SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Jadelle® sine inserter 2 x 75 mg implant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The product consists of two implants. Each implant contains 75 mg levonorgestrel.

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

For a full list of excipients, see section 6.1.

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 Therapeutic indications

Contraception.

Clinical efficacy and safety have been established in women aged 18 to 40 years.

4.2 Posology and method of administration

For subcutaneous use.

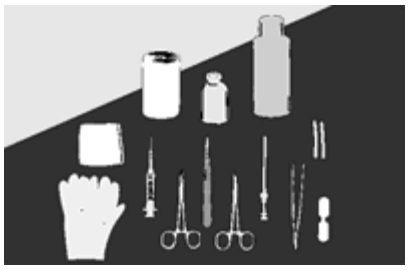
Jadelle is a contraceptive method for long-term (up to five years) use (see section 4.4). The user must be informed that Jadelle implants may be removed at her request at any time.

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

Instructions for insertion of Jadelle implants

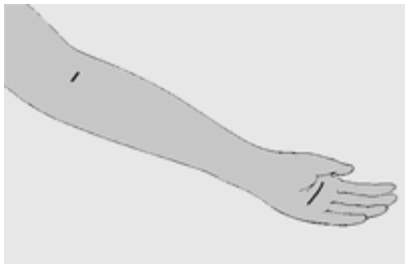
One Jadelle package contains two sterile implants packed in a pouch. Training is required for the insertion and removal procedures, which should preferably be done by a health care professional and the given instructions must be followed closely. The implants are inserted with the disposable sterile 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 anaesthesized. 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.



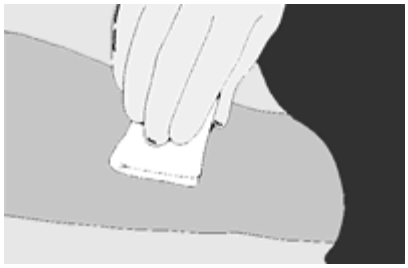
Picture 1
The following equipment is needed for the insertion of Jadelle implants.

- a table for the patient to lie on, and another table or a rest for her arm
- sterile surgical cloths, a sterile tray for the equipment, sterile gloves (free of talc), antiseptic solution for the skin
- local anaesthetic, an anaesthetic needle (5–5.5 cm long) and a 5-ml syringe
- Jadelle Trocar, a scalpel with blade, tweezers
- a skin closure, gauze and compresses.



Picture 2

Ask the patient to lie down on the table with her non-dominant arm extended on a sterile cloth on the other table, at right angles to her body. The implants will be inserted subdermally through an incision, in the shape of a narrow V opening towards the armpit.

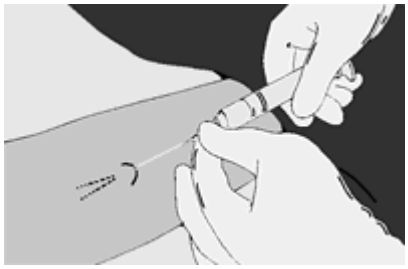


Picture 3

Clean the patient's arm with an antiseptic solution, and cover the arm with either two sterile cloths or a sterile fenestrated drape. The optimal insertion area is in the inner aspect of the upper arm, between the muscles, about 6–8 cm above the fold in the elbow.

Picture 4

Open the 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. NOTE: Always use sterile gloves or forceps when handling the implants. If a rod is contaminated, e.g. falls on the floor, it must be disposed of. Open a new package and continue with the procedure.



Picture 5

First determine any known allergies to the anaesthetic agent or related medicinal products. Fill the syringe with about 2–4 ml of local anaesthetic. Anaesthetize the insertion area by inserting the needle just under the skin about 5 to 5.5 cm in the directions where you are planning to introduce the trocar.

Picture 6

Make a small 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 scapel, though it is not recommended for Jadelle sine inserter.

