SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LNG IUS 20 micrograms/24 hours intrauterine delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levonorgestrel 52 mg. The initial release rate is 20 micrograms /24 hours.

For a full list of excipients, see '*List of excipients*'

3. PHARMACEUTICAL FORM

Intrauterine delivery system (IUS).

The levonorgestrel (LNG) IUS consists of a white or almost white drug core covered with an opaque membrane, which is mounted on the vertical stem of a T-body. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop. The vertical stem of the IUS is loaded in the insertion tube at the tip of the inserter. The IUS and inserter are essentially free of visible impurities.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Contraception Idiopathic menorrhaia
Protection from endometrial hyperplasia during estrogen replacement therapy

4.2 Dosage and method of administration Method of administration

LNG IUS is inserted into the uterine cavity and is effective for five years.

The in vivo dissolution rate is approximately 20 µg/24 hours initially and is reduced to 10 µg/24 hours after five years. The mean dissolution rate of levonorgestrel is about 14 µg/24 hours over the time up to five years.

In women under hormonal replacement therapy, LNG IUS can be used in combination with oral or transdermal estrogen preparations without progestogens.

LNG IUS, when inserted according to the insertion instructions, has a failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7% at 5 years.

- Insertion and removal/replacement

In women of fertile age, LNG IUS is to be inserted into the uterine cavity within seven days of the onset of menstruation. LNG IUS can be replaced by a new system at any time in the cycle. The system can also be inserted immediately after first trimester abortion.

Postpartum insertions should be postponed until the uterus is fully involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation.

When used for endometrial protection during estrogen replacement therapy, LNG IUS can be inserted at any time in an amenorrheic woman, or during the last days of menstruation or withdrawal bleeding.

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

LNG IUS is removed by gently pulling on the threads with a forceps. If the threads are not visible and the system is in the uterine cavity, it may be removed using a narrow tenaculum. This may require dilatation of the cervical canal or other surgical intervention.

The system should be removed after five years. If the user wishes to continue using the same method, a new system can be inserted at the same time.

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 LNG IUS, the system should be checked to be 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.

- Instructions for use and handling

LNG IUS 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 seam of the sterile package is broken, the product should be discarded.

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;

Uterine or cervical malignancy;

Progestogen-dependent tumors;

Undiagnosed abnormal uterine bleeding;

Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity;

Conditions associated with increased susceptibility to infections;

Acute liver disease or liver tumor;

Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use

LNG IUS 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:

migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia

exceptionally severe headache

jaundice

marked increase of blood pressure

severe arterial disease such as stroke or myocardial infarction

LNG IUS may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis. Antibiotic prophylaxis should be administered to these patients when inserting or removing the IUS.

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of LNG IUS.

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

LNG IUS is not the method of first choice for young nulligravid women, nor for postmenopausal women with advanced uterine atrophy.

Due to the limited exposure in LNG IUS trials in the indication protection from endometrial hyperplasia during estrogen replacement therapy, the available data are not sufficient to confirm or refute a risk for breast cancer when LNG IUS is used in this indication.

Medical examination/consultation

Before insertion, the woman must be informed of the efficacy, risks and side effects of LNG IUS. A physical examination including pelvic examination, examination of the breasts, and a cervical smear should be performed. Pregnancy and sexually transmitted diseases should be excluded, and genital infections have to be successfully treated. The position of the uterus and the size of the uterine cavity should be determined. Fundal positioning of LNG IUS is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximize efficacy. Therefore, the instructions for the insertion should be followed carefully. Insertion and removal may be associated with some pain and bleeding. The procedure may precipitate fainting as a vasovagal reaction, or a seizure in an epileptic patient.

The women should be re-examined 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

LNG IUS is not suitable for use as a post-coital contraceptive.

Because irregular bleeding/spotting is common during the first months of therapy, it is recommended to exclude endometrial pathology before insertion of LNG IUS.

If the woman continues the use of LNG IUS inserted earlier for contraception, endometrial pathology has to be excluded in case bleeding disturbances appear after commencing estrogen replacement therapy.

If bleeding irregularities develop during a prolonged treatment, appropriate diagnostic measures should also be taken.

Oligo/amenorrhea

In women of fertile age, oligomenorrhea and amenorrhea develop gradually in 57% and 16% of women, respectively. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation.

