SUMMARY OF PRODUCT CHARACTERISTICS
and
PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

AVIBELA® 20 micrograms/24 hours Intrauterine Delivery System

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is levonorgestrel (LNG).

The intrauterine delivery system contains 52 mg levonorgestrel. The initial release of levonorgestrel is approximately 20 micrograms per day. This rate decreases progressively to approximately 6.5 micrograms/day after 8 years. The average *in vivo* release rate of LNG is approximately 13.5 micrograms/day over a period of 8 years.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intrauterine delivery system (IUS).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

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

4.2 Posology and method of administration

Starting Treatment

In female people of fertile age, AVIBELA is inserted into the uterine cavity within seven days of the onset of menstruation. It can be replaced by a new system at any time of the cycle. If AVIBELA is not inserted during the first 7 days of the menstrual cycle and if the provider can be reasonably certain the person is not pregnant, abstinence or a barrier method of contraception (such as condoms) should be used for 7 days to prevent pregnancy.

Post-partum insertion: To reduce the risk of perforation, postpartum insertions should be postponed until the uterus is fully involuted. Do not insert earlier than 4 weeks after delivery. If the client is experiencing significant post-partum bleeding and/or pain then infection or other causes should be excluded before insertion. AVIBELA can also be inserted immediately after the first trimester abortion.

AVIBELA is effective for 8 years in the indication for contraception and 5 years in the indication of heavy menstrual bleeding. For contraception, remove AVIBELA by the end of the eighth year. AVIBELA can be replaced at the time of removal with a new AVIBELA if continued contraceptive protection is desired. For treatment of heavy menstrual bleeding, replace AVIBELA by the end of the fifth year if continued use is needed.

Timing of Insertion

Refer to Table 1 for instructions on when to start use of AVIBELA.

Table 1: When to Insert AVIBELA

Starting AVIBELA in people not currently using hormonal or intrauterine contraception	• AVIBELA can be inserted any time there is reasonable certainty the person is not pregnant. Consider the possibility of ovulation and conception prior to initiation of AVIBELA. • If AVIBELA is inserted after the first 7 days of the menstrual cycle, the client should use a barrier method of contraception (such as condoms) or abstain from vaginal intercourse for 7 days after insertion to prevent pregnancy.
Switching to AVIBELA from an oral, transdermal, or vaginal hormonal contraceptive	• AVIBELA may be inserted at any time during the hormone-free interval of the previous method. • If AVIBELA is inserted during active use of the previous method, continue that method for 7 days after AVIBELA insertion or until the end of the current treatment cycle. • If using continuous hormonal contraception, discontinue that method 7 days after AVIBELA insertion.
Switching to AVIBELA from an injectable progestin contraceptive	• AVIBELA may be inserted at any time. • If AVIBELA is inserted more than 3 months (13 weeks) after the last injection, the client should use a barrier method of contraception (such as condoms) should also be used for 7 days after insertion to prevent pregnancy.
Switching to AVIBELA from a contraceptive implant or another IUS	• Insert AVIBELA on the same day the implant or IUS is removed. • This switch to AVIBELA may be at any time during the menstrual cycle. Back-up contraception is not needed.
Inserting AVIBELA after pregnancy	
• **After first-trimester abortion or miscarriage**	• AVIBELA may be inserted immediately after a first-trimester surgical or completed medical abortion or miscarriage, unless it is a septic abortion. Back-up contraception is not needed.

• **After childbirth or second-trimester abortion or miscarriage**	• If immediate, insert AVIBELA after expulsion/removal of the placenta, unless infection is present. Back-up contraception is not needed. • If not immediate: o Delay inserting AVIBELA a minimum of 4 weeks or until the uterus is fully involuted. o If the client has not yet had a period, consider the possibility of ovulation and conception occurring prior to insertion of AVIBELA. AVIBELA can be inserted any time there is reasonable certainty the person is not pregnant. o If AVIBELA is not inserted during the first 7 days of the menstrual cycle, the client should use a barrier method of contraception (such as condoms) or abstain from vaginal intercourse for 7 days after insertion to prevent pregnancy. The risk of perforation may be increased if an IUS is inserted in a lactating person.

Paediatric population
Safety and effectiveness of AVIBELA have been established in female people of reproductive potential. The safety and effectiveness are expected to be the same for postpubertal female people under the age of 16 as for users 16 years and older. The AVIBELA clinical study on contraception included 11 participants who were 16 to 17 years of age; no differences in safety or effectiveness were identified in these participants through 8 years of use of AVIBELA. Use of this product is not indicated before menarche.

Hepatic impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of LNG released from AVIBELA. AVIBELA is contraindicated in people with liver tumour or acute liver disease.

Instructions for use and handling

AVIBELA is supplied in a sterile pack which should not be opened until required for insertion. The exposed product should be handled with aseptic precautions. AVIBELA is supplied sterile having been sterilized with ethylene oxide. Do not resterilize. For single use only. If the seal of the sterile package is broken, the product should be discarded (see section 6.6 for disposal instructions).

Note: The inserter provided with AVIBELA (see Figure 2) and the Insertion Instructions in this section are not applicable for immediate insertion after childbirth or second-trimester abortion or miscarriage. For immediate insertion, remove AVIBELA from the inserter by pulling AVIBELA out of the top of the inserter and insert according to accepted practice.

Figure 1: Intrauterine Contraceptive System (IUS)

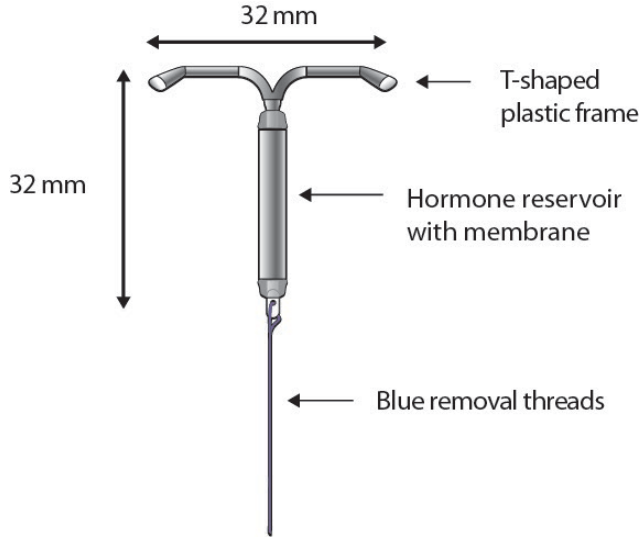
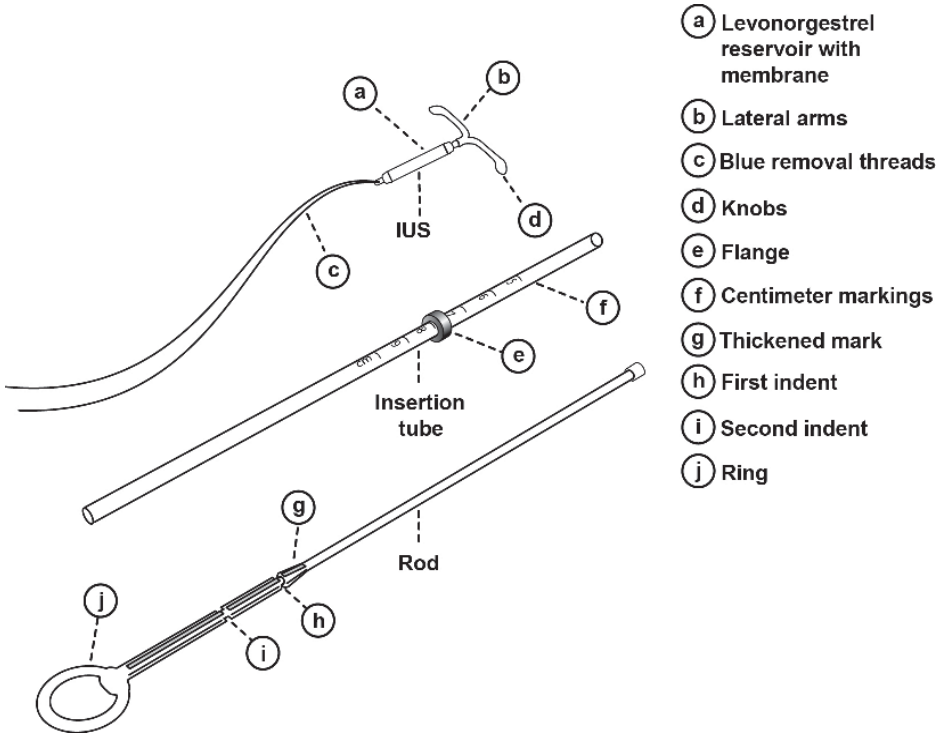


Figure 2: IUS with Inserter



How to insert AVIBELA

AVIBELA 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 labeling before attempting insertion.

