NEW ZEALAND DATA SHEET

1 PRODUCT NAME

JADELLE® levonorgestrel 2 x 75 mg subcutaneous implants

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

JADELLE consists of two implants to be inserted subdermally. Each implant contains 75 mg levonorgestrel.

The release rate of levonorgestrel is about 100 microgram/day at one month after insertion, declining to about 40 microgram/day within one year, to about 30 microgram/day within three years and to about 25 microgram/day within five years.

For full list of excipients, see List of excipients.

3 PHARMACEUTICAL FORM

Subcutaneous implant.

The implants are flexible, sealed, white to off-white rods, about 43 mm in length and 2.5 mm in diameter

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

4.2 Dose and method of administration

For subcutaneous use.

JADELLE is a contraceptive method for long-term (up to five years) use (see Special warnings and precautions for use).

Insertion and Removal/Replacement

The patient must be informed that JADELLE implants may be removed at her request at any time.

Before insertion, the woman must be informed of the efficacy, risks, side effects and bleeding pattern changes to be expected with JADELLE. This discussion should include the information that a small proportion of women (17/1100 or 1.5%) experienced adverse effects from the removal of JADELLE including multiple or long incisions, pain, difficult removals and/or additional visits for the removal.

Training is required for the insertion and removal procedures, which should preferably be done by a healthcare professional and the given instructions must be followed closely. The implants are inserted with the disposable, sterile Trocar just beneath the skin.

Important: the disposable JADELLE Trocar is for single use only. After insertion, the Trocar must be disposed of in an appropriate sharps container. Strict asepsis must be observed here. The implants are inserted in the inner aspect of the upper left arm in right-handed women and in the right arm in left-handed women, approximately 8 cm above the fold in the elbow.

Before insertion, the skin is cleaned with an antiseptic and the insertion area anesthetized. An incision of 2 mm is made in the skin with a scalpel. The implants are inserted with the Trocar subdermally, in the shape of a V opening towards the armpit. Proper insertion will later facilitate removal and result in minimal scarring. After insertion of the second implant, the edges of the incision are pressed together, closed with a skin closure and dressed.

Following insertion, if it is suspected that the system is not in the correct position, it should be removed and a new one inserted.

Instructions for implant insertion

The JADELLE contraceptive method consists of two levonorgestrel releasing implants to be inserted subdermally into the inside of the upper arm.

The basis for successful use of the JADELLE contraceptive method is a correct and carefully performed insertion of the implants. During insertion, special attention should be given to the following:

– asepsis

– correct subdermal placement of the implants

– careful technique to minimize tissue trauma

This will help to avoid infections and scarring of the insertion area on the one hand, and on the other to keep the implants from being inserted too deeply in the tissue. If the rods are placed too deeply, they will be more difficult to remove than correctly placed subdermal rods. The JADELLE method provides up to 5 years of highly effective contraceptive protection. Because the method is intended for long-term use, it is worthwhile spending a little more time than usual in explaining the method to the patient and in performing the insertion.

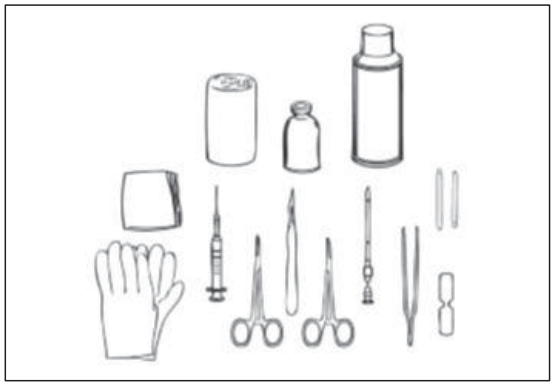
INSERTION

It is preferable to carry out the insertion during the first few days of menstrual bleeding, and at the latest on the 7th day from the onset of the menses. A gynaecological examination should be performed before the insertion of JADELLE implants to exclude genital abnormalities, e.g. tumours. Determine if the patient has any allergies to the antiseptic or anaesthetic to be used or contraindications to progestin-only contraception. If none are found, the implants are inserted using the following procedure.

One JADELLE set consists of two implants in a sterile pouch. The insertion is performed using the disposable sterile trocar for JADELLE insertion (JADELLE Trocar) to place the implants under the skin.

IMPORTANT : the disposable JADELLE Trocar is for single use only!

Picture 1



The following equipment is needed for the insertion:

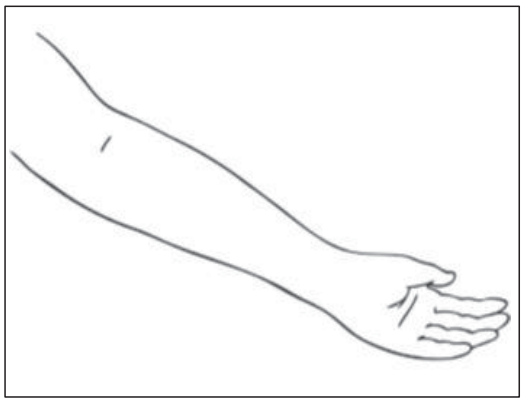
– a table for the patient to lie on

– sterile surgical cloths, sterile tray for the equipment, sterile gloves (free of talc), antiseptic solution

