SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AVIBELA 20 micrograms/24 hours Intrauterine Delivery System

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is Levonorgestrel.

The intrauterine delivery system contains 52 mg levonorgestrel, Ph.Eur. The initial release of levonorgestrel is approximately 20 mcg/day per day and declines progressively to about 50% after 5 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 for up to five years.

Treatment of heavy menstrual bleeding for up to five years. AVIBELA may be particularly useful in women with heavy menstrual bleeding requiring (reversible) contraception.

4.2 Posology and method of administration

Starting Treatment
In women 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 woman is not pregnant, abstinence or a barrier method of contraception (such as condoms and spermicide) 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 six weeks after delivery. If the patient 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 five years in the indications for contraception and heavy menstrual bleeding. Therefore, it should be removed after 5 years of use.

If the user wishes to continue using the same method, a new system can be inserted at the same time, in which case no additional protection is required.

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 women not currently using hormonal or intrauterine contraception	• AVIBELA 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 AVIBELA 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 AVIBELA from an oral, transdermal or vaginal hormonal contraceptive	• AVIBELA 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 seven days after AVIBELA insertion or until the end of the current treatment cycle.
	• If using continuous hormonal contraception, discontinue that method seven 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, a barrier method of contraception (such as condoms and spermicide) should also be used for 7 days after insertion.
Switching to AVIBELA from a contraceptive implant or another IUS	• Insert AVIBELA on the same day the implant or IUS is removed. • AVIBELA may be inserted at any time during the menstrual cycle.
Inserting AVIBELA after abortion or miscarriage	
• **First trimester**	• AVIBELA may be inserted immediately after a first-trimester abortion or miscarriage.

• **Second trimester**	• Do not insert AVIBELA until a minimum of 4 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. • If the woman 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 the provider can be reasonably certain the woman is not pregnant. • If AVIBELA 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 AVIBELA after Childbirth	• Do not insert AVIBELA until a minimum of 4 weeks after delivery, or until the uterus is fully involuted. If involution is delayed, wait until involution is complete before insertion. • If the woman 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 the provider can be reasonably certain the woman is not pregnant. • If AVIBELA 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.

Paediatric population

AVIBELA has not been studied in patients below 16 years of age. AVIBELA is not indicated for use before menarche.

Patients with hepatic impairment

AVIBELA is contraindicated in patients with acute or severe liver disease or liver tumour (see section 4.3).

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. If the seal of the sterile package is broken, the product should be discarded (see section 6.6 for disposal instructions).

Figure 1 Intrauterine Contraceptive System (IUS)