Obtain a complete medical and social history to determine conditions that might influence the selection of AVIBELA for contraception. If indicated, perform a physical examination and appropriate tests for genital or sexually transmitted infections.

Check the expiration date on the box before opening it. **Do not insert AVIBELA after the expiration date.**

Visually inspect the packaging (sealed pouch) containing AVIBELA 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. Complete the pelvic examination, speculum placement, tenaculum placement, and sounding of the uterus before opening the AVIBELA pouch.

Do not open the pouch to insert AVIBELA if the following clinical findings occur:

- 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

In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, please refer to section 4.4.

Please read the following instructions for use carefully as there may be some difference in the type of inserter device compared with other IUSs you have used previously.

Preparation for insertion

Ensure all needed items for AVIBELA insertion are readily available:
- Gloves
- Sterile speculum
- Sterile uterine sound
- Sterile tenaculum
- Antiseptic solution
- AVIBELA with inserter in sealed pouch
- Sterile, blunt-tipped scissors

Additional items that may be useful could include:
- Local anesthesia, needle, and syringe
- Sterile 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 AVIBELA.

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 AVIBELA 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 people with a predisposition to these conditions. Consider administering analgesics prior to insertion.

Use aseptic technique during the entire insertion procedure. Loading and inserting AVIBELA does not require sterile gloves. If not using sterile gloves, complete all steps for loading the IUS (Steps 1-7) inside the pouch. Maintain sterility during insertion; do not touch AVIBELA or parts of any sterile instrument that will pierce tissue (e.g., a tenaculum on the cervix) or go into the uterine cavity.

Insertion procedure

Preparation of client for insertion
- With the client 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.

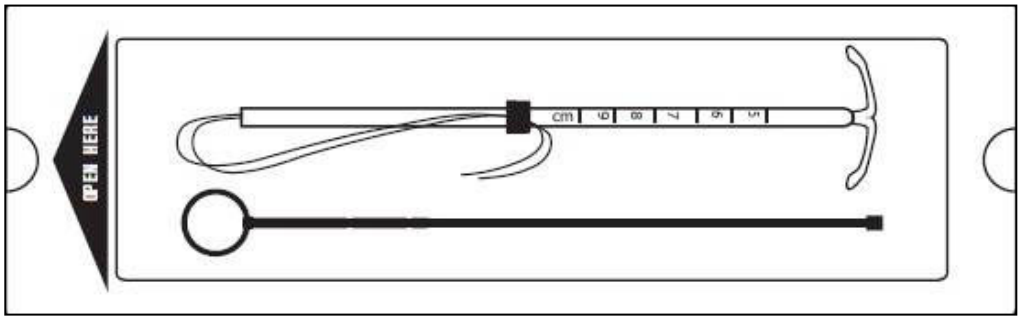
- The uterus should sound to a depth of at least 5.5 cm. Insertion of AVIBELA into a uterine cavity that sounds to less than 5.5 cm may increase the incidence of expulsion, bleeding, pain, perforation, and possibly pregnancy. AVIBELA should not be inserted if the uterus sounds to less than 5.5 cm.
- After ascertaining that the client is appropriate for AVIBELA, open the pouch containing AVIBELA, noting the lot number.

IMPORTANT!
In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine body or cervix. If necessary, remove the system and insert a new, sterile system.

Please report any case of uterine perforation or insertion difficulties via the national reporting system or to the supplier.

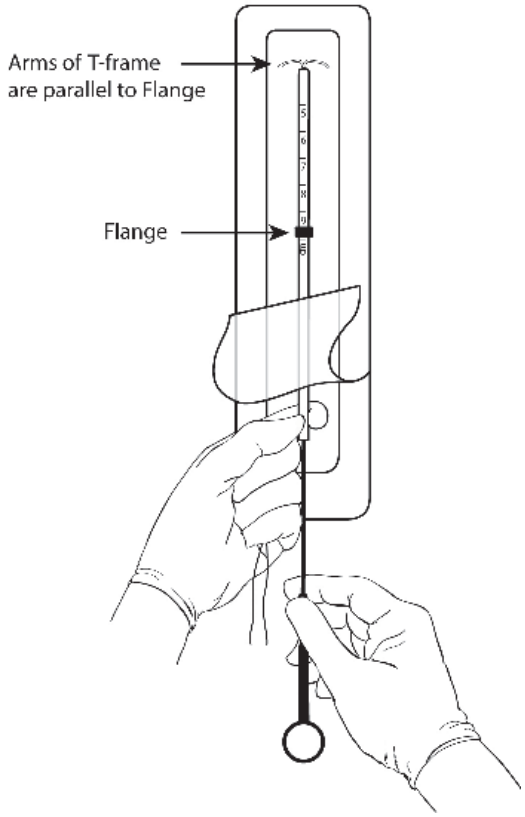
Loading the IUS into the inserter
Step 1
- Place the AVIBELA pouch on a flat surface with the clear side of the pouch facing up (Figure 3).

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



- Open the sterile AVIBELA 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.

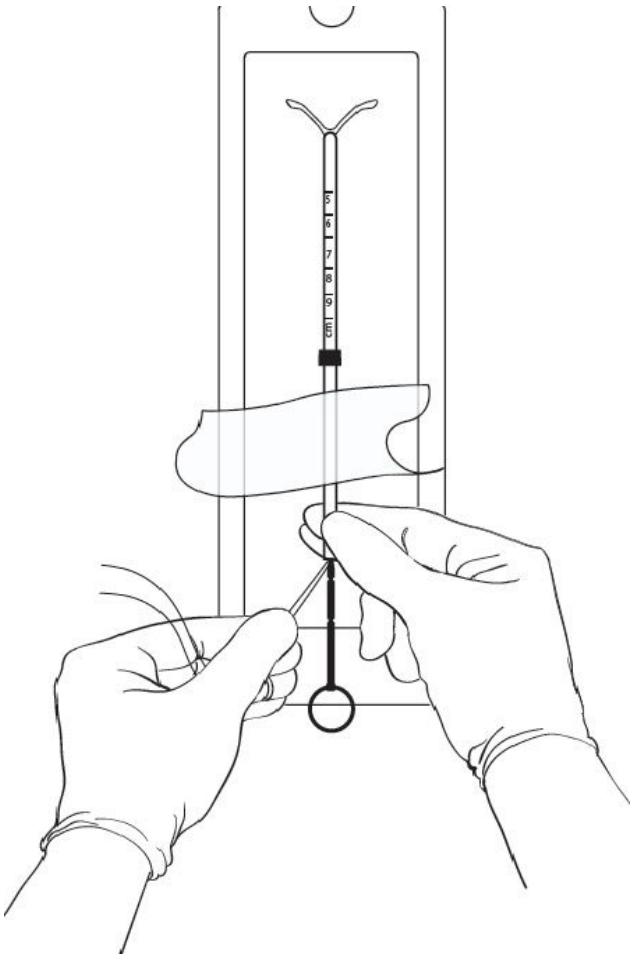
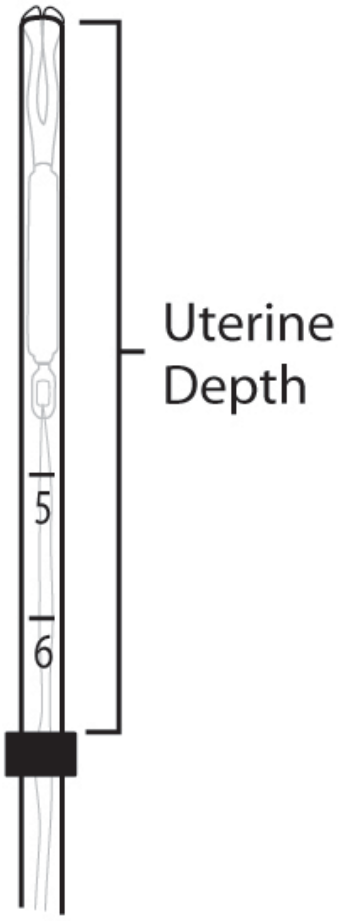


Figure 6: Adjust the flange.

