EMILY
(Levonorgestrel releasing intrauterine system)

BRIEF PRESCRIBING INFORMATION
This information does not include all details needed to use Emily safely and effectively. See full prescribing information for Emily.
Emily (levonorgestrel releasing intrauterine system)
Approval date (India): 2011

INDICATIONS AND USAGE

Emily is a sterile, levonorgestrel releasing intrauterine system indicated for:

- Intrauterine contraception for up to 3 years, in women who have at least one child.
- Treatment of heavy menstrual bleeding for women who suffer from dysfunctional uterine bleeding and who are willing to accept LNG IUD as an alternative to hysterectomy or oral medications.

DOSAGE AND ADMINISTRATION

- Release rate of levonorgestrel is approximately 20 mcg per day; Emily should be replaced after 3 years.
- To be inserted by a trained healthcare provider using strict aseptic technique. Healthcare providers are advised to become thoroughly familiar with the insertion instructions before attempting insertion.
- Patient should be re-examined and evaluated 4 to 12 weeks after insertion; then, yearly or more often if indicated.

DOSAGE FORMS AND STRENGTHS

One sterile intrauterine system consisting of an M-shaped polyethylene frame with a steroid reservoir containing 52 mg levonorgestrel held within an inserter tube.

CONTRAINDICATIONS

- Known or suspected pregnancy
- Current or recurrent pelvic inflammatory disease
- Lower genital tract infection
- Postpartum endometritis
- Undiagnosed abnormal uterine bleeding
- Uterine anomalies including fibroids if they distort the uterine cavity
- Uterine or cervical malignancy
- Known or suspected progestin-dependent neoplasia, including breast cancer
- Cervicitis
- Cervical dysplasia
- Active liver disease or dysfunction
- Actual benign or malignant liver tumors
- Septic abortion within the previous three months
- Hypersensitivity to levonorgestrel or any of the other ingredients in the formulation or component of the container components of EMILY.
- Bacterial endocarditis
- Established immunodeficiency
- Acute malignancies affecting blood or leukemias
- Recent trophoblastic disease with elevated hCG levels

WARNINGS AND PRECAUTIONS

- If pregnancy should occur with Emily in place, remove Emily.
- There is increased risk of ectopic pregnancy
- Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion.
- Before using Emily, consider the risks of PID.
- Bleeding patterns become altered, may remain irregular and amenorrhea may ensue.
- Perforation may occur during insertion. Risk is increased in women with fixed retroverted uteri, during lactation, and postpartum.
- Embedment in the myometrium and partial or complete expulsion may occur.
- Persistent enlarged ovarian follicles should be evaluated.

ADVERSE REACTIONS

The most common adverse reactions reported in clinical trials with a similar device (> 10%users) are uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal/pelvic pain (12.8%) and ovarian cysts (12%).

DRUG INTERACTIONS

- Drugs or herbal products that induce certain enzymes, such as CYP3A4 may decrease the serum concentration of progestins.

USE IN SPECIFIC POPULATIONS

- Small amounts of progestins pass into breast milk resulting in detectable Steroid levels in infant serum.
- Use of this product before menarche is not indicated.
- Use in women over 65 has not been studied and is not approved.

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Emily is indicated for conception control
- Emily is also indicated for the treatment of idiopathic menorrhagia in women accepting the contraceptive use of EMILY.

Following insertion into the uterine cavity, EMILY (levonorgestrel releasing intrauterine system) is effective for up to 3 years. If after 3 years, continued use of EMILY is desired, a new EMILY system should be inserted immediately after the old one is removed.

2 DOSAGE AND ADMINISTRATION

Emily contains 52 mg of levonorgestrel. The invivo dissolution rate is approximately 20 µg levonorgestrel per day.

