Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levosert 52 mg 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 decreases progressively by about 70% after 8 years.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Intrauterine delivery system (IUS).

The product consists of an inserter and levonorgestrel IUS, which is loaded at the tip of the inserter. Inserter components are an insertion tube, plunger, flange, body and slider. The device consists of a white or almost white hormone-elastomer core, mounted on a T-body and covered in opaque tubing, which regulates the release of levonorgestrel. The T-body has a loop at the end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

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

4.2 Posology and method of administration

Posology

Levosert is inserted into the uterine cavity and is effective for eight years in the indication contraception and has a demonstrated efficacy for 3 years for the indication heavy menstrual bleeding. Therefore, Levosert should be removed or exchanged after 8 years of use, or earlier if heavy or bothersome menstrual bleeding returns.

Insertion
It is strongly recommended that Levosert should only be inserted by healthcare professionals who are experienced in IUS insertions and/or have undergone training on the Levosert insertion procedure.

Before insertion, the patient should have been carefully examined in order to detect any contraindication to IUS insertion. Exclude pregnancy before insertion. Consider the possibility of ovulation and conception before using this product. Levosert is not suitable for use as a post-coital contraceptive (see section 4.3 and section 4.4 under Medical examination).

Contraception and heavy menstrual bleeding

Table 1. When to insert Levosert in women of fertile age

Starting Levosert	• Levosert should be inserted into the uterine cavity within 7 days of the onset of menstruation. In this case Levosert provides contraceptive protection upon insertion and no back-up contraception is needed. • If insertion within 7 days of the onset of menstruation is not possible or the woman does not experience regular menses,

	Levosert may be inserted at any time during the menstrual cycle provided that the healthcare professional can reliably exclude the possibility of prior conception. However, in this case immediate contraceptive protection upon insertion is not reliably ensured. Therefore, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for the next 7 days to prevent pregnancy.
Postpartum insertion	In addition to the instructions above (Starting Levosert): Postpartum insertions should be postponed until the uterus is fully involuted, however should not be performed earlier than 6 weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum.
Insertion after first-trimester abortion	Levosert can be inserted immediately after first trimester abortion. In this case no back-up contraception is needed.
Replacing Levosert	Levosert can be replaced by a new system at any time in the menstrual cycle. In this case no back-up contraception is needed.
Changing from another contraceptive method (e.g., combined hormonal contraceptives, implant)	• Levosert can be inserted immediately if it is reasonably certain that the woman is not pregnant. • Need for back-up contraception: If it has been more than 7 days since menstrual bleeding began, the woman should abstain from vaginal intercourse or use additional contraceptive protection for the next 7 days.

In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

After insertion, women should be re-examined after 4 to 6 weeks to check the threads and ensure that the device is in the correct position. Physical examination alone (including checking of threads) may not be sufficient to exclude partial perforation.

Removal/replacement
Levosert is removed by gently pulling on the threads with forceps. If the threads are not visible and the system is found in the uterine cavity on ultrasound exam, it may be removed using a narrow forceps. This may require dilatation of the cervical canal or surgical intervention. After removal of Levosert, the system should be examined to ensure it is intact.

During difficult removals, single cases have been reported of the hormone cylinder sliding over the lateral 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 lateral arms usually prevent complete detachment of the cylinder from the T-body.

Continuation of contraception after removal

- If the woman wishes to continue using the same method, a new system can be inserted immediately following removal of the original system.
- If the woman does not wish to continue using the same method but pregnancy is not desired, the removal should be carried out within 7 days of the onset of menstruation, provided the woman is experiencing regular menses. If the system is removed at some other time during the cycle or the woman does not experience regular menses and the woman has had intercourse within a week, she is at a risk of pregnancy. To ensure continuous contraception a barrier contraceptive method should be used (such as condoms) starting at least 7 days before the removal. After removal, the new contraceptive method should be started immediately (follow the instructions for use of the new contraceptive method).

Special populations

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

Elderly patients

There is no indication for the use of Levosert in postmenopausal women.

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

Renal impairment
Levosert has not been studied in women with renal impairment.

Method of administration

To be inserted by a healthcare professional using aseptic technique.

Levosert is supplied in a sterile pack which should not be opened until required for insertion. Do not resterilise. For single use only. 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). Do not use if the inner package is damaged or open. Do not insert after the expiry date which is stated on the carton and the tray with the peelable lid after EXP. The expiry date refers to the last day of that month.

