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----------

Dosage and Administration, Insertion Instructions (2.3)	01/2016
Dosage and Administration, Patient Follow-up (2.5)	01/2016
Dosage and Administration, Removal of LILETTA (2.6)	01/2016

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

LILETTA is a sterile, levonorgestrel-releasing intrauterine system indicated for prevention of pregnancy for up to 3 years. (1)

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

- Release rate of levonorgestrel (LNG) is 18.6 mcg/day initially and declines progressively to approximately 16.3 mcg/day at 1 year, 14.3 mcg/day at 2 years, and 12.6 mcg/day at 3 years after insertion; LILETTA can be removed at any time but must be removed by the end of the third 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 (4)
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy. (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other progestin-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. (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 and vulvovaginal infections, and acne. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1(800) 272-5525 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised 01/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LILETTA™ is indicated for prevention of pregnancy for up to 3 years. The system should be replaced after 3 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 18.6 mcg/day. This rate decreases progressively to approximately 16.3 mcg/day at 1 year, 14.3 mcg/day at 2 years, and 12.6 mcg/day at 3 years after insertion. The average *in vivo* release rate of LNG is approximately 15.6 mcg/day over a period of 3 years.

LILETTA can be removed at any time but must be removed by the end of the third 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 instructions on when to start use of LILETTA.

Table 1: When to Insert LILETTA

Starting LILETTA in women not currently using hormonal or intrauterine contraception	• 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	• LILETTA may be inserted at any time.
	  ◦ 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	• 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	• 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	
• **First-trimester**	• LILETTA may be inserted immediately after a first-trimester abortion or miscarriage.

• **Second-trimester**	• Do not insert 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 *[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.
Inserting LILETTA after Childbirth	• Do not insert LILETTA until a minimum of 6 weeks after delivery, or until the uterus is fully involuted. If involution is delayed, wait until 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**a) is provided in a sterile pouch and is inserted into the uterine cavity with the provided inserter (Figure 1b) *[see Description (11)]* 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)]*.

Insertion

Figure 1a: LILETTA Intrauterine Contraceptive System (IUS)

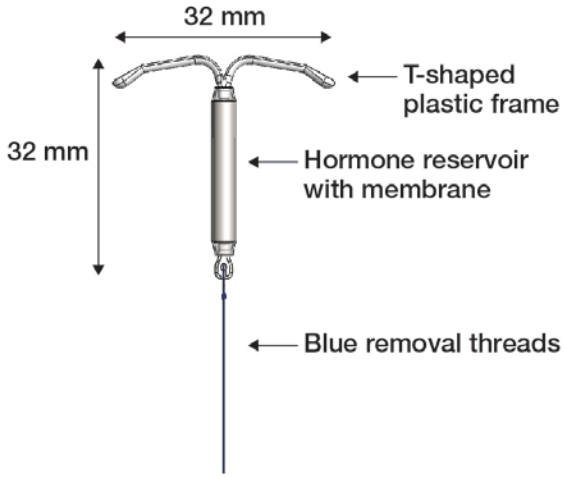
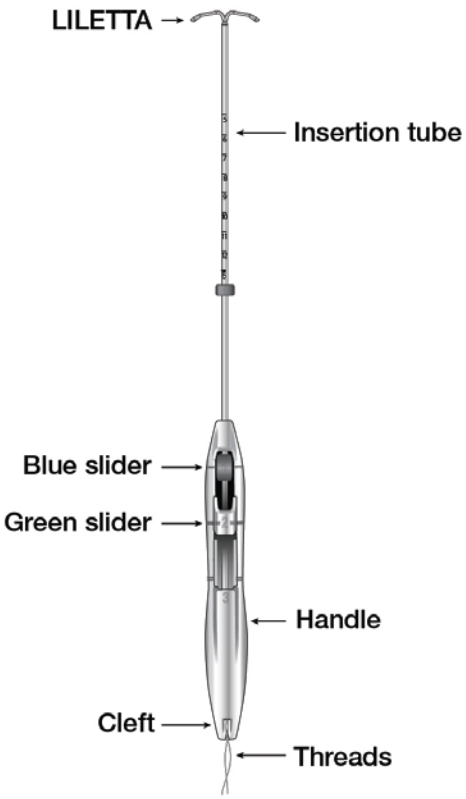