2.1. Insertion Instructions

- In women of fertile age, EMILY should be inserted within seven days of the onset of menstruation.
- The system can also be inserted after first trimester Medical Termination of Pregnancy
- EMILY is not suitable for use as a postcoital contraceptive.
- Before insertion, the patient must be informed of the efficacy, risks and side effects of EMILY.
- A physical examination including pelvic examination, examination of the breasts and cervical smear should be performed.
- Pregnancy and sexually transmitted diseases should be excluded and any genital infections must be successfully treated.
- The position of the uterus and the size of the uterine cavity should be determined.
- Fundal positioning of EMILY is particularly important in order to ensure uniform exposure of the endometrium to the progestogen, prevent expulsion and maximize efficacy.
- Visualize the cervix with the aid of a speculum and thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
- Grasp the upper lip of the cervix with a suitable holding forceps. Gentle traction on the holding forceps has been shown to align the cervical canal with the uterine cavity. The holding forceps should remain in position throughout the insertion procedure to maintain gentle traction on the cervix to facilitate insertion.
- Gently move a uterine sound into the uterine cavity to the fundus to determine the direction of the cervical canal and the utero-cervical length (sound measure), and to exclude a uterine septum, synechiae or sub mucosal fibroids. It is important not to force the insertion. Should the cervical canal be too narrow, consider the need for dilatation and the use of analgesics or paracervical block.

Insertion Procedures

Step 1–Opening of the sterile package

• Wear sterile gloves on your hands.
• Open the sterile package completely.
• Pick up the thread hanging end of inserter tube.

Step 2–Setting the flange

Set the upper edge of the flange to the depth measured during the uterine sounding. (**Figure 1**)

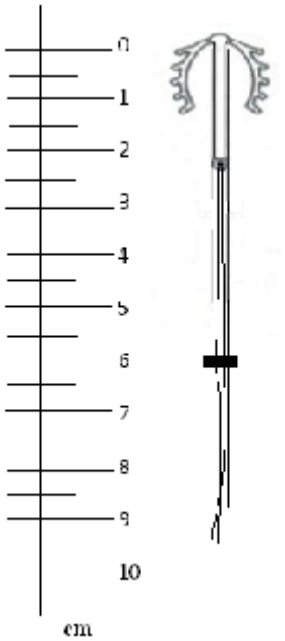


Figure 1: Setting the Flange to the Uterine Depth

Step 3 – EMILY is now ready to be inserted

• Grasp the holding forceps with your one hand and apply gentle traction to align the cervical canal with the uterine cavity.
• While maintaining traction on the cervix, gently advance the insertion tube through the cervical canal and into the uterine cavity **until the flange is 1.5 to 2 cm from the external cervical os**.
• **CAUTION: do not advance flange to the cervix at this step.**
Maintaining the flange 1.5 to 2 cm from the cervical os allows sufficient space for the arms to retain its original shape within the uterine cavity (**Figures 2** and **3**).

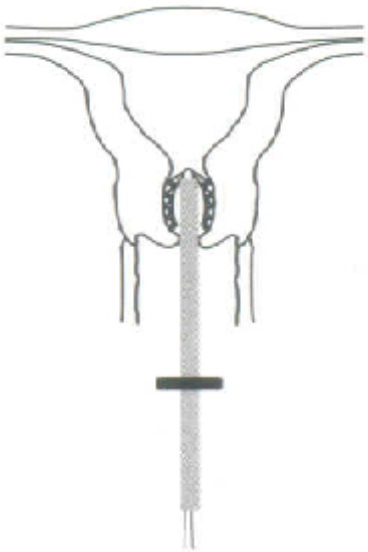


Figure 2: Insertion of EMILY

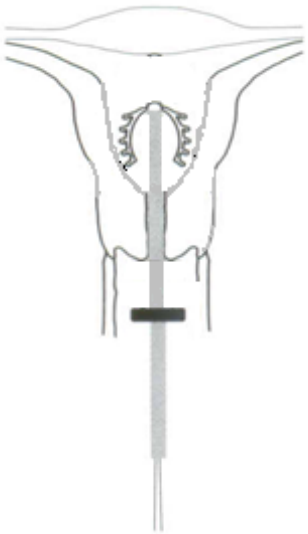


Figure 3: Advancing Insertion Tube until Flange is 1.5 to 2 cm from Cervical OS

Step 4 – Advance to fundal position

• Gently advance the inserter tube into the uterine cavity until the flange meets the cervix and you feel fundal resistance. EMILY should now be in the desired fundal position (**Figure 4**).