– local anaesthetic, anaesthetic needle (5 - 5.5 cm long) and 5 ml syringe

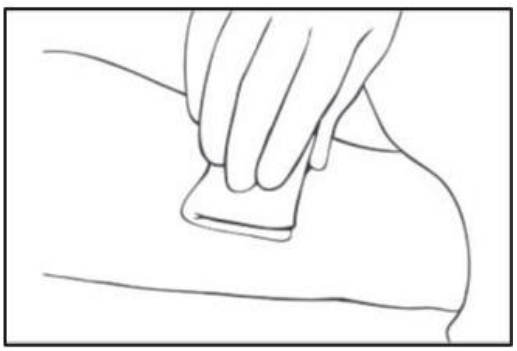
– JADELLE Trocar, a scalpel with blade, tweezers, skin closure, sterile gauze and compresses.

Picture 2



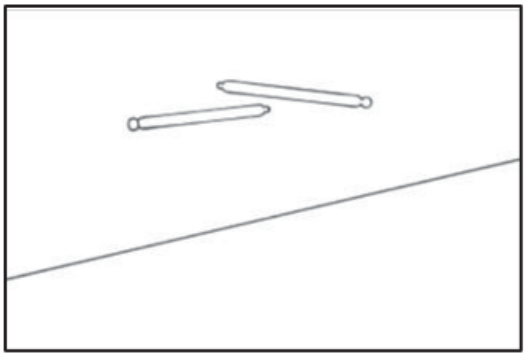
The patient should lie down on the examination table with her non-dominant arm extended on a sterile cloth on the other table, at right angles to her body. The rods will be inserted subdermally through a small transverse 2 mm incision, in the shape of a narrow V, opening towards the armpit.

Picture 3



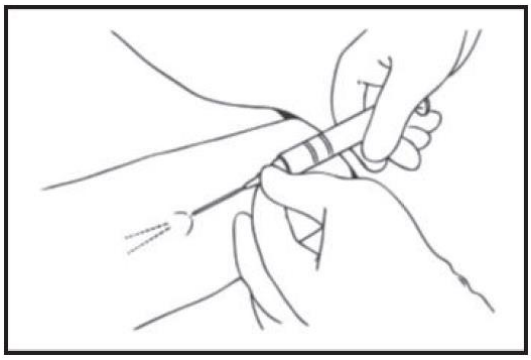
Clean the patient's upper arm with an antiseptic solution and cover the arm with either two sterile clothes or a fenestrated drape. The optimal insertion area is the medial aspect of the upper arm about 6 - 8 cm above the fold of the elbow.

Picture 4



Open the sterile JADELLE pouch by pulling apart the films of the pouch and let the two implants drop on a sterile cloth. Do not touch the inside of the package or its contents with bare hands. There should be two rods. **NOTE: Always use sterile gloves or forceps when handling the rods. If a rod is contaminated, e.g. falls on the floor, leave it for later disposal. Open a new package and continue with the procedure.**

Picture 5



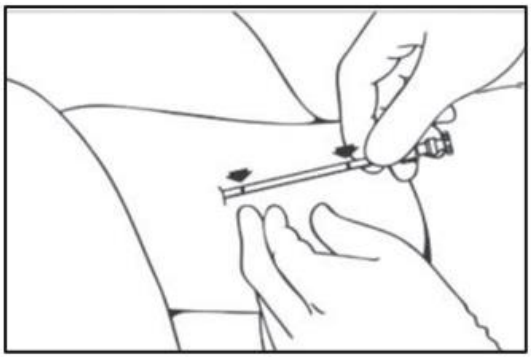
First determine the absence of known allergies to the anaesthetic agent or related drugs. Fill a syringe with 2-4 mL of local anaesthetic. Anaesthetize the insertion area by inserting the needle just under the skin about 5 - 5.5 cm in the directions where you are planning to introduce the trocar.

Picture 6

Make an incision of about 2 mm with the scalpel through the skin.

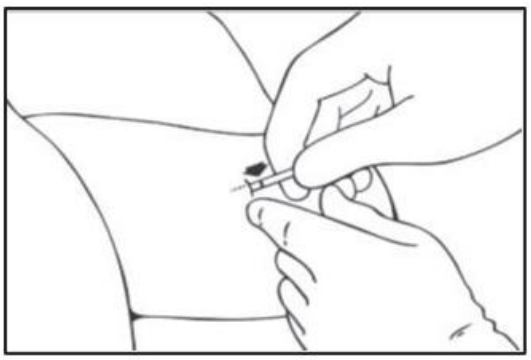
Alternatively, the trocar may be inserted directly through the skin without making an incision with the scalpel, though it is not recommended for JADELLE sine inserter.

Picture 7



The disposable JADELLE Trocar has two marks. One mark is close to the handle and it indicates how far the trocar should be introduced under the skin before the loading of each implant. The mark closest to the tip indicates how much of the trocar should be left under the skin following the insertion of the first implant. When inserting the trocar, avoid touching the part of the trocar that will go under the skin.