Levosert is supplied with a patient reminder card in the outer carton. Complete the patient reminder card and give it to the patient, after insertion.

Preparation for insertion
• Examine the patient to rule out contraindications for the insertion of Levosert (see section 4.3 and section 4.4 under Medical examination).
• Insert a speculum, visualize the cervix, and then thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
• Employ an assistant as necessary.
• Grasp the anterior lip of the cervix with a tenaculum or other forceps to stabilize the uterus. If the uterus is retroverted, it may be more appropriate to grasp the posterior lip of the cervix. Gentle traction on the forceps can be applied to straighten the cervical canal. The forceps should remain in position and gentle counter traction on the cervix should be maintained throughout the insertion procedure.
• Advance a uterine sound through the cervical canal to the fundus to measure the depth. If uterine depth is < 5.5 cm discontinue the procedure. Confirm the direction of the uterine cavity and toexclude any evidence of intrauterine abnormalities (e.g., septum, submucous fibroids) or a previously inserted intrauterine contraceptive which has not been removed. If difficulty is encountered, consider dilatation of the canal. If cervical dilatation is required, consider using analgesics and/or a paracervical block.

Levosert is inserted with the provided inserter into the uterine cavity by carefully following the insertion instructions provided in the box containing the Levosert IUS.

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.
Prior to insertion pregnancy should be excluded and genital infection should be successfully treated. Women should be advised that Levosert does not protect against HIV (AIDS) and other sexually transmitted disease (please refer to the section below on pelvic infections).

The patient should be re-examined 4 to 6 weeks after insertion to check the threads and ensure that the device is in the correct position. Further examinations should be performed where clinically indicated and adapted to the individual woman rather than as routine procedure.

Women should be encouraged to attend cervical and breast screening as appropriate for their age.

Levosert is not for use as a post-coital contraceptive.

Conditions under which Levosert can be used with caution

Levosert 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 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 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 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 levonorgestrel-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 2). These risk factors were independent of the type of IUS/IUD inserted.

Table 2: Incidence of perforation per 1,000 insertions for the entire study cohort, stratified by breast-feeding 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 intrauterine devices (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 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 unless the symptoms fail to resolve within the following 72 hours or unless the women wishes Levosert to be removed. Levosert 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 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 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 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 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 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 has been confirmed.

Partial expulsion may decrease the effectiveness of Levosert.

A partially expelled Levosert 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 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.

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. For details of amenorrhoea rates, see section 5.1.

Treatment review advice for menorrhagia: Levosert 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 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, was approximately 0.12 per 100 woman-years. Women considering Levosert should be counselled on the signs, symptoms and risks of ectopic pregnancy. For women who become pregnant while using Levosert, 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 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 that enrolled 280 women presenting with heavy menstrual bleeding of which 141 received Levosert, ovarian cyst (symptomatic and asymptomatic) was reported in 9.9% patients within 12 months of insertion. In a clinical trial of Levosert which enrolled 1,751 subjects, symptomatic ovarian cysts occurred in approximately 4.5% of subjects using Levosert over 6 years and 0.3 % of subjects discontinued use of Levosert 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.

Psychiatric disorders: 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, 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.

The T-frame of Levosert 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 progestagens 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 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 is not to be used during an existing or suspected pregnancy. In case of an accidental pregnancy with Levosert 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 labour, infection and sepsis). Removal of Levosert 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 levonorgestrel-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. 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 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 3. below reports adverse reactions by MedDRA system organ class (MedDRA SOCs). The frequencies are based on clinical trial data.

Table 3: Adverse reactions

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		
Pregnancy, puerperium and perinatal conditions			Ectopic pregnancy	
Reproductive system and breast disorders	Uterine/vaginal bleeding including spotting, oligomenorrhea, amenorrhea Benign ovarian cysts	Pelvic pain Dysmenorrhoea Vaginal discharge Vulvovaginitis Breast tenderness Breast pain	Uterine perforation* Pelvic inflammatory disease Endometritis Cervicitis Papanicolaou	

		Dyspareunia Uterine spasm	smear normal, class II	
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 in situ, the relative risk of ectopic pregnancy is increased (see section 4.4 and section 4.6).

Reproductive system and breast disorders
Cases of breast cancer have been reported in levonorgestrel IUS users (frequency not known, see section 4.4).