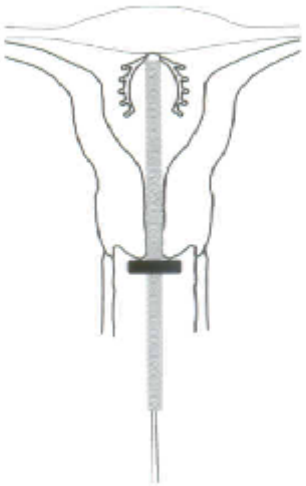


Figure 4: EMILY in the Fundal Position

Step 5 – Release EMILY and withdraw the inserter TUBE

• Pull the Inserter tube all the way down to release EMILY from the insertion tube (**Figure 5**). The threads will release automatically.
• Check that the threads are hanging freely.
Be careful not to pull on the threads as this will displace EMILY.

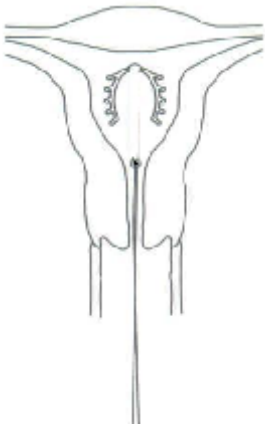


Figure 5: Releasing EMILY from the Insertion Tube

Step 6 – Cut the threads

• Cut the threads perpendicular to the thread length, for example, with sterile curved scissors, leaving about 3 cm length outside the cervix (**Figure 6**).
NOTE: Cutting threads at an angle may leave sharp ends.

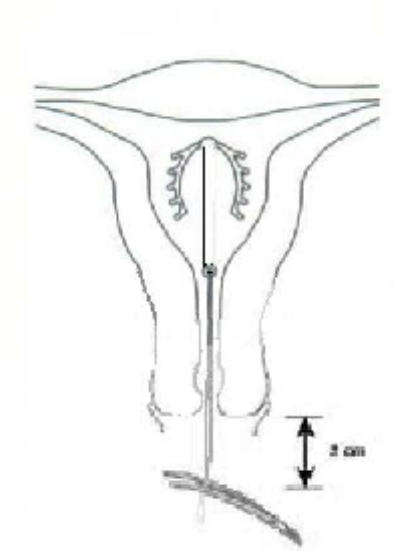


Figure 6: Cutting the Threads

EMILY insertion is now completed.

In case difficulties arise during insertion, the patient complains of pain, or if there is any doubt that the system is not in the correct position, verify with ultrasound or X-ray. Remove the system if it is not positioned properly in the intrauterine cavity and insert a new one. A removed system must never be reinserted.

Use of Sanitary Pads
The use of sanitary pads is recommended during menstruation. Women with Emily inserted should be careful to avoid inadvertently pulling the EMILY removal threads.

2.2 Patient Follow-up

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

2.3 Removal of Emily

- EMILY can be removed by pulling the threads with forceps.
- EMILY system should not remain in the uterus for longer than 3 years.

2.4 Continuation of Contraception after Removal

- A new Emily may be inserted immediately following the removal of the old one
- If a patient with regular cycles wants to start a different birth control method, remove Emily during the first 7 days of the menstrual cycle and start the new method.

3 DOSAGE FORMS AND STRENGTHS

Emily is an intrauterine system consisting of a small white M-shaped frame made from soft, flexible radiopaque plastic. The vertical arm is surrounded by a narrow cylindrical shaped reservoir that contains 52 mg of Levonorgestrel.