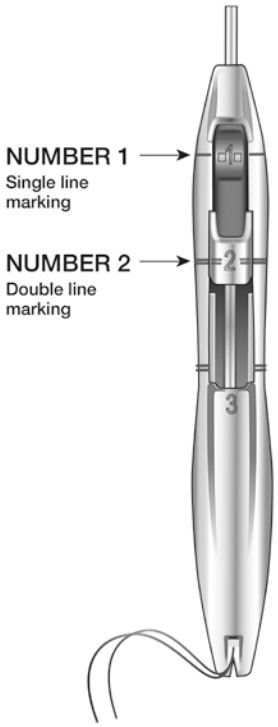
Figure 1b: LILETTA IUS with Inserter



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

The handle of the inserter contains a BLUE slider and a GREEN slider. The handle and sliders are labeled with the numbers 1, 2 and 3 to assist with the insertion process (Figure 2). Moving the sliders achieves the positions required to complete the insertion process.

Figure 2: Inserter Sliders



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, maintain sterility during LILETTA loading and insertion; do not touch LILETTA, the inside of the sterile tray, 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

The overall insertion process is conducted in 5 steps.

Step 1 – Preparation of Patient 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.

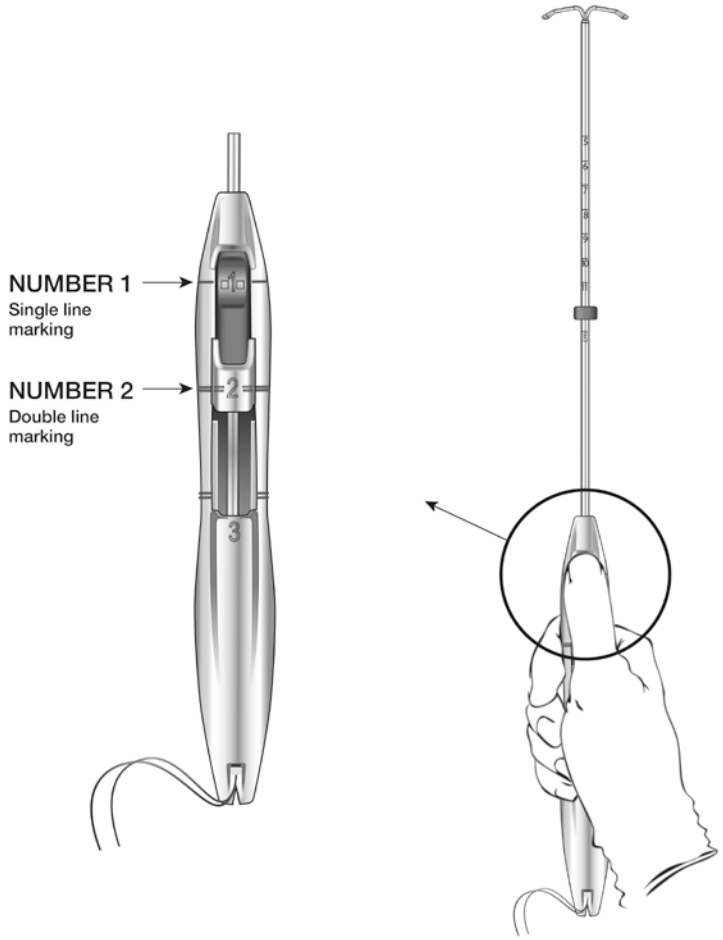
Step 2 – Opening the Sterile LILETTA Packaging

- Remove the pouch containing LILETTA from the box.
- Inspect the pouch and do not use the product if the pouch is damaged.
- Lay the pouch on a flat surface with the opaque side up.
- Completely open the sterile pouch to expose the tray by peeling the opaque side of the pouch back from the handle end toward the inserter tip.
- Remove tray lid.

Step 3 – Loading LILETTA into the Inserter

- Remove the inserter from the tray carefully by gently pulling on the handle, so as not to move the flange out of position.
    - NOTE: Do not attempt to remove the inserter by pulling on the tube.
- Ensure both sliders are fully forward (Figure 3):
    - The handle single line marking will align with the BLUE slider single line marking.
    - The handle double line markings will align with the GREEN slider double line markings.
- Grip the handle keeping your thumb or finger in the groove of the BLUE slider (over the numeral 1) and apply forward pressure while ensuring both sliders are fully forward.

Figure 3: Sliders Completely Forward for Loading LILETTA



- Load LILETTA into the inserter:
    - Ensure the arms of the IUS are horizontal (aligned to the horizontal plane of the handle and flange); adjust the rotation of the IUS as needed using the flat sterile surface of the tray.
    - While maintaining forward pressure on the blue slider, pull the threads straight back until you feel a hard stop. Ensure even tension is applied to both threads when pulling.