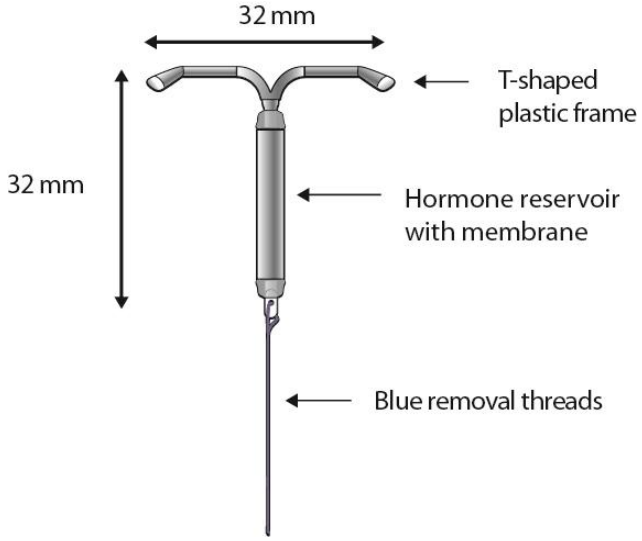
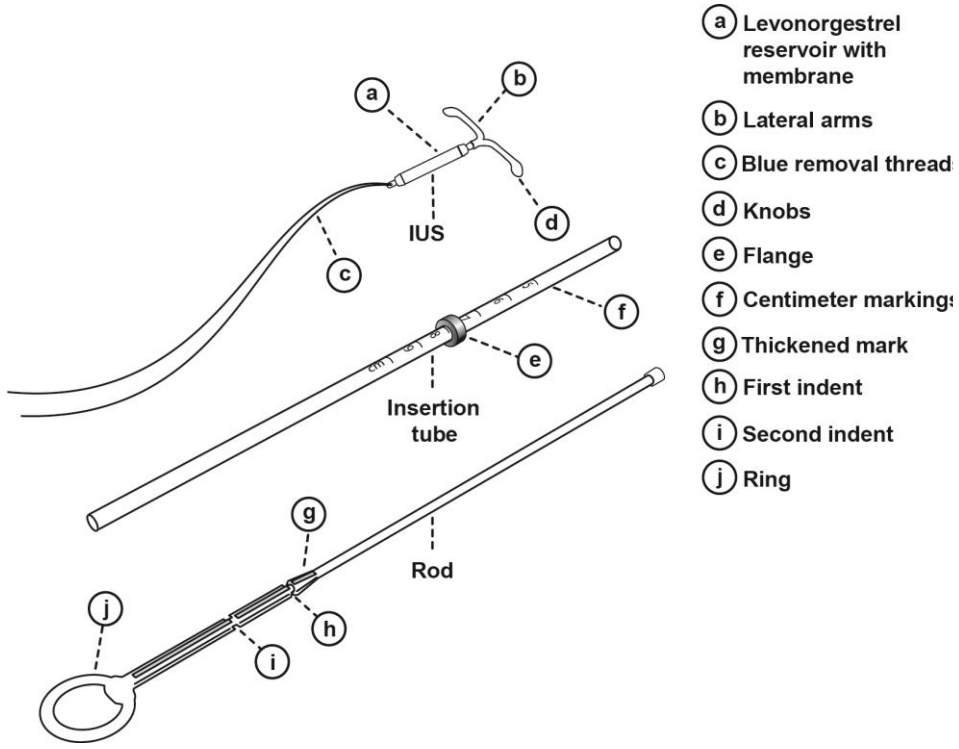


Figure 2: IUS with Inserter



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 patient labeling before attempting insertion.

- Obtain a complete medical and social history to determine conditions that might influence the selection of a levonorgestrel-releasing intrauterine system 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 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.) or product has not been damaged (e.g. crushed, dislodged, etc.). If the packaging has any visual damage that could compromise sterility or performance. Do not use the unit for insertion.
- 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 pouch.
- Do not open the pouch to insert AVIBELA if the cervix is unable to be properly visualized, if the uterus cannot be adequately instrumented (during sounding), or if 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.
- AVIBELA is supplied sterile having been sterilised with ethylene oxide. Do not resterilise. For single use only. Do not use if the inner package is damaged or open. Insert before the month shown on the label.
- AVIBELA is inserted with the provided inserter (Figure 2) into the uterine cavity by carefully following the insertion instructions.

The following insertion instruction will be provided in the box containing the IUS.

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

Planning 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 patients 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.

Preparation for Insertion

- With the patient comfortably in lithotomy position, do a bimanual exam to establish the size, shape, and position of the uterus and to evaluate any signs of uterine infection.
- Gently insert a speculum to visualize the cervix.
- Thoroughly cleanse the cervix and vagina with antiseptic solution.
- Administer cervical anesthetic, if needed.
- Apply a tenaculum to the cervix and use gentle traction to align the cervical canal with the uterine cavity. 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 patient is appropriate for AVIBELA, open the pouch containing AVIBELA.

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.

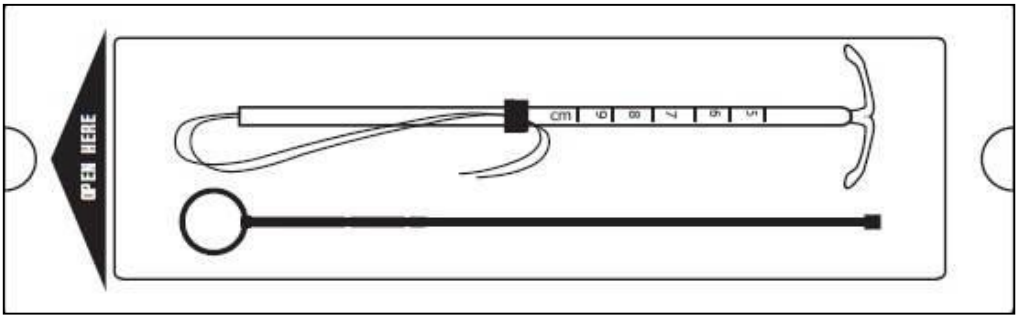
Insertion Procedure

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).