4 CONTRAINDICATIONS

EMILY (Levonorgestrel releasing intrauterine system) is contraindicated in patients with the following conditions:

- Known or suspected pregnancy
- Current or recurrent pelvic inflammatory disease
- Lower genital tract infection
- Postpartum endometritis
- Undiagnosed abnormal uterine bleeding
- Uterine anomalies including fibroids if they distort the uterine cavity
- Uterine or cervical malignancy
- known or suspected progestin-dependent neoplasia, including breast cancer
- Cervicitis
- Cervical dysplasia
- Active liver disease or dysfunction
- Actual benign or malignant liver tumors
- Septic abortion within the previous three months
- Hypersensitivity to levonorgestrel or any of the other ingredients in the formulation or component of the container components of EMILY.
- Bacterial endocarditis
- Established immunodeficiency
- Acute malignancies affecting blood or leukemias
- Recent trophoblastic disease while HCG levels are elevated

5 WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Women with a previous history of ectopic pregnancy, tubal surgery, or pelvic infection carry a higher risk of ectopic pregnancy. Carefully consider the possibility of an ectopic pregnancy in women who become pregnant while having EMILY in place. Pregnancies with EMILY use are rare; however, when a woman becomes pregnant with EMILY in situ, the relative likelihood of ectopic pregnancy is increased. Up to half of the pregnancies that occur with EMILY in place are ectopic. The possibility of ectopic pregnancy should be considered in thecae of lower abdominal pain, especially in association with missed periods, or if an amenorrheic woman starts bleeding. Women who choose EMILY should be told about the risk of ectopic pregnancy, including the possibility of impaired fertility or loss of fertility. Educate women to recognize and report to their physician any signs and symptoms of ectopic pregnancy.

5.2 Intrauterine Pregnancy

EMILY is not to be used during an existing or suspected pregnancy. If pregnancy occurs with EMILY in place, EMILY should be removed since any IUS left in place may increase the risk of abortion and preterm labour. Removal of EMILY or probing of the uterus may result in spontaneous abortion.

5.3 Sepsis

There is very rare chance of streptococcal sepsis associated with EMILY insertion.

5.4 Pelvic Inflammatory Disease (PID)

The inserter provided with EMILY helps protect the system from contamination with microorganisms during insertion, thereby minimizing the risk of pelvic infection. The exposed product should be handled with aseptic precautions.

Known risk factors for pelvic inflammatory disease include multiple sexual partners, frequent intercourse and young age. Less common causes of pelvic inflammatory disease include pelvic actinomycosis and pelvic tuberculosis, both of which are extremely rare. There is an increased risk of PID during 20 days following the insertion of IUDs related to the insertion procedure. Thereafter, the risk of PID during the use of IUDs or EMILY is small. Patients should be advised to report to their physicians promptly if they experience symptoms suggestive of PID.If recurrent endometritis or pelvic infections are experienced or if an acute infection does not respond to treatment within a few days, EMILY must be removed.

5.5 Irregular Bleeding and Amenorrhea

Because irregular menstrual bleeding or spotting is common during the first few months of use, endometrial pathology should be excluded prior to insertion of EMILY. Irregular bleeding patterns in users of EMILY could mask the signs and symptoms of cervical or endometrial cancer. If bleeding irregularities develop after prolonged use, appropriate diagnostic measures should be undertaken.

Prolonged menstrual bleeding may occur during the first few months, however with continued use, bleeding patterns vary from regular scanty menstruation in some women to oligomenorrhea or amenorrhea in others. Oligomenorrhoea or amenorrhea develops gradually in about 20% of users. Reduced bleeding increases the level of blood hemoglobin.

The possibility of pregnancy should be considered if menstruation does not occur after six weeks or more of amenorrhea, following a pattern of regular menses. A pregnancy test is not necessary in amenorrheic women unless indicated by other symptoms.

5.6 Embedment

Embedment of EMILY in the myometrium may occur. Embedment may decrease contraceptive effectiveness and result in pregnancy. An embedded EMILY must be removed. Embedment can result in difficult removal, and may require surgery.

5.7 Perforation

Partial perforation (uterine embedment) or complete perforation of the uterus wall or cervix may occur due to improper insertion, although the perforation may not be detected until later. Pregnancy may result from partial or complete perforation. If partial or complete perforation occurs, EMILY must be located and removed; surgery may be required. Partial perforation (uterine embedment) can result in difficult removal.
Delayed detection of perforation may result in complications (eg. adhesions, peritonitis, intestinal perforation and obstruction, abscesses and erosion of adjacent viscera). The number of uterine perforations is linked to the experience of the person inserting the system.