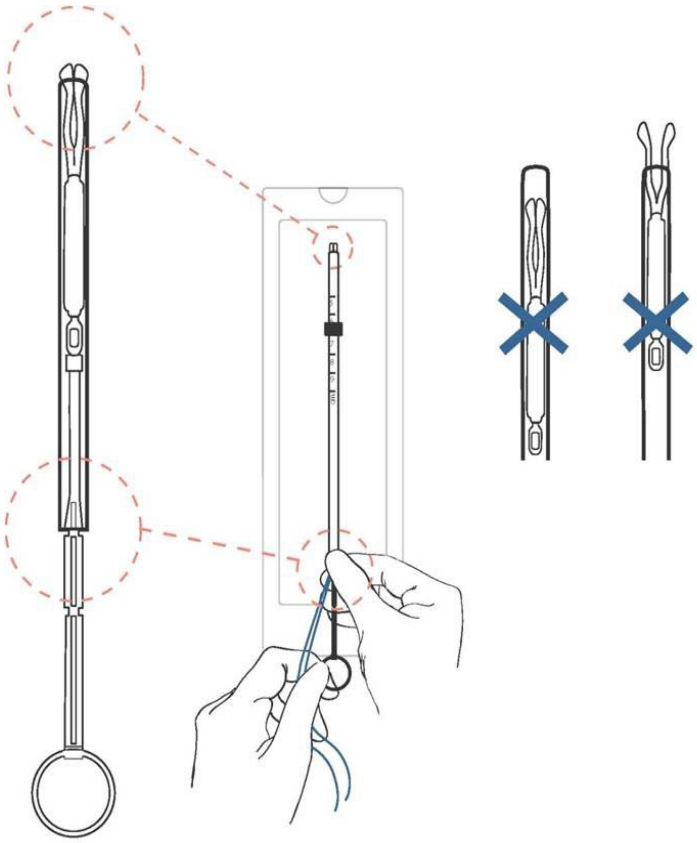


Step 5
- Hold the insertion tube and the rod firmly with one hand.
- With the other hand, adjust the position of the flange (through the sterile packaging if not using sterile gloves) by moving the tube to correspond to the sound measurement (Figure 6).
- The top end of the flange should be at the measurement 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.

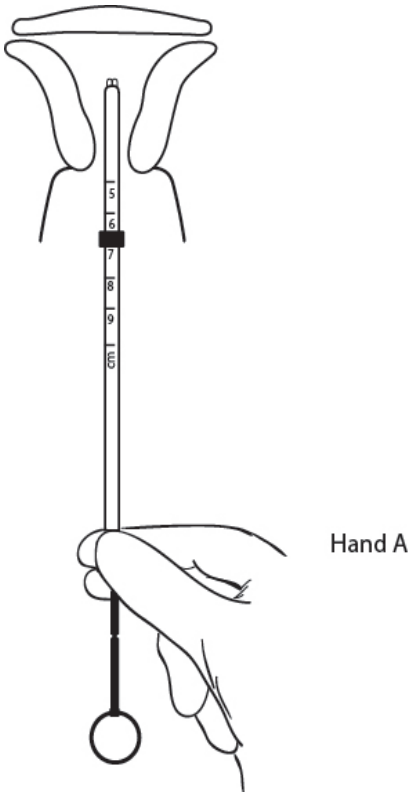
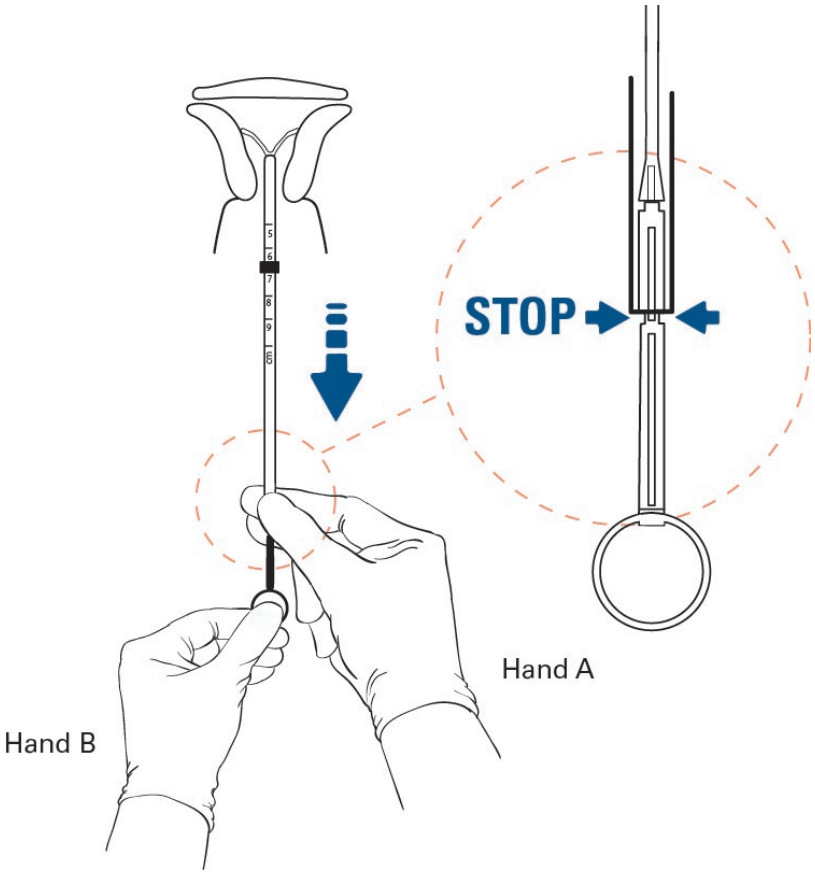


Figure 9: Hold the rod still and pull back the tube until the second indent on the rod.



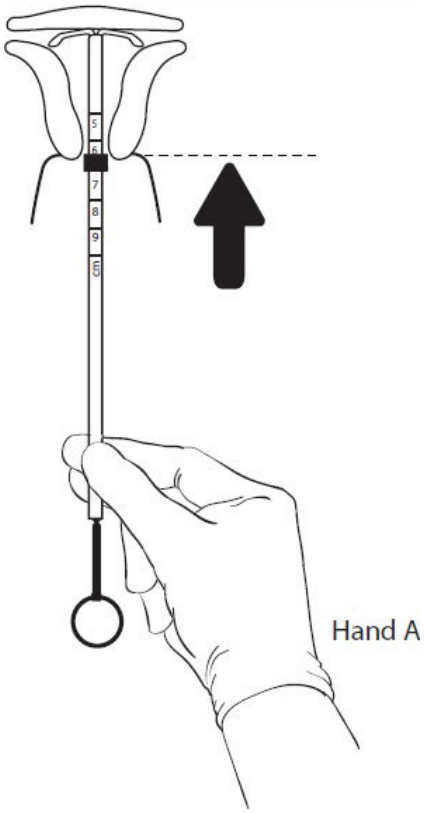
Step 2
- Release hold on the tenaculum.
- Hold the insertion tube with the fingers of one hand (Hand A) and the rod with the fingers of the other hand (Hand B).
- Hold the rod still (Hand B), relax the firmness of the pinch on the tube, and pull the insertion tube back with Hand A to the edge of the 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.

