RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH028 trade name][†]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The product is a set of two rods, each containing 75mg of levonorgestrel, the active ingredient, for a total of 150mg.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sub-dermal implant

The implant is a set of two flexible, cylindrical, sealed, white or off-white rods. Each implant is about 44 mm in length and 2.4 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception

Safety and efficacy of [RH028 trade name] have been demonstrated for 3 years of use.

4.2 Posology and method of administration

Posology

For subdermal use.

[RH028 trade name] is a contraceptive method for three years of use. Once the implants are inserted they may be removed at the request of the user at any time (see 4.4 Special warnings and precautions for use).

Method of administration

Instructions for insertion and removal of the implants

One [RH028 trade name] pouch contains two sterile rods. Only health care providers trained in both insertion and removal should perform these procedures. Aseptic technique must be followed during implant insertion and removal to prevent infection. Contaminated waste must be properly disposed of and instruments and other items should be decontaminated, thoroughly cleaned, and sterilized by autoclaving or dry heat, or high-level disinfected.

Preparation for implant insertion

The following sterile instruments and supplies are needed for insertion of implants:

- sterile dry surgical drape;
- a sterile tray for the equipment;
- a bowl for the antiseptic soaked cotton balls;
- sterile pair of surgical gloves (free of talc);
- a 3-5 mL syringe and a 5-5.5 cm long needle (22-gauge);
- filter needle (if local anesthetic is supplied in glass ampule);

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

- a scalpel with blade;
- tweezers;
- a skin closure or adhesive bandage or gauze with surgical tape;
- gauze and compresses and
- set of two rods in sterile pouch.

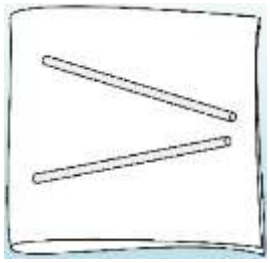
The following non-sterile supplies are recommended for insertion of implants:

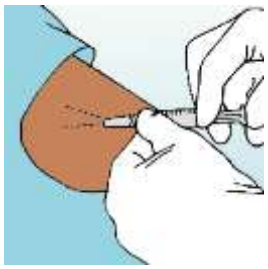
- examining table for the patient to lie on;
- soap for washing the arm;
- ballpoint pen or marker;
- antiseptic solution for the skin and
- 2mL local anesthetic.

Getting ready for insertion procedure

- Explain the procedure to the client and encourage questions.
- Determine that required sterile or high-level disinfected instruments and implants are present.
- Wash hands thoroughly and dry them.
- Check to be sure that the client has thoroughly washed and rinsed her entire arm.
- Position the woman's arm and place a clean, dry cloth under her arm.
- Mark position on arm for insertion of rods 6 cm to 8 cm above the elbow folder (this should form a "V" pattern).
- Put on sterile pair of hand gloves.

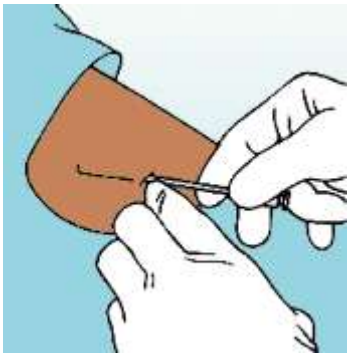
Pre-insertion tasks



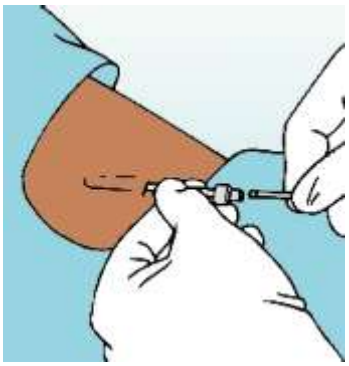


- Set up sterile field and place implant rods and trocar on it.
- Prep insertion site with antiseptic solution.
- Place sterile or high-level disinfected drape over arm.
- Inject 2mL of local anesthetic applied just under the skin, raising a wheal at the insertion point and advancing up to 5 cm along the first insertion track, injecting 1mL of local anesthetic along the track as you withdraw. Without completely removing the needle, reorient to the second insertion track, advance up to 5 cm, and again inject 1mL of local anesthetic along track as needle is withdrawn. Let the arm rest for approximately 5 minutes and check for anesthetic effect before making skin incision.