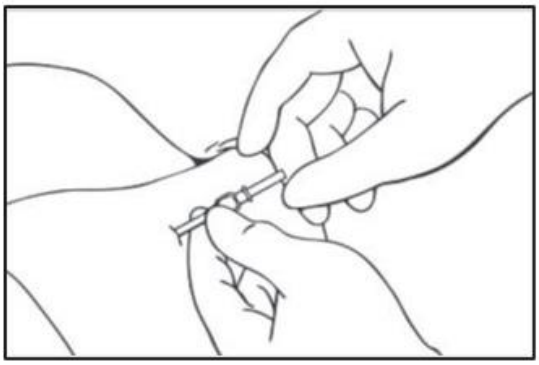
Picture 8



Once the tip of the trocar is inserted, it should be pointed upwards toward the skin to keep the rods in a superficial plane. 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 rods and could make removal more difficult.

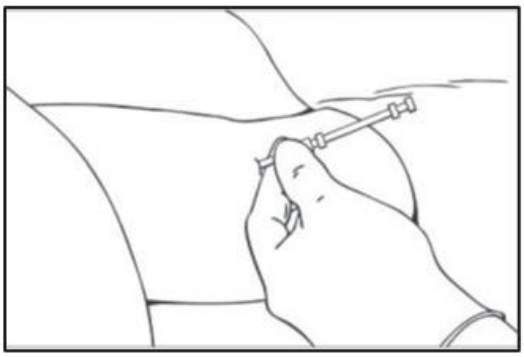
Advance the trocar beneath the skin about 5.5 cm from the incision to the mark closest to the handle of the trocar. Do not force the trocar, and if you feel any resistance, try another direction.

Picture 9



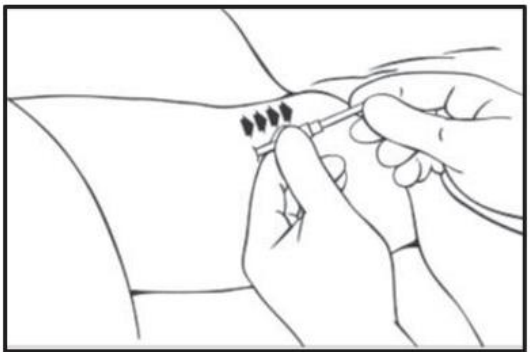
Remove the plunger when the trocar is advanced to the correct mark and load the first rod into the trocar either with tweezers or fingers.

Picture 10



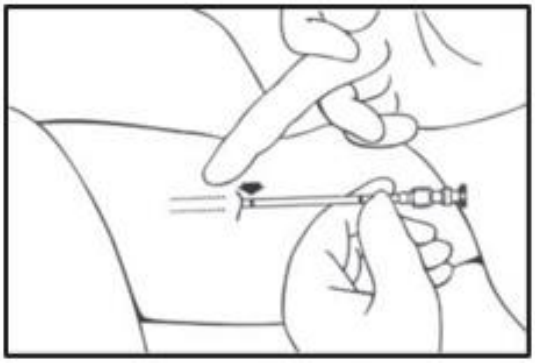
Push the implant gently with the plunger to the tip of the trocar until you feel resistance. Never force the plunger.

Picture 11



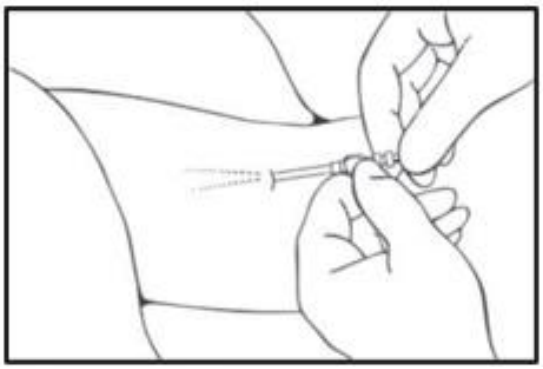
Hold the plunger steady and pull the trocar back along it until it touches the handle of the plunger. It is important to keep the plunger steady and not to push the rod into the tissue. Do not completely remove the trocar until both rods have been placed. The trocar is withdrawn only to the mark closest to its tip.

Picture 12



When you can see the mark near the tip of the trocar in the incision, the implant has been released and will remain in place beneath the skin. You can check this by palpation.

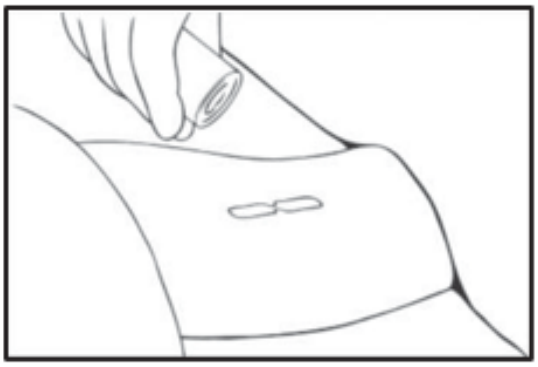
Picture 13



The second implant is inserted at the side of first one, to form a V shape. Fix the position of the first rod with the left forefinger and advance the trocar along the side of the finger. This will ensure a suitable distance between implants.

To prevent expulsions leave a distance of about 5 mm between the incision and the ends of the implants. You can check their correct position by cautious palpation of the insertion area.