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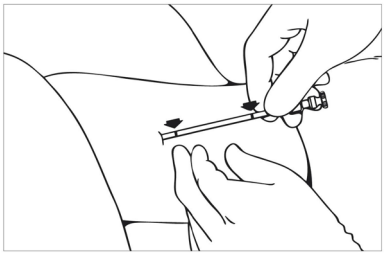


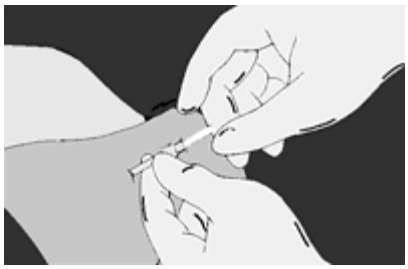
Picture 7

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

Picture 8

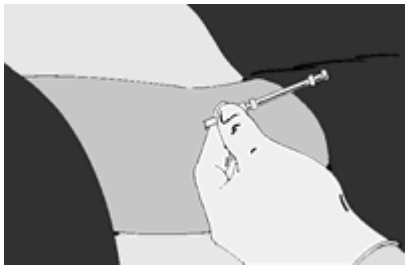
Once the tip of the trocar is beneath the skin, direct it along the skin so that the implants will be placed just beneath the skin. Throughout the insertion procedure, the trocar should be oriented with the bevel up. It is important to hold the trocar just beneath the skin by the tenting the skin with the trocar, because otherwise the implants may be inserted too deep and their removal is more difficult.

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



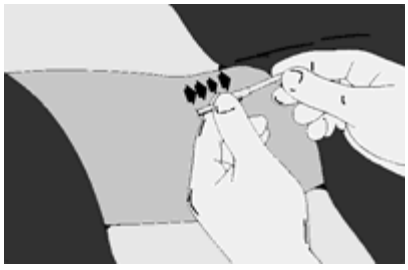
Picture 9

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



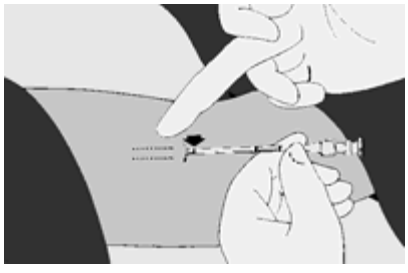
Picture 10

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



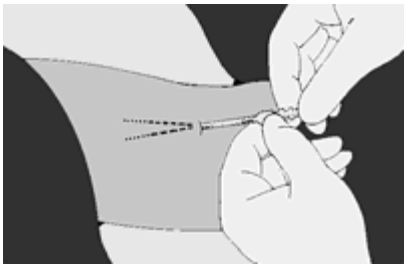
Picture 11

Hold the plunger steady and pull the trocar cautiously back along it until it touches the handle of the plunger. It is important to keep the plunger steady and not push the implant into the tissue. Pull the trocar only up to the mark near the tip. Remove it completely only after both implants have been inserted.



Picture 12

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



Picture 13

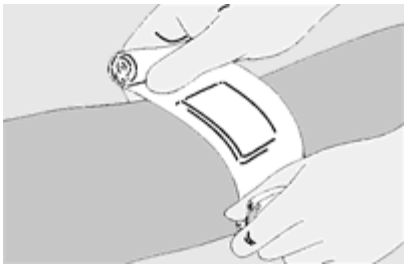
Insert the second implant at the side of the first one to form a V shape. Follow the previous implant with your left-hand forefinger and advance the trocar along the side of the finger. This will ensure a suitable distance between the implants.

To prevent expulsions, leave a distance of about 0.5 cm 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 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 compresses, and wrap enough gauze around the arm to ensure haemostasis. Observe the patient at the clinic for a few minutes before she is discharged.

Advise the patient to keep the insertion area dry for three 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, usually after 3–5 days.

Starting the use of Jadelle implants

No preceding hormonal contraceptive use in the past month
Jadelle implants should be inserted within seven 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 seven days after the insertion.

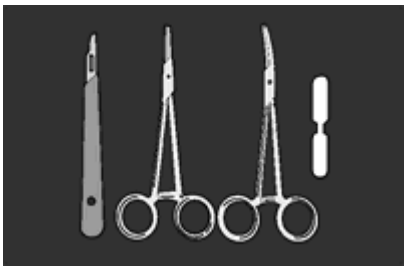
Changing from a combined hormonal contraceptive (combined oral contraceptive /COC), vaginal ring or transdermal patch
Jadelle should preferably be inserted on the day after the last active tablet of previous combined oral contraceptive but at the latest on the day after the 7th day of the tablet free 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)
The woman may switch any day from the minipill, from another implant on the day of its removal, and from an injectable when the next injection is due.