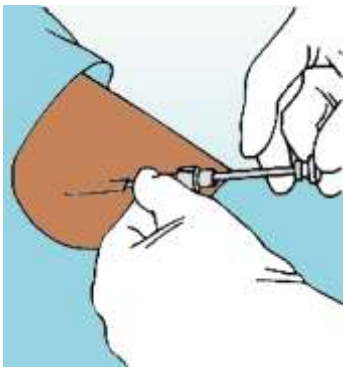
Step by Step implant insertion instructions:



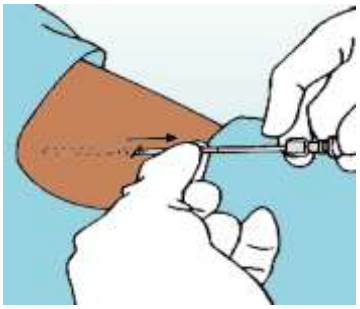
Step 1: Make a small incision with a scalpel in the skin on the inside of the upper arm. Alternatively, use the trocar to puncture the skin. Insert the tip of the trocar beneath the skin at a shallow angle. Gently advance the trocar superficially under the skin with the bevel facing up while tenting the skin. Tenting of the skin enables the implant to be placed under the skin and not deeper into the arm. The rod should be placed parallel to the skin. *Take great care not to insert trocar into the arm muscle. Note:* The trocar has two marks on it. The mark closest to the hub indicates how far the trocar should be introduced under the skin to place the implants. The mark closest to the tip indicates how much of the trocar should remain under the skin following placement of the first implant.



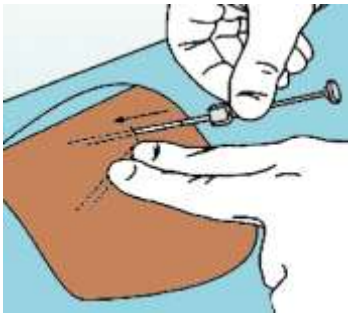
Step 2: When the trocar has been inserted to the mark closest to the hub, remove the obturator and load the first implant into the trocar, using thumb and forefinger.



Step 3: Using the obturator to push, gently advance the implant towards the tip of the trocar until you feel resistance. Never force the obturator.

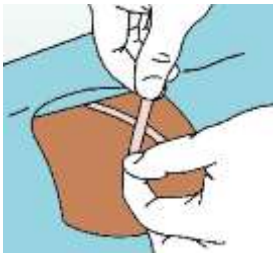


Step 4: Holding the obturator stationary, withdraw the trocar to the mark closest to the trocar tip. The implant should be released under the skin at this point. It is important to keep the obturator stationary and to avoid pushing the implant into the tissue. Do not completely remove the trocar until both implants have been placed.



Step 5: To place the second implant, align the trocar so that the second implant will be positioned at about a 30˚ angle relative to the first implant. Repeat steps 3-4. The rods are placed in the shape of a V opening toward the shoulder. Leave a distance of about 5 mm between the incision and the tips of the implants. Remove the trocar and immediately dispose of it in a sharps container.

Post-insertion tasks



- Remove drape and wipe the client's skin with alcohol.
- Bring edges of incision together and close it using surgical tape, then cover it with tape on a sterile gauze (2x2) or an adhesive bandage.
- Apply pressure dressing snuggly.
- Instruct client regarding wound care:
  - Keep the area around the insertion site dry and clean for at least 48 hours.
  - Leave the gauze pressure bandage in place for 48 hours and the surgical tape or adhesive bandage in place until the incision heals (normally 3-5 days).
- Discuss with the client what to do if she experiences any problems following insertion or side effects from the implant.
- Advise client that she can have the rods removed at any time if she desires.
- Make return visit appointment, if necessary.
- Observe the client for at least 15-20 minutes before discharging.

Timing of insertion

Implants may be inserted at any time during the menstrual cycle when it is reasonably certain that the client is not pregnant or at risk of being pregnant.