Picture 14



After the insertion, press the edges of the incision together and close the incision with a sterile skin closure. Suturing the incision is not necessary and may even increase scarring.

IMPORTANT: after insertion, the disposable JADELLE Trocar cannot be used for further insertions. The trocar must be disposed of in an appropriate sharps container.

Picture 15

Cover the insertion area with a dry compress and wrap enough gauze around the arm to ensure haemostasis. Observe the patient at the clinic 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 for 3 days and give her a copy of the JADELLE patient information leaflet, in which you have entered the date of insertion and the date of the first control visit. The gauze and the bandage may be removed as soon as the incision has healed, normally after 3-5 days.

How to start JADELLE

No preceding hormonal contraceptive use (in the past month)

JADELLE should be inserted within 7 days from the onset of menstrual bleeding. If the implants are inserted at any other time, pregnancy must be reliably excluded before insertion and an additional non-hormonal contraceptive method used for at least 7 days after the insertion.

Changing from a combined hormonal contraceptive (combined oral contraceptive, vaginal ring or transdermal patch)

JADELLE should preferably be inserted on the day after the last active tablet of the previous combined oral contraceptive (COC), but at the latest on the day after the tablet-free interval or placebo tablet phase.

In the latter case, the woman should be advised to additionally use a barrier contraceptive method during the tablet-free interval or placebo tablet phase.

In case a vaginal ring or transdermal patch has been used, JADELLE should preferably be inserted on the day of removal of the last ring or patch of a cycle pack, but at the latest when the next application would have been due.

Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill, another implant, or an IUS on the day of its removal, or from an injectable when the next injection would be due.

Following first-trimester abortion

JADELLE may be inserted immediately. When doing so, no additional contraceptive measures are needed.

Following delivery or second-trimester abortion

JADELLE may be inserted immediately after the second trimester abortion or childbirth. If inserted later than 21 days after childbirth, pregnancy should be reliably excluded and additional non-hormonal contraceptive precautions taken for a minimum of 7 days after the insertion.

Removal of JADELLE

JADELLE implants may be removed at any time for medical or personal reasons but they must be removed after five years from the insertion at the latest. The implants may be removed at any time of the menstrual cycle. Loss of contraceptive effect occurs immediately, and another contraceptive method should be used unless pregnancy is desired.

When starting the removal of implants, the skin is cleaned and a local anaesthetic is infiltrated under the implant ends. A skin incision of 4 mm is made with a scalpel below the bottom of the V. The implants are removed using a small (e.g. Mosquito) forceps. The implants should be removed very gently. This will take more time than the insertion. The implants may be nicked, cut or broken off during removal.

If removal proves difficult or both implants cannot be removed, the patient should be asked to return for a second visit after the removal area has healed. A non-hormonal method of contraception should be used until both implants have been completely removed. If the patient wishes to continue using this method, a new set of JADELLE implants may be inserted through the same incision, either in the same or in the opposite direction.

Following removal pregnancy may occur at any time.

Instructions for implant removal

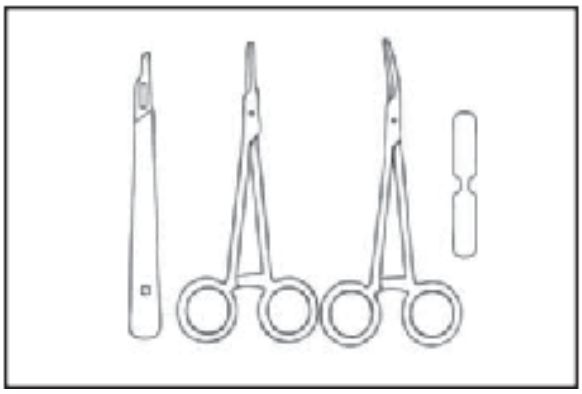
Described below is a removal procedure which was used during the clinical trials for the JADELLE implants. As with many surgical procedures, variations of the technique have appeared and some have been published. No one particular procedure routinely appears to have advantage over another.

Removal should not be attempted if the clinician cannot locate the implant (either by palpation or imaging (soft tissue x-ray or ultrasound)) prior to the removal procedure.

It is recommended that implant removals be done only on certain, pre-scheduled days, so that preparations for carrying out the procedure can be facilitated. Removal of the rods should be performed very gently and will usually take more time than the insertion. Rods are sometimes nicked, cut or broken during removal. If removal of the rod(s) proves difficult, close the incision and bandage the wound, and have the patient return for another visit. The remaining rod(s) will be easier to remove after the area is healed. A non-hormonal method of contraception should be used until both rods are completely removed.

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

Picture 16



The following additional equipment is needed for removal:

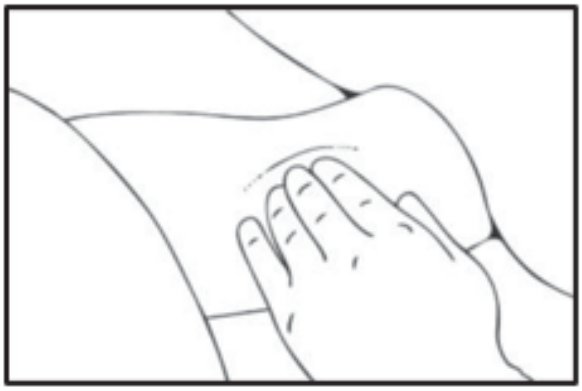
– local anaesthetic, anaesthetic needle and syringe

– a scalpel

– two different sizes of forceps (Mosquito and Crile)

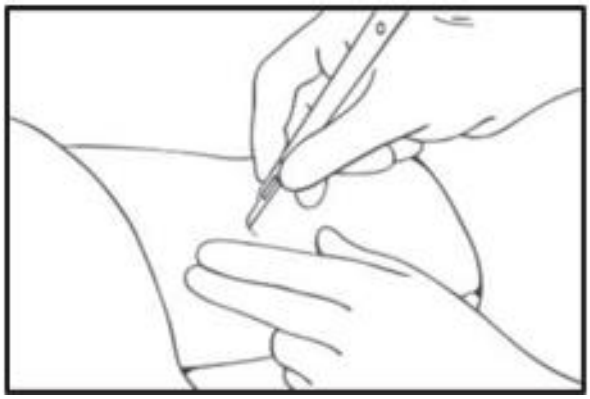
– skin closure, sterile gauze and compresses.

Picture 17



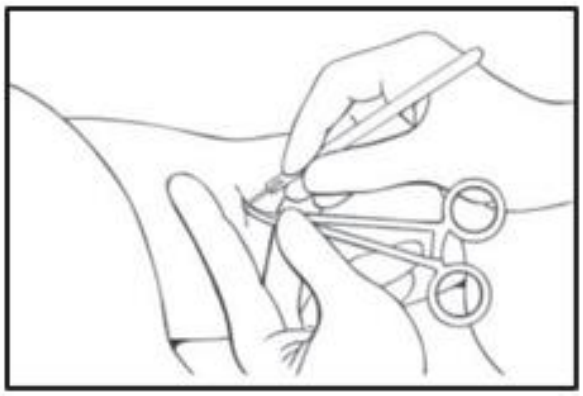
Locate the implants by palpation, possibly marking their position with a marker pen. If they cannot be palpated, they may be located by ultrasound or soft tissue X-ray. Inject a small amount of local anaesthetic under the ends of the implants that are closer to each other. Anaesthetic injected over the implants may obscure their position and make removal more difficult. If necessary, more anaesthetic can be given in small amounts at a time.

Picture 18



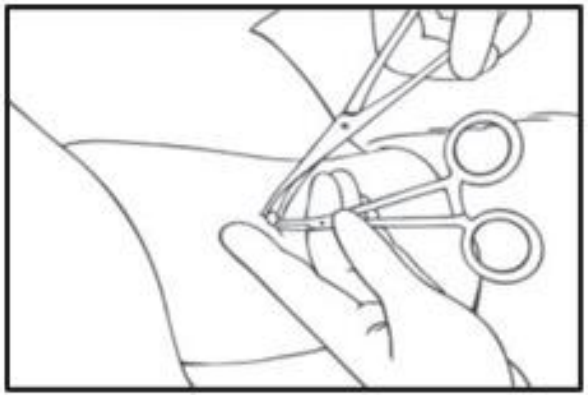
Make a 2-4-mm incision with the scalpel close to the ends of the implants. Keep the incision small.

Picture 19



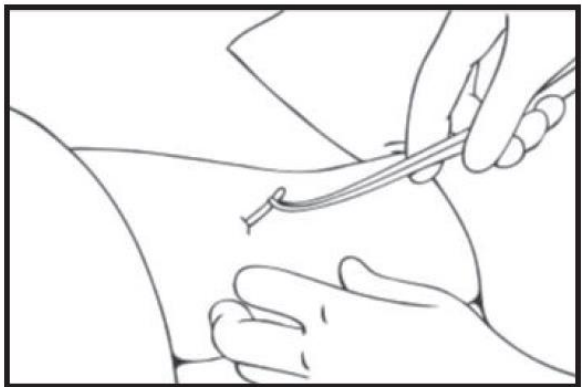
Push each implant with your fingers gently towards the incision. When the tip is visible in the incision, grasp it with the Mosquito forceps. Use the scalpel to very gently open the tissue capsule around the rod.

Picture 20



Grasp the end of the rod with the second forceps (Crile).

Picture 21



Remove the implant gently. Repeat the procedure for the second implant.

Measure the length of the removed implants to make sure the patient had JADELLE implants and not other contraceptive implants. The length should be 43 mm.

After the procedure is completed, close the incision and bandage it as after insertion. The arm should be kept dry for a few days.

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.

4.3 Contraindications

- Hypersensitivity to levonorgestrel or any other component of JADELLE
- Known or suspected pregnancy
- Active venous thromboembolic disorder
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex hormone-dependent malignancies
- Undiagnosed vaginal bleeding

4.4 Special warnings and precautions for use

Warnings

Clinical trials have shown the contraceptive efficacy of JADELLE implants to decrease after the fourth year of use. Consequently, the removal of JADELLE implants and their change into new implants could be considered after 4 years of use, especially in women weighing over 60 kg (see Pharmacodynamic properties). The serum levonorgestrel concentration is lower at the end of the implant use and it is inversely related to body weight.