The following adverse reactions have been reported in connection with the insertion or removal procedure of Levosert: 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.

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

Clinical efficacy

Contraception trial

When inserted according to the insertion instructions, Levosert offers contraceptive protection. Contraceptive efficacy of Levosert was investigated in a large clinical trial. The cumulative pregnancy rate calculated as the Pearl Index (PI) in women aged 16 to 35 years at study entry was 0.15 (95% CI: 0.02, 0.55) at the end of year 1 and 0.18 (95% CI: 0.09, 0.33) at the end of year 8. The cumulative and year-by-year Pearl Indexes are shown in the table below:

Table 4: Cumulative and Year-by-Year Pearl Index in the Primary Efficacy Population (16-35 years old at study entry)

Year	**Pregnancies**	**Number of subjects***	**Cumulative**			**Year-by-Year**		
			Cycles	**PI**	**(95% CI)**	**Cycles**	**PI**	**(95% CI)**
Year 1	2	1,276	17,175	**0.15**	(0.02, 0.55)	17,175	0.15	(0.02, 0.55)
Year 2	4	1,035	31,380	**0.25**	(0.09, 0.54)	14,205	0.37	(0.10, 0.94)
Year 3	1	860	43,140	**0.21**	(0.08, 0.43)	11,760	0.11	(0.00, 0.62)
Year 4	1	720	53,031	**0.20**	(0.08, 0.39)	9,891	0.13	(0.00, 0.73)
Year 5	1	597	61,368	**0.19**	(0.09, 0.36)	8,337	0.16	(0.00, 0.87)
Year 6	0	500	68,284	**0.17**	(0.08, 0.33)	6,916	0.00	(0.00, 0.69)
Year 7**	2	406	73,930	**0.19**	(0.10, 0.35)	5,646	0.46	(0.06, 1.66)
Year 8**	0	302	78,229	**0.18**	(0.09, 0.33)	4,299	0.00	(0.00, 1.12)

CI = Confidence Interval, PI = Pearl Index

** completed the respective year*

*** 406 and 302 subjects completing Year 7 and Year 8, respectively, 380 and 257 subjects were ≤ 39 years old at the beginning of the respective years of use*

Supportive analyses for Year 7 and Year 8 of the year-by-year non-cumulative PI excluding 28-day cycles during which a subject reported one or more days of use of another birth control method from the denominator and using a subset of the efficacy population limited to subjects age 35 or less at the beginning of the year had a total of 3,873 × 28-day cycles with a PI of 0.67 (0.08, 2.42) and a total of 2,677 × 28-day cycles with a PI of 0.00 (0.00, 1.79), respectively.

19% of Levosert users became amenorrhoeic by the end of the first year of use, 27% by the end of the second year of use, 36% 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, 40% by the end of the sixth year of use, 39% at the end of the seventh year of use, and 39% at the end of the eighth year of use.

Heavy menstrual bleeding

In the clinical trial evaluating women with heavy menstrual bleeding (≥ 80 mL per menstrual cycle), Levosert 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 20.4 micrograms/day levonorgestrel from Levosert decreases to 17.7 micrograms/day during the first year, 15.3 micrograms/day during the second year, 13.3 micrograms/day during the third year, 11.5 micrograms/day during the fourth year, 10.0 micrograms/day during the fifth year, 8.7 micrograms/day at sixth year, 7.5 micrograms/day during the seventh year, and 6.5 micrograms/day during the eighth year. Levonorgestrel is delivered directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 88 ± 37 pg/mL after 8 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. Keep the pouch in the outer carton in order to protect from light.

6.5 Nature and contents of container

Levosert IUS with the inserter device is individually packed into a peel pouch that is made up of 2 sheets: thermoformed pouch (polyester) package with a peelable lid.

Each pack contains one or five Levosert in peel pouch or pouches, that is single packed into one or five separated folding cartons with the patient information leaflet and the patient reminder card.

Pack sizes:
One Intrauterine System with the inserter device.
Five Intrauterine System with the inserted device.
Multipack five packs of one Intrauterine System with one 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 is supplied in a sterile pack which should not be opened until required for insertion. Each system should be handled with aseptic precautions. 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 and inserter should be disposed of in this manner. The outer carton package and the inner pouch 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

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of latest renewal: 22nd January 2020

10 DATE OF REVISION OF THE TEXT

October 2025