Note on backup methods of contraception

Extra "backup" contraceptive precautions should be advised in many circumstances, as outlined below. These should be described to the patient as including barrier methods (e.g. condoms) and refraining from sex altogether. The patient should be advised that the "rhythm" or "temperature" methods are *not* adequate for backup. (Changes in body temperature and cervical mucus that normally take place during the menstrual cycle may not occur during the use of [RH028 trade name] implants.)

No contraceptive use

If the woman has been using no contraception, advise her to use a backup method or refrain from sexual intercourse for 7 days after insertion**.**

- If insertion is done within 7 days of the start of the woman's usual monthly bleeding, there is no need for a backup method. If insertion is done more than 7 days after the start of the woman's usual monthly bleeding, a backup method should be used for the first 7 days following insertion.
- If the woman is switching from an IUD, she can have implants inserted immediately.

Switching from a hormonal method

- If the woman has been using a hormonal method consistently and correctly, or if it is otherwise reasonably certain that she is not pregnant, the implant may be inserted immediately. There is no need to wait for the next monthly bleeding. No backup method is needed.
- If switching from injectables, the woman can have implant inserted on the date when the repeat injection would have been given. There is no need for a backup method.

Switching from copper or Levonorgestrel IUD

- If the woman is currently in her first 7 days of monthly bleeding, insert the implant now and remove the IUD. There is no need for a backup method.
- If the implant is desired 7 days or more after the end of her last monthly bleeding and she has had intercourse since the last monthly bleeding, it may be inserted at once. The IUD should be left in place until after her next monthly bleeding.
- If the implant is desired 7 days or more after the end of her last monthly bleeding, and she has ***not*** had intercourse since the last monthly bleeding, the IUD can stay in place and be removed during her next monthly bleeding, or the IUD can be removed and she can use a backup method for the next 7 days.

Breastfeeding

- If the woman's monthly bleeding has not returned, she can have implants inserted any time between giving birth and 6 months, with no need for a backup method.
- If the woman's monthly bleeding has returned, she can have implants inserted as advised for women having menstrual cycles (see previous page).

No monthly bleeding (not related to childbirth or breastfeeding)

She can have implants inserted any time it is reasonably certain she is not pregnant. She will need a backup method for the first 7 days after insertion.

After miscarriage or abortion

Immediately.

- If implants are inserted within 7 days after first- or second-trimester miscarriage or abortion, there is no need for a backup method.

If it is more than 7 days after first or second trimester miscarriage or abortion:

- she can have implants inserted any time it is reasonably certain she is not pregnant. She will need a backup method for the first 7 days after insertion.

After taking emergency contraceptive pills (ECPs)

Implants can be inserted within 7 days after the start of her next monthly bleeding, or any other time it

is reasonably certain she is not pregnant. Give her a backup method, or oral contraceptives to start the day after she finishes taking the ECPs, to use until the implants are inserted.

Implant Removal

[RH028 trade name] should be removed after 3 years of use.

The implants can be removed, for personal or medical reasons, at the request of the client at any time. The implants should be removed by the end of the third year. Removal of implants can be done at any time in the menstrual cycle.

Preparation for implant removal

The following items are needed for removal:

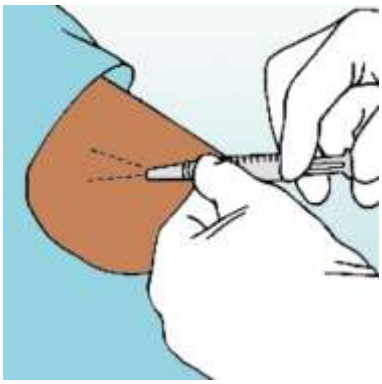
- examining table for the woman to lie on;
- soap for washing the arm;
- ballpoint pen or marker;
- sterile dry surgical drape;
- a bowl for the antiseptic solution;
- pair of sterile surgical gloves;
- antiseptic solution for the skin;
- 2 mL local anesthetic;
- a sterile tray for the equipment;
- a sterile 3-5 mL syringe and a 2.5-4 cm long needle (22-gauge);
- scalpel with #11 blade;
- 1 curved and 1 straight Crile or Kelly forceps;
- 1 tissue forceps (optional) and
- a skin closure or adhesive bandage or sterile gauze with surgical tape.