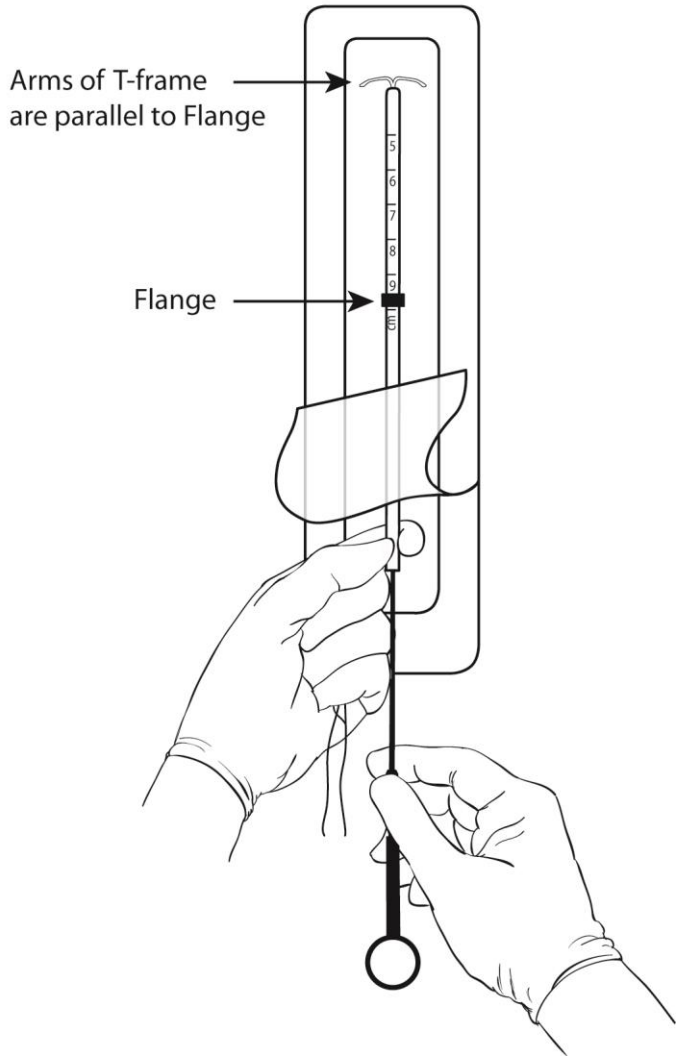
Figure 3: Place the AVIBELA pouch on a flat surface.



- 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 not to pull the IUS down at the same time (Figure 4).

Step 3

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

Step 4

- While holding the insertion tube and the rod firmly between the fingers and thumb of one hand, pull downward on both blue threads with the other hand to draw the IUS into the insertion tube (Figure 5).

- The arms of the IUS should be kept in a horizontal plane, parallel to the flat side of the flange (refer to Figure 4).
- Do not pull the IUS all of the way through the insertion tube; only pull the threads until the IUS is loaded at the top of the insertion tube. *Note: If you accidentally remove the IUS completely out of the insertion tube, do not use or attempt to re-load.*