The effects of JADELLE on clotting factors are varied. In patients with a history of thromboembolic disease, JADELLE should only be used if other contraceptive methods are unsuitable and after careful assessment of the risk benefit ratio. Thromboembolic and cardiovascular undesirable effects have been reported in users of other levonorgestrel implants. Cases of stroke, myocardial infarction, pulmonary embolism and deep venous thrombosis have been reported in users of other levonorgestrel implants, as they have been in users of any hormonal contraceptive method, but a causal relationship with the contraceptive method has not been established.

Patients who develop arterial or venous thrombotic or embolic disease, or suspicion thereof, should have their JADELLE implants removed (see Large and Small Surgical Procedures). Thrombophlebitis

and superficial phlebitis have occurred more commonly in the arm of insertion. Some cases have been associated with trauma to that arm.

Expulsion of an implant may occur before the incision has healed if the implants have been inserted very near the skin surface or too close to the incision or when the insertion site is infected. An expelled implant must always be replaced with a new, sterile implant.

Reports have been published on slight displacement of similar levonorgestrel implants, most of which have involved minor changes in the position of the implants. Infrequent reports on significant displacement (a few to several centimetres) have been received. Some of these cases have been associated with pain or discomfort. In the event of displacement, the removal technique may have to be modified and may involve additional incisions or visits.

Altered serum lipoprotein levels have been observed in clinical trials on JADELLE. Although statistically significant decreases in total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein) and triglycerides have been detected, all mean values have remained within the normal ranges. The long-term clinical significance of these changes has not been determined.

Caution should be observed in prescribing JADELLE implants for patients with recognised risk factors for, or any predisposition to arterial disease.

If a sustained hypertension develops during the use of JADELLE, or if a significant increase in blood pressure does not adequately respond to anti-hypertensive therapy, the use of JADELLE should be discontinued.

If a patient has a history of or develops focal or crescendo type migraine or exhibits worsening of such migraine during the use of JADELLE, the situation should be carefully assessed.

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist. The patient may be advised to stop wearing contact lenses for a while or completely.

Altered glucose tolerance and insulin sensitivity in oral glucose tolerance tests has been reported in users of JADELLE in some studies. The clinical significance of these findings is unknown but diabetic patients using JADELLE should be carefully monitored. A gain in weight is possible during the use of JADELLE.

If cholestatic hepatitis or jaundice develops in a patient with JADELLE, the implants must be removed. Mild or moderate transient rise in total serum bilirubin is usual at the start of the implant use. A slightly increased risk of cholelithiasis has been reported during the use of other levonorgestrel implants of similar type. Levonorgestrel metabolism may be slower than normal in patients with impaired liver function.

Removal of JADELLE should also be considered in women who become significantly depressed, since the symptom may be hormone related. Women with a history of depression should be carefully monitored and removal of JADELLE considered if clear symptoms develop.

Steroid contraceptives may cause some degree of fluid retention, which may result in weight gain. JADELLE should be prescribed with caution to patients with conditions that might be aggravated by fluid retention, and their condition should be monitored closely during the use of JADELLE.

Idiopathic intracranial hypertension has been reported on rare occasions in users of levonorgestrel implants. Evidence is based on isolated reports only. This diagnosis should be considered if persistent

headache and/or visual disturbances occur in a woman with JADELLE, particularly if the patient is obese or has recently gained weight. If idiopathic intracranial hypertension is diagnosed, JADELLE should be removed.

JADELLE implants affect the menstrual bleeding pattern in most women. Irregular, prolonged and intermenstrual bleeding, spotting and amenorrhoea have been reported. In general, such irregularities decrease with continuing use. Significant blood loss leading to anaemia is rare, and average concentrations of haemoglobin normally rise slightly in JADELLE users.

Since some users of JADELLE experience periods of amenorrhoea, missed menstrual periods should not be relied on as the sole means of diagnosing pregnancy. A pregnancy test should be performed whenever pregnancy is suspected. Six or more weeks of amenorrhoea after a period of regular menses may indicate pregnancy. The implants should be removed if pregnancy occurs.

Ectopic pregnancy occurs rarely with levonorgestrel implants: at a rate less than 1 per 1000 woman-years. If a woman using JADELLE presents with lower abdominal pain or is found to be pregnant, she should be examined to exclude ectopic pregnancy.

Follicles develop during the use of JADELLE but their atresia may be delayed and they may continue to grow beyond the normal size. In most women, such enlarged follicles will disappear spontaneously. In rare cases, however, they may twist or rupture, causing abdominal pain. Even in the presence of symptoms, conservative management is indicated but ectopic pregnancy must be excluded. Surgical intervention is rarely warranted.

In some rare cases autoimmune diseases such as scleroderma, LED (lupus erythematosus disseminata) or rheumatoid arthritis have been reported in users of levonorgestrel implants. No causal relationship to implants containing levonorgestrel has been established. Both during pregnancy and during the use of sex steroids, the following conditions have been observed, without confirmed relationship to the use of progestogens: cholestatic icterus and/or itching, cholelithiasis, haemolytic-uremic syndrome, herpes gestationis, and hearing loss associated with otosclerosis.