Removal procedure

Getting ready for removal procedure

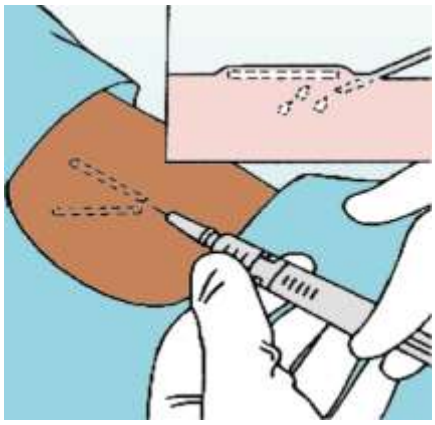
- Determine that required sterile or high-level disinfected instruments are present.
- Check that the client has thoroughly washed and rinsed her arm.
- Explain the procedure to the client and encourage questions.
- Position the woman's arm and place a clean, dry cloth under her arm.
- Palpate the rods to determine point of removal.
- Mark position on arm where the tip of the rods is palpated.

Pre-removal tasks



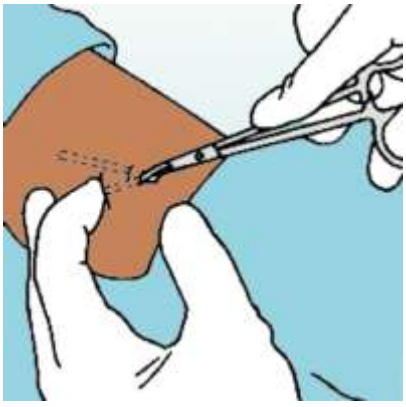
- Wash hands thoroughly and dry clean them.
- Put on sterile pair of hand gloves.
- Arrange instruments and supplies.
- Prep removal site with antiseptic solution twice.
- Place sterile or high-level disinfected drape over arm.
- Inject 1mL of local anesthetic applied at the incision site and under the end of the rods.
- Check for anesthetic effect before making skin incision.

Step by Step implant removal instructions:



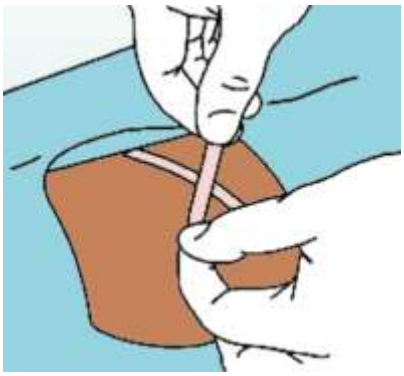
Step 1: Before starting the removal, the implants must be located by palpation with ungloved fingers and the position of each rod marked. To help view the proximal tip near the insertion incision (bottom of the V), push down on the distal end of the implant. After cleaning the skin with an antiseptic, a small amount of local anesthetic is infiltrated **under** the implant ends. Anesthetic injected over the implants may obscure their position and make removal more difficult.

Step 2: A **small** skin incision of 2-4 mm is made close to the ends of the implants (below the bottom of the V). Do not make a large incision.



Step 3: Push each implant gently with your fingers towards the incision. When the tip is visible in the incision, grasp it with the straight Crile/Kelly forceps and gently pull out the rod without twisting or pulling on the rod, as this may lead to rod breakage.

If the tip of the implant does not become visible in the incision, gently insert the curved Crile/Kelly forceps into the incision, trying to grasp the implant. Flip the forceps over with your other hand and with the scalpel, carefully dissect the tissue around the implant to expose it and then grasp the implant with the straight Crile/Kelly forceps. The implant can then be removed, being careful to avoid a twisting or pulling motion.



If the implant is encapsulated, grasp and stabilize the exposed rod with the curved Crile/Kelly forceps. Use the scalpel to very gently make a small incision into the tissue sheath to expose the tip of the rod. Use the tip of the scalpel to gently separate the encapsulated tissue from the rod, moving distally, keeping light but steady traction on the rod until the rod is completely freed from the tissue.

After the procedure is completed, close the incision and bandage it as after insertion. The arm should be kept dry for 24-28 hours.

NOTE: *Mosquito forceps can be used if Crile/Kelly forceps are not available; however, use of Crile/Kelly forceps has been shown to minimize damage to the implants during removal.*

The implants should be removed very gently. This will take more time than the insertion. The implants may be nicked, cut or broken 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 [RH028 trade name] may be inserted through the same incision, either in the same or in the opposite direction. Loss of contraceptive effect occurs practically immediately after removal, and another contraceptive method should be applied unless pregnancy is desired. Following removal, pregnancy may occur at any time.