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

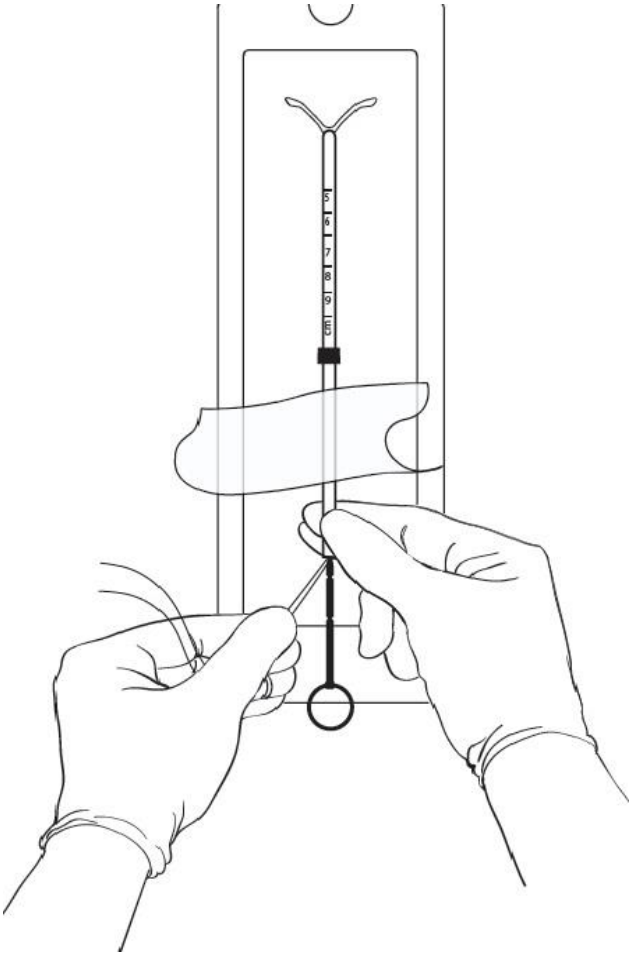
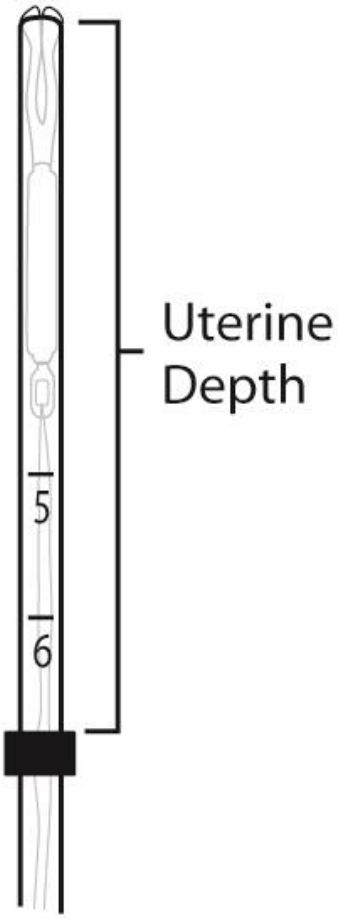


Figure 6: Adjust the Flange.



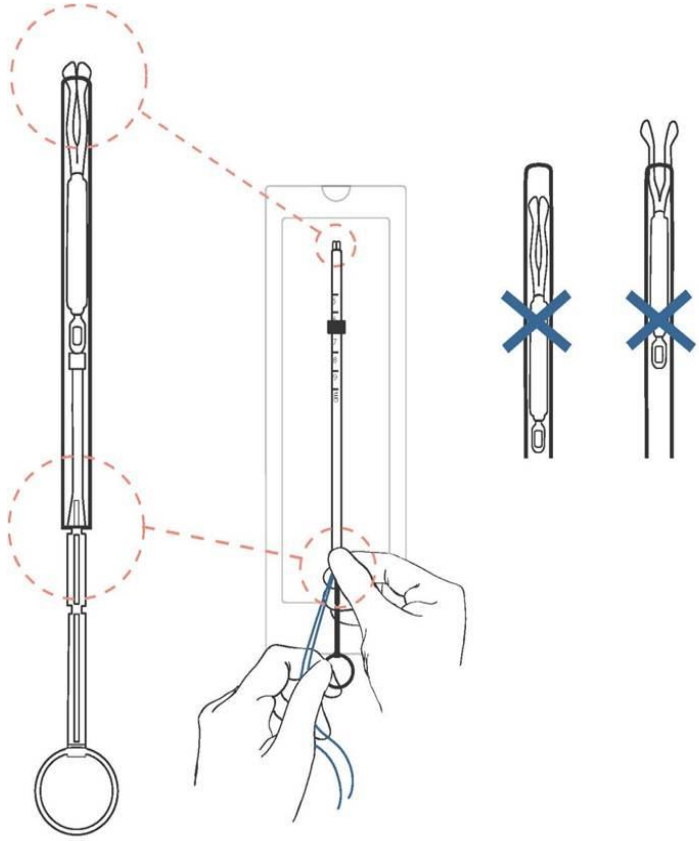
Step 5

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

Step 6

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

Figure 7: Final IUS Positioning



ENSURE A HEMISPHERICAL DOME IS ACHIEVED.
When the IUS is in the correct position, the lower end of the tube will be aligned approximately at the upper edge of the upper indent on the rod.