When LNG IUS is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year.

Pelvic infection

Known risk factors for pelvic inflammatory disease are multiple sexual partners. Pelvic infection may have serious consequences and it may impair fertility and increase the risk of ectopic pregnancy.

As with other gynecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUD insertion, although this is extremely rare.

If the woman experiences recurrent endometritis or pelvic infections or if an acute infection is severe or does not respond to treatment within a few days, LNG IUS must be removed.

Expulsion

Symptoms of the partial or complete expulsion of any IUD may include bleeding or pain. However, the system can be expelled from the uterine cavity without the woman noticing it leading to loss of contraceptive protection. Partial expulsion may decrease the effectiveness of LNG IUS. As LNG IUS decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion.

A displaced LNG IUS should be removed. A new system can be inserted at that time.

The woman should be advised how to check the threads of LNG IUS.

Perforation

Perforation or penetration of the uterine corpus or cervix by an intrauterine contraceptive may occur rarely, most often during insertion and may decrease the effectiveness of LNG IUS. Such a system must be removed. The risk of perforations may be increased in post-partum insertions (see *'Dosage and method of administration'*), in lactating women, and in women with fixed retroverted uterus.

Ectopic pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrheic woman starts bleeding. The ectopic pregnancy rate with LNG IUS is approximately 0.1% per year. The absolute risk of ectopic pregnancy in LNG IUS users is low. However, when a woman becomes pregnant with LNG IUS in situ, the relative likelihood of ectopic pregnancy is increased.

Lost threads

If the retrieval threads are not visible at the cervix on follow-up examinations, pregnancy must be excluded. The threads may have been drawn up into the uterus or cervical canal and may reappear during the next menstrual period. If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, the system may have been expelled. Ultrasound diagnosis may be used to ascertain the correct position of the system. If ultrasound is not available or successful, X-ray may be used to locate LNG IUS.

Ovarian cysts

Since the contraceptive effect of LNG IUS is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. Ovarian cysts have been reported as adverse drug reactions in approximately 7% of women using LNG IUS. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

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.

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, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). The influence of these drugs on the efficacy of LNG IUS is not known, but it is not

believed to be of major importance due to the local mechanism of action.

4.6 Pregnancy and lactation Pregnancy

The use of LNG IUS during an existing or suspected pregnancy is contraindicated (see 4.3 Contraindications).

If the woman becomes pregnant when using LNG IUS removal of the system is recommended, since any intrauterine contraceptive left in situ may increase the risk of abortion and preterm labor. Removal of LNG IUS or probing of the uterus may result in spontaneous abortion. If the woman wishes to continue the pregnancy and the system cannot be withdrawn, she should be informed about the risks and the possible consequences of premature birth to the infant. The course of such a pregnancy should be closely monitored. Ectopic pregnancy should be excluded. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Because of the intrauterine administration and the local exposure to the hormone, the possible occurrence of virilizing effects in the fetus should be taken into consideration.

Lactation

About 0.1% of the levonorgestrel dose is transferred to the infant during breast-feeding. However, it is not likely that there will be a risk for the infant with the dose released from LNG IUS, when it is inserted in the uterine cavity. There appears to be no deleterious effect on infant growth or development when using LNG IUS after six weeks postpartum. Progestogen-only methods do not appear to affect the quantity or quality of breast milk.

Fertility

Upon removal of LNG IUS, women return to their normal fertility.

4.7 Effects on ability to drive or use machines

Not known.

4.8 Undesirable effects

Summary of the safety profile

The majority of women experience changes in menstrual bleeding pattern after insertion of LNG IUS. During the first 90 days, prolonged bleeding is experienced by 22% and irregular bleeding by 67% of women after postmenstrual insertion of LNG IUS, decreasing to 3% and 19% at the end of the first year of use, respectively. Concomitantly, amenorrhea is experienced by 0% and infrequent bleeding by 11% during the first 90 days, increasing to 16% and 57% at the end of the first year of use, respectively.

When LNG IUS is used in combination with continuous estrogen replacement therapy, a non-bleeding pattern gradually develops in most women during the first year

Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported with LNG IUS are summarized in the table below. Frequencies are defined as very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000) and unknown. The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs). The frequencies are crude incidences of the events observed in clinical trials in the indications contraception and idiopathic menorrhagia/ heavy menstrual bleeding, including 5091 women and 12,101 woman-years.