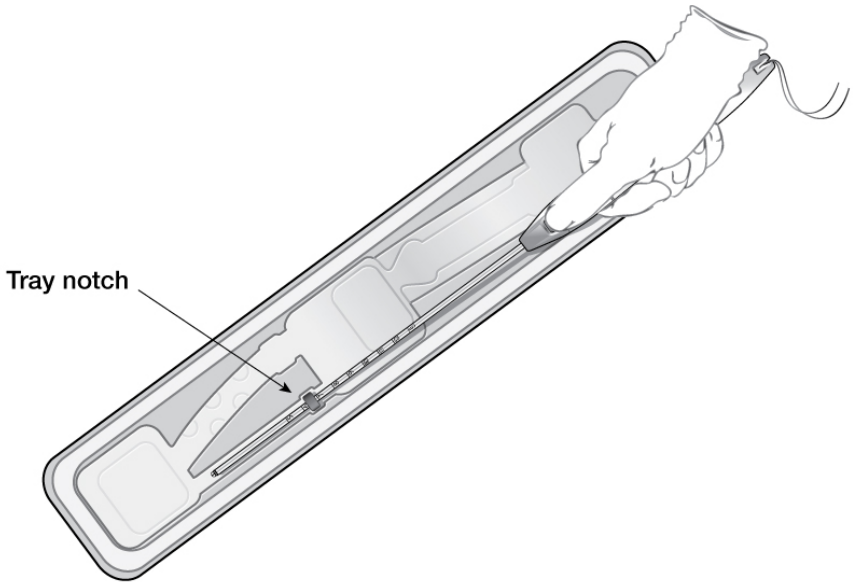
- Pull the threads upward or downward to lock the threads into the cleft at the bottom end of the handle (Figure 4); you must lock the threads in the cleft to prevent the IUS from moving out of the top of the insertion tube.
- After the IUS is loaded, continue to sustain forward pressure on the BLUE slider to maintain a hemispherical dome with the tips of the IUS.
- When correctly loaded, the IUS is completely within the insertion tube with the tips of the arms forming a hemispherical dome at the top of the tube (Figure 5).
- If the IUS is not correctly loaded, *do not attempt insertion*. To re-load LILETTA:
  - Pull the BLUE slider back with your thumb until the groove becomes aligned with the GREEN slider to release the IUS.
  - Manually pull the threads out of the cleft.
  - Return the BLUE slider to the forward position and repeat the loading steps.

Figure 4: Securing the Threads in Cleft

Figure 5: Close-up of Hemispherical Dome at Tip of Tube

- Adjust the flange to the measured uterine depth based on sounding. To adjust, place the flat side of the flange in the tray notch (Figure 6) or against a sterile edge inside of the tray. Slide the insertion tube as necessary to move the flange to the correct measurement. Ensure the flat sides of the flange are in the same horizontal plane as the handle. If, at any step, there is a need to touch a sterile surface, sterile gloves should be used.

Figure 6: Adjusting the Flange

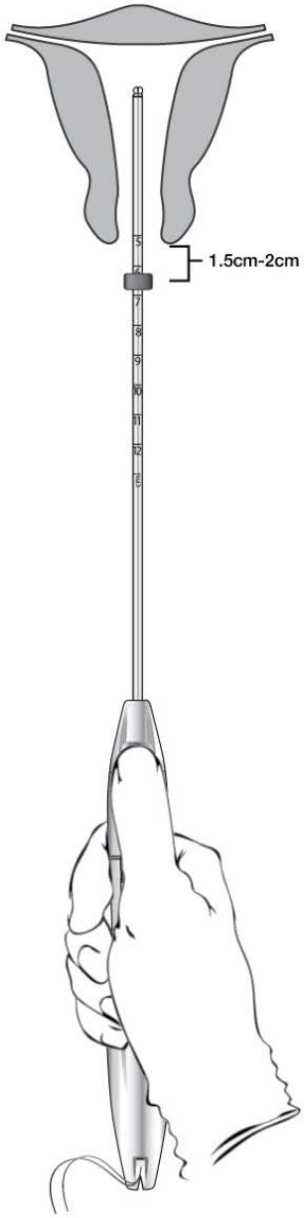


- If an adjustment to the curvature of the insertion tube is required to accommodate the anatomical orientation of the uterus, you may bend or straighten the insertion tube, but do not touch above the flange unless using sterile gloves. When bending the tube, avoid sharp bends to prevent kinking.