Step 7

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

- The IUS is completely within the insertion tube with the knobs of the arms forming a hemispherical dome at the top of the tube.

- The top of the rod is touching the bottom of the IUS.
- The blue threads are hanging through the end of the insertion tube.
- The flange is marking the depth of the uterus based on pre-insertion sounding.

Step 8

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

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

IUS Insertion into the Uterus

Step 1

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

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

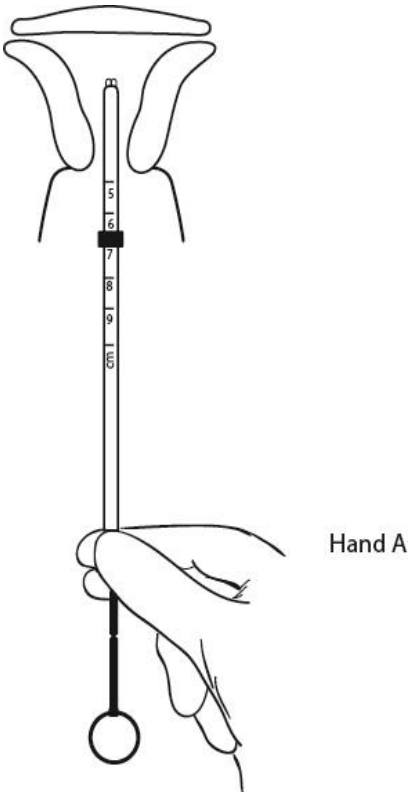
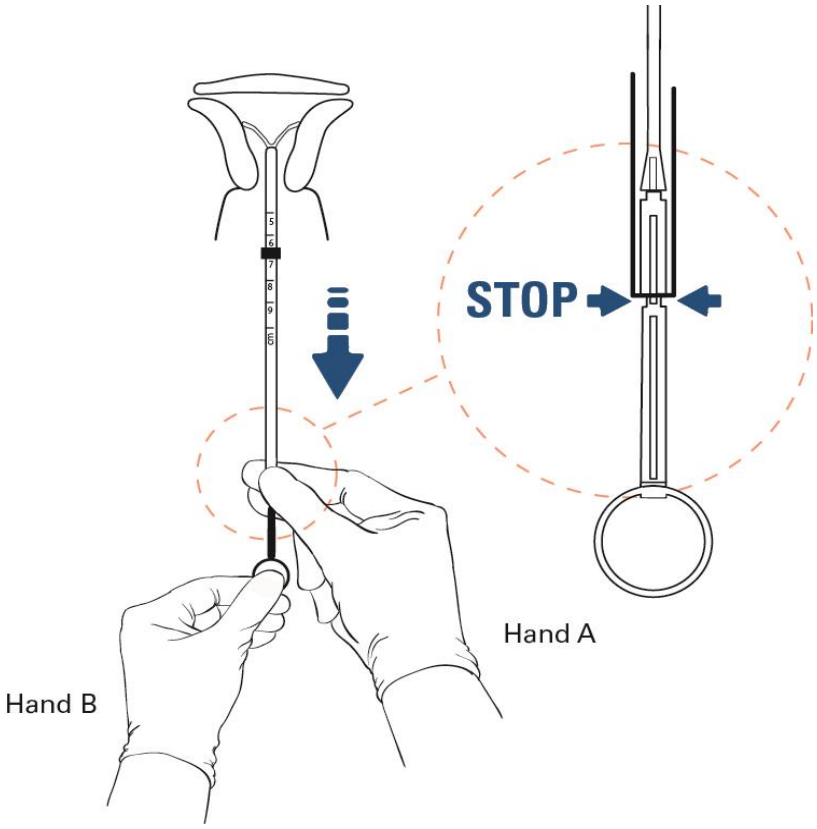


Figure 9: Hold the rod still and pull back the tube until the second indent on the rod.