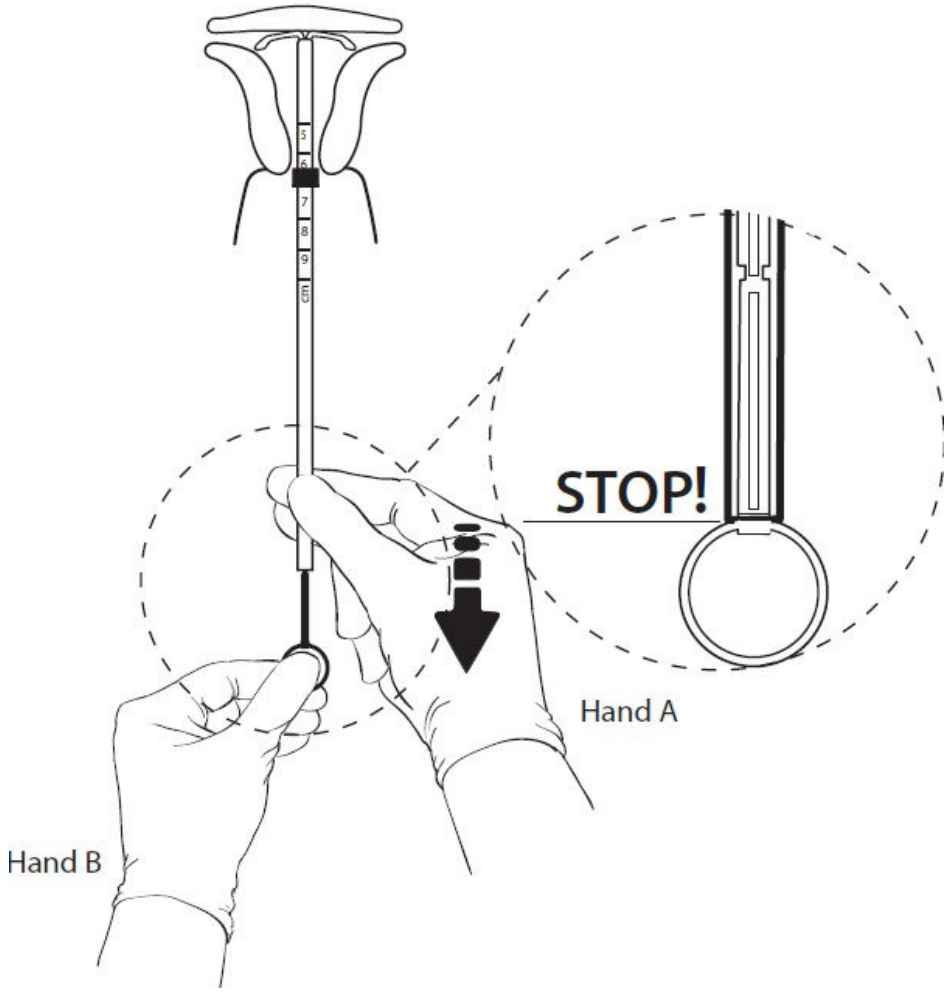
Figure 10: After 10 – 15 seconds, advance to the fundus while holding both the rod and the tube.



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 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

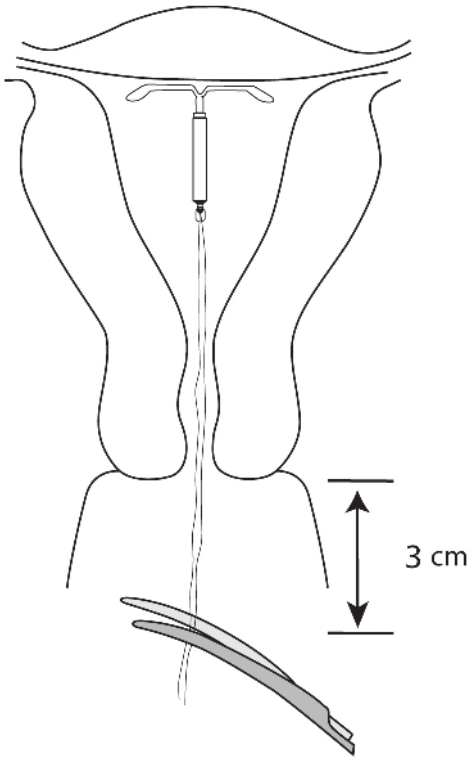
- Completely remove the insertion tube.

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).
- Do not apply tension or pull on the threads when cutting to prevent displacing the IUS.

Note: Do not cut threads at an angle as this may leave sharp ends.

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



Insertion of AVIBELA is now complete.

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

Client counseling and record-keeping

Counsel the client on what to expect following AVIBELA insertion. Discuss expected bleeding patterns with AVIBELA use. Review the signs and symptoms associated with infection, perforation, and expulsion that may occur with use of AVIBELA.

Prescribe analgesics, if indicated.

Client follow-up

The healthcare provider should consider re-examining and evaluating clients 4 to 6 weeks after insertion and during routine care, or more frequently if clinically indicated. The IUS threads should be checked during each evaluation.

Removal of AVIBELA

Planning and timing of removal
If pregnancy is desired, AVIBELA can be removed at any time.

If pregnancy is not desired, AVIBELA can be removed at any time; however, a contraceptive method should be started prior to removal of AVIBELA. Counsel clients that they are at risk of pregnancy if they have intercourse in the week prior to removal without use of a backup contraceptive method.

For contraception, AVIBELA should be removed after 8 years. AVIBELA can be replaced at the time of removal with a new AVIBELA if continued contraceptive protection is desired. For treatment of heavy menstrual bleeding, AVIBELA should be replaced at the end of the fifth year if continued treatment is needed.

Preparation for removal
Ensure all needed items for AVIBELA removal are readily available:
- Gloves
- Sterile speculum
- Sterile forceps

Additional items that may be required:
- Local anesthetic, needle, and syringe
- Sterile os finder and/or cervical dilators
- Ultrasound with abdominal probe
- Sterile tenaculum
- Antiseptic solution
- Sterile long, narrow forceps or intrauterine thread retriever

Removal may be associated with some pain and/or bleeding or vasovagal reactions (e.g., syncope, bradycardia, or seizure), especially in people with a predisposition to these conditions.

After removal of AVIBELA, examine the system to ensure that it is intact. The hormone cylinder may slide over and cover the horizontal arms, giving the appearance of missing arms. This does not require further intervention if the system is verified to be intact.

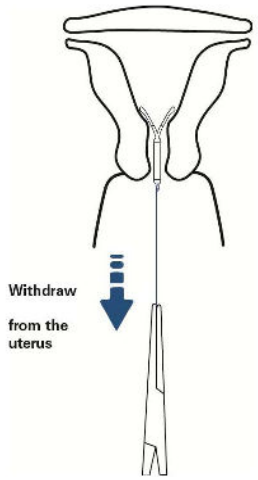
Breakage, embedment in the myometrium, or perforation of AVIBELA can make removal difficult. IUS breakage may be associated with removal. Analgesia, paracervical anesthesia, cervical dilation, alligator forceps or other grasping instrument, or hysteroscopy may assist in removal.

Removal procedure
With the client comfortably in lithotomy position, place a speculum and visualize the cervix.

When the threads of AVIBELA 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 AVIBELA. 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 AVIBELA are not visible:
- Determine location of the IUS and exclude embedment or perforation by ultrasound examination.
- If the IUS is in the uterine cavity, thoroughly cleanse the cervix and vagina with antiseptic solution. Use a thread retriever to capture the threads or a long, narrow forceps (e.g., Alligator forceps) to grasp AVIBELA. Consider use of a tenaculum, cervical anesthesia, cervical dilators, and/or ultrasound guidance as needed. If AVIBELA 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 AVIBELA



Continuation of contraception after removal
If a client wishes to continue using AVIBELA or another intrauterine contraceptive, insertion can occur immediately after removal.

