Data Sheet

JADELLE®

Subcutaneous Implants
Levonorgestrel 2 x 75 mg

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.

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.

Clinical Particulars

Therapeutic Indications

Contraception.

Dosage 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 and instructions must be followed closely. The implants are inserted with a trocar just beneath the skin. 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.

The patient should be advised to keep the insertion area dry for 3 days. The gauze and the bandage may be removed as soon as the incision has healed, normally after 3 - 5 days.

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

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 oral contraceptive (COC)

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.

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 for women who are not breast-feeding. 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. Breast-feeding women should not start to use JADELLE earlier than six weeks after delivery.

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) forcep. 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.

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

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 also 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.

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 and venous disease.

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.

Benign intracranial hypertension has been reported on rare occasions in users of other levonorgestrel implants. 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 oestrogen-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 Diseases including HIV infections and AIDS

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

Large and Small Surgical Procedures

JADELLE implants do not contain oestrogen 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.

Interaction with other Medicines

Interactions

The effect of hormonal contraceptives may be impaired by medicines which induce liver enzymes including primidone, barbiturates, phenytoin, carbamazepine, rifampicin and oxcarbazepine; griseofulvin is also suspected.

Additional non-hormonal (barrier) methods of contraception should be used during the time of concomitant medication with these and other enzyme inducing agents and for four weeks after cessation of therapy with the inducing medicines. For women on long-term therapy with hepatic enzyme inducers, another method of contraception should be considered.

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 over into milk but the quantities do not seem to affect the child. Levels of levonorgestrel obtained with JADELLE do not affect the quality or quantity of breast milk. Breast-feeding mothers are, however, advised not to start using JADELLE until 6 weeks post partum.

Effects on Ability to Drive or Use Machines

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

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 pruritis, 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 Pruritis Skin discolouration		
Renal and urinary	Urinary tract symptoms		
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 of an implant is uncommon but may occur before the insertion area 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 by a new, sterile implant.

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

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 also Warnings and Precautions for Use).

Overdose

There is no experience of overdose with JADELLE.

Pharmacological Properties

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.

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.

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.

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. The metabolic pathways of levonorgestrel are known partly. One of them is 16β-hydroxylation. Concentrations of the metabolites, particularly sulfate conjugates, are higher than those of levonorgestrel.

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.

Preclinical Safety Data

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

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

Pharmaceutical Particulars

List of Excipients

- Silicone elastomers
- Colloidal anhydrous silica

Incompatibilities

Not applicable.

Shelf Life

5 years (60 months).

Special Precautions for Storage

Store below 30^{o}C.

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 contain two 75 mg implants for insertion.

Instructions for Use/Handling

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

Medicine Classification

Prescription Medicine

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Date of Preparation

30 August 2010