Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levosert SHI 52mg Intrauterine Delivery System

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is levonorgestrel.

The intrauterine delivery system contains 52 mg levonorgestrel. The initial release of levonorgestrel is approximately 20 micrograms per day and declines progressively by about 60 % after 6 years.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intrauterine delivery system (IUS).

The product consists of levonorgestrel IUS (Figure 1b) and an inserter. The inserter is partially preloaded with the levonorgestrel IUS. The IUS consists of a T-shaped polyethylene frame (T-frame) with a drug reservoir around the vertical stem (Figure 1a). The drug reservoir is covered by an opaque membrane. The T-frame has an eyelet at one end of the vertical stem and two horizontal arms at the other end. A blue removal thread is attached to an eyelet at the end of the vertical stem of the T-frame. The T-frame of Levosert SHI contains barium sulphate, which makes it visible in X-ray examination.
The size of the T-body is 32x32 mm and the diameter of the insertion tube is 4.8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

Treatment of heavy menstrual bleeding. Levosert SHI may be particularly useful in women with heavy menstrual bleeding requiring (reversible) contraception.

4.2 Posology and method of administration

Starting treatment

In women of fertile age, Levosert SHI is inserted into the uterine cavity within seven days of the onset of menstruation. It can be replaced by a new system at any time of the cycle.

Post-partum insertion: To reduce the risk of perforation, postpartum insertions should be postponed until the uterus is fully involuted. Do not insert earlier than six weeks after delivery. If the patient is experiencing significant postpartum bleeding and/or pain then infection or other causes should be excluded before insertion. Levosert SHI can also be inserted immediately after the first trimester abortion.

Levosert SHI is effective for six years in the indication contraception and has a demonstrated efficacy for 3 years for the indication heavy menstrual bleeding. Therefore, Levosert SHI should be removed or exchanged after 6 years of use, or earlier if heavy or bothersome menstrual bleeding returns.

If the user wishes to continue using the same method, a new system can be inserted at the same time, in which case no additional protection is required.

Paediatric population
Levosert SHI has not been studied in patients below 16 years of age. Levosert SHI should not be used before menarche.

Hepatic impairment
Levosert SHI is contraindicated in patients with liver tumour or other acute or severe liver disease (see section 4.3).

Instructions for use and handling

Levosert SHI is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. If the seal of the sterile package is broken, the product should be discarded (see section 6.6 for disposal instructions).

How to insert Levosert SHI

It is strongly recommended that Levosert SHI should only be inserted by physicians/health care professionals who are experienced in levonorgestrel IUS insertions and/or have undergone sufficient training for levonorgestrel IUS insertion.

In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, please refer to section 4.4.

Levosert SHI is supplied sterile having been sterilised with ethylene oxide. Do not resterilise. For single use only. Do not use if the inner package is damaged or open. Insert before the last day of the month shown on the label.

Levosert SHI (figure 1a) is provided in a tray sealed with a peel-off lid, and is inserted with the provided inserter (figure 1b) into the uterine cavity by carefully following the insertion instructions.

The following insertion instruction will be provided in the box containing the IUS.

Please read the following instructions for use carefully as there may be some difference in the type of inserter device compared with other intrauterine devices (IUDs) you have used previously.

Description
Figure 1a: Levosert SHI Intrauterine Contraceptive System (IUS)