If a client 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 AVIBELA 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 AVIBELA if removal is to occur at other times during the cycle.

If a client with irregular cycles or amenorrhea wants to start a different birth control method, start the new method at least 7 days before AVIBELA removal.

If AVIBELA is removed but no other contraceptive method has already been started, the new contraceptive method can be started on the day AVIBELA is removed. The client should use a backup barrier method of contraception (e.g., condoms) or abstain from vaginal intercourse for 7 days to prevent pregnancy.

4.3 Contraindications

AVIBELA is contraindicated when one or more of the following conditions exist:
- Pregnancy
- For use as post-coital contraception (emergency contraception)
- Congenital or acquired uterine anomaly, including leiomyomas, that distorts the uterine cavity and would be incompatible with correct IUS placement
- Acute pelvic inflammatory disease (PID)
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical malignancy
- 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 tumour (benign or malignant)
- Conditions associated with increased susceptibility to pelvic infections
- A previously inserted IUS that has not been removed
- A history of hypersensitivity reaction to any component of AVIBELA. Reactions may include rash, urticaria, and angioedema.

4.4 Special warnings and precautions for use

Medical examination

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

Exclude underlying endometrial pathology (e.g., polyps or cancer) prior to the insertion of AVIBELA in people with persistent or uncharacteristic bleeding because irregular bleeding/spotting is common during the first months of AVIBELA use and may preclude adequate assessment after insertion. AVIBELA is contraindicated in people with uterine bleeding of unknown etiology.

Exclude underlying congenital or acquired uterine anomalies, including leiomyomas, that distort the uterine cavity and would be incompatible with correct IUS placement.

Ensure a previously inserted IUS has been removed prior to insertion of AVIBELA.

Assess whether the client is at increased risk of pelvic infection (e.g., unprotected sex, history of PID, or acquired immune deficiency syndrome [AIDS]). AVIBELA does not protect against HIV/STI transmission.

Conditions under which AVIBELA can be used with caution

Use AVIBELA 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

Consider removing AVIBELA if any of the following conditions arise during use:

- Uterine or cervical malignancy
- Jaundice

Insertion/removal warnings and precautions

General information:
Insertion and removal may be associated with some pain and/or bleeding or vasovagal reactions (e.g., diaphoresis, syncope, bradycardia, or seizure), especially in people with a predisposition to these conditions. In case of difficult insertion and/or exceptional pain or bleeding during or after insertion, physical examination and ultrasound should be performed immediately to exclude perforation of the uterine corpus or cervix (see also 'Perforation'). Consider administering analgesics prior to insertion.

Sepsis:
Severe infection or sepsis, including Group A streptococcal sepsis (GAS), have been reported following insertion of 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 AVIBELA is essential to minimize serious infections such as GAS.

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

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

If perforation is suspected the IUS should be removed as soon as possible; surgery may be required. Delayed detection or removal of AVIBELA 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 1000 insertions for lactating women, compared to 1.0 per 1,000 insertions for non-lactating women.

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

Pelvic inflammatory disease or endometritis:
Insertion of AVIBELA is contraindicated in the presence of known or suspected PID or endometritis. As well, it is contraindicated in people with untreated acute cervicitis or vaginitis (including bacterial vaginosis), known chlamydial or gonococcal cervical infection, or other known lower genital tract infections, until the infection is controlled. IUSs have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion. Assess risk factors for infection accordingly.

People who use AVIBELA should be counseled to promptly notify a healthcare professional if they develop lower abdominal or pelvic pain, fever, chills, unusual or malodorous discharge, unexplained bleeding, genital lesions or sores, or dyspareunia. In such circumstances, perform a pelvic examination promptly to evaluate for possible pelvic infection. Remove AVIBELA in cases of recurrent PID or endometritis, or if an acute pelvic infection is severe or does not respond to treatment.

In the clinical study on contraception with AVIBELA, pelvic infection was diagnosed in 0.8% of participants. Pelvic infection was diagnosed as PID in 0.5% of participants and as endometritis in 0.3% of participants. Infections occurred following variable duration-of-use. One participant diagnosed with PID and two participants diagnosed with endometritis developed the infection within a week of AVIBELA insertion. One case of endometritis was diagnosed at 39 days after AVIBELA insertion. The remaining 11 cases of PID and endometritis were diagnosed more than six months after insertion, including one at 30 days after IUS removal. In the clinical studies on heavy menstrual bleeding with AVIBELA, there was one participant diagnosed with PID approximately 5 months after AVIBELA insertion.

PID and endometritis are often associated with a sexually transmitted infection (STI), and AVIBELA does not protect against STIs. The risk of PID or endometritis is greater for people who have multiple sexual partners, and for people whose sexual partner(s) have multiple sexual partners. People who have had PID or endometritis are at increased risk for a recurrence or re-infection. Other risk factors for these infections include unprotected sex and acquired immune deficiency syndrome (AIDS).

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

In people with suspected PID or endometritis, obtain microbial specimens, including those for sexually transmitted infections, and initiate antibiotic treatment promptly. After initiation of antibiotic treatment, the IUS may be removed or kept in place. The client should continue to receive antibiotic treatment according to current recommendations and should have close follow-up.

If the client opts for discontinuing IUS use, remove AVIBELA after initiation of antibiotic treatment to avoid the potential risk for bacterial spread resulting from the removal procedure.

If the client opts for ongoing IUS contraception, the client may forego immediate removal of AVIBELA after initiation of antibiotic treatment. However, the client should have close clinical follow-up. If no clinical improvement occurs within 48–72 hours of initiating treatment, IUS removal is appropriate with continued antibiotic therapy, as indicated.

In the AVIBELA clinical study on contraception, 12 of the 14 participants who developed PID or endometritis were successfully treated without removal of AVIBELA (one of the 14 participants developed PID 30 days after removal).

Actinomycosis has been associated with IUS use. Symptomatic clients with known actinomycosis infection should have AVIBELA removed and receive antibiotics. Actinomycetes can be found in the genital tract cultures in healthy people 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 AVIBELA removal and treatment. When possible, confirm a Pap test diagnosis with cultures.

Complications leading to failure

Expulsion:
Partial or complete expulsion of AVIBELA may occur, resulting in the loss of contraceptive protection. In the clinical study on contraception with AVIBELA, an overall expulsion rate of 4.1% over 8 years was reported, with a rate of 2.4% in nulliparous participants and 6.4% in parous participants. The majority (70.4%) occur in the first 12 months, with 23.9% occurring in the first three months and 42.3% in the first six months, cumulatively. Risk of expulsion is increased for people with a history of heavy menstrual bleeding of greater than normal BMI at the time of insertion. In a clinical study on treatment of heavy menstrual bleeding with AVIBELA, 8.6% of participants experienced expulsions, with two-thirds occurring within the first 90 days. About 90% of the expulsion occurred in overweight or obese participants.

Expulsion may be associated with symptoms of bleeding or pain, or it may be asymptomatic and go unnoticed. AVIBELA typically decreases menstrual bleeding over time; therefore, an increase in menstrual bleeding may be indicative of an expulsion. Consider further diagnostic imaging, such as sonography or X-ray, to confirm expulsion if AVIBELA is not found in the uterus.

The risk of expulsion is increased with insertions performed immediately after delivery; it appears to be increased with insertions performed after second-trimester abortion, based on limited data.

Remove a partially expelled AVIBELA. If expulsion has occurred, a new AVIBELA may be inserted when there is reasonable certainty the client is not pregnant.

Lost threads:
At removal, 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, (e.g., expulsed or perforated the uterus). Exclude pregnancy and verify the location of AVIBELA by an appropriate diagnostic method (e.g., ultrasonography, X-ray, or gentle exploration of the cervical canal with a suitable instrument). If AVIBELA is displaced, remove it. A new AVIBELA may be inserted at that time or during the next menses if it is certain that conception has not occurred. If AVIBELA is in place with no evidence of perforation, no intervention is indicated.