Adverse reactions in clinical trials in the indication protection from endometrial hyperplasia during

estrogen replacement therapy (including 514 women and 1218.9 woman-years) were observed at a similar frequency unless specified by footnotes.

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
Immune system disorders					Hypersensitivity including rash, urticaria and angioedema
Psychiatric disorders		Depressed mood/ Depression			
Nervous system disorders	Headache	Migraine			
Gastrointestinal disorders	Abdominal/pelvic pain	Nausea			
Skin and subcutaneous tissue disorders		Acne Hirsutism	Alopecia		
Musculosceletal, connective tissue and bone disorders		Back pain**			
Reproductive system and breast disorders	Bleeding changes including increased and decreased menstrual bleeding, spotting, oligomenorrhoea and amenorrhoea Vulvovaginitis* Genital discharge*	Upper genital tract infection Ovarian cyst Dysmenorrhea Breast pain** Intra-uterine contraceptive device expelled (complete and partial)		Uterine perforation	
Investigations					Blood pressure increased

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

*Endometrial protection trials: “common”

**Endometrial protection trials: “very common”

Description of selected adverse reactions

When a woman becomes pregnant with LNG IUS in situ, the relative risk of ectopic pregnancy is increased.

The removal threads may be felt by the partner during intercourse.

The risk of breast cancer is unknown when LNG IUS is used in the indication protection from endometrial hyperplasia during estrogen replacement therapy. Cases of breast cancer have been

reported (frequency unknown, see section *'Special warnings and special precautions of use'*).

The following ADRs have been reported in connection with the insertion or removal procedure of LNG IUS:

Procedural pain, procedural bleeding, insertion-related vasovagal reaction with dizziness or syncope. The procedure may precipitate a seizure in an epileptic patient.

Cases of sepsis (including group A streptococcal sepsis) have been reported following IUD insertion (see section *'special warnings and precautions for use'*).

Overdose

Not relevant.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Levonorgestrel is a progestogen with anti-estrogenic activity used in gynecology in various ways: as the progestogen component in oral contraceptives and in hormonal replacement therapy, or alone for contraception in progestogen-only pills and subdermal implants. Levonorgestrel can also be administered into the uterine cavity with an intrauterine delivery system. This allows a very low daily dosage, as the hormone is released directly into the target organ.

LNG IUS has mainly local progestogenic effects in the uterine cavity. The high levonorgestrel concentration in the endometrium down-regulates endometrial estrogen and progesterone receptors, making the endometrium insensitive to the circulating estradiol and a strong antiproliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction are observed during use of LNG IUS. Thickening of the cervical mucus prevents passage of the sperm through the cervical canal. The local milieu of the uterus and of the ovarian tubes inhibits sperm mobility and function, preventing fertilization. Ovulation is inhibited in some women.

The menstrual pattern is a result of the direct action of the levonorgestrel on the endometrium and does not reflect the ovarian cycle. There is no clear difference in follicle development, ovulation or estradiol and progesterone production in women with different bleeding patterns. In the process of inactivation of the proliferation of the endometrium there can be an initial increase of spotting during the first months of use. Thereafter, the strong suppression of the endometrium results in the reduction of the duration and volume of menstrual bleeding during use of LNG IUS. Scanty flow frequently develops into oligomenorrhea or amenorrhea. Ovarian function is normal and estradiol levels are maintained, even when users of LNG IUS are amenorrhoeic.

5.2 Pharmacokinetic properties

The active ingredient of LNG IUS is levonorgestrel. Levonorgestrel is directly released into the uterine cavity. The in vivo release rate of levonorgestrel is initially approximately 20 µg/24 hours and declines to 10 µg/24 hours after 5 years.

Absorption

Following insertion, levonorgestrel is released into the uterine cavity without delay based on serum concentration measurements. The high local drug exposure in the uterine cavity leads to a strong concentration gradient via the endometrium to the myometrium (gradient endometrium to myometrium >100-fold), and to low concentrations of levonorgestrel in serum (gradient endometrium to serum>1000-fold).