The risk of perforation may be increased in lactating women, women with abnormal uterine anatomy or with fixed retroverted uteri and postpartum insertions. To reduce the possibility of perforation postpartum, EMILY insertion should be delayed until a minimum of 6 weeks after delivery or until uterine involution is complete. If involution is delayed, consider waiting until12 weeks postpartum. Inserting EMILY immediately after first trimester abortion is not known to increase the risk of perforation, but insertion after second trimester abortion should be delayed until uterine involution is complete.
To reduce the possibility of perforation, it is important to follow the recommended insertion technique.

5.8 Expulsion

Symptoms of the partial or complete expulsion of EMILY may include bleeding or pain; however, a system may be expelled from the uterine cavity without the patient noticing it. Partial expulsion may decrease the effectiveness of EMILY. Since EMILY decreases menstrual flow, an increase in menstrual flow may indicate an expulsion. A displaced system should be removed. A new system can be inserted at that time and the patient should be advised on how to check for the presence of the system by feeling for the removal threads.

5.9 Ovarian Cysts

Since the contraceptive action of EMILY is due mainly to its local effect on the uterus, 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 the follicles are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia. In most cases, the enlarged follicles disappear spontaneously over a two to three month period. Should this not occur, continued ultrasound monitoring and other diagnostic or therapeutic measures are recommended. Rarely, surgical intervention may be required.

5.10 Breast Cancer

In a previous study, the incidence rate of breast cancer in 17,360 LNG-IUS users (a total of > 58,000 women years with LNG-IUS, and > 150,000 women years of follow-up) was not statistically significantly different compared to the occurrence of breast cancer in4, 863 control women.

5.11 Patient Evaluation and Clinical Considerations

- A complete medical and social history, including that of the partner, should be obtained to determine conditions that might influence the selection of an IUD for contraception.
- Special attention must be given to ascertaining whether the woman is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome (AIDS), I.V. drug abuse), or has a history of PID unless there has been a subsequent intrauterine pregnancy. Emily is contraindicated in these women.
- A physical examination should include a pelvic examination, a Pap smear, examination of the breasts, and appropriate tests for any other forms of genital or other sexually transmitted diseases, such as gonorrhea and chlamydia laboratory evaluations, if indicated. Use of Emily in patients with vaginitis or cervicitis should be postponed until proper treatment has eradicated the infection and until it has been shown that the cervicitis is not due to gonorrhea or Chlamydia.
- Irregular bleeding may mask symptoms and signs of endometrial polyps or cancer. Because irregular bleeding/spotting is common during the first months of Emily use, exclude endometrial pathology prior to the insertion of Emily in women with persistent or uncharacteristic bleeding. If unexplained bleeding irregularities develop during the prolonged use of Emily, appropriate diagnostic measures should be taken.
- **The healthcare provider should determine that the patient is not pregnant**. The possibility of insertion of Emily in the presence of an existing undetermined pregnancy is reduced if insertion is performed within 7 days of the onset of a menstrual period. Emily can be replaced by a new system at any time in the cycle. Emily can be inserted immediately after first trimester abortion.
- Emily should not be inserted until 6 weeks postpartum or until involution of the uterus is complete in order to reduce the incidence of perforation and expulsion. If involution is substantially delayed, consider waiting until 12 weeks postpartum.

- Patients with certain types of valvular or congenital heart disease and surgically constructed systemic-pulmonary shunts are at increased risk of infective endocarditis. Use of Emily in these patients may represent a potential source of septic emboli. Patients with known congenital heart disease who may be at increased risk should be treated with appropriate antibiotics at the time of insertion and removal.
- Patients requiring chronic corticosteroid therapy or insulin for diabetes should be monitored with special care for infection.

Emily should be used with caution in patients who have:

- Coagulopathy or are receiving anticoagulants
- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- Exceptionally severe headache
- Marked increase of blood pressure
- Severe arterial disease such as stroke or myocardial infarction.