Bleeding pattern alternations

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

Contraception study:
The amenorrhea rates observed in the AVIBELA clinical study on contraception are shown in Table 2. The bleeding and spotting days, based on 28-day equivalents, are shown in Table 3. In this study, 2.5% of participants discontinued AVIBELA due to bleeding complaints.

Table 2: Amenorrhea Rates Last 90-Day Interval of Year

Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Amenorrhea Rate*	19%	27%	37%	37%	40%	40%	39%	39%

*Amenorrhea is defined as no bleeding and/or spotting.

Table 3: Bleeding and Spotting Days per 28-Day Cycle Equivalent

28-Day Cycle Equivalent N*	**Cycle 1 N=1,691**		**Cycle 4 N=1,593**		**Cycle 7 N=1,519**		**Cycle 13 N=1,395**		**Cycle 26 N=1,109**	
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

*N includes all AVIBELA participants in the clinical study on contraception.

Heavy menstrual bleeding study:
The amenorrhea rates observed in an AVIBELA clinical study on treatment of heavy menstrual bleeding (HMB) in the US are shown in Table 4. Amenorrhea developed in 19% of AVIBELA study participants by Cycle 6.

Table 4: Amenorrhea Rates for 28-Day Treatment Cycles

28-Day Cycle N	**Baseline** N=87	**Cycle 1** N=87	**Cycle 2** N=88	**Cycle 3** N=88	**Cycle 4** N=82	**Cycle 5** N=82	**Cycle 6** N=79
Amenorrhea Rate*	0%	3%	8%	11%	13%	17%	19%

*Amenorrhea is defined as no bleeding and/or spotting. Percentages within each cycle are based on the number of participants who completed the cycle.

The bleeding and spotting days, based on 28-day cycle equivalents, are shown in Table 5. In this study, 3.8% of AVIBELA participants discontinued due to bleeding complaints.

Table 5: Bleeding and Spotting Days from Baseline to Treatment Cycle 3 and Cycle 6

28-Day Cycle N*	**Baseline** N=87		**Cycle 3** N=88		**Cycle 6** N=79	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Number of Bleeding Days	4.9	1.5	3.7	3.8	2.2	3.5
Number of Spotting Days	1.8	1.1	7.3	7.0	5.1	5.8

*N includes participants with at least one complete 28-day cycle of product-use. Calculations are based on complete 28-day cycles (at least 23 days in length).

Resumption of menses after discontinuation:
In the AVIBELA clinical study on contraception, 651 of 652 (99.8%) participants 16-35 years of age at enrollment that were evaluated resumed menses after AVIBELA removal. This excludes twelve participants (9 became pregnant, 2 had a hysterectomy, and 1 had ovulatory dysfunction).

Other bleeding pattern changes:
If a significant change in bleeding develops during prolonged use, conduct diagnostic tests to assess possible endometrial pathology. Consider the possibility of pregnancy, including ectopic pregnancy, if menstruation does not occur within six weeks of the onset of a previous menstruation. After excluding pregnancy, repeat pregnancy tests are generally not necessary in amenorrheic people unless indicated by other signs of pregnancy or pelvic pain.

Other risks during use

Ectopic pregnancy:
Evaluate clients for ectopic pregnancy if they become pregnant with AVIBELA in place because the likelihood of a pregnancy being ectopic is increased with use of an IUS. Approximately half of pregnancies that occur with an IUS 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 menses or new onset bleeding in an amenorrheic person. If an ectopic pregnancy is confirmed, AVIBELA should be removed.

The incidence of ectopic pregnancy in the clinical study on contraception with AVIBELA, which excluded participants with a history of ectopic pregnancy who did not have a subsequent intrauterine pregnancy, was approximately 0.12 per 100 women-years. There were no ectopic pregnancies in the clinical studies on heavy menstrual bleeding with AVIBELA. The risk of ectopic pregnancy in people who have a history of ectopic pregnancy and use AVIBELA is unknown. People 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.

People who use AVIBELA should be informed about recognizing the signs and symptoms of ectopic pregnancy and promptly reporting them to their healthcare provider, and about the associated risks of ectopic pregnancy (e.g., loss of fertility).

Ovarian cysts:
The contraceptive effect of AVIBELA is mainly due to its local effects within the uterus; therefore, ovulatory cycles with follicular rupture usually occur in people of fertile age using AVIBELA. 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. In the clinical study on contraception, symptomatic ovarian cysts occurred in 4.7% of participants using AVIBELA over the course of 8 years, and 0.3% of participants discontinued use of AVIBELA because of an ovarian cyst. In the clinical study on treatment of heavy menstrual bleeding in the US, symptomatic ovarian cysts occurred in 1.0% of participants using AVIBELA over the course of 6 months.

Evaluate persistent ovarian cysts. Surgical intervention is not usually required but may be necessary in some cases, and occurred in 1 (0.06%) of participants in the AVIBELA clinical study on contraception. Discuss this risk with clients, as indicated.

Breast cancer:
People who currently have or have had breast cancer, or have a suspicion of breast cancer, should not use hormonal contraception, including AVIBELA, because some breast cancers are hormone-sensitive.

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

General information

Post-coital contraception: AVIBELA is not for use as a post-coital contraceptive.

4.5 Interaction with other medicinal products and other forms of interaction

No drug-drug interaction studies have been conducted with AVIBELA. Contraceptive effect of AVIBELA is mediated via the direct release of levonorgestrel into the uterine cavity and is unlikely to be affected by drug interactions via enzyme induction or inhibition.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Septic abortion:
If a client becomes pregnant with an IUS in place, septic abortion—potentially including 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. AVIBELA is contraindicated in people who have had an infected abortion in the prior 3 months.

Continuation of pregnancy:
If a client becomes pregnant with AVIBELA in place and if AVIBELA cannot be removed or the client chooses not to have it removed, warn the client that failure to remove AVIBELA increases the risk of miscarriage, sepsis, premature labor, and premature delivery. Prenatal care should include counseling about

these risks and instructions to immediately report 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.

Local exposure to levonorgestrel:
Published studies report no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins in a pregnant person. There have been isolated cases of virilization of the external genitalia of the female fetus following local exposure to LNG during pregnancy with an LNG IUS in place. Animal reproduction studies have not been conducted with AVIBELA.

Breastfeeding

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. Isolated cases of decreased milk production have been reported with another LNG-releasing IUS. There are no reports of adverse effects in breastfed infants with maternal use of progestin-only contraceptives. The infant's developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AVIBELA, underlying maternal conditions, and any potential adverse effects from AVIBELA on the infant.

The incidence of uterine perforation appears higher in lactating people.

Fertility

The use of levonorgestrel IUS has not been demonstrated to alter the course of female fertility after removal of the IUS. In the AVIBELA clinical study on contraception, 651 of 652 (99.8%) participants 16-35 years of age at enrollment that were evaluated resumed menses after AVIBELA removal. This excludes twelve participants (9 became pregnant, 2 had a hysterectomy, and 1 had ovulatory dysfunction).

4.7 Effects on ability to drive and use machines

AVIBELA has no known influence on the ability to drive or use machines.

4.8 Undesirable effects

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

Clinical study on contraception

The data described below reflect exposure of 1,751 generally healthy participants, 16 to 45 years of age, to AVIBELA in a large, multi-center contraceptive study conducted in the US. Participants included 1,401 exposed for 1 year and 380 who completed 8 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 participants who received AVIBELA were Caucasian (78.4%) or Black/African American (13.3%); 14.7% of participants were of Hispanic ethnicity. Mean BMI of AVIBELA participants was 26.9 kg/m^2 (range 15.8 – 61.6 kg/m^2); 25.1% had a BMI ≥ 30 kg/m^2 of which 5.3% had a BMI ≥ 40 kg/m^2. The data cover more than 80,221 28-day cycles of AVIBELA exposure. The frequencies of reported adverse drug reactions represent crude incidences.

