JADELLE®

1. NAME OF THE MEDICINAL PRODUCT
Jadelle® 2 x 75 mg implants

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
The product 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 3 years, and to about 25 microgram/day within five years.

3. PHARMACEUTICAL FORM
Implant

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

4. CLINICAL PARTICULARS
4.1 Indication(s)
Contraception.

4.2 Dosage and method of administration
4.2.1 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). The user must be informed that Jadelle implants may be removed at her request at any time.

Paediatric population
There is no relevant indication for the use of Jadelle before menarche.

One sterile Jadelle package contains two sterile implants packed in a pouch. Training is required for the insertion and removal procedures, which should preferably be done by a health care 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. A transverse incision of 2 mm is made in the skin with a scalpel. The implants are placed with the trocar subdermally, in the shape of a V opening towards the armpit. Proper insertion will facilitate later 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.

4.2.2 Dosage regimen

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/COC), vaginal ring or transdermal patch

Jadelle should preferably be inserted on the day after the last active tablet of previous combined oral contraceptive but at the latest on the day after the 7th day of the tablet free interval or placebo tablet. 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 another progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill, from another implant or the IUS on the day of its removal, 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 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 the Jadelle method 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 5 years from the insertion at the latest. The implants may be removed at any time of the menstrual cycle. Loss of contraceptive effect occurs practically immediately, and another contraceptive method should be applied 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 2 - 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 the 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.

4.3 Contraindications

- Hypersensitivity to levonorgestrel or any other component of Jadelle, mentioned in section 6.1
- 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 tumors (benign or malignant)
- Known or suspected sex hormone-dependent malignancies
- Undiagnosed vaginal bleeding

4.4 Special Warnings and Precautions for use

4.4.1 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 should be considered after 4 years of use, especially with women weighing over 60 kg (see section '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 have 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 section '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 centimeters) 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.

Special caution should be observed in prescribing Jadelle implants for patients with recognized 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 antihypertensive 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.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment. 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 amenorrhea have been reported. In general, such irregularities decrease with continuing use. Significant blood loss leading to anemia is rare, and average concentrations of hemoglobin normally rise slightly in Jadelle users.

Since some users of Jadelle experience periods of amenorrhea, 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 amenorrhea 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, hemolytic-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 using combined oral contraceptives (COCs), mainly using 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 dignosed in ever-users tends to be less advanced clinically than the cancers diagnosed in never-users.

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

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.

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.

4.4.2 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 physician 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.

4.4.3 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 immobilization for some other reason.

4.4.4 Instructions for 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 medicinal products and other forms of interaction

4.5.1 Effects of other medicinal products on Jadelle

Interactions can occur with drugs 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 drugs 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 drug 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 already be observed after a few days of treatment.

Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy 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.
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.

4.5.2 Effects of Jadelle on other medicinal products

Jadelle may affect the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

4.5.3 Other forms of interactions

Laboratory Test
The use of contraceptive steroids may influence the results of certain laboratory tests.

4.6 Fertility, pregnancy and lactation

4.6.1 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 OCs containing levonorgestrel prior to pregnancy, nor of a teratogenic effect when OCs were inadvertently used during pregnancy. No studies are available on the effect Jadelle during or prior to pregnancy.

4.6.2 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.

4.7 Effects on ability to drive or use machines
No effects on ability to drive and use machines have been observed.

4.8 Undesirable Effects
4.8.1 Summary of the safety profile
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 amenorrhea), cervicitis, vaginal discharge, genital pruritus, pelvic pain, breast pain, weight gain.

4.8.2 Tabulated list of adverse reactions

Organ system	**Common undesirable effects >1/100, <1/10**	**Uncommon undesirable effects >1/1000, <1/100**	**Rare undesirable effects >1/10000, <1/1000**
Psychiatric	mood changes, depression, changes in libido		
Nervous system	migraine		
Cardiac	palpitation, chest pain		
Vascular	hypertension, varicose veins		
Respiratory	dyspnea		
Gastrointestinal	abdominal discomfort		
Hepato-biliary	rise in total serum bilirubin		

Skin	acne, contact dermatitis, alopecia, hypertrichosis, rash, pruritus, skin discoloration		
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

4.8.3 Description of selected adverse reactions

Expulsion or displacement of Jadelle may be possible (see also section '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 also section 'Special warnings and precautions for use').

4.9 Overdose

There is no experience of overdose with Jadelle.

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 multicenter 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, 0.0 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.

5.2.1 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.

5.2.2 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.

5.2.3 Metabolism / Biotransformation
Levonorgestrel (LNG) is extensively metabolized. 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 LNG. The available in vitro data suggest that CYP mediated biotransformation reactions may be of minor relevance for LNG compared to reduction and conjugation.

5.2.4 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 feces (16 to 48%). After removal of the implants, serum levonorgestrel concentrations decrease below 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 other parts of the CCDS.
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
Colloidal anhydrous silica.
Silicone elastomers

6.2 Incompatibilities
Not applicable

6.3 Shelf Life and Storage Conditions
Please refer to labels.

Do not store above 30°C

6.4 Nature and contents of container
The implants are flexible, sealed, white or off-white rods, about 43 mm in length and 2.5 mm in diameter.

The sterile implants are packed in a moulded polyethylene terephtalate blister package sealed with a coated, spunbonded polyethylene film.

Manufacturer
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