants is less than 1%. (This means that less than one woman out of every 100 who uses Jadelle® implants may get pregnant each year.)

\_\_\_\_\_ I have been told that I can have Jadelle® implants taken out at any time and for any reason. I have also been told that, if I have trouble finding a health care provider to remove them, I can call (800) 934-5556 for help.

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\_\_\_\_\_ I understand that the Jadelle® implants are made of a hormone embedded in a flexible solid state silicone polymer.

\_\_\_\_\_ I have been told that Jadelle® implants are implanted under the skin of my arm during an in-office surgical procedure.

\_\_\_\_\_ I have been told that the Jadelle® implants must be removed at the end of 5 years. The removal procedure is also an in-office surgical procedure and may cause more discomfort and scarring than the insertion procedure.

\_\_\_\_\_ I have been told about the side effects of Jadelle® implants, including that most women have changes in their menstrual bleeding. I have been told that the side effects may vary in severity from one woman to another.

\_\_\_\_\_ I have been told about warning signs that may indicate serious conditions and know that I should seek medical attention if any warning signs appear.

\_\_\_\_\_ I have been told that I need to receive a medical checkup yearly and at any time I am having problems.

\_\_\_\_\_ I have been told that Jadelle® implants do not protect me from HIV infection (AIDS) or any other sexually transmitted disease.

\_\_\_\_\_ I have considered all the information in this brochure and voluntarily choose to have Jadelle® implants inserted by:

\_\_\_\_\_  
(Name of Health-Care Provider)

\_\_\_\_\_  
(Patient Signature)

\_\_\_\_\_  
(Date)

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WITNESSED BY:

The patient above has signed this brochure in my presence after I counseled her and answered her questions.

\_\_\_\_\_  
(Health-Care Provider Signature)

\_\_\_\_\_  
(Date)

I have provided an accurate translation of this information to the patient whose signature appears above. She has stated that she understands the information and has had an opportunity to have her questions answered.

\_\_\_\_\_  
(Signature of Translator)

\_\_\_\_\_  
(Date)