The most common adverse reactions during the AVIBELA clinical study on contraception (occurring in ≥ 5% of participants) are shown in Table 6. The most common adverse reactions during the first year of use were acne (11.4%), bacterial vaginitis (9.0%), and vulvovaginal mycotic infection (7.9%).

The table below reports adverse reactions by MedDRA system organ class (MedDRA SOCs). The frequencies are based on AVIBELA contraception clinical study data.

Table 6: Most Common Adverse Reactions in AVIBELA Participants in the Phase 3 Clinical Study on Contraception

Organ System	Very common:	Common:	Uncommon:	Rare:

	>1/10	≥1/100 to <1/10	≥1/1000 to <1/100	≥1/10000 to <1/1000
Gastrointestinal disorders	• Nausea or vomiting • Abdominal pain/discomfort	• Abdominal distension • Constipation • Dyspepsia • Diarrhoea	• Oedema abdomen • Peripheral oedema	
Infections and infestations	• Vaginal bacterial infections • Vulvovaginal mycotic infections		• Pelvic inflammatory disease • Endometritis	
Injury, poisoning and procedural complications	Procedural bleeding	• Intrauterine contraceptive device expelled • Procedural pain	• Perforation • Intrauterine contraceptive device migration	
Investigations		Weight increased		
Musculoskeletal and connective tissue disorders		• Back pain • Pain in extremity		
Nervous system disorders		• Headache • Migraine • Presyncope • Dizziness • Syncope		
Pregnancy, puerperium and perinatal conditions			Ectopic pregnancy	
Psychiatric disorders		• Anxiety • Depression • Mood changes • Insomnia • Libido decreased	• Exacerbation of bipolar disorder • Suicidality	
Reproductive system and breast disorders		• Dysmenorrhea • Dyspareunia • Breast tenderness/pain • Menstruation irregular • Metrorrhagia • Ovarian cysts • Pelvic discomfort/pain • Uterine spasm • Vaginal discharge • Vulvovaginal dryness/discomfort • Ovarian cyst • Menorrhagia • Coital bleeding • Vaginal odour • Vaginal haemorrhage	• Amenorrhea • Polymenorrhea	

Skin and subcutaneous tissue disorders	Acne	Alopecia		

In the clinical study, 20.1% of AVIBELA participants discontinued prematurely due to an adverse reaction. The most common adverse reactions reported by participants as reason for discontinuation were expulsion (4.1%), bleeding complaints (2.5%), acne (1.4%), dysmenorrhea (1.0%), weight increased (1.0%), mood swings (0.8%), uterine spasm (0.7%), dyspareunia (0.6%) and pelvic pain (0.6%). Two participants discontinued the clinical study due to PID and one due to endometritis. The most common adverse reactions reported by participants as reason for discontinuation during the first year of use were expulsion (2.9%) and acne (0.7%).

In the clinical study, serious adverse reactions related to AVIBELA were ectopic pregnancies, ovarian cysts, and IUS perforation requiring laparoscopic surgery.

Clinical studies on treatment of heavy menstrual bleeding

The data for adverse reactions experienced by study participants being treated for heavy menstrual bleeding include exposure of 385 participants to an LNG-releasing IUS, 246 of which used AVIBELA, across two clinical studies. The adverse reaction profile in the clinical studies on heavy menstrual bleeding were consistent with the adverse reaction profile for AVIBELA participants in the contraception study as shown in Table 6.

A non-comparative, open-label clinical study conducted in the US exposed 105 generally healthy participants, 18 to 50 years of age, to AVIBELA for up to 6 months. The participants had no contraindications to AVIBELA and had confirmed heavy menstrual bleeding (≥ 80 mL menstrual blood loss [MBL] per menses), determined using the alkaline hematin method. Participants with any structural (e.g., leiomyomas > 2 cm in greatest diameter or more than 3 leiomyomas > 1.5 cm in greatest diameter) or diagnosed pathophysiologic conditions that may cause heavy uterine bleeding were excluded. The study population was 64.8% White, 23.8% African American, and 11.4% Other; 9.5% of enrolled participants were of Hispanic ethnicity. The median BMI was 29.7 kg/m^2 (with 23.8% overweight and 48.6% obese). The median baseline MBL was 143.2 mL. Approximately 11% of AVIBELA study participants discontinued prematurely due to an adverse reaction. The most common adverse reactions leading to discontinuation were expulsions (4.8%) and bleeding pattern alterations (3.8%).

A multiple-center, randomized, parallel group, single-blind clinical study in Eastern Europe was conducted to assess the therapeutic equivalence of AVIBELA and MIRENA in participants with heavy menstrual bleeding, with an extension phase through three years of use. A total 280 participants were randomized, of which 141 were exposed to AVIBELA. Approximately 17% of AVIBELA study participants discontinued prematurely due to an adverse reaction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system or to the local partner. Clients are encouraged to call their healthcare provider if they have any concerns about AVIBELA and may also report any suspected adverse reactions via the national reporting system or to the local partner. Contact information for the national reporting systems and local partners can be found at www.avibelapv.com.

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
- Hypersensitivity (including rash, urticaria, and angioedema)
- Increased blood pressure
- Device breakage
- Dizziness

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

AVIBELA has mainly local progestogenic effects in the uterine cavity which change the endometrium and may lead to alterations in the menstrual bleeding pattern. High local concentrations of LNG lead to morphological changes including stromal pseudo-decidualization, glandular atrophy, a leukocytic infiltration, and a decrease in glandular and stromal mitoses.

In clinical studies with other LNG-releasing IUSs with an LNG release rate similar to AVIBELA, approximately 45-75% of menstrual cycles were ovulatory.

Clinical efficacy

Clinical study on contraception:
The efficacy of AVIBELA for contraception was studied in a multicenter, randomized, open-label clinical study conducted in the US that enrolled 1,910 generally healthy participants aged 16 to 45 years, 1,751 of whom received AVIBELA. AVIBELA was inserted in 1,011 (58%) nulliparous and 740 (42%) parous participants. Participants 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 demographic profile of enrolled participants who received AVIBELA are as follows: White 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 study had no limit on weight (minimum or maximum) or BMI (range was 15.8 – 61.6 kg/m^2). The mean BMI of AVIBELA participants 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 participants 16 to 35 years of age, 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 8-year pregnancy rate was calculated by the life table method, based on a total of eleven pregnancies that occurred after the onset of treatment and within 7 days after AVIBELA removal or expulsion. Table 7 shows the annual PI for each of the eight years and the calculated cumulative life table pregnancy rates through years 1, 2, 3, 4, 5, 6, 7, and 8. For Year 7 and Year 8, participants who were more than 39 years of age at the beginning of the respective study year were excluded from the efficacy analysis.

Table 7: Contraceptive Efficacy: Pregnancy Rates

Year	**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	0.50 (0.22, 1.10)
Year 3	11,760	0.11 (0.00, 0.62)	43,140	0.60 (0.29, 1.27)
Year 4	9,891	0.13 (0.00, 0.73)	53,031	0.73 (0.36, 1.48)
Year 5	8,337	0.16 (0.00, 0.87)	61,368	0.89 (0.45, 1.74)
Year 6	6,916	0.00 (0.00, 0.69)	68,284	0.89 (0.45, 1.74)
Year 7*	5,280	0.49 (0.06, 1.78)	73,564	1.37 (0.71, 2.62)
Year 8*	3,657	0.00 (0.00, 1.31)	77,221	1.37 (0.71, 2.62)

*Excludes participants >39 years of age at the beginning of the respective year.

Conception rates after the removal of AVIBELA were assessed and appeared consistent with conception rates in the general population having regular unprotected sexual intercourse for 12 months.

Of 244 participants who desired pregnancy after study discontinuation, 63.1% conceived within 6 months after removal of AVIBELA and 83.2% conceived within 12 months after removal of AVIBELA.