5.12 Insertion Precautions

- EMILY is not the contraceptive method of first choice for young subjects,
- EMILY is intended for use only in women of child-bearing age.
- EMILY is not suitable for use as a postcoital contraceptive.

5.13 Continuation and Removal

- Re examine and evaluate patients 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.
- If the threads are not visible, they may have retracted into the uterus or broken, or Emily may have broken, perforated the uterus, or been expelled. If the length of the threads has changed from the length at time of insertion, the system may have become displaced. Pregnancy must be excluded and the location of Emily verified, for example, by sonography, X-ray, or by gentle exploration of the uterine cavity with a probe. If Emily is displaced, remove it. A new Emily may be inserted at that time or during the next menses if it is certain that conception has not occurred. If Emily is in place with no evidence of perforation, no intervention is indicated.
- Promptly examine users with complaints of pain, odorous discharge, unexplained bleeding, fever, genital lesions or sores.
- Consider the possibility of ectopic pregnancy in the case of lower abdominal pain especially in association with missed periods or if an amenorrheic woman starts bleeding.

In the event a pregnancy is confirmed during Emily use:

- Determine whether pregnancy is intrauterine or ectopic and, if so, take appropriate measures.
- Inform patient of the risks of leaving Emily in place or removing it during pregnancy and of the lack of data on long-term effects on the offspring of women who have had Emily in place during conception or gestation
- If possible, Emily should be removed after the patient has been warned of the risks of removal. If removal is difficult, the patient should be counseled and offered pregnancy termination.
- If Emily is left in place, the patient's course should be followed closely.

In the event of a sexually transmitted disease during Emily use:
The use of a barrier method as a partial protection against acquiring sexually transmitted diseases should be strongly recommended.
Emily should be removed for the following medical reasons*:*

- New onset menorrhagia and/or metrorrhagia producing anemia
- Sexually transmitted disease
- Pelvic infection; endometritis
- Symptomatic genital actinomycosis
- Intractable pelvic pain
- Severe dyspareunia
- Pregnancy
- Endometrial or cervical malignancy
- Uterine or cervical perforation.

Removal of the system should also be considered if any of the following conditions 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.

5.14 Glucose Tolerance
Combination and progesrtogen-only oral contraceptives, including those containing levonorgestrel, may affect glucose tolerance in some users. Diabetic patients, and those with family history of diabetes, should be observed closely to detect any alterations in carbohydrate metabolism. Young diabetic patients whose disease is of recent origin, well controlled and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be closely observed. There are no changes in mean daily insulin requirements in women with Type 1 Diabetes Mellitus using LNG-IUS over a 12-month period.

6 ADVERSE REACTIONS
The most commonly occurring adverse events (i.e., in greater than 10% of users) with levonorgestrel-releasing intrauterine systems are uterine/vaginal bleeding (including frequent, prolonged or heavy bleeding, spotting, oligomenorrhea, amenorrhea) and benign ovarian cysts.

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

7 DRUG INTERACTIONS
Drug-Drug Interactions
The effect of hormonal contraceptives may be impaired by drugs which induce liver enzymes, including primidone, barbiturates, phenytoin, carbamazepine, rifampicin and griseofulvin. The influence of these drugs on the efficacy of EMILY (levonorgestrel-releasing intrauterine system) has not been studied, but it is not believed to be of major importance due to the local action of EMILY.

Drug-Food Interactions - Interactions with food have not been established.
Drug-Herb Interactions - Interactions with herbal products have not been established.
Drug-Laboratory Test Interactions - Interactions with laboratory tests have not been established.

Tissue Specimens
Pathologists should be advised of EMILY therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

Drug-Lifestyle Interactions
The effect of EMILY on the ability to drive or to use machines has not been studied. Patients should be advised not to drive or use machines until they know how they react to EMILY.

8 USES IN SPECIFIC POPULATIONS

8.1 Pregnancy
EMILY is not to be used during an existing or suspected pregnancy. If pregnancy occurs with EMILY in place, EMILY should be removed since any IUS left in place may increase the risk of abortion and preterm labour. Removal of EMILY or probing of the uterus may result in spontaneous abortion.

8.2 Nursing Mothers
Hormonal contraceptives are not recommended as the contraceptive method of first choice in breast-feeding women. A published study indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel could be transferred to the newborn via milk.

Although levonorgestrel has been found in the breast milk of women using EMILY, there does not appear to be a detrimental effect on growth or development of breast-fed infants whose mothers started using the product after six weeks postpartum. Progestogen-only contraceptive methods do not appear to affect the quantity and quality of breast milk.

8.3 Pediatric Use
EMILY is not the contraceptive method of first choice for young.
Use of this product before menarche is not indicated.

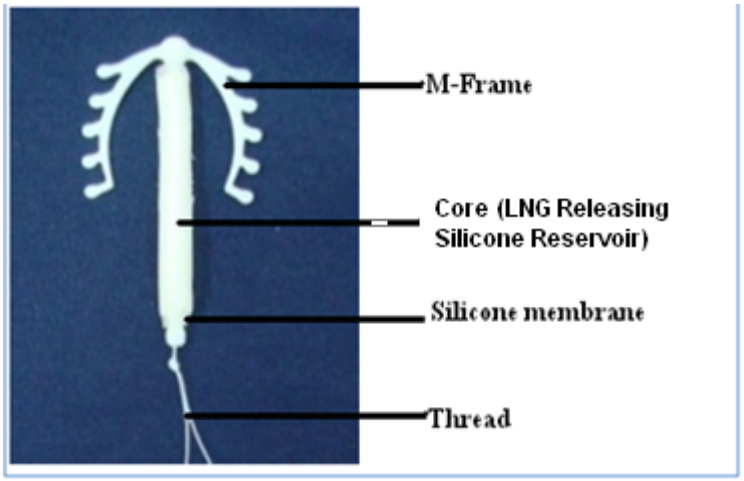
8.4 Geriatric Use
EMILY is not indicated for use in postmenopausal women

8.5 Hepatic Impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of levonorgestrel released from Emily.

8.6 Renal Impairment
No studies were conducted to evaluate the effect of renal disease on the disposition of levonorgestrel released from Emily.

9 DESCRIPTION OF THE DEVICE

Route of Administration- Intra-uterine
Dosage Form/Strength - Intrauterine system /52 mgLevonorgestrel
Clinically Relevant Non-medicinal Ingredients - Barium sulphate, iron oxide, polydimethylsiloxane, Polyethylene, silica



EMILY (Levonorgestrel-releasing intrauterine system)

EMILY is an intrauterine delivery system (IUS) consisting of a small white M-shaped frame made from soft, flexible plastic. The vertical arm is surrounded by a narrow cylindrical shaped reservoir that contains Levonorgestrel. The reservoir contains a total of 52 mg of Levonorgestrel and the membrane around the core regulates the release of Levonorgestrel. Two fine plastic threads are attached to the tip of the vertical arm. These threads are intended to be used for removal of the system and also serve to check its presence once it is in place.

EMILY works by slowly releasing Levonorgestrel into the uterus at a rate of approximately 20 micrograms per day. This amount of Levonorgestrel prevents pregnancy and decrease the abnormally heavy menstrual blood loss. EMILY contains a total of 52 mg of Levonorgestrel which is enough to prevent pregnancy for 3 years. For preventing pregnancy, EMILY is as effective as oral contraceptives. EMILY can be used for the treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. Clinical experience with similar imported devices for over 3 years in India has shown good efficacy for treating idiopathic menorrhagia.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

EMILY works by slowly releasing Levonorgestrel into the uterus at a rate of approximately 20 micrograms per day. This amount of Levonorgestrel:

• reduces the normal monthly thickening of the lining of the uterus.
• thickens the cervical mucus which prevents passage of sperm through the cervical canal.

10.2 Pharmacodynamics

The contraceptive action of EMILY is due mainly to the local progestogenic effect of Levonorgestrel on the uterine cavity. The use of EMILY does not alter the course of future fertility; nearly 90% of women wishing to become pregnant conceive within 24 months after removal of the system. Endometrial histology has been investigated in clinical studies examining the intrauterine release of levonorgestrel at rates ranging from 10 to 40µg/day. Subjects with exposure to continuous levonorgestrel release anywhere from 3 to 84 months showed endometrial glandular atrophy and decidualized stroma throughout the period. Local inflammation and focal necrosis compatible with the intrauterine mode of administration were observed.

10.3 Pharmacokinetics

Absorption

The intrauterine release of Levonorgestrel results in the absorption of the drug into the systemic circulation**.**

Distribution

The drug can be detected in plasma within 15 minutes of insertion and maximum concentrations are seen within a few hours. Following intrauterine insertion of EMILY, the initial release rate of levonorgestrel is 20 µg per day. This provides stable plasma levonorgestrel concentrations which, after the first few weeks, stabilize at between 150 to 200 pg/ml in women of fertile age.

Metabolism

The terminal half-life in serum is in the range of 14 to 20 hours after single-dose administration. Levonorgestrel is excreted as metabolites at about equal proportion in urine and faeces. The metabolites have little or no pharmacological activity. The principal metabolite in urine is tetrahydronorgestrel which accounts for approximately 25% of the radioactivity recovered from the urine after administration of radio labelled Levonorgestrel.

11. NONCLINICAL TOXICOLOGY AND CLINICAL EXPERIENCE

Toxicology studies were performed on all the components of EMILY: Core LNG- releasing silicone reservoir, membrane and unfilled silicone polymer, cured PDMS, the polyethylene "M-body" and the polyethylene "removal threads" and were found to be confirming to ISO 10993 standards. Mutagenicity studies showed that the Core- LNG releasing Silicon reservoir levonorgestrel was not genotoxic. Other tests done include bioburden analysis, Spore viability, sterility and trace element analysis and was found to be confirming to industry standards.

Clinical experience

Extensive clinical data exists for the safety and efficacy of Levonorgestrel releasing intra uterine systems as a method of contraception as well as for treatment of idiopathic menorrhagia.

12. STORAGE AND HANDLING

Store at room temperature, between 15°C and 30°C. Protect from moisture and direct sunlight.
Keep out of reach of children and pets.

Special Handling Instruction

EMILY (levonorgestrel-releasing intrauterine system) should be handled with aseptic precautions. Used EMILY systems should be considered bio hazardous waste and disposed off accordingly. Care should be taken to ensure the remaining hormonal ingredients are not introduced into water/sewer systems.

Packaging

Each EMILY (levonorgestrel-releasing intrauterine system) contains 52 mg of levonorgestrel in a cylindrical-shaped reservoir composed of a matrix of levonorgestrel and polydimethylsiloxane. The reservoir is mounted on the vertical arm of an M-shaped frame made of polyethylene and covered with a rate-controlling membrane of polydimethylsiloxane and silica. The M-frame is pigmented with barium sulphate. The polyethylene removal threads attached to the M-frame are pigmented with black iron oxide. EMILY is available in a carton of one sterile unit. Each EMILY is packaged in a pouch with an inserter tube.

Patients should be counseled that this product does not protect against HIV infection (AIDS) and Other sexually transmitted diseases (STDs).

- Inform the patient that irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her healthcare provider.
- Instruct the patient to contact her healthcare provider if she experiences any of the following:

    - A stroke or heart attack
    - Develops very severe or migraine headaches
    - Unexplained fever Yellowing of the skin or whites of the eyes, as these may be signs of serious liver problems
    - She thinks she is pregnant
    - Pelvic pain or pain during sex
    - She or her partner becomes HIV positive
    - She might be exposed to sexually transmitted diseases (STDs)
    - Unusual vaginal discharge or genital sores
    - Severe vaginal bleeding or bleeding that lasts a long time, or if she misses a menstrual period
    - Cannot feel Emily's threads.

Instruct the patient on how to check after her menstrual period to make certain that the threads still protrude from the cervix and caution her not to pull on the threads and displace Emily. Inform her that there is no contraceptive protection if Emily is displaced or expelled.

Manufactured and Marketed by:

HLL Lifecare Limited
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HLL Bhavan
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