4.3 Contraindications

- Hypersensitivity to levonorgestrel or any other component of [RH028 trade name]
- Current (history of) breast cancer
- Other diagnosed or suspected sex hormone-dependent neoplasia
- Severe liver disease, infection or tumor
- Thromboembolic disease
- Unexplained vaginal bleeding
- Systemic lupus erythematous with positive or unknown antiphospholipid antibodies

4.4 Special warnings and precautions for use

Warnings

Clinical trials have demonstrated the contraceptive efficacy of [RH028 trade name] for three years of use. 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.

Breakage of [RH028 trade name] at or near removal occurred at a rate of 16% over 4 years in the pivotal clinical trial.

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 levonorgestrel implants. 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 levonorgestrel implants on clotting factors have varied. In patients with a history of thromboembolic disease, [RH028 trade name] 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 [RH028 trade name] 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 [RH028 trade name] for patients with recognized risk factors for or any predisposition to arterial disease.

If a sustained hypertension develops during the use of [RH028 trade name] implants, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, the use of [RH028 trade name] 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 [RH028 trade name], 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 levonorgestrel implants in some studies. The clinical significance of these findings is unknown but diabetic patients using [RH028 trade name] should be carefully monitored. A gain in weight is possible during the use of [RH028 trade name].

If cholestatic hepatitis or jaundice develops in a patient with [RH028 trade name], 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.

Removal of [RH028 trade name] 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 [RH028 trade name] considered if clear symptoms develop.

Steroid hormones may cause some degree of fluid retention, which may result in weight gain. The use of [RH028 trade name] 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 [RH028 trade name].

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 [RH028 trade name], particularly if the patient is obese or has recently gained weight. If idiopathic intracranial hypertension is diagnosed, [RH028 trade name] should be removed.

[RH028 trade name] 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 [RH028 trade name] users.

Since some users of [RH028 trade name] 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 [RH028 trade name] 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 [RH028 trade name] 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.

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.

Large and small surgical procedures

[RH028 trade name] implants do not contain estrogen and, therefore, the use of [RH028 trade name], 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 [RH028 trade name] to patients. A copy of the leaflet should be given to each patient. The advantages and disadvantages of [RH028 trade name], 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

Effects of other medicinal products on [RH028 trade name]

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 [RH028 trade name] 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 [RH028 trade name] 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.

[RH028 trade name] 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) and diltiazem can increase plasma concentrations of the progestin.

Substances with variable effects on the clearance of levonorgestrel:
When co-administered, many HIV medications can decrease or increase plasma concentrations of levonorgestrel (decrease [e.g. nevirapine, etravirine, efavirenz], or increase [ritonavir, darunavir/ritonavir, lopinavir/ritonavir, atazanavir/ritonavir, tipranavir/ritonavir, and (fos)amprenavir/ritonavir, indinavir]). These changes may be clinically relevant in some cases.
(Note: Women with HIV were excluded from the pivotal clinical study.)

Effects of [RH028 trade name] on other medicinal products

[RH028 trade name] 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.

Other forms of interaction

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests. [RH028 trade name] 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 [RH028 trade name]. 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 inadvertent foetal exposure to combinations of oestrogens and progestogens indicate no teratogenic or fetotoxic effect. No studies are available on the effect of [RH028 trade name] during or prior to pregnancy.

Levonorgestrel passes over into milk but epidemiological studies to date have not revealed serious adverse effects on the child. Levels of levonorgestrel obtained with implants do not affect the quality or quantity of breast milk.

4.7 Effects on ability to drive and use machines

[RH028 trade name] has no effects on the ability to drive and use machines.

4. 8 Undesirable Effects

The following undesirable effect has been reported during the pivotal clinical trial with [RH028 trade name]:

Very common (occurring in more than 10% of users):

Breakage of the implant during or near removal.