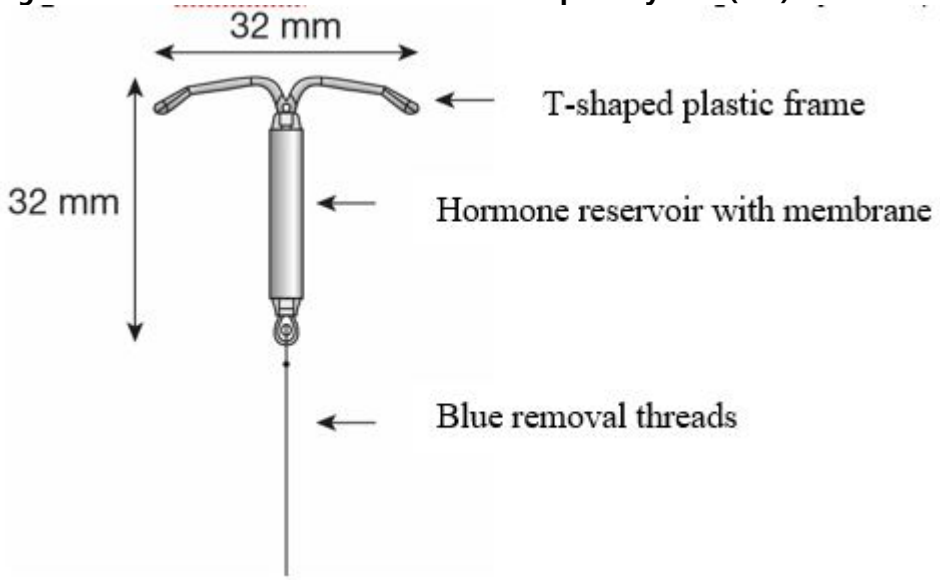

Figure 1b: Levosert SHI IUS with inserter

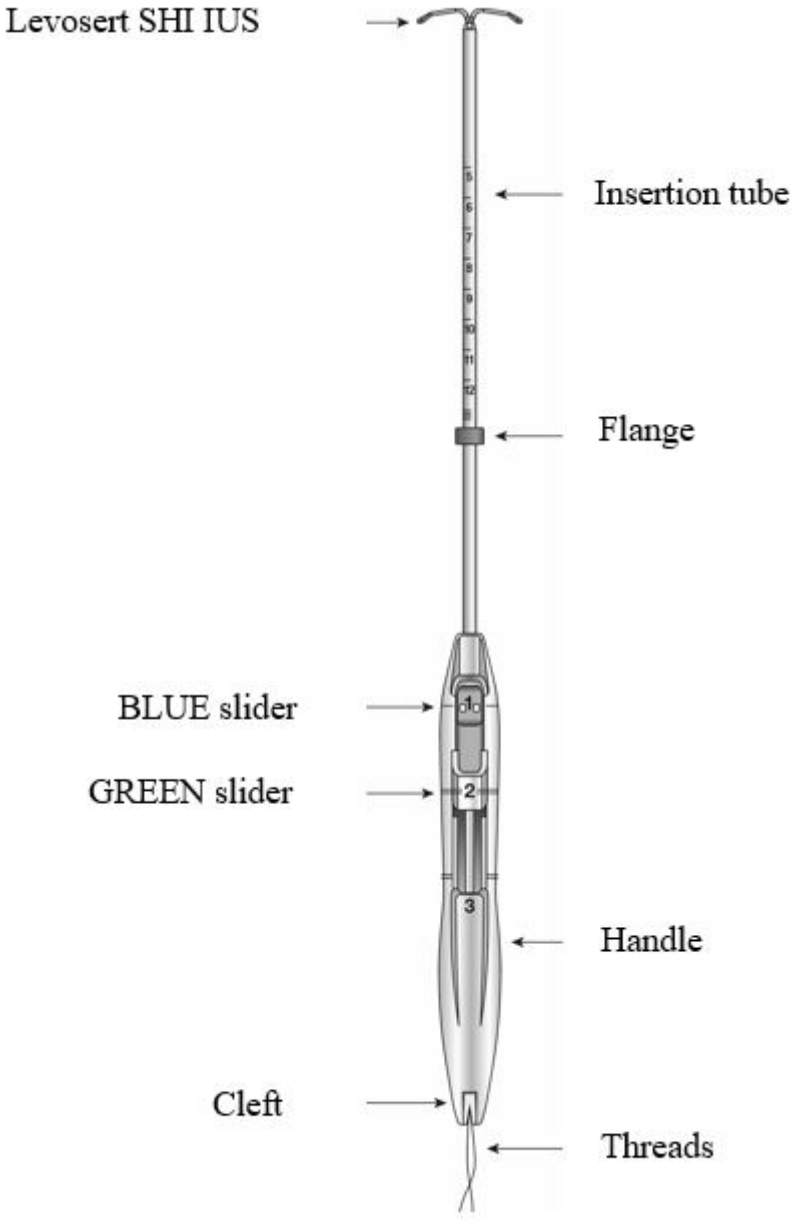

Figure 2: Inserter sliders

• Levosert SHI is packaged partially preloaded within the inserter. The threads are passed through the insertion tube, and exit through an opening in the handle at the cleft.

• The handle of the inserter contains a BLUE slider labelled with the number 1 and a GREEN slider labelled with the number 2, and the handle is labelled with the number 3 to assist with the insertion process.

• Moving the sliders achieves the positions required to complete the insertion process.

Conditions for use

1. In women of fertile age, Levosert SHI is inserted within seven days of the onset of menstruation. It can be replaced by a new system at any time of the cycle.
2. It is strongly recommended that Levosert SHI should only be inserted by physicians/health care professionals who have undergone sufficient training and have read carefully these instructions before Levosert SHI insertion.
3. Levosert SHI is supplied in a sterile packwhich should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. Do not use if the inner package is damaged or open.
4. Determine the position (anteversion, retroversion) and size of the uterus by a gynaecological examination. Exclude pregnancy and contraindications.
5. Place a speculum, use appropriate antiseptic solution to clean the vagina and cervix.
6. Use cervical dilators if cervical stenosis is diagnosed. Do not force to overcome resistance. If cervical dilatation is required, consider using analgesics and/or a paracervical block.
7. Grasp the cervix with a Tenaculum forceps and apply a gentle traction in order to straighten alignment of the cervical canal and uterine cavity.
8. Determine the uterine depth by hysterometry. If uterine depth is < 5.5 cm discontinue the procedure.

Preparation for insertion

Step 1: Opening the sterile Levosert SHI packaging

- Remove the sealed tray containing Levosert SHI from the box.
- Inspect the sealed tray and do not use the product if the packaging, inserter or IUS is damaged.
- Lay the tray on a flat surface with the peel-off lid side up.
- Remove peel-off lid.

Step 2: Removing inserter from tray (Figure 3)
Figure 3

• To remove the inserter from the tray, grasp the handle below the sliders and twist gently (Figure 3).

NOTE: Do not attempt to remove the inserter by pulling on the tube.

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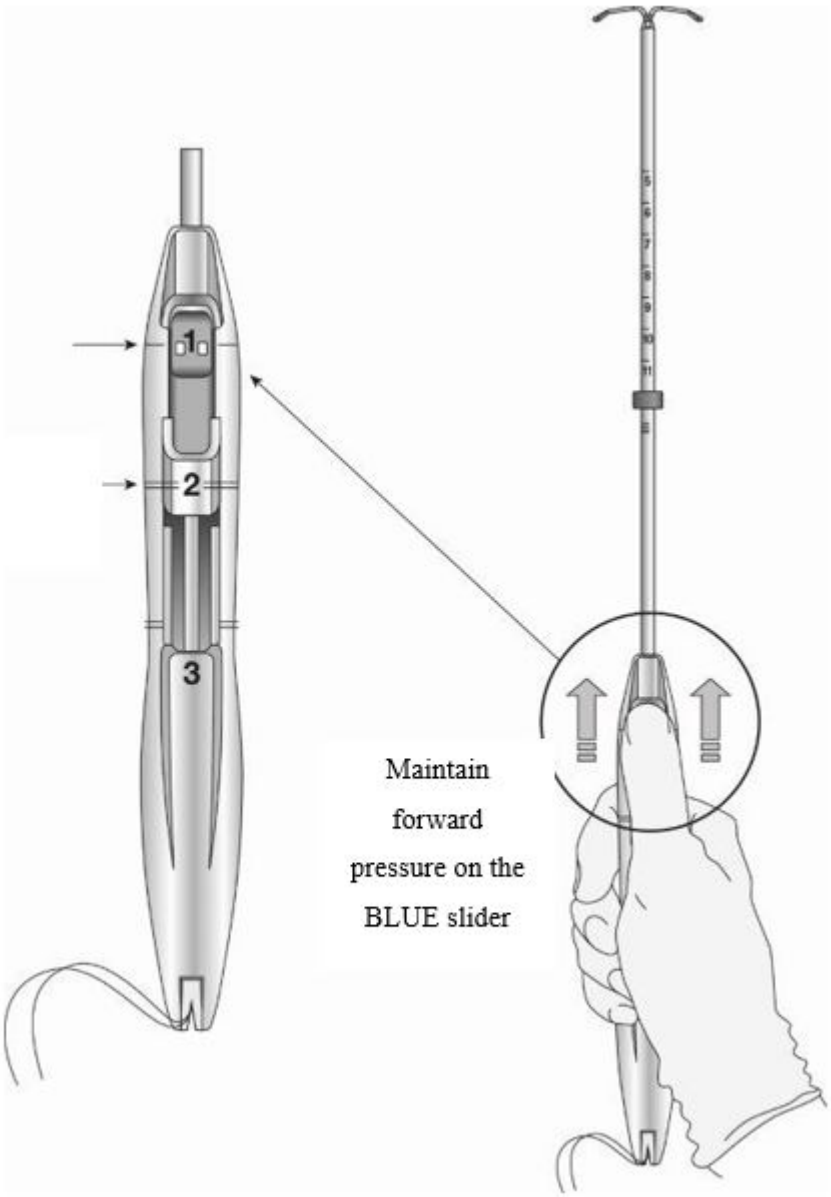
Step 3: Sliders completely forward for loading Levosert SHI (Figure 4)
Figure 4