Following first-trimester abortion
Jadelle may be inserted immediately. When doing so, no additional contraceptive measures are needed.

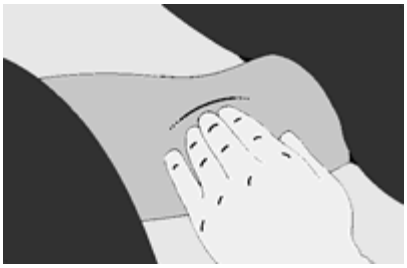
Following delivery or second-trimester abortion
Jadelle may be inserted immediately after childbirth or second-trimester abortion. If inserted later than 21 days after childbirth, pregnancy should be reliably excluded and additional non-hormonal contraceptive precautions taken for a minimum of seven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

Removal of Jadelle implants
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 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 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.



Picture 16

The following equipment is needed for removal:
- local anaesthetic, an anaesthetic needle and a syringe
- a scalpel
- two different types of forceps (Mosquito and Crile)
- a skin closure, gauze and compress

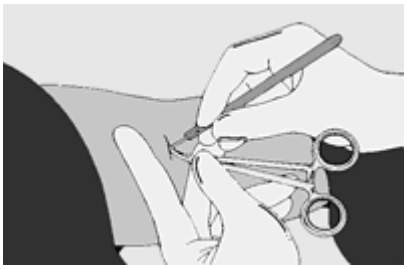


Picture 17

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.

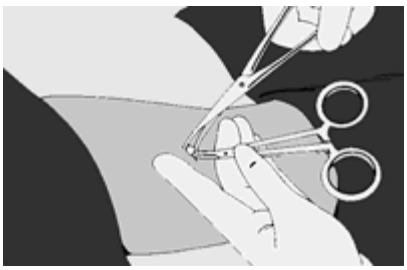
Picture 18

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



Picture 19

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



Picture 20

Grasp the end of the implant 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. The length of Jadelle implants is 43 mm. This will ensure that the patient has had two Jadelle implants and not other contraceptive implants.
After the procedure is completed, close the incision and bandage it as after incision. The arm should be kept dry for a few days.

Following removal, pregnancy may occur at any time.

4.3 Contraindications

Hypersensitivity to levonorgestrel or any other component of Jadelle,
undiagnosed vaginal bleeding,
diagnosed or suspected sex hormone dependent neoplasia,
presence or history of severe hepatic disease as long as liver function values have not returned to normal
benign or malignant liver tumour,
thromboembolic disease.

4.4 Special warnings and special 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 should be considered after four years of use, especially in women weighing over 60 kg (see 5.1). The serum levonorgestrel concentration is lower at the end of the implant use and it is inversely related to the user's body weight.

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) and 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.
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. Patients who develop thrombotic or embolic disease 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.

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 implants, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, the use of Jadelle implants 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 loss of vision 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 tests have 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. A 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 hormones may cause some degree of fluid retention, which may result in weight gain. The use of Jadelle should be considered carefully in 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 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 must 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, 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.

Even though there is no clear causal connection between the use of oral contraceptives and breast cancer, a meta-analysis of 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). The increased risk gradually disappears during the course of 10 years after cessation of COC use. The risk of having breast cancer diagnosed in progestogen-only contraceptive users is possibly of a similar magnitude to that associated with COCs.

Precautions
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 and precautions 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. Women with a family history of breast cancer or who have benign breast nodules or mastopathy should be monitored with particular care.

Women should be advised that Jadelle implants do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

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 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.

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 levornorgestrel (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.

Jadelle users should be warned of the possibility of decreased contraceptive efficacy when using medicinal products exhibiting enzyme-inducing activity such as those mentioned above: Breakthrough bleeding and unintended pregnancies have been reported.

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.

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

When co-administered with sex hormones, many HIV/HCV protease inhibitors and non-nucleoside 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.