Distribution

Levonorgestrel is bound non-specifically to serum albumin and specifically to SHBG. About 1-2% of the circulating levonorgestrel is present as free steroid and 42-62% is specifically bound to SHBG. During the use of LNG IUS, the concentration of SHBG declines. Accordingly, the fraction bound to

SHBG decreases during the treatment and the free fraction increases. The mean apparent volume of distribution of levonorgestrel is about 106 L.

After insertion of LNG IUS, levonorgestrel is detectable in serum after 1 hour. The maximum concentration is reached within 2 weeks after insertion. **Error! Bookmark not defined.**In correspondence with the declining release rate, the median serum concentration of levonorgestrel declines from 206 pg/ml (25^{th} to 75^{th} percentiles: 151 pg/ml to 264 pg/ml) at 6 months to 194 pg/ml (146 pg/ml to 266 pg/ml) at 12 months, and to 131 pg/ml (113 pg/ml to 161 pg/ml) at 60 months in women of reproductive age weighing above 55 kg.

Body weight and serum SHBG concentration have been shown to affect systemic levonorgestrel concentration i.e. low body weight and/or a high SHBG level increase levonorgestrel concentration. In women of reproductive age with a low body weight (37 to 55 kg) the median serum concentration of levonorgestrel is about 1.5-fold higher.

In postmenopausal women using LNG IUS together with non-oral estrogen treatment, the median serum concentration of levonorgestrel declines from 257 pg/ml (25^{th} to 75^{th} percentiles: 186 pg/ml to 326 pg/ml) at 12 months to 149 pg/ml (122 pg/ml to 180 pg/ml) at 60 months. When LNG IUS is used together with oral estrogen treatment, the serum levonorgestrel concentration at 12 months is increased to approx. 478 pg/ml (25^{th} to 75^{th} percentiles: 341 pg/ml to 655 pg/ml) due to the induction of SHBG by oral estrogen treatment.

Biotransformation

Levonorgestrel is extensively metabolized. The major metabolites in the plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel. Based on in vitro and in vivo studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel, CYP2E1, CYP2C19 and CYP2C9 may also be involved, but to a smaller extent.

Elimination

The total clearance of levonorgestrel from plasma is approximately 1.0 ml/min/kg. Only trace amounts of levonorgestrel are excreted in unchanged form. The metabolites are excreted with the feces and urine at an excretion ratio of about 1. The excretion half-life which is mainly represented by metabolites, is about 1 day.

Linearity/ non-linearity

The pharmacokinetics of levonorgestrel is dependent on the concentration of SHBG, which itself is influenced by estrogens and androgens. During use of LNG IUS a mean SHBG decrease of about 30% was observed**Error! Bookmark not defined.**, which leads to a decrease of levonorgestrel in serum indicating non-linear pharmacokinetics of levonorgestrel with regard to time. Based on the mainly local action of LNG IUS, no impact on the efficacy of LNG IUS is expected.

Preclinical safety data

The preclinical safety evaluation revealed no special hazard for humans based on studies of safety pharmacology, toxicity, genotoxicity, and carcinogenic potential of levonorgestrel. Levonorgestrel is a well-established progestogen. The safety profile following systemic administration is well documented. A study in monkeys with intrauterine delivery of levonorgestrel for 12 months confirmed local pharmacological activity with good local tolerance and no signs of systemic toxicity. No embryotoxicity was seen in the rabbit following intrauterine administration of levonorgestrel. The safety evaluation of the elastomer components of the hormone reservoir, polyethylene materials of the product, and combination of elastomer and levonorgestrel, based on both the assessment of genetic toxicology in standard in vitro and in vivo test systems and on biocompatibility tests in mice, guinea pigs, rabbits and in vitro test systems have not revealed bio- incompatibility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polydimethylsiloxane elastomer Silica,
colloidal anhydrous Polyethylene
Barium sulphate

Iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30 °C.
Keep out of reach of children

6.4 Nature and contents of container

PEGT/PE Blister pack: 1 x 1

Instructions for use / handling

See document "*Insertion Instructions*"

7. MARKETING AUTHORISATION HOLDER:

MANUFACTURED BY

Bayer Oy,

Pansiontie 47,

20210 Turku, Finland

8. MARKETING AUTHORIZATION HOLDER

16833

9. DATE OF LAST REVISION OF TEXT

13/01/2026