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 taking combined oral contraceptives (COCs), mainly taking estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in progestogen-only contraceptive users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. The breast cancer diagnosed in OC ever-users tends to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely malignant liver tumours, have been reported in users of hormonal contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women using JADELLE.

Medical Examination/Consultation

Before initiating or reinstituting treatment, a complete medical and family history should be taken. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications and warnings for use. The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given and to contact her doctor if any problems occur at the insertion area. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

The insertion area should be examined at every control visit. If undiagnosed, persistent or recurrent vaginal bleeding occurs, appropriate measures should be taken to rule out malignancy.

Sexually Transmitted Infections including HIV infections and AIDS

JADELLE is intended to prevent pregnancy. It does not protect against sexually transmitted infections (STIs), including HIV infections (AIDS).

Large and Small Surgical Procedures

JADELLE implants do not contain estrogen and, therefore, the use of JADELLE, as well as of other similar contraceptives, may usually be continued during surgical procedures. However, if a high risk of thrombosis exists, consideration should be given to appropriate prophylactic measures. Due to a risk of thromboembolism, the removal of implants may be considered either in connection with surgery or with prolonged immobilisation for some other reason.

Instructions to the Patient

The package contains a patient information leaflet to facilitate explaining the characteristics of JADELLE to patients. A copy of the leaflet should be given to each patient. The advantages and disadvantages of JADELLE, other methods of contraception and of not using any contraceptive method should be explained thoroughly to the patient. In addition, information should be given on implant insertion and removal.

4.5 Interaction with other medicines and other forms of interaction

Effects of other Medicines on JADELLE

Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones and which may lead to changes in the uterine bleeding profile and/or contraceptive failure.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to JADELLE or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation.

Substances increasing the clearance of levonorgestrel (diminished efficacy of JADELLE by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, efavirenz, and possibly also oxcarbazepine, topiramate, bosentan, felbamate, griseofulvin and products containing St. John's Wort.

Enzyme induction can be observed after a few days of treatment.

Maximal enzyme induction is generally seen within a few weeks. After the cessation of therapy with other medicines, enzyme induction may be sustained for about 4 weeks.

Substances with variable effects on the clearance of levonorgestrel, e.g.:

When co-administered with sex hormones, many HIV/HCV protease inhibitors and nonnucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of the progestin (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir, nevirapine, efavirenz] or increase [e.g., indinavir and atazanavir/ritonavir, etravirene]).

These changes may be clinically relevant in some cases.

Substances decreasing the clearance of levonorgestrel (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the progestin.

Effects of JADELLE on other Medicines

JADELLE may affect the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease (e.g. lamotrigine).

Other Forms of Interactions

Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis.

Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation

Pregnancy

The implants should be removed if pregnancy occurs during treatment with JADELLE. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used oral contraceptives containing levonorgestrel prior to pregnancy, nor of a teratogenic effect when oral contraceptives were inadvertently used during pregnancy. No studies are available on the effect of JADELLE during or prior to pregnancy.

Lactation

Levonorgestrel passes into milk but the available data show no adverse effects on infant growth and development. Levels of levonorgestrel obtained with JADELLE do not affect the quality or quantity of breast milk.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

The following undesirable effects have been reported during clinical trials with JADELLE:

Very common undesirable effects (occurring in more than 10% of users): headache, nervousness, dizziness, nausea, changed menstrual bleeding (frequent, irregular or prolonged menstrual bleeding, spotting, amenorrhoea), cervicitis, vaginal discharge, genital pruritus, pelvic pain, breast pain, weight gain.

Most users of JADELLE can expect variation in menstrual bleeding patterns such as irregular menstrual bleeding, prolonged episodes of bleeding or spotting, heavy bleeding, bleeding or spotting between periods, no bleeding at all or a combination of these patterns. In a combined clinical report representing 3 clinical studies out of 1243 women 174 (14%) of the JADELLE users discontinued their treatment before 5 years due to menstrual problems.

In the same report, the following very common side effects (occurring in more than 10% of users) were reported over the first five years: headache (30.5%), vaginal discharge (30.3%), pelvic pain (24.4%), weight increase (22.4%), genital pruritus (16.3%), cervicitis (14.8%), vaginal fungal infection (14.8%), dizziness (14.5%), breast pain (12.6%), nausea (11.6%), acne (10.9%) and bleeding at the injection site (10.8%).

Organ System	**Common undesirable effects** **> 1/100, < 1/10**	**Uncommon undesirable effects** **> 1/1000, < 1/100**	**Rare undesirable effects** **>1/10,000, < 1/1000**
Psychiatric	Mood changes Depression Changes in libido		
Nervous system	Migraine		
Cardiac	Palpitation Chest pain		
Vascular	Hypertension Varicose veins		
Respiratory	Dyspnoea		
Gastro-intestinal	Abdominal discomfort		
Hepato-biliary	Rise in total serum bilirubin		
Skin	Acne Contact dermatitis Alopecia Hypertrichosis Rash Pruritus Skin discolouration		
Renal and urinary	Urinary tract symptoms		

Organ System	Common undesirable effects > 1/100, < 1/10	Uncommon undesirable effects > 1/1000, < 1/100	Rare undesirable effects >1/10,000, < 1/1000
Reproductive system and breast	Vaginitis Ovarian cysts Benign breast nodules Breast discharge		
General disorders and administration site	Itching at insertion site General pain Fatigue Back pain Weight loss	Bruising at insertion site Infection at the implant site	Expulsion of implant Arm pain Numbness Tingling and scarring Difficulty in removal of the implant Ulnar nerve damage associated with removal of the implant Hyperpigmentation over the implant site

Expulsion or displacement of JADELLE may be possible (see Special warnings and precautions for use).