4.5.2 Effects of Jadelle on other medicinal products

Jadelle may affect the metabolism of other medicinal products. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).
Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

4.5.3 Other forms of interaction

*Laboratory test*s

The use of contraceptive steroids may influence the results of certain laboratory tests. Jadelle implants may have the following effects on the results of some endocrine laboratory tests:

1. Reduce the concentration of SHBG (sex hormone binding globulin)
2. Decrease thyroxine concentration in serum and elevate the values in triiodothyronine binding test.

4.6 Pregnancy and lactation

The implants must be removed if pregnancy occurs during the use of Jadelle. Animal studies have shown that very high doses of progestogenic substances may cause masculinization of female foetuses. The results of most epidemiological studies to date with relevant inadvertant foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or foetotoxic effect. No studies are available on the effect of Jadelle during or prior to pregnancy.

Levonorgestrel passes into milk, but at therapeutic doses of Jadelle no effects on the breastfed newborns/infants are anticipated. 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 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):

Disturbance of menstrual bleeding patterns, such as frequent, irregular or prolonged menstrual bleeding, spotting, oligomenorrhoea or amenorrhoea, are the most common undesirable effects, occurring in the majority of users during the first year. 14% of users discontinued the use of Jadelle because of bleeding pattern disturbances during five years. Other very common undesirable effects are: headache, nervousness, dizziness, nausea, cervicitis, vaginal discharge, genital pruritus, pelvic pain, breast pain, weight gain.

Organ system	Very common undesirable effects >1/10	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, dyspareunia		
Nervous system	headache, nervousness, dizziness	migraine		
Cardiac		palpitation, chest pain		
Vascular		hypertension, varicose veins		
Respiratory		dyspnoea		
Gastrointestinal	nausea	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		
Reproductive system and breast	Disturbance of menstrual bleeding patterns, such as frequent, irregular or prolonged menstrual bleeding, spotting, oligomenorrhoea or amenorrhoea, cervicitis, vaginal discharge, genital pruritus, pelvic pain, breast pain	vaginitis, ovarian cysts, benign breast nodules, breast discharge		
General disorders and administration site	weight gain	itching near the insertion site, general pain, fatigue, backpain, weight loss	bruising at insertion site, infection at insertion 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 migration of Jadelle may be possible (see also section 4.4).

On rare occasions, ectopic pregnancies have been reported (see also section 4.4 Special warnings and precautions for use).

In users of similar levonorgestrel implants in various countries, limited blistering, ulceration or 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 4.4).

The occurrence of chloasma has been reported with the use of other levonorgestrel implants.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no experience of overdose with Jadelle.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens, levonorgestrel

ATC code: G03AC03

The active ingredient in Jadelle implants, levonorgestrel, is a synthetic progestogen. The levonorgestrel released from the implants 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 clinical multicentre trials involving 1393 women observed for 4657 woman-years. 525 women completed five years of use. The Pearl index during five years was 0.17 per 100 woman-years (95% confidence interval 0.04–0.30). During the fifth year, the annual Pearl index was 0.84 per 100 woman-years (95% confidence interval 0.09–1.57). The annual pregnancy rate per 100 users was 0.1 ± 0.1 at one, two and three years, 0.0 ± 0.0 at four years, and 0.8 ± 0.5 (SE) at five years. Regarding the different weight groups, the annual pregnancy rate during year 5 was 0.9 ± 0.9 per 100 users weighing less than 50 kg, 0.5 ± 0.5 per 100 users weighing 50–59 kg, 1.1 ± 0.7 per 100 users weighing 60–69 kg, and 1.1 ± 1.1 per 100 users weighing 70 kg or more. In all women with body weight of 60 kg or more, the annual pregnancy rates per 100 users were 0.2 ± 0.2 during year 1, 0.2 ± 0.2 during year 2, 0.3 ± 0.3 during year 3, 0.0 ± 0.0 during year 4, and 1.1 ± 0.6 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 three 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.

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 twofold 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.

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.

Elimination

There is wide interindividual variation in the metabolic clearance rate. This is believed to be the reason for the wide variation in the 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 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 sections of the SmPC.

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

Polydimethyl siloxanes
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The two sterile implants are packed into a bag manufactured from a spunbonded PE film and a PET/PE film.

6.6 Special precautions for disposal and other handling

Information on insertion and removal is provided in section 4.2.

7. DATE OF REVISION OF THE TEXT

May 2021