Step 4 – Inserting LILETTA into the Uterus

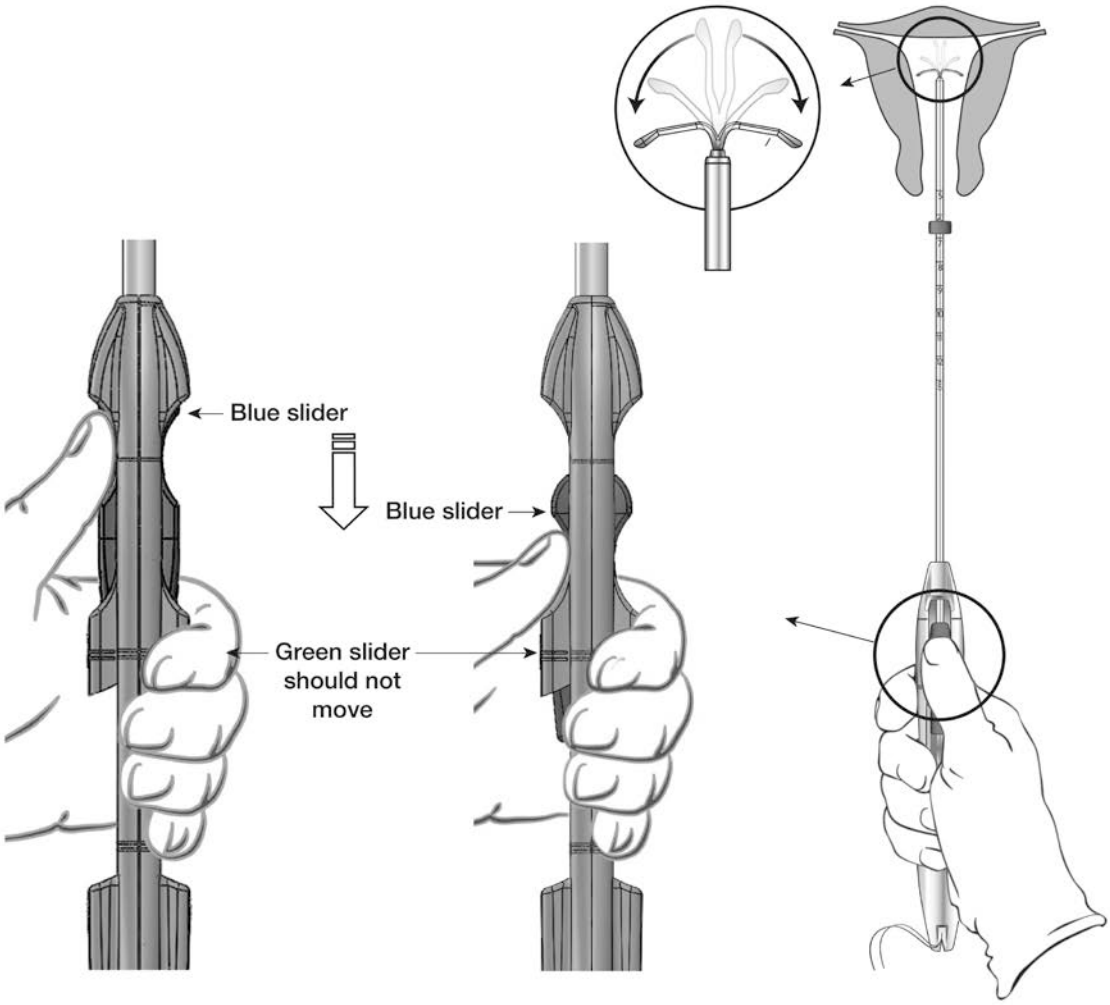
- Apply gentle traction on the tenaculum while inserting the loaded insertion tube through the cervical os. Advance the tube until the upper edge of the flange is 1.5-2 cm from the external cervical os (Figure 7). Maintain forward pressure on the BLUE slider throughout the insertion process.
    - DO NOT advance flange to the cervix at this time.
    - DO NOT force the inserter. If necessary, dilate the cervical canal.

Figure 7: Advancing Insertion Tube until Flange is 1.5 to 2 cm from the External Cervix



- Using your thumb or finger, gently slide only the BLUE slider back until you feel resistance. The BLUE and GREEN sliders will merge together to form a common thumb recess. Do not move the BLUE slider any more than is necessary to create the recess. Maintain the GREEN slider so that the double line markings on the slider and the insertion handle remain aligned (Figure 8). This will allow the IUS arms to open in the lower uterine segment**.** Do not pull the sliders back any further as this could result in premature release of the IUS at the incorrect location.