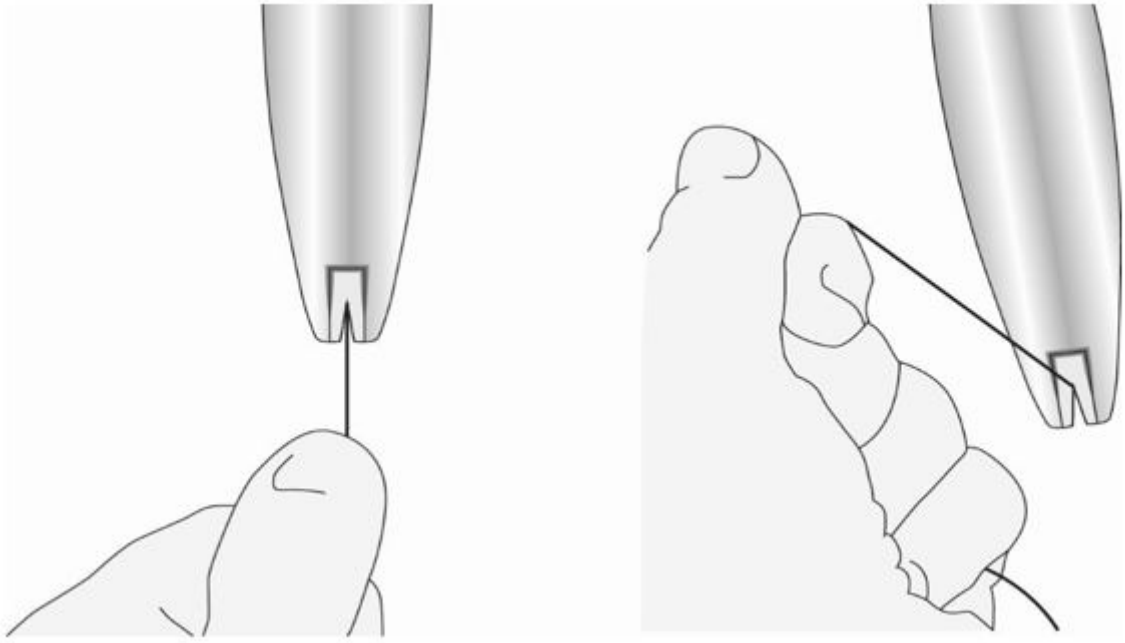


- The BLUE slider (labelled with the number 1) has a single line marking that will align with the handle's single line marking.
- The GREEN slider (labelled with the number 2) has a double line marking that will align with the handle's double line marking.
- Grip the handle keeping your thumb or finger in the groove of the BLUE slider (over the numeral 1) and apply **forward pressure** while ensuring both sliders are **fully forward**.

Step 4: Load Levosert SHI into the inserter

- Ensure the arms of the IUS are horizontal (aligned to the horizontal plane of the handle and flange); adjust the rotation of the IUS as needed using the flat sterile surface of the tray.
- While maintaining **forward pressure** on the blue slider, gently pull the threads **straight** back to load Levosert SHI into the insertion tube. Ensure even tension is applied to both threads when pulling. Pull the threads upward or downward to lock the threads into the cleft at the bottom end of the handle (Figure 5); you must **lock the threads** in the cleft to prevent the IUS from moving out of the top of the insertion tube. Once the threads are locked in the cleft, **stop holding the threads**.

Figure 5: Locking the threads in cleft

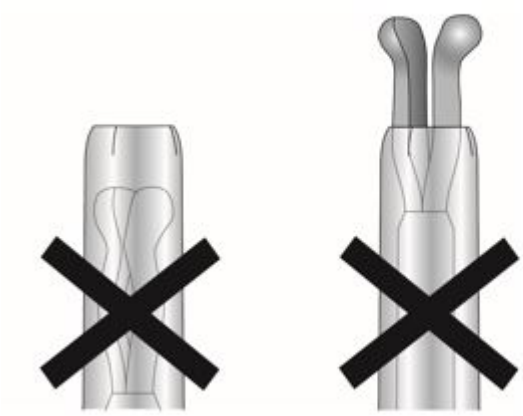


- After the IUS is loaded, continue to sustain **forward pressure** on the BLUE slider to maintain a hemispherical dome with the tips of the IUS.
- When correctly loaded, the IUS is completely within the insertion tube with the tips of the arms forming a hemispherical dome at the top of the tube (Figure 6, Zoom 1).

Figure 6: Position of the IUS in the insertion tube
Zoom 1

The knobs of the lateral arms must be closely opposed to each other, slightly above the upper extremity of the insertion tube (Zoom 1).

Zoom 2



• If the IUS is not correctly loaded (Zoom 2), *do not attempt insertion*.

• To re-load Levosert SHI:
- Pull the BLUE slider back with your thumb until the groove becomes aligned with the GREEN slider to release the IUS.
- Manually pull the threads out of the cleft.
- Return the BLUE slider to the forward position and repeat the loading steps.

Step 5: Adjusting the flange (Figure 7)
Figure 7

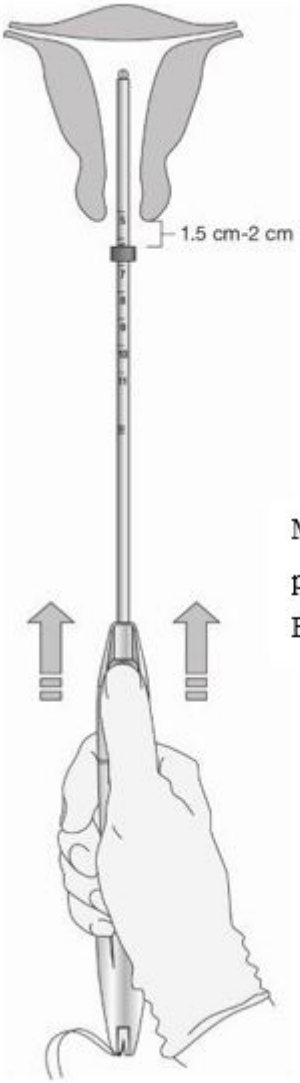
• Adjust the flange to the measured uterine depth based on sounding. To adjust, place the flat side of the flange in the tray notch (Figure 7) or against a sterile edge inside of the tray. Slide the insertion tube as necessary to move the flange to the correct measurement. Ensure the flat sides of the flange are in the same horizontal plane as the handle.

• If an adjustment to the curvature of the insertion tube is required to accommodate the anatomical orientation of the uterus, you may bend or straighten the insertion tube. When bending the tube, avoid sharp bends to prevent kinking.

• Once the flange has been properly positioned, avoid contact with flange against objects that can change its position (e.g. tray, speculum, tenaculum, etc.).

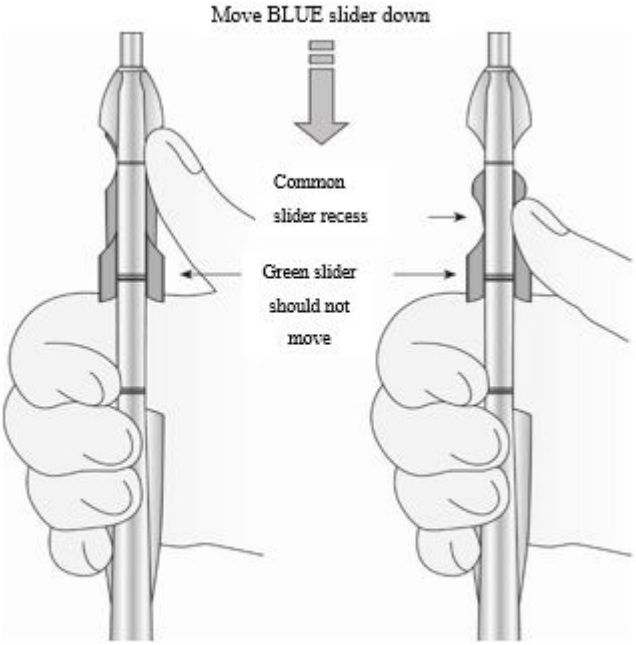
Note: If, at any step, there is a need to touch the flange or another sterile surface, sterile gloves should be used.

Step 6: Inserting Levosert SHI into the uterus (Figure 8)
Figure 8



• Apply gentle traction on the tenaculum and continue to apply **forward pressure** on the BLUE slider while inserting the loaded insertion tube through the cervical os. Advance the tube until the upper edge of the flange is 1.5-2 cm from the external cervical os (Figure 8). Maintain forward pressure on the BLUE slider throughout the insertion process.
- DO NOT advance flange to the cervix at this time.
- DO NOT force the inserter. If necessary, dilate the cervical canal.

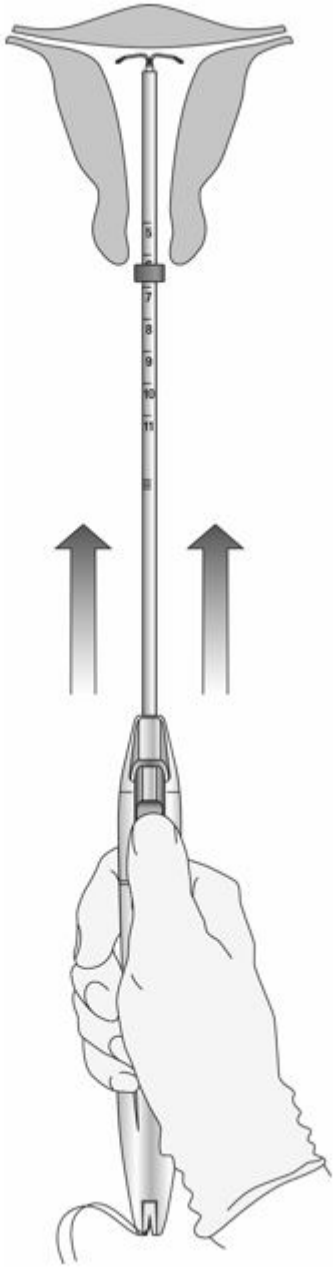
Step 7: Releasing and opening the arms of the IUS
Figure 9



- Using your thumb or finger, gently slide only the BLUE slider back until you feel resistance. The BLUE and GREEN sliders will merge together to form a common slider recess. Do not move the BLUE slider any more than is necessary to create the recess. Maintain the GREEN slider so that the double line markings on the slider and the insertion handle remain aligned (Figure 9). This will allow the IUS arms to open in the lower uterine segment. Do not pull the sliders back any further as this could result in premature release of the IUS at the incorrect location.

- Wait 10-15 seconds to allow for the arms of the IUS to fully open.

Figure 10: Move Levosert SHI into the fundal position

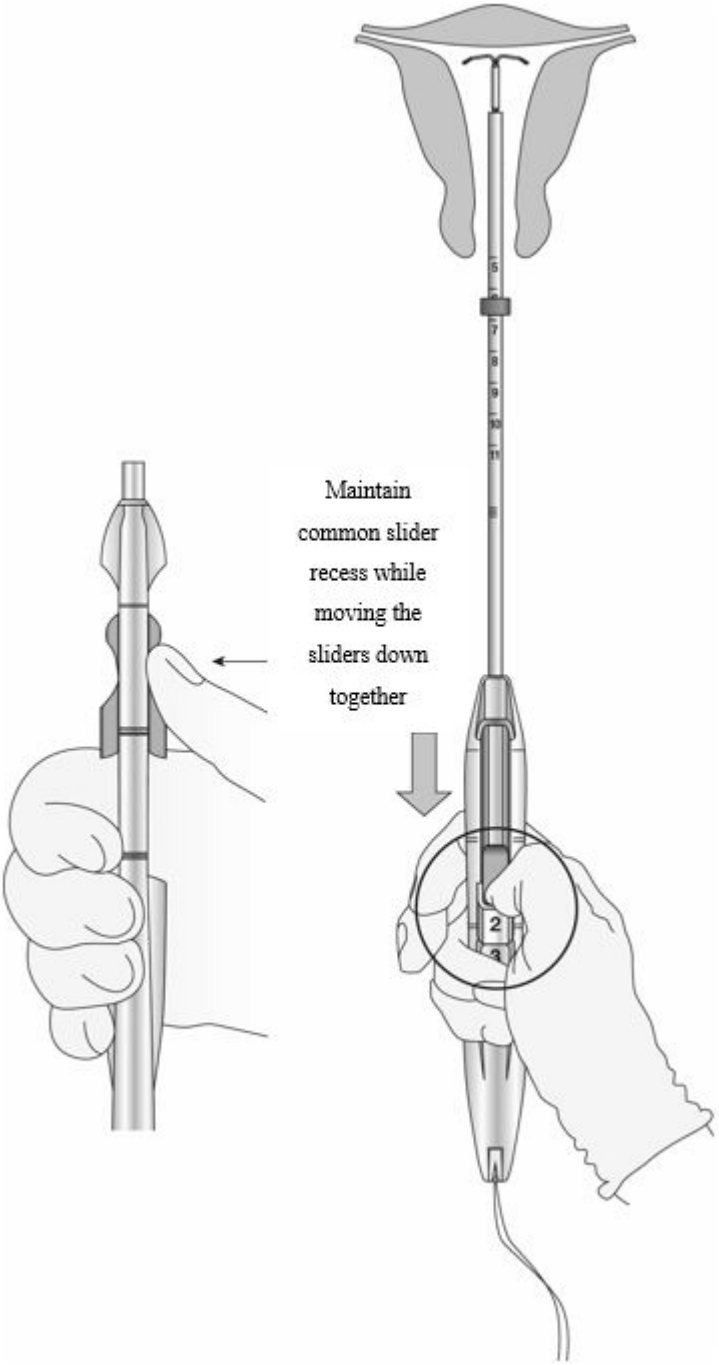


• Without moving the sliders, advance the inserter until the flange touches the cervix. If fundal resistance is encountered, do not continue to advance. Levosert SHI is now in the fundal position (Figure 10).

Note: Fundal position is important to prevent expulsions.

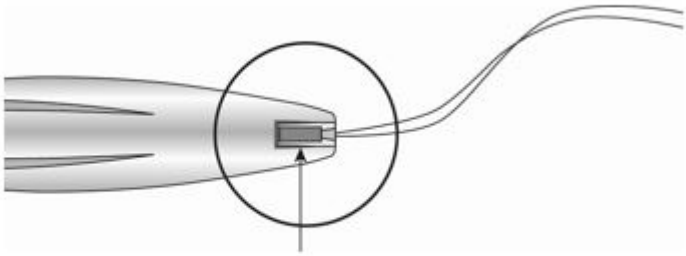
Step 8: Releasing Levosert SHI and procedure completion

Figure 11: Releasing Levosert SHI from the inserter tube



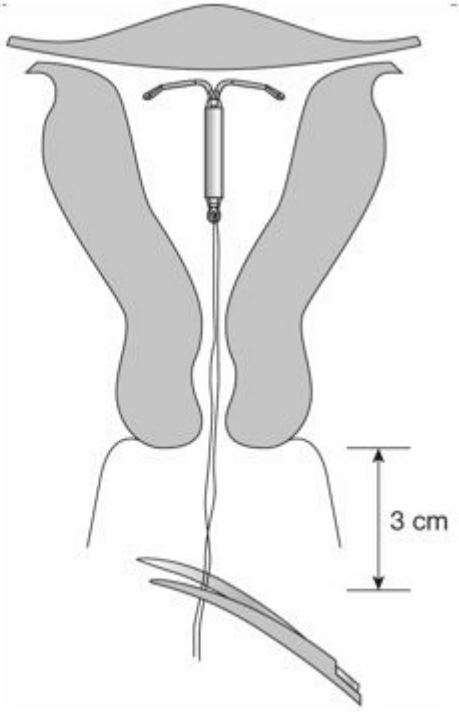
• While holding the inserter steady and maintaining its position relative to the cervix, move **both** sliders (BLUE and GREEN) together while maintaining the common slider recess down toward the number 3 on the handle (Figure 11) until a click is heard and the GREEN indicator at the bottom of the handle is visible (Figure 12).

Figure 12: Green indicator visible and threads released from cleft



• Look at the cleft to ensure the threads were properly released (Figure 12); if not released or if a click is not heard, grasp the threads and gently pull the threads out of the cleft.

Figure 13: Cut the threads about 3 cm from the cervix



• Withdraw the inserter from the uterus.

• Use blunt-tipped sharp scissors to cut the IUS threads perpendicular to the thread length, leaving about 3 cm outside of the cervix (Figure 13).

Note: Do not cut threads at an angle as this may leave sharp ends.

• Do not apply tension or pull on the threads when cutting to prevent displacing the IUS.

Insertion of Levosert SHI is now complete.

Important information to consider during or after insertion:

- If you suspect the IUS is not in the correct position:
- Check insertion with an ultrasound or other appropriate radiologic test.
- If incorrect insertion is suspected, remove Levosert SHI. Do not reinsert the same Levosert SHI IUS after removal.

IMPORTANT!

In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine body or cervix. If necessary remove the system and insert a new, sterile system.

Please report any case of uterine perforation or insertion difficulties via:

HPRA Pharmacovigilance

Website: www.hpra.ie

How to remove Levosert SHI

Levosert SHI is removed by gently pulling on the threads with forceps. If the threads are not visible and the device is in the uterine cavity, it may be removed using a narrow tenaculum or intrauterine thread retriever. This may require dilatation of the cervical canal.

If pregnancy is not desired, the removal should be carried out during the menstruation in women of fertile age, provided that there appears to be a menstrual cycle. If the system is removed in the mid-cycle and the woman has had intercourse within a week, she is at a risk of pregnancy unless a new system is inserted immediately following removal.

After removal of Levosert SHI, the device should be checked to ensure it is intact. During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them together inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

4.3 Contraindications

- Known or suspected pregnancy;
- Current or recurrent pelvic inflammatory disease;
- Lower genital tract infection;
- Postpartum endometritis;
- Infected abortion during the past three months;
- Cervicitis, cervical dysplasia;
- Suspected or confirmed uterine or cervical malignancy;
- Liver tumour or other acute or severe liver disease;
- Congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity;
- Undiagnosed abnormal uterine bleeding;
- Conditions associated with increased susceptibility to infections;
- Current or suspected hormone dependent tumours such as breast cancer (see section 4.4);
- Acute malignancies affecting the blood or leukaemias except when in remission;
- Recent trophoblastic disease while hCG levels remain elevated;
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Medical examination
Before insertion, a complete personal and family medical history should be taken. Physical examination should be guided by this and by the contraindications and warnings for use. Pulse and blood pressure should be measured and a bimanual pelvic examination performed to establish the orientation of the uterus. The patient should be re-examined six weeks after insertion and further examinations should be performed where clinically indicated and adapted to the individual woman rather than as routine procedure. Prior to insertion pregnancy should be excluded and genital infection should be successfully treated.
Women should be advised that Levosert SHI does not protect against HIV (AIDS) and other sexually transmitted disease (please refer to the section below on pelvic infections).
Women should be encouraged to attend cervical and breast screening as appropriate for their age.

Conditions under which Levosert SHI can be used with caution
Levosert SHI may be used with caution after specialist consultation, or removal of the system should be considered, if any of the following conditions exist or arise for the first time during treatment:
- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- Unusually severe or unusually frequent headache
- Jaundice
- Marked increase of blood pressure
- Malignancies affecting the blood or leukaemias in remission
- Use of chronic corticosteroid therapy
- Past history of symptomatic functional ovarian cysts
- Active or previous severe arterial disease, such as stroke or myocardial infarction
- Severe or multiple risk factors for arterial disease
- Thrombotic arterial or any current embolic disease
- Acute venous thromboembolism

Levosert SHI may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis.

Irregular bleedings may mask some symptoms and signs of endometrial polyps or cancer, and in these cases diagnostic measures have to be considered.

In general, women using Levosert SHI should be encouraged to stop smoking.

Insertion / removal warnings and precautions
General information: Insertion and removal may be associated with some pain and bleeding. In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine corpus or cervix (see also 'Perforation').

The procedure may precipitate fainting as a vasovagal reaction or a seizure in an epileptic patient. In the event of early signs of a vasovagal attack, insertion may need to be abandoned or the system removed. The woman should be kept supine, the head lowered and the legs elevated to the vertical position if necessary in order to restore cerebral blood flow. A clear airway must be maintained; an airway should always be at hand. Persistent bradycardia may be controlled with intravenous atropine. If oxygen is available it may be administered.

Perforation: Perforation of the uterine corpus or cervix may occur, most commonly during insertion, although it may not be detected until sometime later. This may be associated with severe pain and continued bleeding. If perforation is suspected the system should be removed as soon as possible; surgery may be required.

The incidence of perforation during or following Levosert SHI insertion in the clinical trial, which excluded breast-feeding women, was 0.1%.

In a large prospective comparative non-interventional cohort study in IUS/IUD users (N = 61,448 women), the incidence of perforation was 1.3 (95% CI: 1.1-1.6) per 1,000 insertions in the entire study cohort; 1.4 (95% CI: 1.1-1.8) per 1,000 insertions in the cohort for another LNG-IUS and 1.1 (95% CI: 0.7-1.6) per 1,000 insertions in the copper IUD cohort.
The study showed that both breast-feeding at the time of insertion and insertion up to 36 weeks after giving birth were associated with an increased risk of perforation (see Table 1). These risk factors were independent of the type of IUS/IUD inserted.

Table 1: Incidence of perforation per 1,000 insertions for the entire study cohort, stratified by breastfeeding and time since delivery at insertion (parous women)

	Breast-feeding at time of insertion	Not breast-feeding at time of insertion
Insertion ≤ 36 weeks after delivery	5.6 (95% CI 3.9-7.9; n=6,047 insertions)	1.7 (95% CI 0.8-3.1; n=5,927 insertions)
Insertion > 36 weeks after delivery	1.6 (95% CI 0.0-9.1; n=608 insertions)	0.7 (95% CI 0.5-1.1; n=41,910 insertions)

Breast-feeding at the time of insertion and insertion up to 36 weeks after giving birth were confirmed as risk factors also in the subgroup that were followed up for 5 years.

The risk of perforation may be increased in postpartum insertions (see section 4.2), in lactating women and in women with a fixed retroverted uterus.
Re-examination after insertion should follow the guidance given above under the heading "Medical examination" above, which may be adapted as clinically indicated in women with risk factors for perforation.

Pelvic infection: In users of copper IUDs, the highest rate of pelvic infections occurs during the first month after insertion and decreases later.
Known risk factors for pelvic inflammatory disease are multiple sexual partners, frequent intercourse and young age. Pelvic infection may have serious consequences as it may impair fertility and increase the risk of ectopic pregnancy. As with other gynaecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUS insertion, although this is extremely rare.

For women using Levosert SHI with symptoms and signs suggestive of pelvic infection, bacteriological examinations are indicated and monitoring is recommended even with discrete symptoms, and appropriate antibiotics should be started. There is no need to remove Levosert SHI unless the symptoms fail to resolve within the following 72 hours or unless the woman wishes Levosert SHI to be removed. Levosert SHI must be removed if the woman experiences recurrent endometritis or pelvic infection, or if an acute infection is severe.

Complications leading to failure

Expulsion: In clinical trials with Levosert SHI in the indication contraception, the incidence of expulsion was low (<4% of insertions) and in the same range as reported for other IUDs and IUSs. Symptoms of partial or complete expulsion of Levosert SHI may include bleeding or pain. However, a system can be expelled from the uterine cavity without the woman noticing it, leading to loss of contraceptive protection. As Levosert SHI decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion.

Risk of expulsion is increased in

- Women with history of heavy menstrual bleeding (including women who use Levosert SHI for treatment of heavy menstrual bleeding)
- Women with greater than normal BMI at the time of insertion; this risk increases gradually with increasing BMI

Woman should be counselled on possible signs of expulsion and how to check the threads of Levosert SHI and advised to contact a healthcare professional if the threads cannot be felt. A barrier contraceptive (such as a condom) should be used until the location of Levosert SHI has been confirmed.

Partial expulsion may decrease the effectiveness of Levosert SHI.

A partially expelled Levosert SHI should be removed. A new system can be inserted at the time of removal, provided pregnancy has been excluded.

Lost threads: If the retrieval threads are not visible at the cervix on follow-up examination, first exclude pregnancy. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If they cannot be found, they may have broken off, the system may have been expelled, or rarely the device may be extra-uterine after having perforated the uterus. An ultrasound should be arranged to locate the device and alternative contraception should be advised in the meantime. If an ultrasound cannot locate the device and there is no evidence of expulsion, a plain abdominal X-ray should be performed to exclude an extra-uterine device.