In users of similar levonorgestrel implants in various countries limited blistering, ulceration and sloughing have been observed rarely.

During the use of other levonorgestrel implants of similar type, very rare cases of cholestatic hepatitis, jaundice, bilirubinemia and thromboembolic complications have been reported (see Special warnings and precautions for use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

There is no experience of overdose with JADELLE. For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The active ingredient in JADELLE implants, levonorgestrel, is a synthetic progestogen. Levonorgestrel released from JADELLE has been shown to affect ovarian function in various ways, ranging from absence of follicular and luteal activity through normal follicular activity but deficient luteal activity to normal ovulatory patterns. Levonorgestrel causes thickening of the cervical mucus, thus preventing passage of spermatozoa into the uterus. It also suppresses the endometrium and may prevent implantation of the blastocyst.

The contraceptive efficacy of JADELLE was studied in multicentre trials involving 1393 women observed for 4657 woman-years. The Pearl Index during five years was 0.17 per 100 woman-years. The annual pregnancy rate per 100 users was 0.1 at one, two and three years, 0.00 at four years, and 0.8 at five years. In all women with body weight 60 kg or more the annual pregnancy rates per 100 users were 0.2 during year 1, 0.2 during year 2, 0.3 during year 3, 0.0 during year 4 and 1.1 during year 5.

After removal of the implants, women return quickly to their normal fertility. When women had JADELLE implants removed for planned pregnancy, 45% became pregnant within 3 months and 86% within a year.

The efficacy of JADELLE does not depend on patient compliance

5.2 Pharmacokinetic properties

The only active ingredient in JADELLE is levonorgestrel, a progestogen. The implants are inserted subdermally, and they have been shown to provide effective contraception over the intended five years lifetime of the product.

Absorption

Levonorgestrel is released from the implants directly into tissue fluid. Maximum serum levonorgestrel concentrations of approximately 772 pg/mL are reached 48 hours after insertion. After the initial phase, levonorgestrel concentrations decline to 435 pg/mL within one month, 355 pg/mL within six months, 341 pg/mL within one year, and 277 pg/mL within five years.

Distribution

Serum levonorgestrel concentrations are inversely related to body weight. The difference is approximately 2-fold between women weighing 50 and 70 kg. However, due to the great variation in serum levonorgestrel concentrations and in individual response, serum concentrations alone are not predictive of the risk of pregnancy in an individual woman. In JADELLE implant users, serum levonorgestrel concentrations are substantially below those observed in women taking oral contraceptives containing levonorgestrel.

In serum, levonorgestrel is mainly bound to sex hormone binding globulin (SHBG). Levonorgestrel lowers SHBG concentrations within a few days, reducing the total serum levonorgestrel concentrations.

Metabolism/ Biotransformation

Levonorgestrel is extensively metabolised. The most important metabolic pathways are the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β and 16β, followed by conjugation. CYP3A4 is the main enzyme involved in the oxidative metabolism of levonorgestrel. The available in vitro data suggest that CYP mediated biotransformation reactions may be of minor relevance for levonorgestrel compared to reduction and conjugation.

Elimination/ Excretion

There is wide interindividual variation in the metabolic clearance rate. This is believed to be the reason for the wide variation in serum levonorgestrel levels in various users. The elimination half-life of levonorgestrel is 13 to 18 hours. Levonorgestrel and its metabolites are primarily excreted in the urine (40 to 68%) and partly in faeces (16 to 48%). After removal of the implants, serum levonorgestrel concentrations decrease below the detection limit within 5 to 14 days.

5.3 Preclinical safety data

The toxicity profile of levonorgestrel is well-established and reveals no particular human health risks beyond those discussed in the Data Sheet.

Mutagenicity and biocompatibility testing gave no indication of genotoxicity or unacceptable local tolerance of levonorgestrel or the non-active polymeric components of JADELLE.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Silicone elastomers
- Colloidal anhydrous silica.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 Months.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

The sterile implants are packed in a moulded polyethylene terephtalate blister package sealed with a coated, spunbonded polyethylene film. If the seam of the sterile package is broken, the product should be discarded.

Each pack contains two 75 mg implants for insertion.

6.6 Special precautions for disposal

No special requirements.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Instructions for Use/Handling

Information on insertion and removal is provided in the Dosage and Administration section.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Bayer New Zealand Limited
P O Box 2825
Shortland Street

Auckland 1140
New Zealand

Free phone 0800 233 988

www.bayer.co.nz

9 DATE OF FIRST APPROVAL

9 September 2015

10 DATE OF REVISION OF THE TEXT

3 November 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
4.2	Addition of detailed instructions for implant insertion/removal.