The following very common undesirable effects have also been reported during clinical trials with LNG-releasing implants including [RH028 trade name]:

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. 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, lower abdominal pain	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 breasts	disturbance of menstrual bleeding patterns, such as frequent, irregular or prolonged menstrual bleeding, spotting, dysmenorrhoea, 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, breakage of implant during removal, implant site pain	itching near the insertion site, general pain, fatigue, 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
Infection and Infestations	Vaginal infection			
Musculoskeletal and connective tissue disorders	Back pain			

Expulsion or migration of [RH028 trade name] may be possible (see also section 4.4).

On rare occasions, ectopic pregnancies have been reported (see also section 4.4).

In users of similar levonorgestrel implants, 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, bilirubinaemia 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 is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions via their national authorities, or to the manufacturer at safety.dahua@ddreg.in.

4.9 Overdose
No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: progestogens, levonorgestrel

ATC code: G03AC03

The active ingredient in [RH028 trade name], levonorgestrel, is a synthetic progestin.
The primary pharmacologic action of levonorgestrel is its anti-fertility effect. Levonorgestrel has been shown to affect ovarian function in various ways. This ranges from: the absence of follicular and luteal activity through to normal follicular activity but deficient luteal activity to normal ovulatory patterns. Levonorgestrel causes thickening of the cervical mucus, thus preventing the passage of spermatozoa into the uterus. It also suppresses the endometrium and may prevent implantation of the blastocyst.

The contraceptive efficacy of [RH028 trade name] was studied in a population of 514 women assigned to use the product in the Dominican Republic. The Pearl Index (number of pregnancies per 100 woman years) for [RH028 trade name] during the first three years was 0.18 (95% confidence interval 0.20 to 0.65). However, during year four the Pearl index rose significantly to 3.54 (95% confidence interval 1.53 to 6.97). The overall Pearl Index over four years was 0.74 (95% confidence interval 0.36 to 1.37).

Pharmacokinetic values for levonorgestrel with [RH028 trade name] were significantly lower after 2 years than with the comparator product, Jadelle. The geometric mean ratios (GMR) for total levonorgestrel for [RH028 trade name] versus Jadelle at 24, 36 and 48 months were 0.81, 0.78 and 0.68.

5.2 Pharmacokinetic properties

Absorption
Levonorgestrel is released from the [RH028 trade name] directly into tissue fluid. Maximum plasma levonorgestrel concentrations of approximately 833 ± 367 pg/mL are reached about 5.4 days after insertion. After the initial phase, levonorgestrel concentrations decline to 430 ± 205 pg/mL within one

month, 351 ± 210 pg/mL within six months, 311 ± 197 pg/mL within one year. Plasma levonorgestrel concentrations are inversely related to body weight. However, due to the great variation in plasma levonorgestrel concentrations and in individual response, plasma concentrations alone are not predictive of the risk of pregnancy in an individual woman. Considerable inter- and intra-individual variation occurs, and serum drug concentrations are affected by individual clearance rates and body weight, among other factors. In [RH028 trade name] users, plasma levonorgestrel concentrations are substantially below those observed in women taking oral contraceptives containing levonorgestrel.

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

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

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Dimethylsiloxane/methylvinylsiloxane copolymer core
Silicone tubing
Polydimethylsiloxane adhesive

6.2 Incompatibilities
Not applicable

6.3 Shelf life
60 months

6.4 Special precautions for storage
Do not store above 30°C.

Keep the product in the provided outer carton to protect from light

Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

[RH028 trade name] is supplied in a sterile primary package containing a set of two levonorgestrel implant-rods. The primary package is a laminated pouch of Polyethylene Terephthalate (PET) and Polyethylene (PE) designed for pharmaceutical packaging. Ten sets of [RH028 trade name] are packaged in a cardboard secondary package. CE marked disposable trocars are supplied separately with [RH028 trade name] in a 1:1 ratio, and it is not assessed by prequalification.

6.6 Special precautions for disposal and other handling

Information on insertion and removal is provided in section 4.2.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Shanghai Dahua Pharmaceutical Co. Ltd.
3503 Changzheng Road, Chongming County
Shanghai, China
Email: distribution@dahua-sh.com
Telephone: 86-21-5931-1132
Fax: 86-21-5931-1132

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

RH028

9. DATE OF FIRST PREQUALIFICATION

30 July 2017

10. DATE OF REVISION OF THE TEXT

September 2021.

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines