

LILETTA- levonorgestrel intrauterine device
Actavis Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LILETTA® safely and effectively. See full prescribing information for LILETTA.

LILETTA (levonorgestrel-releasing intrauterine system)

Initial U.S. Approval: 2015

----- **RECENT MAJOR CHANGES** -----

Indications and Usage (1) 10/2017

Dosage and Administration (2.1) 10/2017

Warnings and Precautions (5.5) 10/2017

----- **INDICATIONS AND USAGE** -----

LILETTA is a sterile, levonorgestrel-releasing intrauterine system indicated for prevention of pregnancy for up to 4 years. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Release rate of levonorgestrel (LNG) is 19.5 mcg/day initially and declines progressively to approximately 17.0 mcg/day at 1 year, 14.8 mcg/day at 2 years, 12.9 mcg/day at 3 years and 11.3 mcg/day at 4 years after insertion; LILETTA can be removed at any time but must be removed by the end of the fourth year. (2)
- To be inserted by a trained healthcare provider using strict aseptic technique. Follow insertion instructions exactly as described. (2.3)
- Patient should be re-examined and evaluated 4 to 6 weeks after insertion and once a year thereafter, or more frequently if clinically indicated. (2.5)

----- **DOSAGE FORMS AND STRENGTHS** -----

- One intrauterine system consisting of a T-shaped polyethylene frame with a drug reservoir containing 52 mg LNG, packaged within a sterile inserter. (3)

----- **CONTRAINDICATIONS** -----

- Pregnancy or suspected pregnancy (4)
- Use for post-coital contraception (emergency contraception) (4)
- Congenital or acquired uterine anomaly that distorts the uterine cavity and would be incompatible with correct IUS placement (4)
- Acute pelvic inflammatory disease (PID) or endometritis or a history of PID unless there has been a subsequent intrauterine pregnancy (4)
- Infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other hormone-sensitive cancer (4)
- Uterine bleeding of unknown etiology (4)
- Untreated acute cervicitis or vaginitis or other lower genital tract infections (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- Increased susceptibility to pelvic infections (4)
- A previously inserted IUS that has not been removed (4)
- Hypersensitivity to any component of LILETTA (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Remove LILETTA if pregnancy occurs with LILETTA in place and LILETTA is in the uterus. If pregnancy occurs, there is increased risk of ectopic pregnancy (including loss of fertility), pregnancy loss, septic abortion (including septicemia, shock and death) and premature labor and delivery. (5.1, 5.2)
- Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion. (5.3)
- Before using LILETTA, consider the risks of PID. (5.4)
- Perforation may occur and reduce contraceptive effectiveness. Risk is increased if inserted in women with fixed retroverted uteri, during lactation, and postpartum. (5.5)

- Partial or complete expulsion may occur. (5.6)
- Evaluate persistent enlarged ovarian follicles or ovarian cysts. (5.7)
- Bleeding patterns become altered, may remain irregular and amenorrhea may ensue. (5.8)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions reported in clinical trials (> 10% users) are vaginal bacterial infections, vulvovaginal mycotic infections and acne. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LILETTA[®] is indicated for prevention of pregnancy for up to 4 years. The system should be replaced after 4 years if continued use is desired.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Over Time

LILETTA contains 52 mg of levonorgestrel (LNG). Initially, LNG is released at a rate of 19.5 mcg/day. This rate decreases progressively to approximately 17.0 mcg/day at 1 year, 14.8 mcg/day at 2 years, 12.9 mcg/day at 3 years and 11.3 mcg/day at 4 years after insertion. The average *in vivo* release rate of LNG is approximately 15.4 mcg/day over a period of 4 years.

LILETTA can be removed at any time but must be removed by the end of the fourth year. LILETTA can be replaced at the time of removal with a new LILETTA if continued contraceptive protection is desired.

2.2 Timing of Insertion

Refer to Table 1 for instruction on when to start use of LILETTA.

Table 1: When to Insert Liletta

| | |
|--|---|
| <p>Starting LILETTA in women not currently using hormonal or intrauterine contraception</p> | <ul style="list-style-type: none"> • LILETTA can be inserted any time the provider can be reasonably certain the woman is not pregnant. Consider the possibility of ovulation and conception prior to initiation of this product. • If LILETTA is inserted after the first 7 days of the menstrual cycle, the patient should use a barrier method of contraception (such as condoms and spermicide) or abstain from vaginal intercourse for 7 days after insertion to prevent |
|--|---|

| | |
|---|--|
| | pregnancy. |
| Switching to Liletta from an oral, transdermal or vaginal hormonal contraceptive | <ul style="list-style-type: none"> • LILETTA may be inserted at any time. <ul style="list-style-type: none"> • May be inserted during the hormone-free interval of the previous method. • If inserted during active use of the previous method, continue that method for 7 days after LILETTA insertion or until the end of the current treatment cycle. • If using continuous hormonal contraception, discontinue that method 7 days after LILETTA insertion. |
| Switching to LILETTA from an injectable progestin contraceptive | <ul style="list-style-type: none"> • LILETTA may be inserted at any time. • If LILETTA is inserted more than 3 months (13 weeks) after the last injection, a barrier method of contraception (such as condoms and spermicide) should also be used for 7 days after insertion. |
| Switching to LILETTA from a contraceptive implant or another IUS | <ul style="list-style-type: none"> • Insert LILETTA on the same day the implant or IUS is removed. • LILETTA may be inserted at any time during the menstrual cycle. |
| Inserting Liletta after abortion or miscarriage | |
| <ul style="list-style-type: none"> • First-trimester | <ul style="list-style-type: none"> • LILETTA may be inserted immediately after a first-trimester abortion or miscarriage. |
| <ul style="list-style-type: none"> • Second-trimester | <ul style="list-style-type: none"> • Delay inserting LILETTA until a minimum of 6 weeks after second-trimester abortion or miscarriage, or until the uterus is fully involuted. If involution is delayed, wait until involution is complete before insertion [<i>see Warnings and Precautions (5.5, 5.6)</i>]. • If the woman has not yet had a period, consider the possibility of ovulation and conception occurring prior to insertion of LILETTA. [<i>See Contraindications (4), Warnings and Precautions (5.2), and FDA-Approved Patient Labeling.</i>] LILETTA can be inserted any time the provider can be reasonably certain the woman is not pregnant. • If LILETTA is not inserted during the first 7 days of the menstrual cycle, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for 7 days after insertion to prevent pregnancy. |
| | <ul style="list-style-type: none"> • Delay inserting LILETTA until a minimum of 6 weeks after delivery, or until the uterus is fully involuted. If involution is delayed, wait until |

Inserting Liletta after Childbirth

involution is complete before insertion [see *Warnings and Precautions (5.5, 5.6)*].

- If the woman has not yet had a period, consider the possibility of ovulation and conception occurring prior to insertion of LILETTA. [See *Contraindications (4), Warnings and Precautions (5.2), and FDA-Approved Patient Labeling.*] LILETTA can be inserted any time the provider can be reasonably certain the woman is not pregnant.
- If LILETTA is not inserted during the first 7 days of the menstrual cycle, a barrier method of contraception should be used or the patient should abstain from vaginal intercourse for 7 days after insertion to prevent pregnancy.
- There appears to be an increased risk of perforation in lactating women. [See *Warnings and Precautions (5.5)*.]

2.3 Insertion Instructions

LILETTA (Figure 1) is provided in a sterile pouch [see *Description (11)*] and is inserted into the uterine cavity with the provided inserter (Figure 2) by carefully following the insertion instructions. Do not use if the seal of the sterile package is broken or appears compromised. Use strict aseptic techniques throughout the insertion procedure [see *Warnings and Precautions (5.3)*].

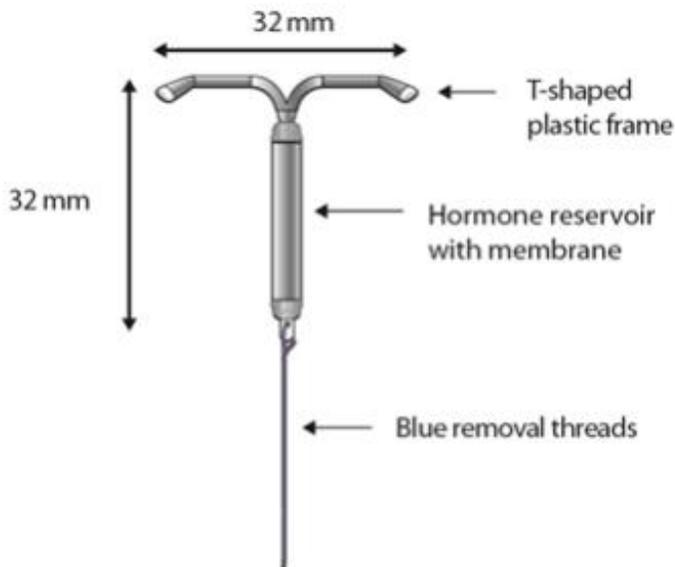


Figure 1 LILETTA Intrauterine Contraceptive System (IUS)

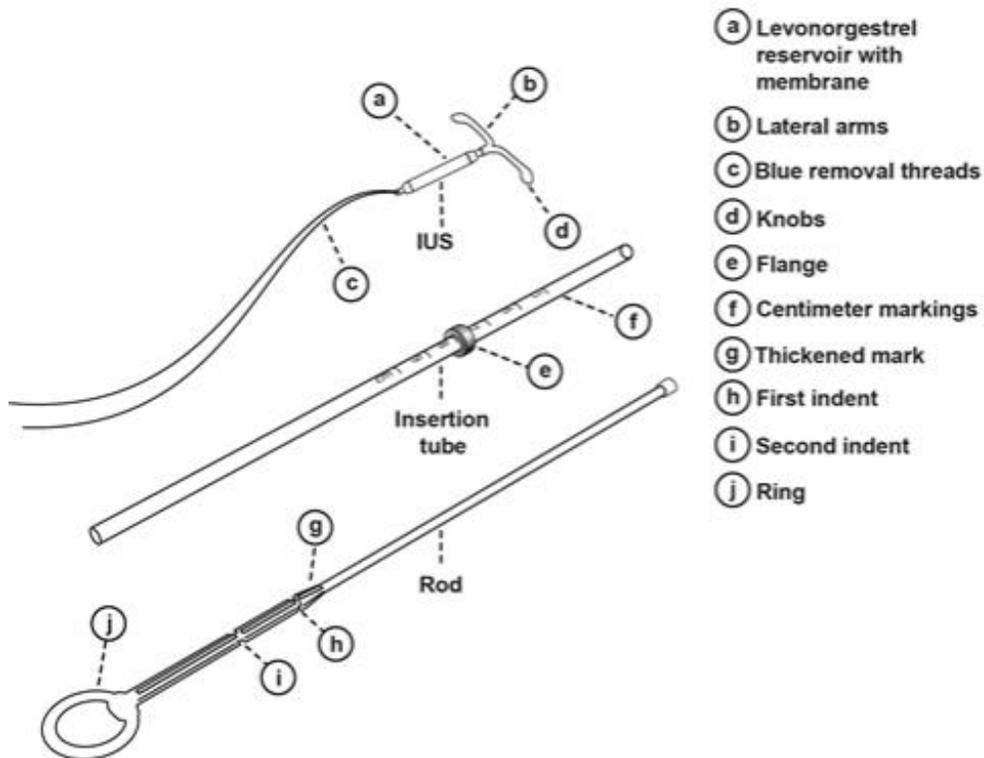


Figure 2: LILETTA IUS with Inserter

Insertion

LILETTA should only be inserted by a trained healthcare provider. Healthcare providers should become thoroughly familiar with the product, product educational materials, product insertion instructions, prescribing information, and patient labeling before attempting insertion of LILETTA.

- Obtain a complete medical and social history to determine conditions that might influence the selection of LILETTA for contraception. If indicated, perform a physical examination and appropriate tests for genital or sexually transmitted infections. [See *Contraindications (4) and Warnings and Precautions (5.4, 5.10).*]
- Check the expiration date on the box before opening it. **Do not insert LILETTA after the expiration date.**
- Visually inspect the packaging (sealed pouch) containing LILETTA to verify that the packaging has not been damaged (e.g., torn, punctured, etc.). If the packaging has any visual damage that could compromise sterility, do not use the unit for insertion [see *Warnings and Precautions (5.3)*].
- Ensure that the patient understands the contents of the Patient Information Booklet and obtain consent. A sample consent form that includes the lot number is on the last page of the Patient Information Booklet.
- Complete the pelvic examination, speculum placement, tenaculum placement, and sounding of the uterus before opening the LILETTA pouch.
- Do not open the pouch to insert LILETTA if:
 - the cervix is unable to be properly visualized
 - the uterus cannot be adequately instrumented (during sounding)
 - the uterus sounds to less than 5.5 cm

Planning for Insertion

- Ensure all needed items for LILETTA insertion are readily available:
 - Gloves

- Speculum
- Sterile uterine sound
- Sterile tenaculum
- Antiseptic solution
- LILETTA with inserter in sealed pouch
- Sterile, blunt-tipped scissors
- Additional items that may be useful could include:

- Local anesthesia, needle, and syringe
- Os finder and/or cervical dilators
- Ultrasound with abdominal probe
- Exclude pregnancy and confirm that there are no other contraindications to the insertion and use of LILETTA.
- Follow the insertion instructions exactly as described in order to ensure proper insertion.
- If you encounter cervical stenosis at any time during uterine sounding or LILETTA insertion, use cervical dilators, not force, to overcome resistance. If necessary, dilation, sounding, and insertion may be performed with ultrasound guidance.
- Insertion may be associated with some pain and/or bleeding or vasovagal reactions (e.g., diaphoresis, syncope, bradycardia, or seizure), especially in patients with a predisposition to these conditions. Consider administering analgesics prior to insertion.

Use aseptic technique during the entire insertion procedure. Loading and inserting LILETTA can be done with or without sterile gloves. If not using sterile gloves, complete all steps for loading the IUS (Steps 1-7) inside the pouch. Maintain sterility during LILETTA insertion; do not touch LILETTA or parts of any sterile instrument that will pierce tissue (e.g., a tenaculum on the cervix) or go into the uterine cavity. If, at any step, there is a need to touch a sterile surface, sterile gloves should be used.

Preparation for Insertion

- With the patient comfortably in lithotomy position, do a bimanual exam to establish the size, shape, and position of the uterus and to evaluate any signs of uterine infection.
- Gently insert a speculum to visualize the cervix.
- Thoroughly cleanse the cervix and vagina with antiseptic solution.
- Administer cervical anesthetic, if needed.
- Apply a tenaculum to the cervix and use gentle traction to align the cervical canal with the uterine cavity. If the uterus is retroverted, it may be more appropriate to grasp the lower lip of the cervix. Keep the tenaculum in position and maintain gentle traction on the cervix throughout the insertion procedure.
- Carefully sound the uterus to measure its depth.
- The uterus should sound to a depth of at least 5.5 cm. Insertion of LILETTA into a uterine cavity that sounds to less than 5.5 cm may increase the incidence of expulsion, bleeding, pain, perforation, and possibly pregnancy. LILETTA should not be inserted if the uterus sounds to less than 5.5 cm.
- After ascertaining that the patient is appropriate for LILETTA, replace contaminated glove(s) and open the pouch containing LILETTA.

Insertion Procedure

Loading the IUS into the Inserter

Step 1

- Place the LILETTA pouch on a flat surface with the clear side of the pouch facing up (Figure 3).

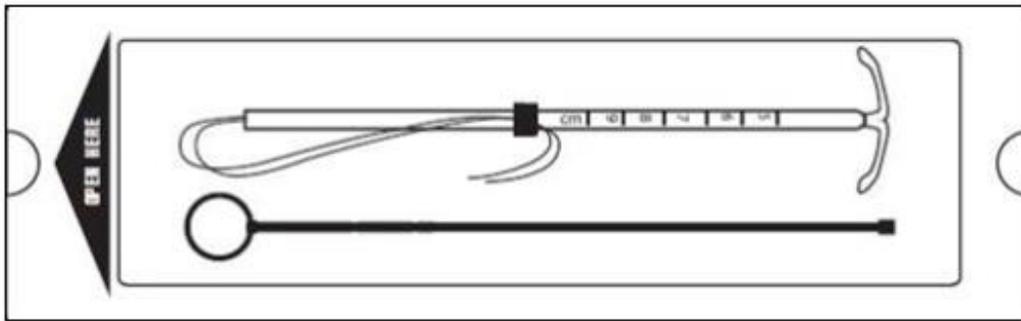


Figure 3: Place the LILETTA pouch on a flat surface.

- Open the sterile LILETTA pouch from the bottom (end with the rod ring) approximately 1/3 of the way until the lower ends of the IUS threads, the rod, and the insertion tube are exposed (Figure 4).

If using sterile gloves, you can open the pouch completely before putting on the sterile gloves.

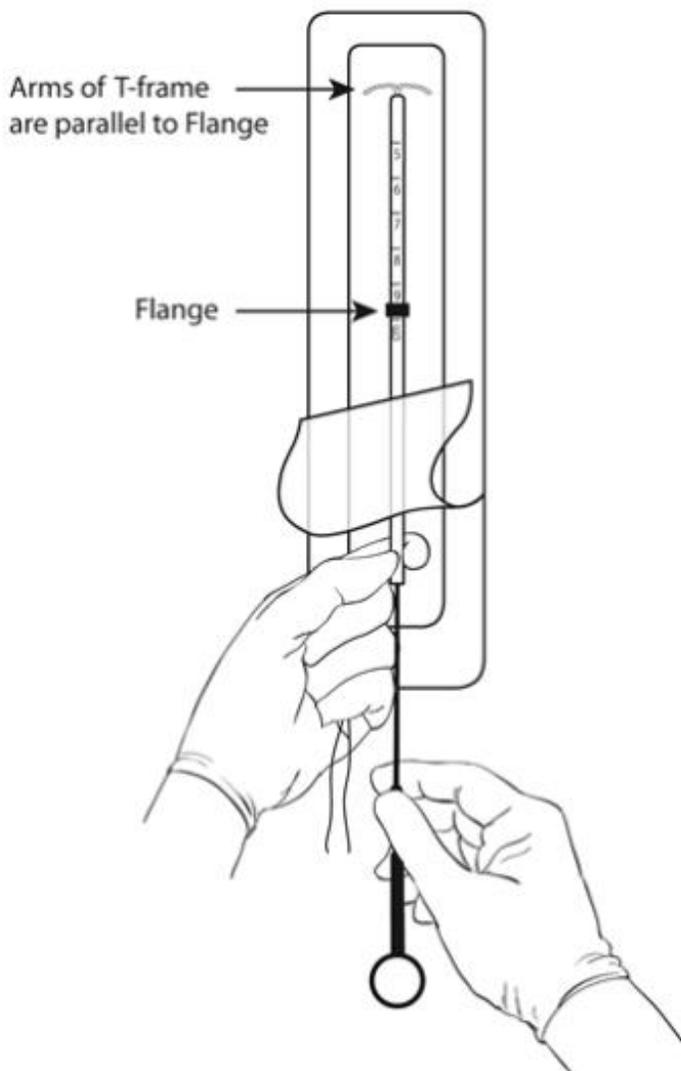


Figure 4: Release the threads from the flange and insert the rod.

Step 2

- Pull back the blue threads to dislodge them from the flange.
- Be careful to not pull the IUS down at the same time (Figure 4).

Step 3

- Hold the exposed end of the insertion tube containing the IUS (Figure 4) while keeping the end of the insertion tube with the IUS inside the packaging.
- Remove the rod from the pouch.
- Do not touch the end of the rod that will go into the insertion tube.
- Place the rod into the insertion tube (alongside the IUS threads) to about the 5 cm marking (Figure 4).

Step 4

- While holding the insertion tube and the rod firmly between the fingers and thumb of one hand, pull downward on both blue threads with the other hand to draw the IUS into the insertion tube (Figure 5).
- The arms of the IUS should be kept in a horizontal plane, parallel to the flat side of the flange (refer to Figure 4).
- Do not pull the IUS all of the way through the insertion tube; only pull the threads until the IUS is loaded at the top of the insertion tube. *Note: If you accidentally remove the IUS completely out of the insertion tube, do not use or attempt to re-load.*

Figure 5: Pull on the threads to pull the IUS into the tube.

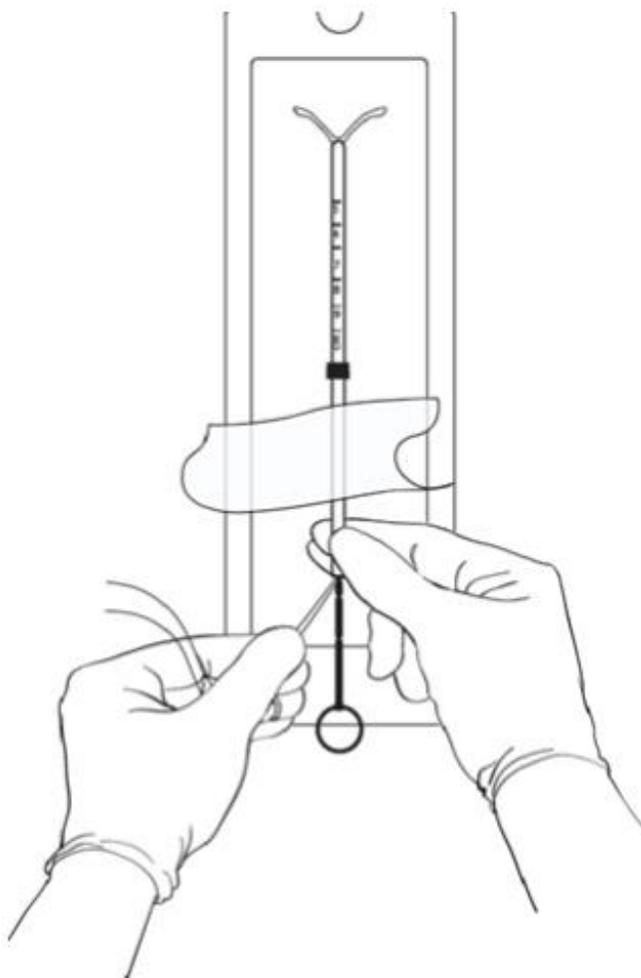
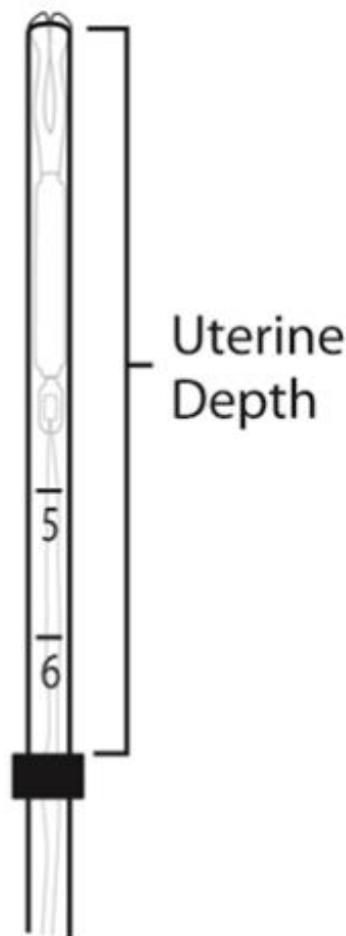


Figure 6: Adjust the Flange.



Step 5

- Hold the insertion tube and the rod firmly with one hand.
- With the other hand, adjust the position of the flange (through the sterile packaging if not using sterile gloves) by moving the tube to correspond to the sound measurement (Figure 6).
- The top end of the flange should be at the measurement corresponding to the sounded depth of the uterus.

Step 6

- Final IUS positioning: position the IUS in the tube so that the knobs of the lateral arms are opposed to each other and protrude slightly above the tip of the insertion tube to form a hemispherical dome (Figure 7).
- Hold the tube at its proximal end between your fingers and thumb of one hand.
- With the other hand, while pulling on the blue threads, slowly advance the rod forward to adjust the position of the IUS.
- When the IUS tips are in the correct position (slightly protruding), pinch and hold the proximal end of the tube firmly to maintain rod position.
- The proximal end of the insertion tube will be approximately at the top of the first indent on the rod (Figure 7).

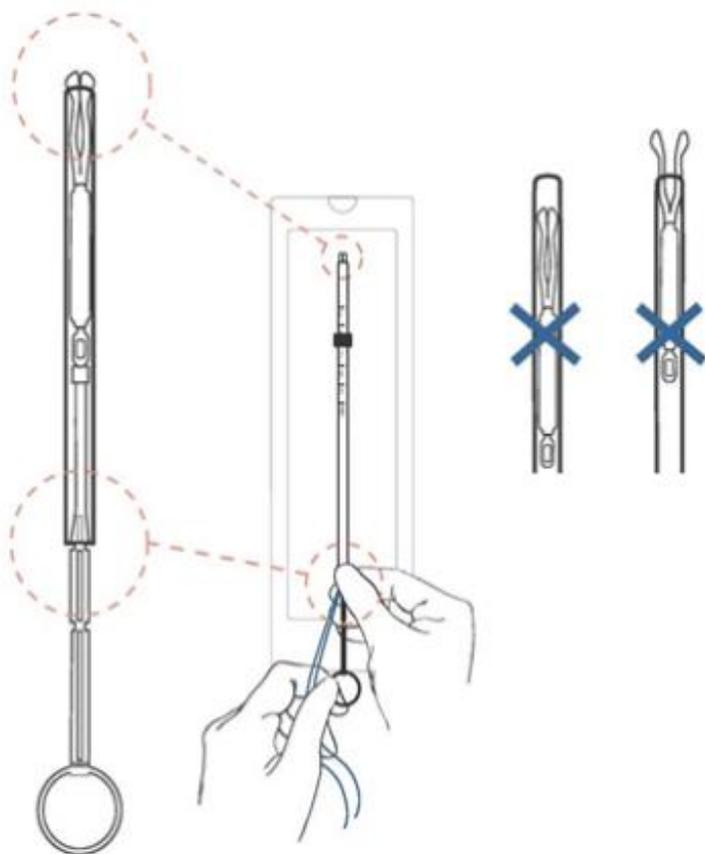


Figure 7: Final IUS Positioning

ENSURE A HEMISPHERICAL DOME IS ACHIEVED.

When the IUS is in the correct position, the lower end of the tube will be aligned approximately at the upper edge of the upper indent on the rod.

Step 7

Check to make sure the IUS is correctly loaded. You should note the following:

- The IUS is completely within the insertion tube with the knobs of the arms forming a hemispherical dome at the top of the tube.
- The top of the rod is touching the bottom of the IUS.
- The blue threads are hanging through the end of the insertion tube.
- The flange is marking the depth of the uterus based on pre-insertion sounding.

Step 8

Remove the loaded IUS insertion tube from the pouch while holding the lower end of the tube firmly between your fingers and thumb.

If not using sterile gloves, do not touch the flange and any part of the insertion tube above the flange during this step and through the IUS insertion procedure.

IUS Insertion into the Uterus

Step 1

- Apply gentle traction on the tenaculum to straighten the alignment of the cervical canal and uterine cavity.
- While still firmly pinching the proximal end of the insertion tube to maintain the IUS in the correct position (Hand A), slide the loaded IUS insertion tube through the cervical canal until the upper edge of the flange is approximately 1.5 – 2.0 cm from the cervix (Figure 8).
- DO NOT advance flange to the cervix at this step.
- DO NOT force the inserter. If necessary, dilate the cervical canal.

Figure 8: While holding the rod and the tube, advance into the uterine cavity. Advance to 1.5 – 2.0 cm from the cervix.

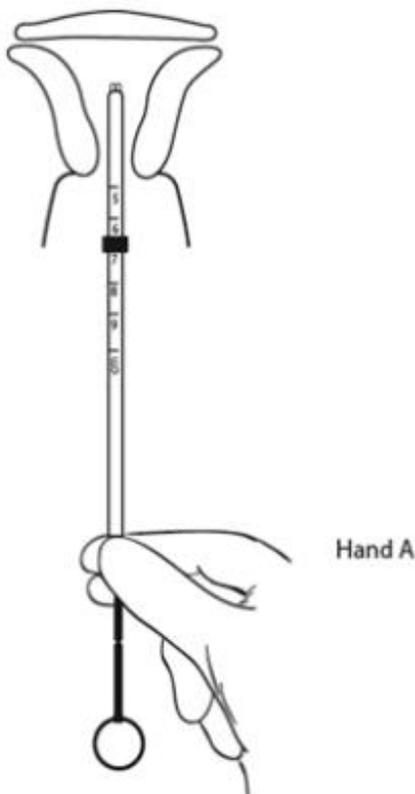
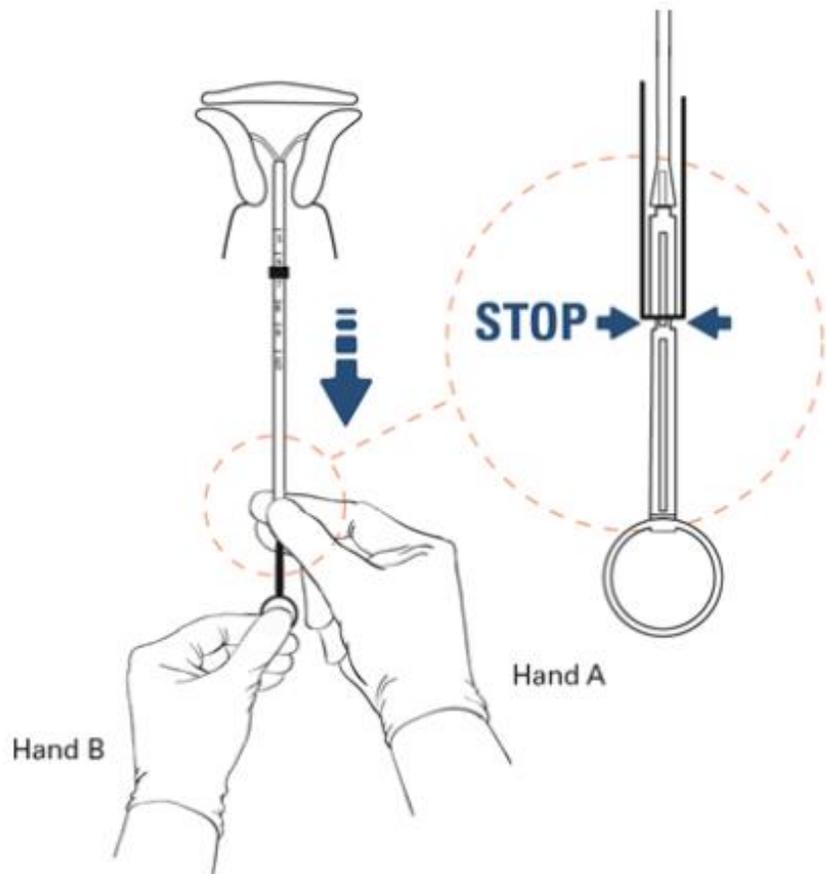


Figure 9: Hold the rod still and pull back the tube until the second indent on the rod.



Step 2

- Release hold on the tenaculum.
- Hold the insertion tube with the fingers of one hand (Hand A) and the rod with the fingers of the other hand (Hand B).

- Hold the rod still (Hand B), relax the firmness of the pinch on the tube, and pull the insertion tube back with Hand A to the edge of the second indent of the rod (Figure 9).
- This will allow the IUS arms to open in the lower uterine segment.

Step 3

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

Step 4

- Apply gentle traction with the tenaculum before advancing the IUS.
- With Hand A still holding the proximal end of the tube, advance both the insertion tube and rod simultaneously up to the uterine fundus (Figure 10). You will feel slight resistance when the IUS is at the fundus.
- The flange should be touching the cervix when the IUS reaches the uterine fundus.

Note: Fundal positioning is important to prevent expulsion.

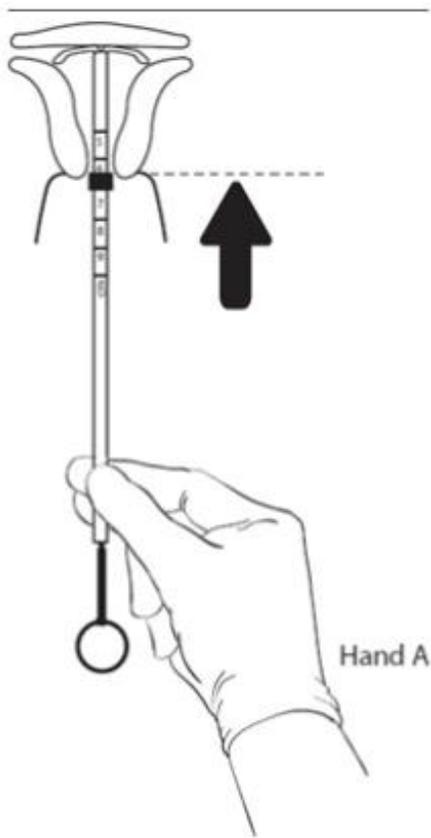


Figure 10: After 10 – 15 seconds, advance to the fundus while holding both the rod and the tube.

Step 5

- Hold the rod still (Hand B) while pulling the insertion tube back with Hand A to the ring of the rod (Figure 11).

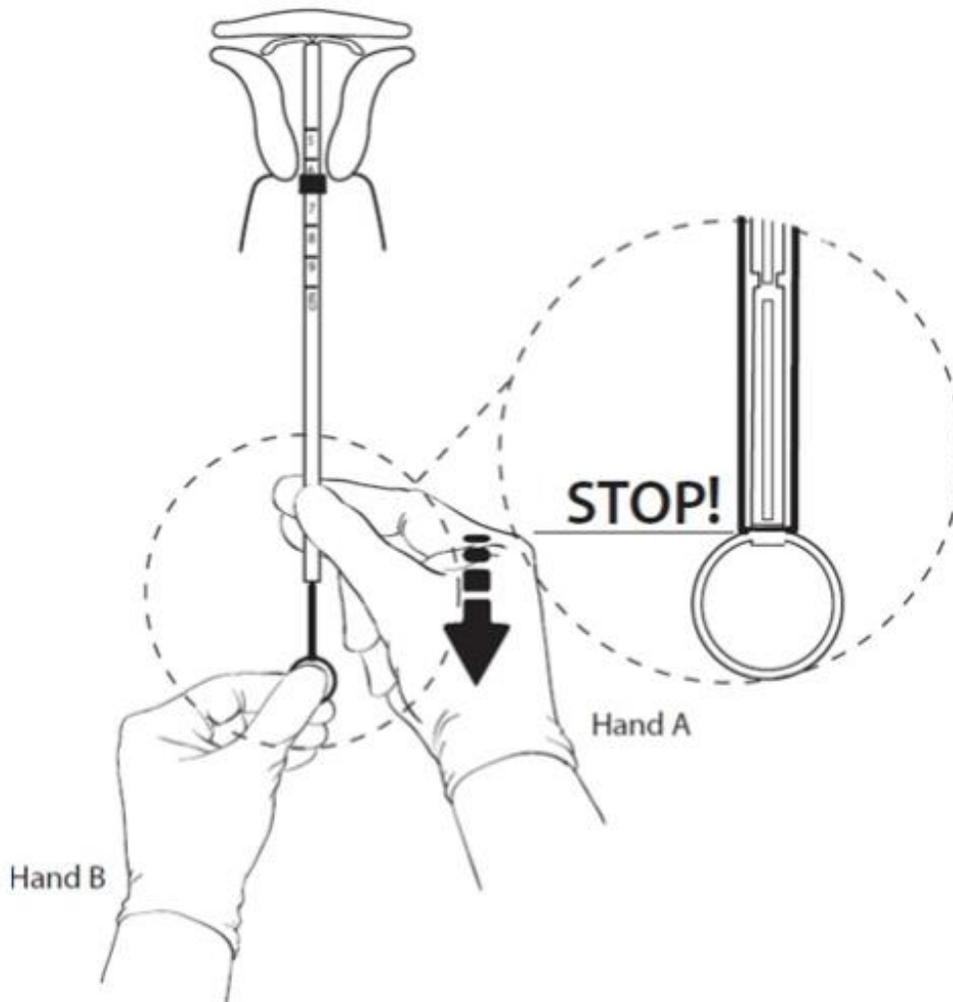


Figure 11: Hold the rod still and pull back the tube to the ring on the rod.

Step 6

- While holding the inserter tube with Hand A, withdraw the rod from the insertion tube all of the way out to prevent the rod from catching on the knot at the lower end of the IUS.

Note: Ensure the tube is held firmly in place until the rod is completely pulled outside of the tube as there will be some slight resistance while removing the rod from the tube.

Step 7

- Completely remove the insertion tube.

Step 8

- Use blunt-tipped sharp scissors to cut the IUS threads perpendicular to the thread length, leaving about 3 cm outside of the cervix (Figure 12). *Note: Do not cut threads at an angle as this may leave sharp ends.*
- Do not apply tension or pull on the threads when cutting to prevent displacing the IUS.

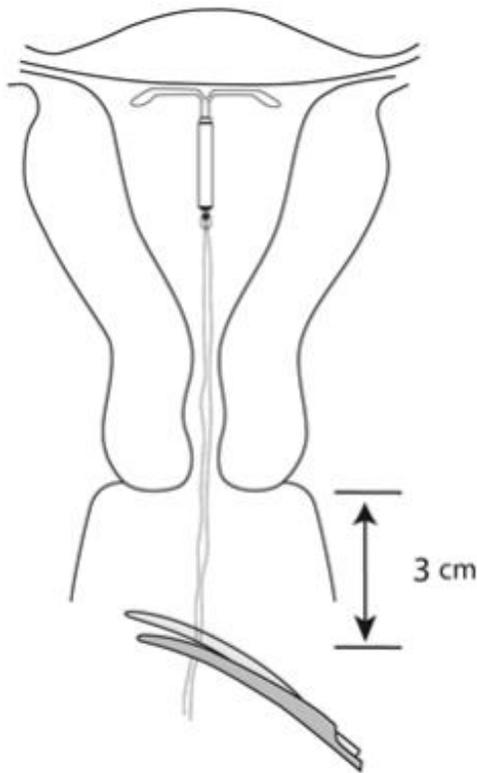


Figure 12: Cut the threads about 3 cm from the cervix

Insertion of LILETTA is now complete.

Important information to consider during or after insertion:

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

Difficult insertion

- If insertion is difficult because the uterus cannot be appropriately instrumented, consider the following measures:
 - Use of cervical anesthesia to make sounding and manipulation more tolerable.
 - Use of dilators to dilate the cervix if needed to allow passage of the sound or inserter.
 - Abdominal ultrasound guidance during dilation and/or insertion.
 - If there is clinical concern, exceptional pain, or bleeding during or after insertion, take appropriate steps, such as physical examination and ultrasound, immediately to exclude uterine perforation [see *Warnings and Precautions (5.5)*].

2.4 Patient Counseling and Record-Keeping

- Keep a copy of the consent form and LILETTA lot number for your records.
- Counsel the patient on what to expect following LILETTA insertion. Give her the Patient Information Booklet, which includes the website address (www.LILETTA.com). Discuss expected bleeding patterns with LILETTA use. Review the signs and symptoms of LILETTA expulsion. [See *Patient Counseling Information (17)*].
- Prescribe analgesics, if indicated.

2.5 Patient Follow-Up

Re-examine and evaluate patients 4 to 6 weeks after insertion and once a year thereafter, or more frequently if clinically indicated. The healthcare provider should check strings during each routine and

follow-up visit.

2.6 Removal of LILETTA

Timing of Removal

- If pregnancy is desired, LILETTA can be removed at any time.
- If pregnancy is not desired, LILETTA can be removed at any time; however, a contraception method should be started prior to removal of LILETTA [see *Dosage and Administration (2.5)*]. Counsel your patient that she is at risk of pregnancy if she has intercourse in the week prior to removal without use of a backup contraceptive method.
- LILETTA should be removed after 4 years. LILETTA can be replaced at the time of removal with a new LILETTA if continued contraceptive protection is desired.

Planning for Removal

- Ensure all needed items for LILETTA removal are readily available:
 - Gloves
 - Speculum
 - Sterile forceps
 - Additional items that may be required could include:
 - Local anesthetic, needle, and syringe
 - Os finder and/or cervical dilators
 - Ultrasound with abdominal probe
 - Sterile tenaculum
 - Antiseptic solution
 - Long, narrow forceps
- Removal may be associated with some pain and/or bleeding or vasovagal reactions (e.g., syncope, bradycardia, or seizure), especially in patients with a predisposition to these conditions.
- After removal of LILETTA, examine the system to ensure that it is intact.

Removal Instructions

- With the patient comfortably in lithotomy position, place a speculum and visualize the cervix.
- When the threads of LILETTA are visible:
 - Remove the IUS by applying traction on the threads with forceps (Figure 13).
 - The arms of the device will fold upward as it is withdrawn from the uterus.
 - If the IUS cannot be removed with traction on the threads, perform an ultrasound examination to confirm location of the IUS, including assessment for partial or total perforation. If the IUS is in the uterus, use long, narrow forceps to grasp LILETTA. Consider use of a tenaculum, cervical anesthesia, cervical dilators, and/or ultrasound guidance as needed.
 - After removal, examine the system to ensure it is intact.
- If the threads of LILETTA are not visible:
 - Determine location of the IUS by ultrasound examination.
 - If the IUS is in the uterine cavity, use long, narrow forceps (e.g., Alligator forceps) to grasp LILETTA. Consider use of a tenaculum, cervical anesthesia, cervical dilators, and/or ultrasound guidance as needed. If LILETTA cannot be removed using the above techniques, consider hysteroscopic evaluation for removal.
 - If the IUS is not in the uterine cavity, consider an abdominal x-ray or CT scan to evaluate if the IUS is in the abdominal cavity. Consider laparoscopic evaluation for removal, as clinically indicated.
 - After removal, examine the system to ensure it is intact.

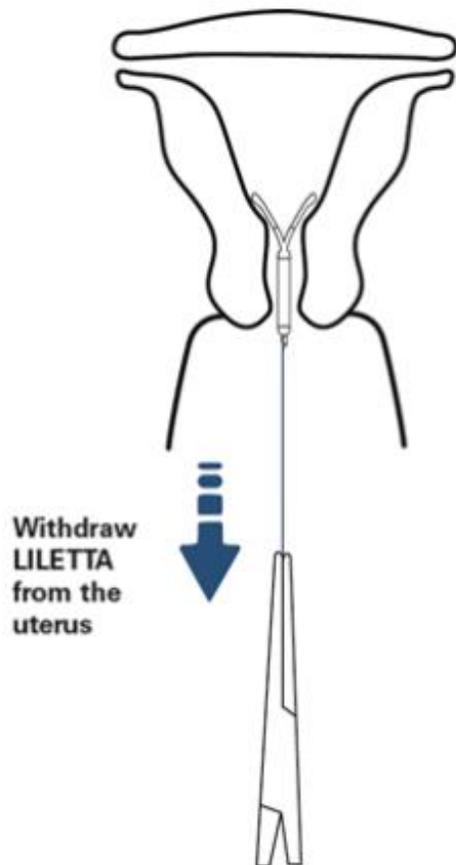


Figure 13: Removal of LILETTA

2.7 Continuation of Contraception After Removal

- If a patient wishes to continue using LILETTA or another intrauterine contraceptive, insertion can occur immediately after removal.
- If a patient with regular cycles wants to start a different birth control method, time the removal and initiation of a new method to ensure continuous contraception. Either remove LILETTA during the first 7 days of the menstrual cycle and start the new method or start the new method at least 7 days prior to removing LILETTA if removal is to occur at other times during the cycle.
- If a patient with irregular cycles or amenorrhea wants to start a different birth control method, start the new method at least 7 days before LILETTA removal.
- If LILETTA is removed but no other contraceptive method has already been started, the new contraceptive method can be started on the day LILETTA is removed. The patient should use a backup barrier method of contraception (e.g., condoms and spermicide) or abstain from vaginal intercourse for 7 days to prevent pregnancy.

3 DOSAGE FORMS AND STRENGTHS

LILETTA is a levonorgestrel-releasing intrauterine system consisting of a T-shaped polyethylene frame with a drug reservoir containing 52 mg levonorgestrel, packaged within a sterile inserter.

4 CONTRAINDICATIONS

The use of LILETTA is contraindicated when one or more of the following conditions exist:

- Pregnancy or suspected pregnancy
- For use as post-coital contraception (emergency contraception)
- Congenital or acquired uterine anomaly, including fibroids, that distorts the uterine cavity and would

be incompatible with correct IUS placement

- Acute pelvic inflammatory disease (PID) or endometritis or a history of PID unless there has been a subsequent intrauterine pregnancy
- Infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia
- Known or suspected breast cancer or other hormone-sensitive cancer, now or in the past
- Uterine bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis, including bacterial vaginosis, known chlamydial or gonococcal cervical infection, or other lower genital tract infections until infection is controlled
- Acute liver disease or liver tumor (benign or malignant)
- Conditions associated with increased susceptibility to pelvic infections [see *Warnings and Precautions (5.4)*]
- A previously inserted IUS that has not been removed
- Hypersensitivity to any component of LILETTA [see *Adverse Reactions (6.2)*]

5 WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Evaluate women for ectopic pregnancy if they become pregnant with LILETTA in place because the likelihood of a pregnancy being ectopic is increased with LILETTA. Approximately half of pregnancies that occur with LILETTA in place are likely to be ectopic. Also 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. If an ectopic pregnancy is confirmed, LILETTA should be removed.

The incidence of ectopic pregnancy in the clinical trial with LILETTA, which excluded women with a history of ectopic pregnancy who did not have a subsequent intrauterine pregnancy, was approximately 0.16 per 100 women-years. The risk of ectopic pregnancy in women who have a history of ectopic pregnancy and use LILETTA is unknown. Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection have a higher risk of ectopic pregnancy. Ectopic pregnancy may require surgery and may result in loss of fertility.

Tell women who choose LILETTA about the risks of ectopic pregnancy, including the loss of fertility. Teach them to recognize and report to their healthcare provider promptly any signs of ectopic pregnancy.

5.2 Intrauterine Pregnancy

If pregnancy occurs while using LILETTA, determine if LILETTA is in the uterus. If LILETTA is in the uterus, attempt to remove LILETTA because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Removal of LILETTA or probing of the uterus may also result in spontaneous abortion. In the event of an intrauterine pregnancy with LILETTA, consider the following:

Septic abortion

In patients becoming pregnant with an IUS in place, septic abortion – with septicemia, septic shock, and death – may occur. Septic abortion typically requires hospitalization and treatment with intravenous antibiotics. Septic abortion may result in spontaneous abortion or a medical indication for pregnancy termination. Should severe infection of the uterus occur, hysterectomy may be required, which will result in permanent infertility.

Continuation of pregnancy

If a woman becomes pregnant with LILETTA in place and if LILETTA cannot be removed or the woman chooses not to have it removed, warn her that failure to remove LILETTA increases the risk of

miscarriage, sepsis, premature labor, and premature delivery. Prenatal care should include counseling about these risks and that she should report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of fluid, or any other symptom that suggests complications of the pregnancy.

5.3 Sepsis

Severe infection or sepsis, including Group A streptococcal sepsis (GAS), have been reported following insertion of other LNG-releasing IUSs. In some cases, severe pain occurred within hours of insertion followed by sepsis within days. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of LILETTA is essential in order to minimize serious infections such as GAS.

5.4 Pelvic Inflammatory Disease or Endometritis

Insertion of LILETTA is contraindicated in the presence of known or suspected PID or endometritis or a history of PID unless there has been a subsequent intrauterine pregnancy [see *Contraindications (4)*]. IUSs have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion.

In the clinical trial with LILETTA, pelvic infection was diagnosed in 0.8% of women. The infection was diagnosed as PID in 0.5% of women and as endometritis in 0.3% of women. One woman diagnosed with PID developed the infection within a week of LILETTA insertion, while the remainder were diagnosed more than six months after insertion. The cases of endometritis had onset less than 40 days after LILETTA insertion except for one occurring at 43 months after insertion.

Counsel women who receive LILETTA to notify a healthcare provider if they have complaints of lower abdominal or pelvic pain, odorous discharge, unexplained bleeding, fever, or genital lesions or sores. In such circumstances, perform a pelvic examination promptly to evaluate for possible pelvic infection. Remove LILETTA in cases of recurrent PID or endometritis, or if an acute pelvic infection is severe or does not respond to treatment.

Women at increased risk for PID or endometritis

PID and endometritis are often associated with a sexually transmitted infection (STI), and LILETTA does not protect against STIs. The risk of PID or endometritis is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Women who have had PID or endometritis are at increased risk for a recurrence or re-infection. In particular, ascertain whether the woman is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome [AIDS], IV drug abuse).

Asymptomatic PID or endometritis

PID or endometritis may be asymptomatic but still result in tubal damage and its sequelae.

Treatment of PID or endometritis

Following a diagnosis of PID or endometritis, or suspected PID or endometritis, perform appropriate testing for sexually transmitted infection and initiate antibiotic therapy promptly. LILETTA does not need to be removed immediately if the woman needs ongoing contraception (1). In the LILETTA clinical trial, 12 of the 14 women who developed PID or endometritis were successfully treated without removal of LILETTA.

Reassess the woman in 48-72 hours. If no clinical improvement occurs, continue antibiotics and consider removal of LILETTA. If the woman wants to discontinue use, remove LILETTA after antibiotics have been started to avoid the potential risk for bacterial spread resulting from the removal procedure. Guidelines for PID or endometritis treatment are available from the Centers for Disease Control (CDC), Atlanta, Georgia (1).

Actinomycosis

Actinomycosis has been associated with IUS use. Symptomatic women with known actinomycosis infection should have LILETTA removed and receive antibiotics. Actinomycetes can be found in the genital tract cultures in healthy women without IUSs. The significance of actinomyces-like organisms on Pap test in an asymptomatic IUS user is unknown, and so this finding alone does not always require LILETTA removal and treatment. When possible, confirm a Pap test diagnosis with cultures.

5.5 Perforation

Perforation (total or partial, including penetration/embedment of LILETTA in the uterine wall or cervix) may occur, most often during insertion, although the perforation may not be detected until sometime later. Perforation may reduce contraceptive efficacy and result in pregnancy. This may be associated with severe pain and continued bleeding.

The incidence of perforation during or following LILETTA insertion in the clinical trial, which excluded breastfeeding women, was 0.1%.

If perforation is suspected the IUS should be removed as soon as possible, surgery may be required. Delayed detection or removal of LILETTA in case of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses, and erosion of adjacent viscera.

In a large prospective comparative non-interventional cohort study with another IUS the incidence of uterine perforation was reported as 6.3 per 1,000 insertions for lactating women, compared to 1.0 per 1,000 insertions for non-lactating women.

The risk of perforation may be increased if LILETTA is inserted when the uterus is fixed retroverted or not completely involuted during the post-partum period. Delay LILETTA insertion a minimum of six weeks or until involution is complete following a delivery or a second trimester abortion.

5.6 Expulsion

Partial or complete expulsion of LILETTA may occur, resulting in the loss of contraceptive protection. In the clinical trial with LILETTA, an overall expulsion rate of 3.7% was reported, with a rate of 2.1% in nulliparous women and 5.7% in parous women. Expulsion may be associated with symptoms of bleeding or pain, or it may be asymptomatic and go unnoticed. LILETTA typically decreases menstrual bleeding over time; therefore, an increase in menstrual bleeding may be indicative of an expulsion.

The risk of expulsion may be increased when the uterus is not completely involuted at the time of insertion. Delay LILETTA insertion a minimum of 6 weeks or until uterine involution is complete following a delivery or a second trimester abortion.

Remove a partially expelled LILETTA. If expulsion has occurred, a new LILETTA may be inserted within 7 days after the onset of a menstrual period after pregnancy has been ruled out.

5.7 Ovarian Cysts

Because the contraceptive effect of LILETTA is mainly due to its local effects within the uterus, ovulatory cycles with follicular rupture usually occur in women of fertile age using LILETTA. Sometimes atresia of the follicle is delayed and the follicle may continue to grow. Most ovarian cysts that occur during use of LNG-releasing IUSs are asymptomatic and disappear spontaneously during two to three months of observation. Cysts that cause clinical symptoms can result in pelvic or abdominal pain or dyspareunia. Symptomatic ovarian cysts occurred in 4.3% of subjects using LILETTA, and 0.3% of subjects discontinued use of LILETTA because of an ovarian cyst.

Evaluate persistent ovarian cysts. Surgical intervention is not usually required, but may be necessary in some cases. Discuss this risk with patients who choose to use LILETTA.

5.8 Bleeding Pattern Alterations

LILETTA can alter the bleeding pattern and result in spotting, irregular bleeding, heavy bleeding, oligomenorrhea, and amenorrhea. During the first three to six months of LILETTA use, the number of bleeding and spotting days may be increased and bleeding patterns may be irregular. Thereafter, the number of bleeding and spotting days usually decreases but bleeding may remain irregular.

In the LILETTA clinical trial, amenorrhea developed in approximately 19% of LILETTA users by the end of the first year of use, in 27% by the end of the second year of use, in 37% by the end of the third year of use and 41% by the end of the fourth year of use. In the trial, 2.2% of LILETTA subjects discontinued due to bleeding complaints. Table 2 shows the bleeding and spotting days based on 28-day cycle equivalents.

Table 2: Mean Number of Bleeding and Spotting Days per 28-Day Cycle Equivalent

| 28-Day Cycle Equivalent | Cycle 1 N=1,691 | | Cycle 4 N=1,593 | | Cycle 7 N=1,519 | | Cycle 13 N=1,395 | | Cycle 26 N=1,108 | |
|--------------------------------|----------------------------|-----|----------------------------|-----|----------------------------|-----|-----------------------------|-----|-----------------------------|-----|
| Days on treatment | 1-28 | | 85-112 | | 169-196 | | 337-364 | | 674-728 | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Number of bleeding days | 5.8 | 5.2 | 2.3 | 3.3 | 1.6 | 2.7 | 1.2 | 2.4 | 0.8 | 1.8 |
| Number of spotting days | 9.0 | 5.9 | 4.3 | 4.2 | 3.2 | 3.6 | 2.7 | 3.4 | 1.9 | 2.8 |

Note: Includes all LILETTA subjects.

In the LILETTA clinical trial, 429 of 439 (97.7%) women evaluated experienced menses after LILETTA removal. Excluding nine women who became pregnant or had a hysterectomy before having a return of their menses, 429 of 430 (99.8%) had a return of their menses, 99.1% within three months.

If a significant change in bleeding develops during prolonged use, take appropriate diagnostic measures to rule out endometrial pathology. Consider the possibility of pregnancy if menstruation does not occur within six weeks of the onset of a previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are generally not necessary in amenorrheic women unless indicated, for example, by other signs of pregnancy or by pelvic pain.

5.9 Breast Cancer

Women who currently have or have had breast cancer, or have a suspicion of breast cancer, should not use hormonal contraception, including LILETTA, because some breast cancers are hormone-sensitive [see *Contraindications (4)*].

Spontaneous reports of breast cancer have been received during postmarketing experience with another LNG-releasing IUS. Observational studies have not provided consistent evidence of an increased risk of breast cancer with use of a LNG-releasing IUS.

5.10 Clinical Considerations for Use and Removal

Obtain a complete medical and social history, including partner status, to determine conditions that might influence the selection of an IUS for contraception.

Because irregular bleeding/spotting is common during the first months of LILETTA use, exclude endometrial pathology (polyps or cancer) prior to the insertion of LILETTA in women with persistent or uncharacteristic bleeding.

Special attention must be given to ascertaining whether the woman is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome [AIDS], IV drug abuse), or has a history of PID unless there has been a subsequent intrauterine pregnancy. LILETTA does not protect against HIV/STI transmission. [See *Warnings and Precautions (5.4)*].

Use LILETTA with caution after careful assessment if any of the following conditions exist, and consider removal of the IUS if any of them arise during use:

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

In addition, consider removing LILETTA if any of the following conditions arise during use [*see Contraindications (4)*]:

- Uterine or cervical malignancy
- Jaundice

If the threads are not visible or are significantly shortened, they may have broken or retracted into the cervical canal or uterus. Consider the possibility that the IUS may have been displaced, (for example, expelled or perforated the uterus) [*see Warnings and Precautions (5.5, 5.6)*]. Exclude pregnancy and verify the location of LILETTA, for example, by sonography, by X-ray, or by gentle exploration of the cervical canal with a suitable instrument [*see Dosage and Administration (2.6)*]. If LILETTA is displaced, remove it. A new LILETTA may be inserted at that time or during the next menses if it is certain that conception has not occurred. If LILETTA is in place with no evidence of perforation, no intervention is indicated.

5.11 Magnetic Resonance Imaging (MRI) Information

LILETTA is MR Safe.

6 ADVERSE REACTIONS

The following serious or otherwise important adverse reactions are discussed elsewhere in the labeling:

- Ectopic Pregnancy [*see Warnings and Precautions (5.1)*]
- Intrauterine Pregnancy [*see Warnings and Precautions (5.2)*]
- Group A Streptococcal Sepsis (GAS) [*see Warnings and Precautions (5.3)*]
- Pelvic Inflammatory Disease or Endometritis [*see Warnings and Precautions (5.4)*]
- Perforation [*see Warnings and Precautions (5.5)*]
- Expulsion [*see Warnings and Precautions (5.6)*]
- Ovarian Cysts [*see Warnings and Precautions (5.7)*]
- Bleeding Pattern Alterations [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure of 1,751 generally healthy 16- to 45-year-old women to LILETTA in a large, multi-center contraceptive trial conducted in the US, including 1,409 exposed for 1 year and 837 subjects who completed 4 years of use; 58% were nulliparous (mean age 25.1 ± 4.3 years) and 42% were parous (mean age 30.3 ± 6.1 years). Most women who received LILETTA were Caucasian (78.4%) or Black/African American (13.3%); 14.7% of women were of Hispanic ethnicity. The clinical trial had no upper or lower weight or BMI limit. Mean BMI of LILETTA subjects was 26.9 kg/m^2 (range $15.8 - 61.6 \text{ kg/m}^2$); 25.1% had a BMI $\geq 30 \text{ kg/m}^2$, of which 5.3% had a BMI $\geq 40 \text{ kg/m}^2$. The data cover more than 59,000 28-day cycles of LILETTA exposure. The frequencies of

reported adverse drug reactions represent crude incidences.

The most common adverse reactions during the LILETTA clinical trial (occurring in $\geq 5\%$ of users) are shown in Table 3.

Table 3: Adverse Reactions in $\geq 5\%$ of LILETTA Users in Phase 3 Clinical Study

| System Organ Class/Preferred Term | % LILETTA Subjects (N = 1,751) |
|--|---------------------------------------|
| Vaginal bacterial infections | 17.9% |
| Vulvovaginal mycotic infections | 17.9% |
| Acne | 14.5% |
| Nausea or vomiting | 9.4% |
| Dyspareunia | 8.8% |
| Headache | 8.7% |
| Breast tenderness or pain | 8.0% |
| Pelvic discomfort or pain | 7.9% |
| Anxiety | 7.6% |
| Abdominal discomfort or pain | 7.4% |
| Depression | 6.4% |
| Weight increased | 5.6% |
| Dysmenorrhea | 5.6% |
| Mood changes | 5.5% |
| Vaginal discharge | 5.3% |
| Back pain | 5.2% |

In the contraceptive trial, 18.3% of LILETTA users discontinued prematurely due to an adverse reaction. The most common adverse reactions leading to discontinuation were expulsion (3.7%) and bleeding complaints (2.2%). The next most common adverse reactions causing discontinuation were acne (1.4%), dysmenorrhea (1.0%), weight increased (1.0%), mood swings (0.8%), uterine spasm (0.7%) and pelvic pain (0.6%). One woman discontinued the clinical study due to PID and one due to endometritis.

In the clinical trial, serious adverse reactions considered related or possibly related to LILETTA were ectopic pregnancies, ovarian cysts, and IUS perforation requiring a laparoscopic surgery.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of LNG-releasing IUSs. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Arterial thrombotic and venous thromboembolic events, including cases of pulmonary emboli, deep vein thrombosis and stroke
- Device breakage
- Hypersensitivity (including rash, urticaria, and angioedema)
- Increased blood pressure

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with LILETTA.

Contraceptive effect of LILETTA is mediated via the direct release of LNG into the uterine cavity and is unlikely to be affected by drug interactions via enzyme induction or inhibition.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LILETTA is contraindicated for use in pregnant women because there is no need for pregnancy prevention in a woman who is already pregnant and LILETTA may cause adverse pregnancy outcomes. If a woman becomes pregnant with LILETTA in place, there is an increased risk of miscarriage, sepsis, premature labor, and premature delivery. Published studies report no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins in a pregnant woman. The background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Animal reproduction studies have not been conducted with LILETTA. Advise a woman of the potential risks if pregnancy occurs with LILETTA in place.

8.2 Lactation

Risk Summary

Published studies report the presence of LNG in human milk. Small amounts of progestins (approximately 0.1% of the total maternal doses) were detected in the breast milk of nursing mothers who used other LNG-releasing IUSs. There are no reports of adverse effects in breastfed infants with maternal use of progestin-only contraceptives. Isolated cases of decreased milk production have been reported with another LNG-releasing IUS. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LILETTA and any potential adverse effects on the breastfed child from LILETTA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of LILETTA have been established in females of reproductive age. Efficacy is expected to be the same for postpubertal females under the age of 16 as for users 16 years and older. Use of this product before menarche is not indicated [see *Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

LILETTA has not been studied in women over age 65 and is not indicated for postmenopausal women.

8.6 Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of LNG released from LILETTA [see *Contraindications (4)*].

8.7 Renal Impairment

No studies were conducted to evaluate the effect of renal disease on the disposition of LNG released from LILETTA.

8.8 Obesity

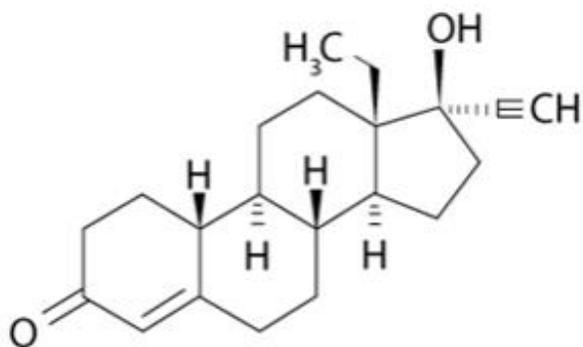
The safety and efficacy of LILETTA have been evaluated in overweight, obese, and morbidly obese patients. There was no apparent effect of BMI or body weight on contraceptive efficacy [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

LILETTA (levonorgestrel-releasing intrauterine system) contains 52 mg of levonorgestrel, a progestin, and is intended to provide an initial release rate of 19.5 mcg/day of levonorgestrel.

Levonorgestrel USP, (-)-13-ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one, the active

ingredient in LILETTA, has a molecular weight of 312.45, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:



11.1 LILETTA

LILETTA consists of a T-shaped polyethylene frame (T-frame) with a drug reservoir around the vertical stem (Figure 14). The T-frame has a loop at one end of the vertical stem and two horizontal arms at the other end. The drug reservoir consists of a cylinder, made of a mixture of 52 mg levonorgestrel and polydimethylsiloxane (PDMS) formed from silicone base, tetra-n-propyl silicate, and stannous octoate. The drug reservoir is covered by a translucent PDMS membrane. The low-density polyethylene of the T-frame is compounded with barium sulfate, which makes it radio-opaque. A blue polypropylene monofilament removal thread is attached to an eyelet at the end of the vertical stem of the T-frame. The polypropylene of the removal thread contains a copper-containing pigment as a colorant. The components of LILETTA, including its packaging, are not manufactured using natural rubber latex.

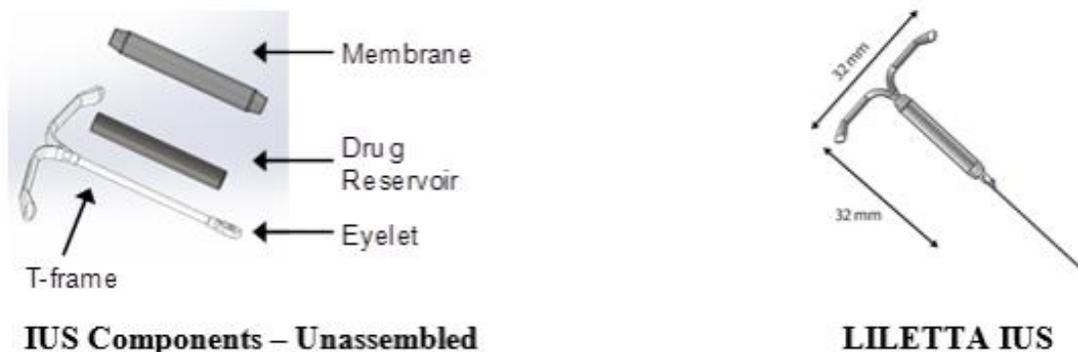


Figure 14: Diagram of LILETTA

11.2 Inserter

The inserter device provided with LILETTA is a single-use, disposable, sterile insertion system (tube, flange, rod; Figure 15), partially preloaded with the IUS product for intrauterine administration.

Once LILETTA has been inserted, the inserter is discarded.



Figure 15: Diagram of Inserter

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The local mechanism by which continuously released LNG provides contraception has not been conclusively demonstrated. Studies of LNG-releasing IUSs suggest several mechanisms for pregnancy prevention: prevention of fertilization due to the thickening of the cervical mucus, which inhibits sperm passage through the cervix, and inhibition of sperm mobility and function (capacitation), and alteration of the endometrium.

12.2 Pharmacodynamics

LILETTA has mainly local progestogenic effects in the uterine cavity. High local concentrations of LNG lead to morphological changes including stromal pseudodecidualization, glandular atrophy, a leukocytic infiltration, and a decrease in glandular and stromal mitoses. Changes in the uterine endometrium may lead to alterations in the menstrual bleeding pattern [see *Warnings and Precautions* (5.8)].

In clinical trials with other LNG-releasing IUSs, ovulation was inhibited in some women but most cycles were ovulatory.

12.3 Pharmacokinetics

Absorption

Low doses of LNG are administered into the uterine cavity with the LILETTA intrauterine delivery system. The initial *in vivo* release rate is 19.5 mcg/day and decreases to 17.0 mcg/day at 1 year, 14.8 mcg/day at 2 years, 12.9 mcg/day at 3 years and 11.3 at 4 years.

In the phase 3 study, systemic LNG concentrations were assessed in a subset of subjects through Month 30 and in all subjects at Month 36 and after. Plasma LNG concentrations following insertion of LILETTA are shown in Table 4.

Table 4: Plasma LNG Concentrations (mean ± SD, pg/mL) Following LILETTA Insertion

| 7 Days (N = 40) | 6 Months (N = 36) | 12 Months (N = 33) | 24 Months (N = 30) | 36 Months (N = 787) | 48 Months (N = 302) |
|--------------------|----------------------|-----------------------|-----------------------|------------------------|------------------------|
| 252 ± 123 | 195 ± 68 | 168 ± 51 | 150 ± 47 | 134 ± 55 | 134 ± 61 |

Distribution

The apparent volume of distribution of LNG at steady-state following oral administration is reported to be approximately 1.8 L/kg. It is about 98.9% protein-bound, principally to sex hormone binding globulin

(SHBG) and, to a lesser extent, serum albumin.

Metabolism

Following absorption, LNG is conjugated at the 17 β -OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3 α , 5 β -tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3 α , 5 α -tetrahydrolevonorgestrel and 16 β -hydroxylevonorgestrel. LNG and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG-containing contraceptive products. *In vitro* studies have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4.

Excretion

About 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The elimination half-life of LNG after a single oral administration is approximately 13.9 \pm 3.2 hours.

Specific Populations

Pediatric: Safety and efficacy of LILETTA have been established in females of reproductive age. The LILETTA clinical trial included 11 subjects aged 16 to 17 years; no pregnancies occurred in these subjects through 4 years of use of LILETTA.

Race: The effect of race on plasma LNG concentrations after LILETTA insertion was assessed in 629 (80%) White subjects, 94 (12%) Black subjects, 34 (4%) Asian subjects, 8 (1%) American Indian/Alaska Native subjects, 17 (2%) multiple-race subjects. Race does not appear to affect LNG concentrations following LILETTA insertion.

Obesity: The LILETTA clinical trial included overweight (24%), obese (24%), and morbidly obese (5%) women. LNG systemic exposure decreased with increasing body weight; however, there was no apparent effect of body mass index (BMI) or body weight on contraceptive efficacy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.9).]

14 CLINICAL STUDIES

14.1 Clinical Trial on Contraception

LILETTA was studied in a multicenter, randomized, open-label clinical trial conducted in the US that enrolled 1,910 generally healthy women aged 16 to 45 years, 1,751 of whom received LILETTA.

LILETTA was inserted in 1,011 (58%) nulliparous and 740 (42%) parous women. Women with a history of ectopic pregnancy, PID, or trophoblastic disease without a subsequent intrauterine pregnancy, who were less than 4 weeks post-pregnancy, had HIV, or were not in a mutually monogamous relationship at study entry were excluded. The demographics of enrolled women who received LILETTA were: Caucasian 78.4%, Black or African American 13.3%, Asian 3.9%, American Indian or Alaska Native 1.2%, Native Hawaiian or Other Pacific Islander 0.3%; 2.9% identified multiple races; 14.7% indicated Hispanic ethnicity. The clinical trial had no upper or lower weight or BMI limit and the BMI range was 15.8 – 61.6 kg/m². The mean BMI of LILETTA subjects was 26.9 kg/m²; 24% were overweight, 24% were obese (BMI \geq 30 kg/m²), and 5% were morbidly obese (BMI \geq 40 kg/m²).

The pregnancy rate calculated as the Pearl Index (PI) in women aged 16 to 35 years, inclusive, was the primary efficacy endpoint used to assess contraceptive reliability. The PI was calculated based on 28-

day equivalent exposure cycles; evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle. The Year 1 PI was based on two pregnancies and the cumulative 4-year pregnancy rate was calculated by the life table method, based on a total of eight pregnancies that occurred after the onset of treatment and within 7 days after LILETTA removal or expulsion. Contraceptive protection did not appear to vary by parity, race or body mass index. Table 5 shows the annual PI for each of the four years and the calculated cumulative life table pregnancy rates through years 1, 2, 3 and 4.

Table 5: Pregnancy Rates

| LILETTA Clinical Trial | Number of 28-Day Cycles of Exposure By Year | Year-by-Year Pearl Index Pregnancy Rate (95% CI) | Cumulative 28-Day Cycles of Exposure | Cumulative Year Life Table Pregnancy Rate (95% CI) |
|-------------------------------|--|---|---|---|
| Year 1 | 17,175 | 0.15 (0.02, 0.55) | 17,175 | 0.14 (0.04, 0.57) |
| Year 2 | 14,205 | 0.37 (0.10, 0.94) | 31,380 | 0.49 (0.22, 1.09) |
| Year 3 | 11,760 | 0.11 (0.00, 0.62) | 43,140 | 0.59 (0.28, 1.25) |
| Year 4 | 9,755 | 0.13 (0.00, 0.74) | 52,895 | 0.73 (0.36, 1.47) |

The use of LILETTA does not appear to alter the course of female fertility after removal of the IUS. Of 153 women who desired pregnancy after study discontinuation, 78% conceived within 6 months following LILETTA removal, and 88% conceived within 12 months after removal of LILETTA.

15 REFERENCES

(1) Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010 Dec 17;59(RR-12):1-110.

16 HOW SUPPLIED/STORAGE AND HANDLING

LILETTA (levonorgestrel-releasing intrauterine system), containing 52 mg levonorgestrel, is packaged together with an inserter in a peelable pouch, and is available in a carton of one sterile unit. NDC # 52544-035-54.

LILETTA is supplied sterile. LILETTA is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner pouch is damaged or opened. Insert before the end of the month shown on the pouch. Store at 20 – 25°C (68 – 77°F), with excursions permitted between 15 – 30°C (59 – 86°F) [See USP Controlled Room Temperature]. Store pouch in outer carton until use to protect from light.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Advise the patient that this product does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).
- Advise the patient about the risks of ectopic pregnancy, including the loss of fertility. Advise her to recognize and report to her healthcare provider promptly any symptoms of ectopic pregnancy, including lower abdominal pain, especially in association with missed periods [see *Warnings and Precautions* (5.1).]
- Advise the patient that if pregnancy occurs while using LILETTA:

- LILETTA will likely need to be removed because leaving it in place may increase the risk of spontaneous abortion and preterm labor; however, removal of LILETTA or probing of the uterus may also result in spontaneous abortion. *[See Warnings and Precautions (5.2).]*
- Septic abortion may occur. Advise her that if LILETTA cannot be removed or she chooses not to have it removed, there may be an increased risk of miscarriage, sepsis, premature labor, and premature delivery. *[See Warnings and Precautions (5.2).]*
- Advise the patient that severe infection or sepsis, including Group A streptococcal sepsis (GAS), can occur within the first few days after LILETTA is inserted. Advise her to contact a healthcare provider immediately if she develops severe pain or fever shortly after LILETTA is inserted. *[See Warnings and Precautions (5.3).]*
- Advise the patient about the possibility of PID or endometritis and that these infections can cause tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death. Advise the patient to recognize and report any symptoms of PID to her healthcare provider promptly, including *[see Warnings and Precautions (5.4)]*:
 - development of menstrual disorders (prolonged or heavy bleeding)
 - unusual vaginal discharge
 - abdominal or pelvic pain or tenderness
 - dyspareunia
 - chills
 - fever
- Advise the patient that perforation may occur, most often during insertion, although the perforation may not be detected until sometime later. Advise her that if perforation occurs, LILETTA will have to be located and removed. Surgery may be required. Advise her that delayed detection or removal of LILETTA in case of perforation may result in *[see Warnings and Precautions (5.5)]*:
 - migration of the IUS outside the uterine cavity
 - adhesions
 - peritonitis
 - intestinal perforations
 - intestinal obstruction
 - abscesses
 - erosion of adjacent viscera
- Review the signs and symptoms of LILETTA expulsion with the patient. Advise the patient on how she can check that the threads still protrude from her cervix, and not to pull on them. Advise her that there is no contraceptive protection if LILETTA is displaced or expelled. *[See Warnings and Precautions (5.6).]*
- Advise the patient regarding the risk of ovarian cysts and that cysts can cause clinical symptoms including pelvic pain, abdominal pain or dyspareunia and infrequently will need surgery. *[See Warnings and Precautions (5.7).]*
- Advise the patient that irregular or prolonged bleeding and spotting, and/or cramps may occur during the first three to six months after insertion. If her symptoms continue or are severe, she should report them to her healthcare provider. *[See Warnings and Precautions (5.8).]*
- Advise the patient that LILETTA is MR Safe and that it is safe for her to have an MRI with LILETTA in place. *[See Warnings and Precautions (5.11).]*
- Advise the patient to contact her healthcare provider if she experiences any of the following:
 - A stroke or heart attack
 - 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
 - Pregnancy or suspected pregnancy
 - Pelvic pain or pain during sex
 - She or her partner becomes HIV positive
 - Possible exposure to sexually transmitted infections (STIs)

- Unusual vaginal discharge or genital sores
- Severe vaginal bleeding or bleeding that lasts a long time, or if she misses a menstrual period
- Inability to feel LILETTA's threads

Complete the Follow-Up Reminder Card and give it to the patient.

LILETTA® and its design are registered trademarks of Odyssea Pharma SPRL, an Allergan affiliate.

Manufactured by:

Odyssea Pharma, Belgium

An affiliated company of Allergan USA, Inc.

Distributed by:

Allergan USA, Inc. Irvine, CA 92612

Marketed by:

Allergan USA, Inc. Medicines360

Irvine, CA 92612 San Francisco, CA 94111

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Patient Information

LILETTA (lye-LET-uh)

(levonorgestrel-releasing intrauterine system)

LILETTA does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).

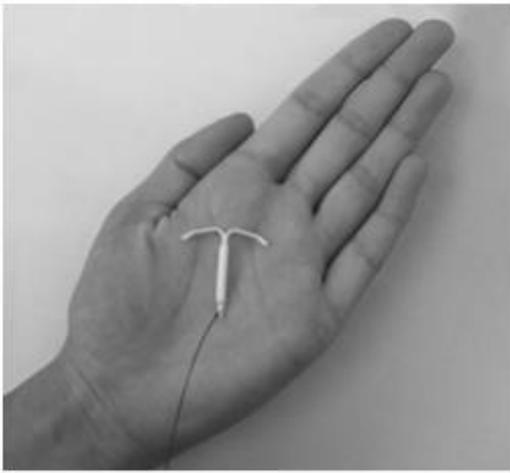
Read this Patient Information carefully before you decide if LILETTA is right for you. This information does not take the place of talking with your gynecologist or other healthcare provider who specializes in women's health. If you have any questions about LILETTA, ask your healthcare provider. You should also learn about other birth control methods to choose the one that is best for you.

What is LILETTA?

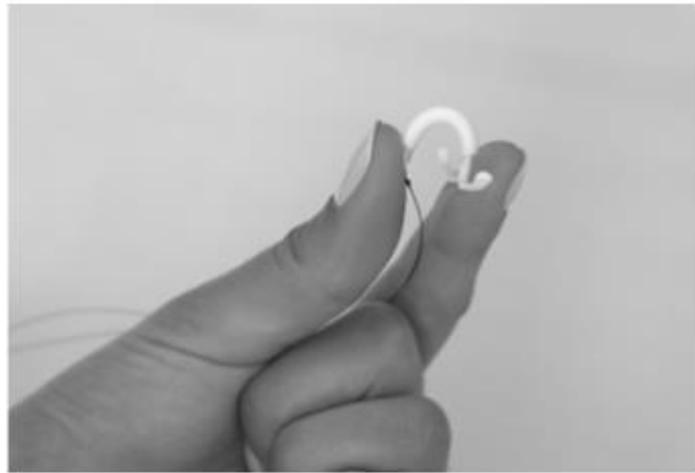
- LILETTA is a hormone-releasing system placed in your uterus by your healthcare provider to prevent pregnancy for up to 4 years.
- LILETTA can be removed by your healthcare provider at any time.
- LILETTA can be used whether or not you have given birth to a child.

LILETTA is a small, flexible plastic T-shaped system that slowly releases a progestin hormone called levonorgestrel (LNG) that is often used in birth control pills. Because LILETTA releases LNG into your uterus, only small amounts of the hormone enter your blood. LILETTA does not contain estrogen.

Two thin threads are attached to the stem (lower end) of LILETTA. The threads are the only part of LILETTA you can feel when LILETTA is in your uterus; however, unlike a tampon string, the threads do not extend outside your body.



LILETTA is small



and flexible

What if I need birth control for more than 4 years?

LILETTA must be removed after 4 years. Your healthcare provider can place a new LILETTA during the same office visit if you choose to continue using LILETTA.

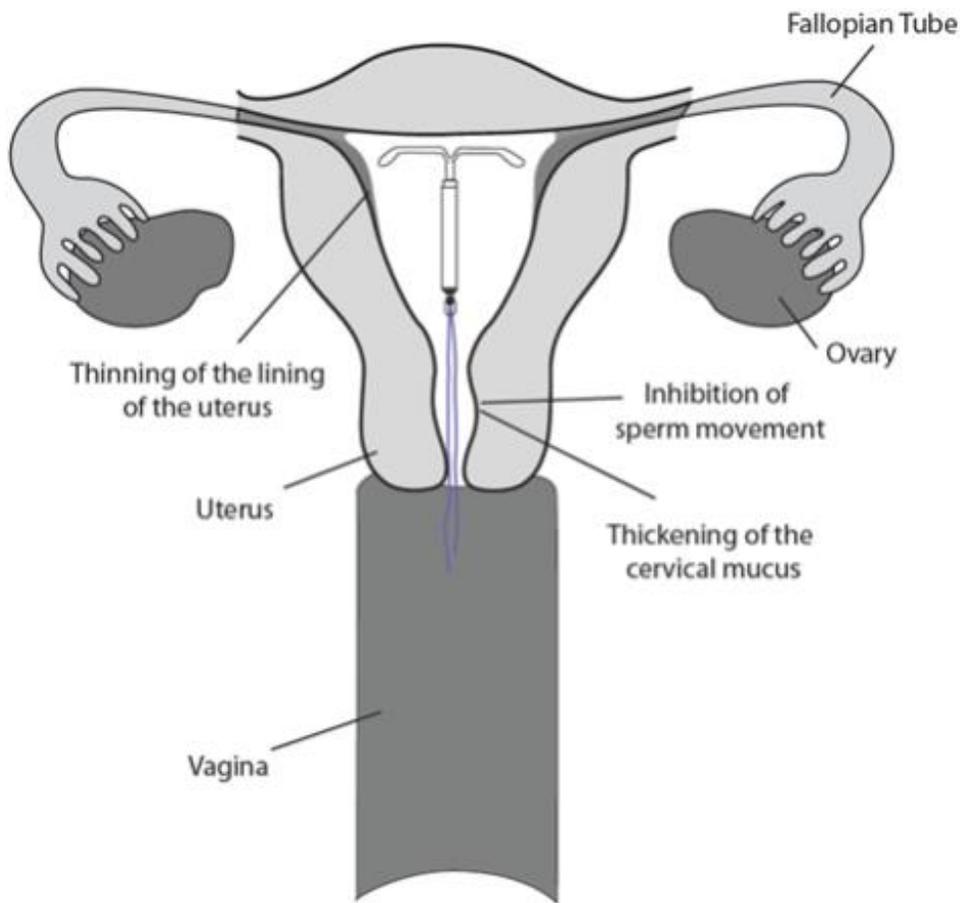
What if I want to stop using LILETTA?

LILETTA is intended for use up to 4 years, but you can stop using LILETTA at any time by asking your healthcare provider to remove it. You could become pregnant as soon as LILETTA is removed, so you should use another method of birth control if you do not want to become pregnant. Talk to your healthcare provider about the best birth control methods for you, because your new method may need to be started 7 days before LILETTA is removed to prevent pregnancy.

What if I change my mind about birth control and want to become pregnant in less than 4 years?

Your healthcare provider can remove LILETTA at any time. You could become pregnant as soon as LILETTA is removed. About 6 out of 7 women who want to become pregnant will become pregnant sometime in the first year after LILETTA is removed.

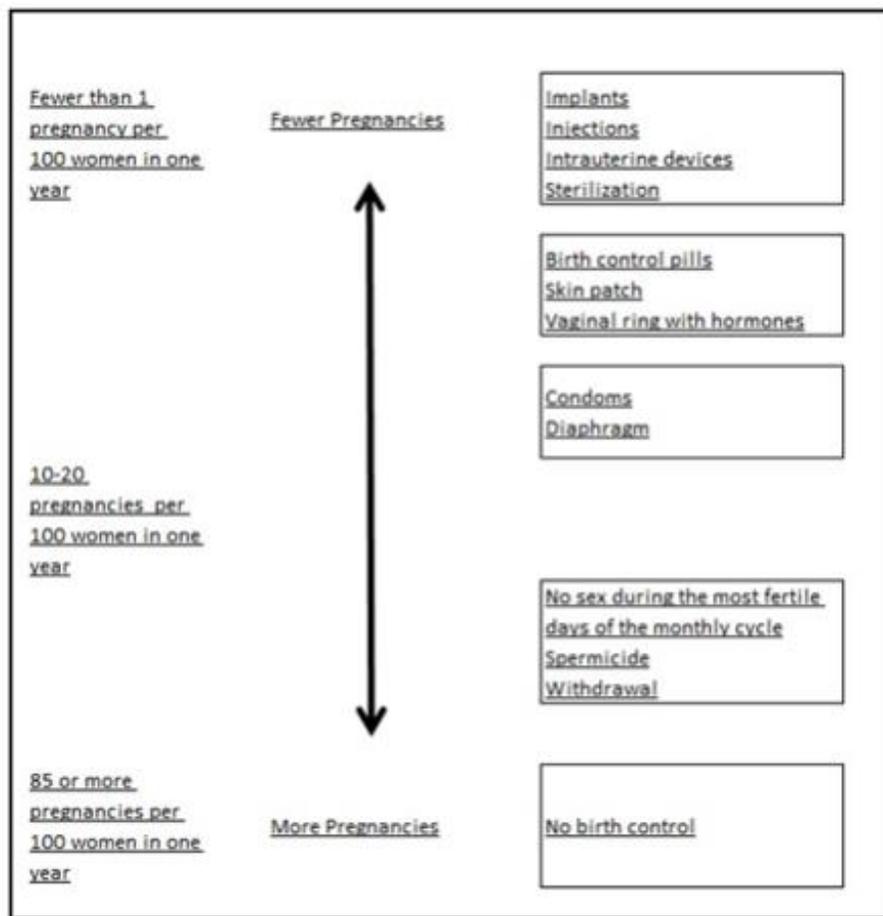
How does LILETTA work? LILETTA may work in several ways including thickening cervical mucus, inhibiting sperm movement, reducing sperm survival, and thinning the lining of your uterus. It is not known exactly how these actions work together to prevent pregnancy.



How well does LILETTA work for contraception?

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.

LILETTA, an intrauterine system (IUS), is in the box at the top of the chart.



Who might use LILETTA?

You might choose LILETTA if you:

- want long-term birth control that provides a low chance of getting pregnant (less than 1 in 100)
- want birth control that works continuously for up to 4 years
- want birth control that is reversible
- want a birth control method that you do not need to take daily
- are willing to use a birth control method that is placed in the uterus
- want birth control that does not contain estrogen

Do not use LILETTA if you:

- are or might be pregnant; LILETTA cannot be used as an emergency contraceptive
- have a serious pelvic infection called pelvic inflammatory disease (PID) or endometritis unless you have had a normal pregnancy after the infection went away have an untreated lower genital infection now
- have had an infection from an abortion within the last 3 months
- can get infections easily. For example, if you:
 - have problems with your immune system
 - have multiple sexual partners or your partner has multiple sexual partners
 - use or abuse intravenous drugs
- have or suspect you might have cancer of the uterus or cervix
- have bleeding from the vagina that has not been explained
- have short-term (acute) liver disease or liver tumor
- have breast cancer or any other cancer that is sensitive to progestin (a female hormone), now or in the past
- have an intrauterine system in your uterus already
- have a condition of the uterus that changes the shape of the uterine cavity, such as large fibroid

tumors

- are allergic to levonorgestrel, silicone, polyethylene, or barium sulfate

Before having LILETTA placed, tell your healthcare provider if you have any medical conditions, including if you:

- **have any of the conditions listed above**
- have had a heart attack
- have had a stroke
- were born with heart disease or have problems with your heart valves
- have problems with blood clotting or take medicine to reduce clotting
- have high blood pressure
- recently had a baby or if you are breastfeeding
- have severe migraine headaches
- have severe or frequent headaches
- have AIDS, HIV, or any other sexually transmitted infection

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How is LILETTA placed?

LILETTA is placed by your healthcare provider during an in-office visit.

First, your healthcare provider will examine your pelvis to find the exact position of your uterus. Your healthcare provider will then clean your vagina and cervix with an antiseptic solution and slide a slim plastic tube containing LILETTA through the cervix into your uterus. Your healthcare provider will then remove the plastic tube, and leave LILETTA in your uterus. Your healthcare provider will trim the threads to the right length. Placement takes only a few minutes.

You may experience pain, bleeding, or dizziness during and after placement. If your symptoms do not pass within 30 minutes after placement, LILETTA may not have been placed correctly. Your healthcare provider will examine you to see if LILETTA needs to be removed or replaced.

Should I check that LILETTA is in place?

Yes, you should check that LILETTA is in proper position by feeling the threads. It is a good habit to do this 1 time a month. Your healthcare provider should teach you how to check that LILETTA is in place. First, wash your hands with soap and water. You can check by reaching up to the top of your vagina with clean fingers to feel the threads. Do not pull on the threads.

If you feel more than just the threads or if you cannot feel the threads, LILETTA may not be in the right position and may not prevent pregnancy. Use non-hormonal back-up birth control (such as condoms and spermicide) and ask your healthcare provider to check that LILETTA is still in the right place.

How soon after placement of LILETTA should I return to my healthcare provider?

Call your healthcare provider if you have any questions or concerns (see “When should I call my healthcare provider?”). Otherwise, you should return to your healthcare provider for a follow-up visit 4 to 6 weeks after LILETTA is placed to make sure that LILETTA is in the right position.

Can I use tampons with LILETTA?

Yes, tampons may be used with LILETTA.

What if I become pregnant while using LILETTA?

Call your healthcare provider right away if you think you are pregnant. If possible, also do a urine pregnancy test. If you get pregnant while using LILETTA, you may have an ectopic pregnancy. This means that the pregnancy is not in the uterus. Unusual vaginal bleeding or abdominal pain especially with missed periods may be a sign of ectopic pregnancy.

Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death. There are also risks if you get pregnant while using LILETTA and the pregnancy is in the uterus. Severe infection, miscarriage, premature labor, premature delivery, and even death can occur with pregnancies that continue with an intrauterine system (IUS). Because of this, your healthcare provider may try to remove LILETTA, even though removing it may cause a miscarriage. If LILETTA cannot be removed, talk with your healthcare provider about the benefits and risks of continuing the pregnancy.

If you continue your pregnancy, see your healthcare provider regularly. Call your healthcare provider right away if you get flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge, or fluid leaking from your vagina. These may be signs of infection.

It is not known if LILETTA can cause long-term effects on the fetus if it stays in place during a pregnancy.

How will LILETTA change my periods?

For the first 3 to 6 months, your period may become irregular and the number of bleeding days may increase. You may also have frequent spotting or light bleeding and cramping. Some women have heavy bleeding during this time. After you have used LILETTA for a while, the number of bleeding and spotting days is likely to lessen. For some women, menstrual periods will stop altogether. When LILETTA is removed, your menstrual periods will likely return to their former pattern.

Is it safe to breastfeed while using LILETTA?

You may use LILETTA when you are breastfeeding if more than 6 weeks have passed since you had your baby. If you are breastfeeding, LILETTA is not likely to affect the quality or amount of your breast milk or the health of your nursing baby. However, isolated cases of decreased milk production have been reported among women using progestin-only birth control pills. The risk of LILETTA becoming attached to (embedded) or going through the wall of the uterus is increased when LILETTA is placed in breastfeeding women.

Will LILETTA interfere with sexual intercourse?

You and your partner should not feel LILETTA during intercourse. LILETTA is placed in the uterus, not in the vagina. In some cases, your partner may feel the threads. If this occurs, or if you or your partner experience pain during sex, talk with your healthcare provider.

Can I have an MRI with LILETTA in place?

LILETTA is MR Safe. It is safe to have an MRI following LILETTA placement.

What are the possible side effects of LILETTA?

LILETTA can cause serious side effects, including:

- **ectopic pregnancy.** If you get pregnant while using LILETTA, you might have an ectopic pregnancy. This means that the pregnancy is not in the uterus. Unusual vaginal bleeding or abdominal pain especially with missed periods may be a sign of ectopic pregnancy. Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.
- **intrauterine pregnancy risks.** There are also risks if you get pregnant while using LILETTA and the pregnancy is in the uterus. Severe infection, miscarriage, premature labor, premature delivery, and even death can occur with pregnancies that continue with an intrauterine system (IUS). Because of this, your healthcare provider may try to remove LILETTA, even though removing it may cause a miscarriage. If LILETTA cannot be removed, talk with your healthcare provider about the benefits and risks of continuing the pregnancy. If, after seeing your healthcare provider, you choose to continue your pregnancy, see your healthcare provider regularly. Call your healthcare provider right away if you get flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge, or fluid leaking from your vagina. These may be signs of infection. It is not known if LILETTA can

cause long-term effects on the fetus if it stays in place during a pregnancy.

- **life-threatening infection.** Life-threatening infection can occur within the first few days after LILETTA is placed. Call your healthcare provider immediately if you develop severe pain or fever shortly after LILETTA is placed.
 - **pelvic inflammatory disease (PID) or endometritis.** Some IUS users get a serious pelvic infection called pelvic inflammatory disease (PID) or endometritis. PID and endometritis are usually sexually transmitted. You have a higher chance of getting PID or endometritis if you or your partner has sex with other partners. PID or endometritis can cause serious problems such as infertility, ectopic pregnancy or pelvic pain that does not go away. PID is usually treated with antibiotics. More serious cases of PID or endometritis may require surgery. Removal of the uterus (hysterectomy) is sometimes needed. In rare cases, infections that start as PID or endometritis can even cause death.
- **perforation.** LILETTA may become attached to (embedded) or go through the wall of the uterus. This is called perforation. If this occurs, LILETTA may no longer prevent pregnancy. If perforation occurs, LILETTA may move outside the uterus and can cause internal scarring, infection, or damage to other organs. You may need surgery to have LILETTA removed if perforation or embedment occurs. The risk of perforation is increased in breastfeeding women.
- **expulsion.** LILETTA may come out of your uterus. This is called expulsion. Expulsion occurs in about 4 out of 100 women, most often in the first year of use. You may become pregnant if LILETTA comes out. If you think that LILETTA has come out, use another birth control method like condoms and spermicide or do not have sex (vaginal intercourse) until you are seen by a healthcare provider.
- **cysts on the ovary.** Some women using LILETTA develop a painful cyst on the ovary. These cysts usually disappear on their own in 2 to 3 months. However, a cyst can cause pain and sometimes cysts will need surgery.
- **changes in bleeding.** You may have bleeding and spotting between menstrual periods, especially during the first 3 to 6 months. Sometimes the bleeding is heavier than usual at first. However, the bleeding usually becomes lighter than usual and may be irregular. Call your healthcare provider if the bleeding remains heavier than usual or increases after it has been light for a while.

Tell your healthcare provider right away if you have any of these signs of PID or endometritis: long-lasting or heavy bleeding, unusual vaginal discharge, low abdominal pain, painful sex, chills, or fever.

The most common side effects of LILETTA include:

| | |
|-------------------------------|---|
| • vaginal bacterial infection | • yeast infection of the outer part of your vagina (vulvovaginal) |
| • acne | • headache |
| • nausea or vomiting | • pain during sex |
| • abdominal pain | • breast pain |
| • pelvic pain | • depression |
| • weight increase | • vaginal discharge |
| • mood changes | • anxiety |

- **Pain, bleeding, or dizziness during and after placement.** If these symptoms do not stop within 30 minutes after placement, LILETTA may not have been placed correctly. Your healthcare provider

PRINCIPAL DISPLAY PANEL

NDC 52544-035-54

RxOnly

Liletta

(levonorgestrel-releasing intrauterine system)

52 mg



LILETTA

levonorgestrel intrauterine device

Product Information

| | | | |
|--------------------------------|-------------------------|---------------------------|---------------|
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Source) | NDC:52544-035 |
| Route of Administration | INTRAUTERINE | | |

Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|--|-------------------|----------|
| LEVONORGESTREL (UNII: 5W7SIA7YZW) (LEVONORGESTREL - UNII:5W7SIA7YZW) | LEVONORGESTREL | 52 mg |

Inactive Ingredients

| Ingredient Name | Strength |
|-----------------------------------|----------|
| DIMETHICONE (UNII: 92RU3N3Y1O) | |
| BARIUM SULFATE (UNII: 25BB7EKE2E) | |

Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|------------------|--|----------------------|--------------------|
| 1 | NDC:52544-035-54 | 1 in 1 CARTON | 02/26/2015 | 01/31/2020 |
| 1 | | 1 in 1 POUCH; Type 4: Device Coated/Impregnated/Otherwise Combined with Drug | | |

Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|--------------------|--|----------------------|--------------------|
| NDA | NDA206229 | 02/26/2015 | 01/31/2020 |

Labeler - Actavis Pharma, Inc. (119723554)

Revised: 7/2018

Actavis Pharma, Inc.