Bleeding irregularities

Irregular bleeding: Levosert SHI usually achieves a significant reduction in menstrual blood loss within 3 to 6 months of treatment. Increased menstrual flow or unexpected bleeding may be indicative of expulsion. If menorrhagia persists then the woman should be re-examined. An assessment of the uterine cavity should be performed using ultrasound scan. An endometrial biopsy should also be considered.

Risk in pre-menopausal women

Because irregular bleeding/spotting may occur during the first months of therapy in pre-menopausal women, it is recommended to exclude endometrial pathology before insertion of Levosert SHI.

When to check for pregnancy in women of childbearing potential: The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation and expulsion should be excluded. A repeated pregnancy test is not necessary in amenorrhoeic subjects unless indicated by other symptoms. In women of fertile age, oligomenorrhoea and/or amenorrhea develops gradually in about 20% of the users.

Treatment review advice for menorrhagia: Levosert SHI usually achieves a significant reduction in menstrual blood loss within 3 to 6 months of treatment. If significant reduction in blood loss is not achieved in these timeframes, alternative treatments should be considered.

Other risks during use

Ectopic pregnancy: The absolute risk of ectopic pregnancy in users of levonorgestrel IUS is low. However, when a woman becomes pregnant with Levosert SHI in situ, the relative likelihood of ectopic pregnancy is increased. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding.

In the conducted clinical study, the overall incidence of ectopic pregnancy with Levosert SHI, was approximately 0.12 per 100 woman-years. Women considering Levosert SHI should be counselled on the signs, symptoms and risks of ectopic pregnancy. For women who become pregnant while using Levosert SHI, the possibility of an ectopic pregnancy must be considered and evaluated.

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry an increased risk of ectopic pregnancy. The risk of ectopic pregnancy in women who have a history of ectopic pregnancy and use Levosert SHI is unknown. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain, especially in connection with

missed periods or if an amenorrhoeic woman starts bleeding. Ectopic pregnancy may require surgery and may result in loss of fertility.

Ovarian cysts: Ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. These enlarged follicles cannot be distinguished clinically from ovarian cysts. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In a clinical trial of Levosert SHI that enrolled 280 women presenting with heavy menstrual bleeding of which 141 received Levosert SHI, ovarian cyst (symptomatic and asymptomatic) was reported in 9.9% patients within 12 months of insertion. In a clinical trial of Levosert SHI which enrolled 1,751 subjects, symptomatic ovarian cysts occurred in approximately 4.5% of subjects using Levosert SHI, over 6 years and 0.3 % of subjects discontinued use of Levosert SHI because of an ovarian cyst.

In most cases, the ovarian cysts disappear spontaneously during two to three months observation. Should this not happen, continued ultrasound monitoring and other diagnostic/therapeutic measures are recommended. Rarely, surgical intervention may be required.

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.

Breast cancer

Risk in pre-menopausal women
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 oestrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer.

The risk of having breast cancer diagnosed in users of progestogen-only methods (POPs, implants and injectables), including Levosert SHI, is possibly of similar magnitude to that associated with COC. However, for progestogen-only contraceptive preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs.

General information
Glucose tolerance: Low-dose levonorgestrel may affect glucose tolerance and blood glucose concentrations should be monitored in diabetic users of Levosert SHI.

Post-coital contraception: Levosert SHI is not for use as a post-coital contraceptive.

The T-frame of Levosert SHI contains barium sulphate so that it can be seen on X-rays.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of progestogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. griseofulvin, rifampicin, rifabutin, nevirapine, efavirenz). On the other hand, substances known to inhibit drug-metabolizing enzymes (e.g. itraconazole, ketoconazole) may increase serum concentrations of levonorgestrel. The influence of these drugs on the contraceptive efficacy of Levosert SHI is not known, but it is not believed to be of major importance due to the local mechanism of action.

4.6 Fertility, pregnancy and lactation

Pregnancy
Levosert SHI is not to be used during an existing or suspected pregnancy. In case of an accidental pregnancy with Levosert SHI in situ (see section 5), ectopic pregnancy should be excluded (see section 4.4) and the system should be removed as soon as possible, as there is a high risk for pregnancy complications (abortion, preterm labor, infection and sepsis). Removal of Levosert SHI or probing of the uterus may also result in spontaneous abortion. Should these procedures not be possible or if the woman wishes to continue the pregnancy, the woman should be informed about these risks, and accordingly, such

pregnancies should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Local exposure to levonorgestrel
In addition, an increased risk of virilising effects in a female foetus because of the intrauterine exposure to levonorgestrel cannot be excluded. There have been isolated cases of masculinisation of the external genitalia of the female foetus following local exposure to levonorgestrel during pregnancy with an LNG-IUS in place.

Breast-feeding
Levonorgestrel is excreted in very small quantities in breast milk after use in levonorgestrel IUS. Since no risk for the child is expected, breast feeding can be continued during use of Levosert SHI. Uterine bleeding has rarely been reported in women using a levonorgestrel IUS during lactation.

Fertility
The use of levonorgestrel IUS does not alter the course of female fertility after removal of the IUS.

4.7 Effects on ability to drive and use machines

Levosert SHI has no known influence on the ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects are more common during the first months after the insertion, and subside during prolonged use.

Very common undesirable effects (occurring in more than 10% of users) include uterine/vaginal bleeding including spotting, oligomenorrhoea, amenorrhoea (see section 5.1) and benign ovarian cysts.

The frequency of benign ovarian cysts depends on the diagnostic method used, and in clinical trials enlarged follicles have been diagnosed in 12% of the subjects using a levonorgestrel IUS. Most of the follicles are asymptomatic and disappear within three months.

The table below reports adverse reactions by MedDRA system organ class (MedDRA SOCs). The frequencies are based on clinical trial data.

System organ class	**Undesirable effects**			
	Very common: ≥ 1/10	**Common: ≥ 1/100 to < 1/10**	**Uncommon: ≥ 1/1,000 to < 1/100**	**Rare: ≥ 1/10,000 to < 1/1,000**
Infections and infestations	Vaginal bacterial infections, Vulvovaginal mycotic infections			
Immune system disorders				Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders		Depressive mood Nervousness Decreased libido		
Nervous system disorders		Headache Migraine Presyncope	Syncope	
Vascular disorders		Dizziness		
Gastrointestinal disorders		Abdominal pain/discomfort Nausea		

		Abdominal distension Vomiting		
Skin and subcutaneous tissue disorders	Acne		Alopecia Hirsutism Pruritus Eczema Chloasma/skin hyperpigmentation	Rash Urticaria
Musculoskeletal and connective tissue disorders		Back pain		
Reproductive system and breast disorders	Uterine/vaginal bleeding including spotting, oligomenorrhoea, amenorrhoea Benign ovarian cysts	Pelvic pain Dysmenorrhoea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain Dyspareunia Uterine spasm	Uterine perforation* Pelvic Inflammatory disease Endometritis Cervicitis Papanicolaou smear normal, class II	
Pregnancy, puerperium and perinatal conditions ectopic pregnancy			Ectopic pregnancy	
General disorders and administration site conditions	Procedural pain Procedural bleeding	Intrauterine contraceptive device expelled	Oedema	
Investigations		Weight increase		

*This frequency is based on a large prospective comparative non-interventional cohort study in IUS/IUD users which showed that breast-feeding at the time of insertion and insertion up to 36 weeks after giving birth are independent risk factors for perforation (see section 4.4). In clinical trials with levonorgestrel IUS that excluded breastfeeding women the frequency of perforation was "rare".

Infections and infestations
Cases of sepsis (including group A streptococcal sepsis) have been reported following IUS insertion (see section 4.4).

Pregnancy, puerperium and perinatal conditions
When a woman becomes pregnant with Levosert SHI in situ, the relative risk of ectopic pregnancy is increased (see 'Special warnings and precautions for use' and 'Fertility, pregnancy and lactation').

Reproductive system and breast disorders
Cases of breast cancer have been reported in levonorgestrel IUS users (frequency unknown, see section 4.4).

The following adverse reactions have been reported in connection with the insertion or removal procedure of Levosert SHI: pain, bleeding, and insertion-related vasovagal reaction with dizziness or syncope (see section 4.4). The procedure may also precipitate a seizure in patients with epilepsy.

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Not applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Intrauterine contraceptives, plastic IUD with progestogen ATC code: G02BA03

Levonorgestrel is a progestogen used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills and subdermal implants. Levonorgestrel can also be administered directly into the uterine cavity as an IUS. This allows a very low daily dosage, as the hormone is released directly into the target organ.
The contraceptive mechanism of action of the levonorgestrel IUS is based mainly on hormonal effects producing the following changes:

- Prevention of proliferation of the endometrium
- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Suppression of ovulation in some women.

The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.

Clinical Efficacy
Contraception Trial
When inserted according to the insertion instructions, Levosert SHI offers contraceptive protection which does not appear to vary by parity, race or body mass index. Contraceptive efficacy of Levosert SHI was investigated in a large clinical trial. The cumulative pregnancy rate calculated as the Pearl Index (PI) in women aged 16 to 35 years, inclusive, was 0.15 (95% CI: 0.02, 0.55) at the end of year 1 and 0.18 (95% CI: 0.08, 0.33) at the end of year 6. 19% of Levosert SHI users becoming amenorrhoeic by the end of the first year of use, 27% by the end of the second year of use, 37% by the end of the third year of use, 37% by the end of the fourth year of use, 40% by the end of the fifth year of use, and 40% by the end of the sixth year of use.

In idiopathic menorrhagia, prevention of proliferation of the endometrium is the probable mechanism of action of levonorgestrel IUS in reducing blood loss.

Heavy Menstrual Bleeding
In the clinical trial evaluating women with heavy menstrual bleeding (≥ 80 mL per menstrual cycle), Levosert SHI achieved a significant reduction in menstrual blood loss within 3 to 6 months of treatment. The volume of menstrual bleeding was decreased by 88% in women with heavy menstrual bleeding by the end of three months of use and 82% reduction was sustained for the duration of the study (12 months), with heavy menstrual bleeding caused by submucosal fibroids may respond less favourably. The effect was maintained during the extension phase of the study (up to 36 months). Reduced bleeding promotes an increase of blood haemoglobin in patients with heavy menstrual bleeding.

5.2 Pharmacokinetic properties

The initial in vivo release rate of 20.1 micrograms/day levonorgestrel from Levosert SHI decreases to 17.5 micrograms/day during the first year and 8.6 micrograms/day at sixth year. Levonorgestrel is delivered directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 93 ± 45 pg/mL after 6 years) resulting in only minor systemic effects.
The pharmacokinetics of levonorgestrel itself have been extensively investigated and reported in the literature. A half-life of 20 hours is considered the best estimate although some studies have reported values as short as 9 hours and others as long as 80 hours. Another important finding, although one in agreement with experience with other synthetic steroids, has been marked differences in metabolic clearance rates among individuals, even when administration was by the intravenous route. Levonorgestrel is extensively bound to proteins (mainly sex hormone binding globulin [SHBG]) and extensively metabolised to a large number of inactive metabolites.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans other than the information already included in other sections of the SmPC. These data are based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Environmental risk assessment studies have shown that levonorgestrel may pose a risk for aquatic compartment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polydimethylsiloxane (PDMS) reservoir
Polydimethylsiloxane (PDMS) membrane
Low density polyethylene T-frame with 20-24% barium sulphate
Polypropylene thread
Copper phthalocyanine blue

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package. This medicinal product does not require any special temperature storage conditions. Keep the sealed tray in the outer carton in order to protect from light.

6.5 Nature and contents of container

Levosert SHI IUS with the inserter device is individually packed into a thermoformed plastic (PETG) tray with a peelable lid (TYVEK-Polyethylene). Sterile trays are packed into a folding carton.

Pack sizes:
One Intrauterine System with the inserter device.
Multipack containing five packs of one Intrauterine System with the inserter device.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

As the insertion technique is different from intrauterine devices, special emphasis should be given to training in the correct insertion technique. Special instructions for insertion are in the package.
Levosert SHI is supplied in a sterile pack which should not be opened until required for insertion. Each system should be handled with aseptic precautions. Once Levosert SHI has been inserted, the inserter has to be discarded.
The active substance levonorgestrel is persistent in the environment.
If the seal of the sterile envelope is broken, the system inside should be disposed of in accordance with the local guidelines for the handling of biohazardous waste. Likewise, a removed Levosert SHI and inserter should be disposed of in this manner. The outer carton package and the inner blister package can be handled as household waste.

This medicinal product may pose a risk to the environment. (See section 5.3) Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyömroi út 19-21
H-1103, Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER

PA1330/022/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th November 2021

10 DATE OF REVISION OF THE TEXT

November 2023