Figure 8: Releasing and Opening the Arms of the IUS

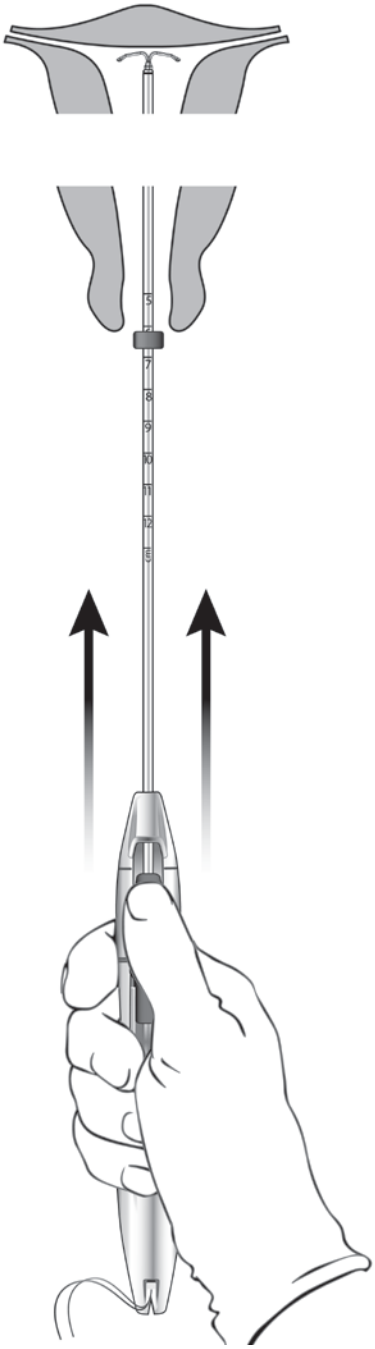


- Wait 10-15 seconds to allow for the arms of the IUS to fully open.

- While maintaining the same slider position, advance the inserter until the flange touches the cervix. If fundal resistance is encountered, do not continue to advance. LILETTA is now in the fundal position (Figure 9).

  Note: Fundal position is important to prevent expulsions.

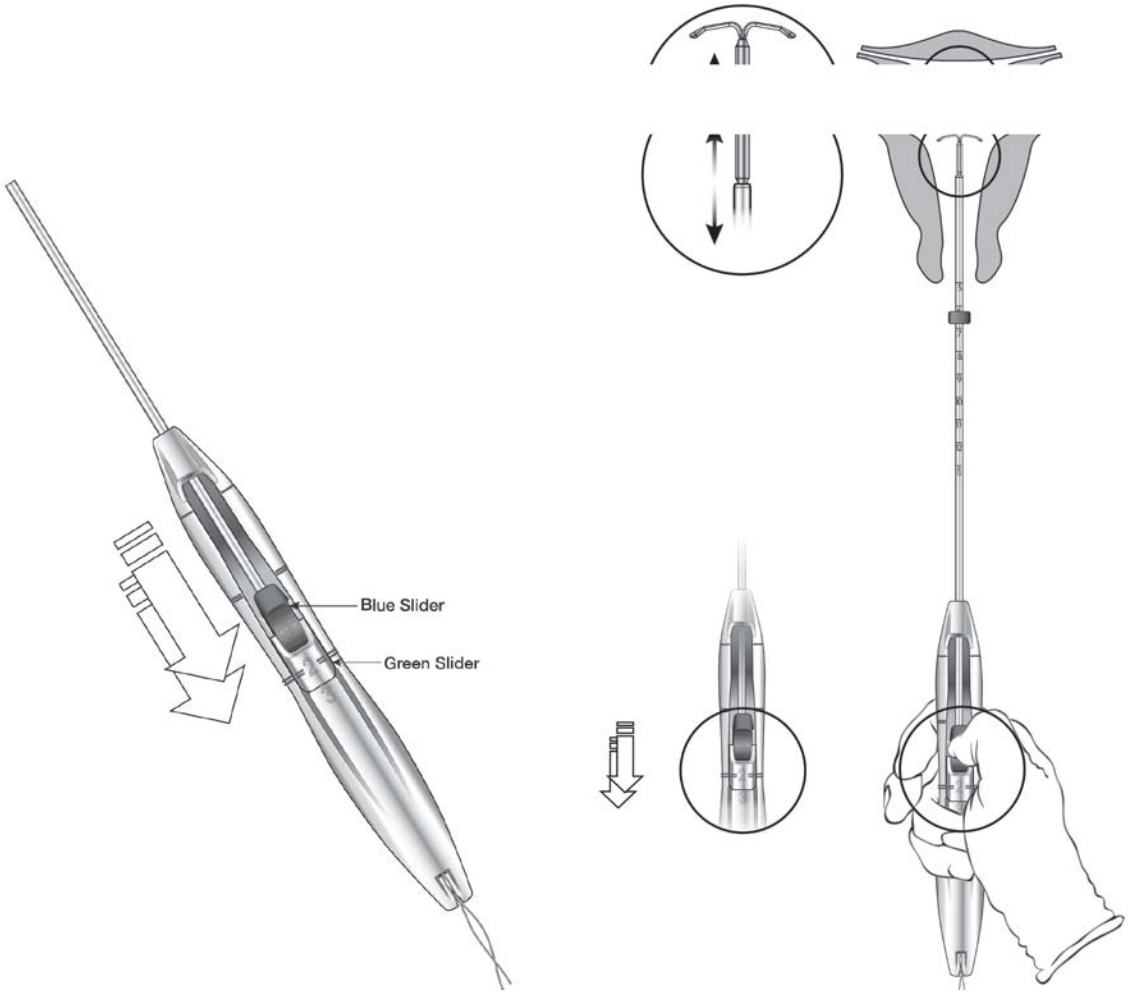
Figure 9: Move LILETTA into the Fundal Position



Step 5 – Releasing LILETTA & Procedure Completion

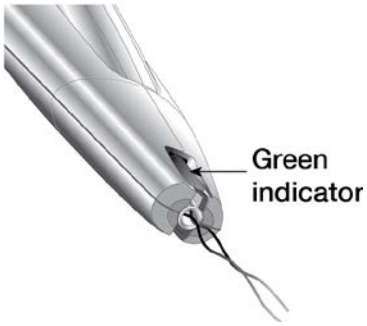
While holding the inserter steady and maintaining its position relative to the cervix, move both sliders (BLUE and GREEN) together down the handle (Figure 10) until a click is heard and the GREEN indicator at the bottom of the handle is visible (Figure 11).

Figure 10: Releasing LILETTA from the Inserter Tube



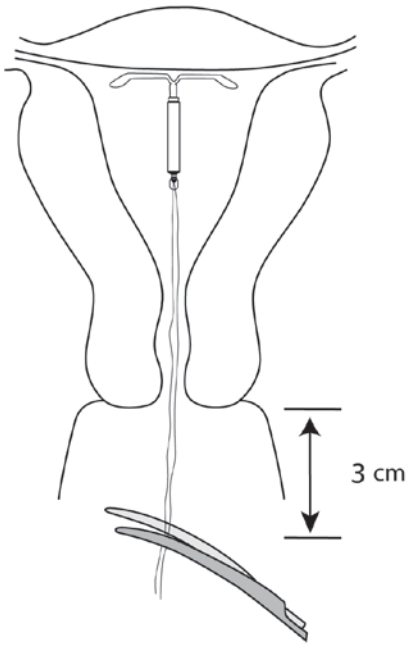
- Look at the cleft to ensure the threads were properly released (Figure 11); if not released, grab the threads and gently pull the threads out of the cleft.

Figure 11: Green Indicator Visible and Threads Released from Cleft



- Remove the inserter from the uterus.
- Use blunt-tipped sharp scissors to cut the IUS threads perpendicular to the thread length, leaving about 3 cm outside of the cervix (Figure 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.

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 3 years. LILETTA can be replaced at the time of removal with a new LILETTA if continued contraceptive protection is desired.

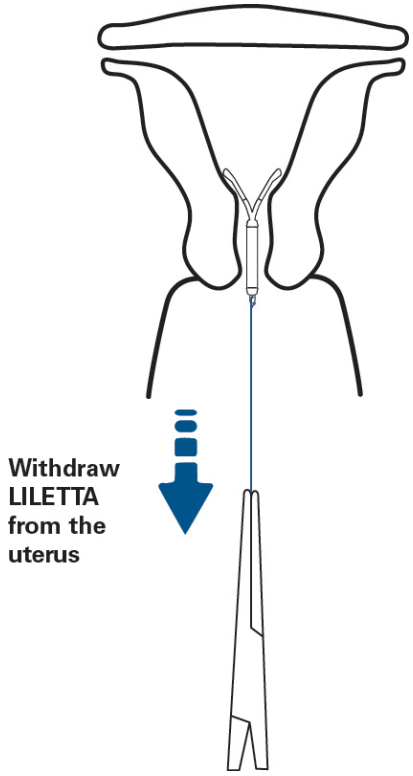
Planning for Removal

- 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 a 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 a 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 pregnancy is not desired and if a woman wishes to continue using LILETTA, a new system can be inserted immediately after removal any time during the cycle.
- 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
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia
- Known or suspected breast cancer or other progestin-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 0.12 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 0.6% of women. The infection was diagnosed as PID in 0.4% of women and as endometritis in 0.2% of women. About 1/3 of women 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.

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, 7 of the 10 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. The incidence of perforation during or following LILETTA insertion in the clinical trial, which excluded breastfeeding women, was 0.1%.

If perforation occurs, locate and remove LILETTA. 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.

A large post-marketing safety study with other IUSs demonstrated an increased risk of perforation in lactating women. The risk of perforation may be increased if LILETTA is inserted when the uterus is fixed and retroverted or not completely involuted during the postpartum 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 3.5% was reported, with a rate of 2.0% in nulliparous women and 5.6% 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 3.4% 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 26% by the end of the second year of use, and in approximately 38% of users by the end of year 3. In the trial, 1.5% 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=1,525**		**Cycle 7 N=1,223**		**Cycle 13 N=791**		**Cycle 26 N=438**	
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	1.5	2.6	1.2	2.3	0.8	1.7
Number of spotting days	8.9	6.0	4.3	4.2	3.0	3.6	2.7	3.4	2.0	2.7

Note: Includes all LILETTA subjects.

In the LILETTA clinical trial, 248 of 255 (97.3%) of women evaluated experienced menses within 3 months after LILETTA removal.

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 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 (2.4)]*. 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 1,412 exposed for 1 year and 383 subjects who completed 3 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 kg/m^2); 25.1% had a BMI ≥ 30 kg/m^2, and 5.3% had a BMI ≥ 40 kg/m^2. The data cover more than 22,000 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 ≥ 5% of users) are shown in Table 3.

Table 3: Adverse Reactions in ≥ 5% of LILETTA Users in Phase 3 Clinical Study

System Organ Class/Preferred Term	% LILETTA Subjects (N = 1,751)
Vaginal infections	13.6%
Vulvovaginal infections	13.3%
Acne	12.3%
Headache or migraine	9.8%
Nausea or vomiting	7.9%
Dyspareunia	7.0%
Abdominal discomfort or pain	6.8%
Breast tenderness or pain	6.7%
Pelvic discomfort or pain	6.1%
Depression or depressed mood	5.4%
Mood changes	5.2%

In the contraceptive trial, 12.3% of LILETTA users discontinued prematurely due to an adverse reaction. The most common adverse reaction leading to discontinuation was expulsion (3.5%), bleeding

complaints (a total of 1.5%). The next most common adverse reactions causing discontinuation were acne (1.3%), mood swings (1.3%), dysmenorrhea (0.6%), and uterine spasm (0.6%). Two women discontinued the clinical study due to PID and one due to endometritis.

In the clinical trial, serious adverse reactions included: suicidality and exacerbations of depression and bipolar disorder, ectopic pregnancy, 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. 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.

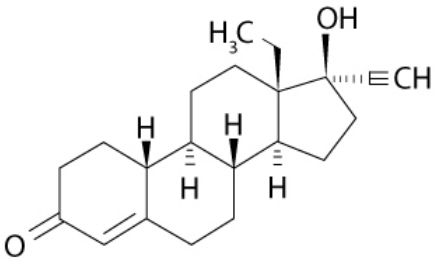
8.8 Obesity

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 18.6 mcg/day of levonorgestrel.

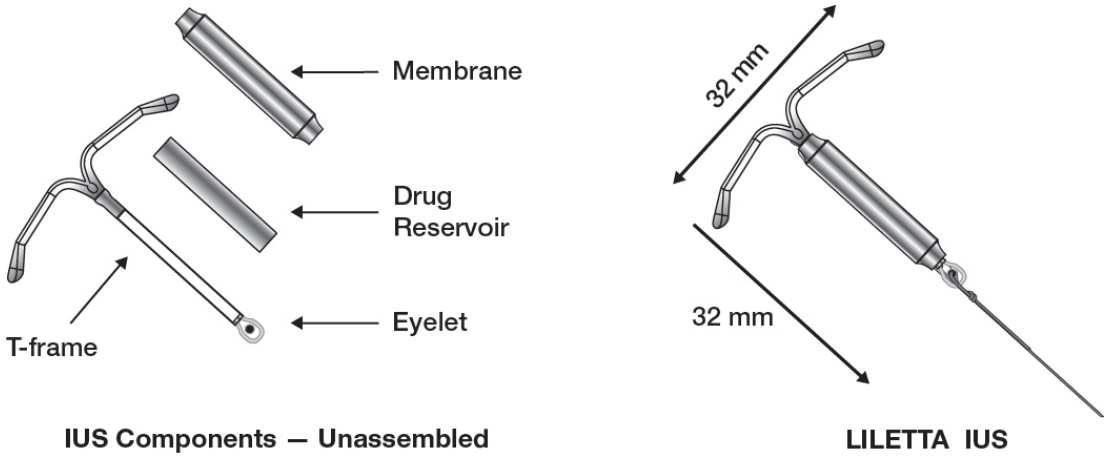
Levonorgestrel USP, (-)-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in LILETTA, has a molecular weight of 312.45, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:



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

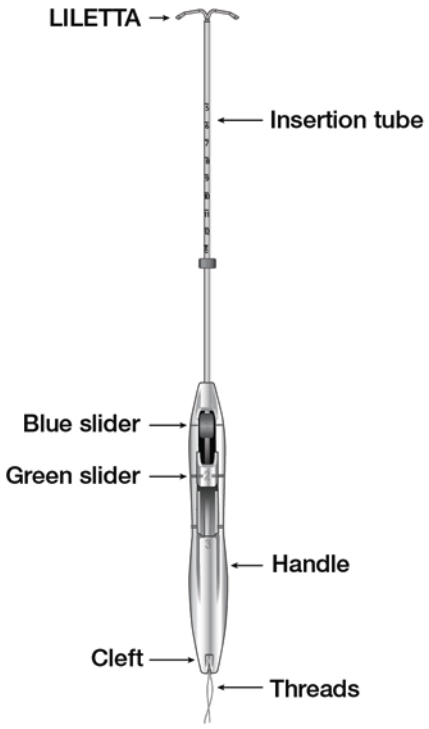


11.2 Inserter

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 and cervix. 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 18.6 μg/day and decreases to 16.3 μg/day at 1 year, 14.3 μg/day at 2 years, and 12.6 μg/day after 3 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. Plasma LNG concentrations following insertion of LILETTA are shown in Table 4.

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

Initial (7 days) (N = 40)	6 Months (N = 36)	12 Months (N = 33)	24 Months (N = 29)	30 Months (N = 9)	36 Months (N = 243)
252 ± 123	195 ± 69	170 ± 50	147 ± 46	133 ± 28	135 ± 51

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 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3α, 5β-tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16β-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 ± 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.

Race: The LILETTA clinical trial included 199 (13%) Black/African American subjects and 226 (15%) subjects of Hispanic ethnicity. 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/m^2. The mean BMI of LILETTA subjects was 26.9 kg/m^2; 24% were overweight, 24% were obese (BMI $\geq$ 30 kg/m^2), and 5% were morbidly obese (BMI $\geq$ 40 kg/m^2).

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 3-year pregnancy rate was calculated by the life table method, based on a total of six 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 calculated cumulative pregnancy rates.

Table 5: Cumulative Pregnancy Rates

LILETTA Clinical Trial	Year 1 Pearl Index	Cumulative 3-Year Life Table
Number of 28-day Cycles of Exposure	17,125	34,711
Pregnancy Rate (95% CI)	0.15 (0.02, 0.55)	0.55 (0.24, 1.23)

Of 68 women who desired pregnancy after study discontinuation, 71% conceived within 6 months following LILETTA removal, and 87% 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 supplied partially preloaded within the inserter and packaged in a clear plastic tray with lid. The tray is sealed in a peelable pouch. Liletta is available in a carton of one sterile unit. NDC # 52544-035-11.

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™ is a trademark of Odyssea Pharma SPRL, an Actavis affiliate.

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Odyssea Pharma, Belgium
An affiliated company of Actavis Pharma, Inc.

Distributed by:
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Parsippany, NJ 07054

Marketed by:
Actavis Pharma, Inc.
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