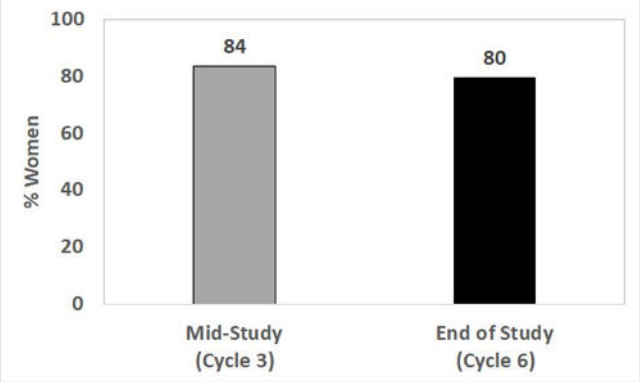
Clinical studies on treatment of heavy menstrual bleeding:
The efficacy of AVIBELA in the treatment of heavy menstrual bleeding was evaluated in two clinical studies.

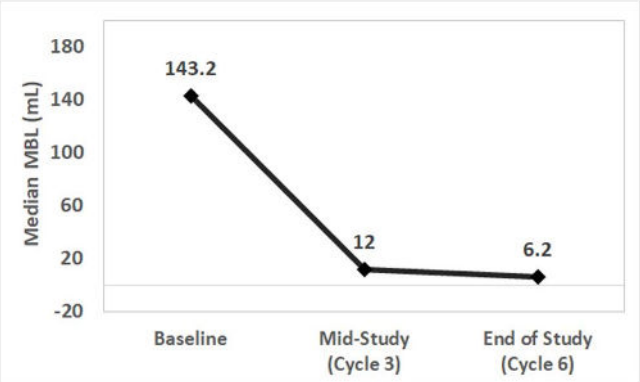
In the US, the efficacy of AVIBELA in the treatment of heavy menstrual bleeding was studied in a non-comparative, open-label clinical study. The study enrolled 105 generally healthy participants 18 to 50 years of age, with no contraindications to AVIBELA, and with confirmed heavy menstrual bleeding (≥ 80 mL menstrual blood loss [MBL] per menses) determined using the alkaline hematin method. Participants with any structural (e.g., leiomyomas > 2 cm in greatest diameter or more than 3 leiomyomas > 1.5 cm in greatest diameter) or diagnosed pathophysiologic conditions that may cause heavy uterine bleeding were excluded. The study population was 64.8% White, 23.8% African American, and 11.4% Other; 9.5% of enrolled participants were of Hispanic ethnicity. The median BMI was 29.7 kg/m^2 (with 23.8% overweight and 48.6% obese). The median baseline MBL was 143.2 mL.

The primary efficacy endpoint was the proportion of participants with successful treatment, defined as (1) an end-of-study MBL volume < 80 mL and (2) ≥ 50% reduction in MBL from baseline to end-of-study. Treatment outcomes with AVIBELA are summarized in Figures 14 and 15. The proportion of participants meeting both criteria defining successful treatment was 80% at the end of the study, with a 95% confidence interval of 71-88% (Figure 17). The quantitative reduction in median MBL volume from baseline to mid-study and to end-of-study is shown in Figure 18. The median MBL percent reduction from baseline to mid-study was 91% and to end-of-study was 96%.

Figure 14: Proportion of Participants with Successful Treatment of HMB Over Time

Figure 15: Median Menstrual Blood Loss (MBL) Over Time





In Eastern Europe, in a clinical study evaluating participants with heavy menstrual bleeding (≥80 mL per menstrual cycle), AVIBELA achieved a significant reduction in menstrual blood loss within 3 to 6 months of treatment. The volume of menstrual bleeding was decreased by 88% in participants with heavy menstrual bleeding by the end of three months of use and 82% reduction was sustained for the duration of the study (12 months), with 15% becoming amenorrheic at the end of the first year and 29% at the end of the third year.

5.2 Pharmacokinetic properties

Low doses of LNG are administered into the uterine cavity with the AVIBELA intrauterine delivery system. The initial *in vivo* release rate is 20.4 mcg/day and decreases to 17.7 mcg/day at 1 year, 15.3 mcg/day at 2 years, 13.3 mcg/day at 3 years, 11.5 mcg/day at 4 years, 10.0 mcg/day at 5 years, 8.7 mcg/day at 6 years, 7.5 mcg/day at 7 years, and 6.5 mcg/day at 8 years.

In the clinical study on contraception, systemic plasma LNG concentrations were assessed in a subset of participants through Month 30 and in all participants in the study at Month 36 and after. Plasma LNG concentrations following insertion of AVIBELA are shown in Table 8.

Table 8: Plasma LNG Concentrations (mean ± SD, pg/mL) Following AVIBELA Insertion

7 Days (n=40)	6 Months (n=36)	12 Months (n=33)	24 Months (n=30)	36 Months (n=914)	48 Months (n=793)	60 Months (n=608)	72 Months (n=243)	84 Months (n=211)	96 Months (n=142)
252±123	195±68	168±51	150±47	132±54	114±52	101±42	92±43	90±38	88±37

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.

Elimination

The elimination half-life of LNG after a single oral administration is approximately 13.9 ± 3.2 hours. 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.

Metabolism
Following absorption, LNG is conjugated at the 17b-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3a, 5b-tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3a, 5a-tetrahydrolevonorgestrel and 16b-hydroxylevonorgestrel. *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.

Specific populations

Racial or ethnic groups:
The effect of race on plasma LNG concentrations after AVIBELA insertion was assessed in 731 (80%) White participants, 106 (12%) Black participants, 40 (4%) Asian participants, 8 (1%) American Indian/Alaska Native participants, and 21 (2%) multiple-race participants. Race does not appear to affect LNG concentrations following AVIBELA insertion.

BMI/Body Weight:
The effect of BMI on LNG exposure was assessed in 687 non-obese (BMI < 30 kg/m^2) and 225 obese participants (BMI ≥ 30 kg/m^2). Plasma LNG concentrations were approximately 21-34% lower in obese participants than in non-obese participants based on data collected from Months 36 to 96. However, since AVIBELA has a mainly local progestogenic effect in the uterine cavity, the clinical relevance of the reduced systemic exposure is unclear.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans other than the information already included in other sections of the SmPC. These data are based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development, and toxicity evaluations of device components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

AVIBELA consists of a T-shaped polyethylene frame (T-frame) with a drug reservoir around the vertical stem (see Figure 1). 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 AVIBELA, including its packaging, are not manufactured using natural rubber latex.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

AVIBELA is supplied sterile. AVIBELA is sterilized with ethylene oxide. Do not re-sterilize. Do not use if the packaging is damaged, or if the packaging is opened. Insert before the end of the month shown on the packaging. Store at 20°C – 25°C (68°F – 77°F), with excursions permitted between 15°C – 30°C (59°F – 86°F) [See USP Controlled Room Temperature]. Store in the original package. Keep the blister in the outer carton in order to protect from light. Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

AVIBELA IUS with the inserter device is individually packed into a peelable pouch and is available in a carton of one sterile unit.

6.6 Special precautions for disposal and other handling

As the insertion technique is different from intrauterine devices, special emphasis should be given to training in the correct insertion technique. Special instructions for insertion are in the package.

AVIBELA is supplied in a sterile pack which should not be opened until required for insertion. Each system should be handled with aseptic precautions. If the seal of the sterile envelope is broken, the system inside should be disposed of in accordance with the local guidelines for the handling of biohazardous waste. Likewise, a removed AVIBELA and inserter should be disposed of in this manner. The outer carton package and the inner blister package can be handled as household waste.

AVIBELA is not for resale or redistribution.

7. SUPPLIER AND MANUFACTURER

Supplied by:
Impact RH360 LLC,
a subsidiary of Medicines360
49 Stevenson St., Suite 1150
San Francisco, CA 94105
Telephone: 1-415-951-8700

Manufactured by:
Odyssea Pharma SPRL
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