Step 2

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

Step 3

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

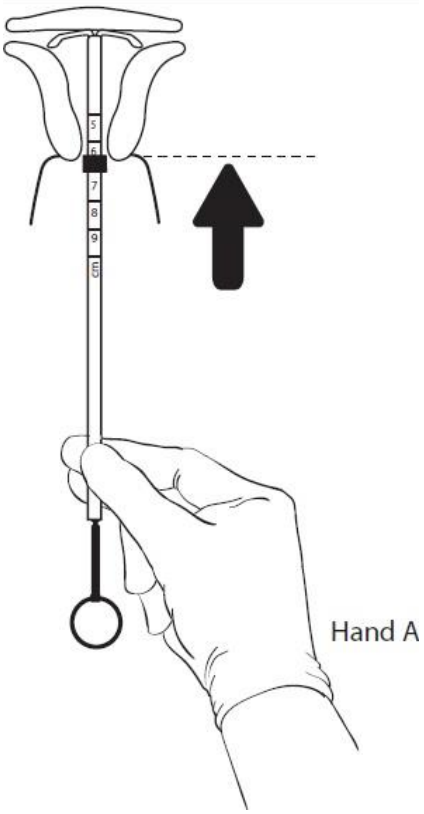
Step 4

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

- The flange should be touching the cervix when the IUS reaches the uterine fundus.

Note: Fundal positioning is important to prevent expulsion.

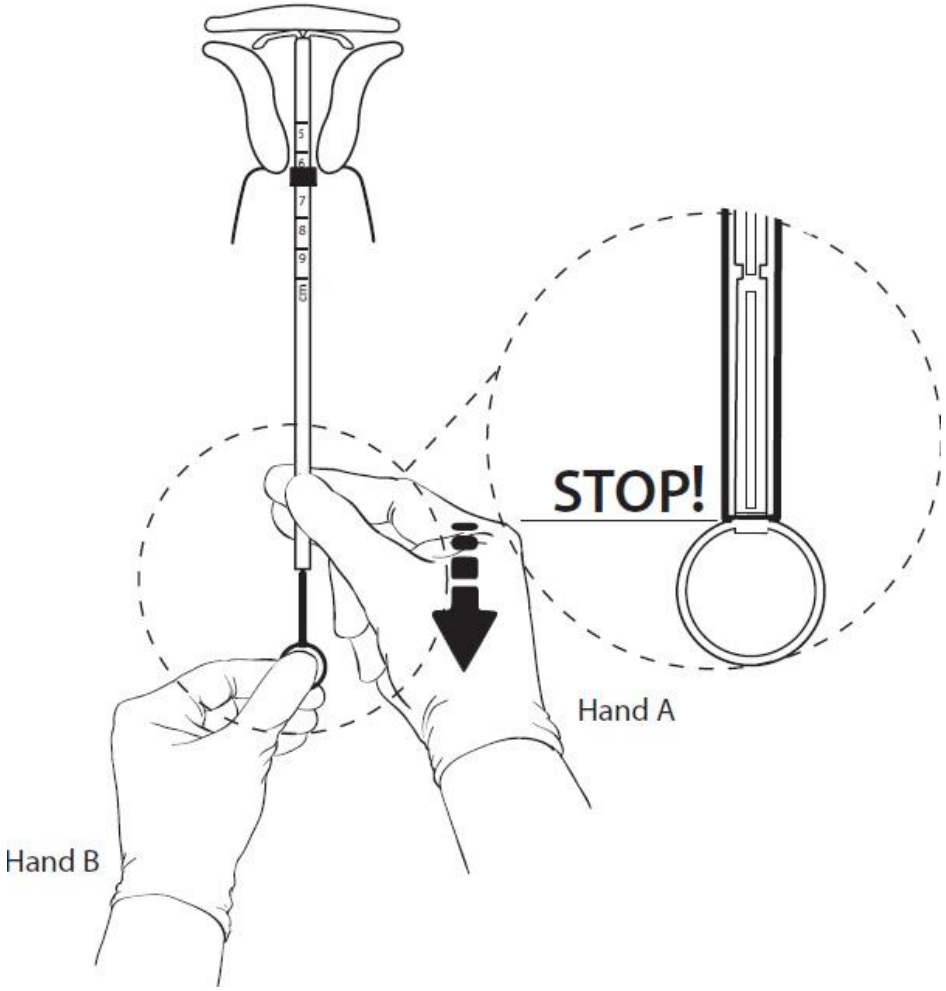
Figure 10: After 10 – 15 seconds, advance to the fundus while holding both the rod and the tube.



Step 5

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

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



Step 6

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

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

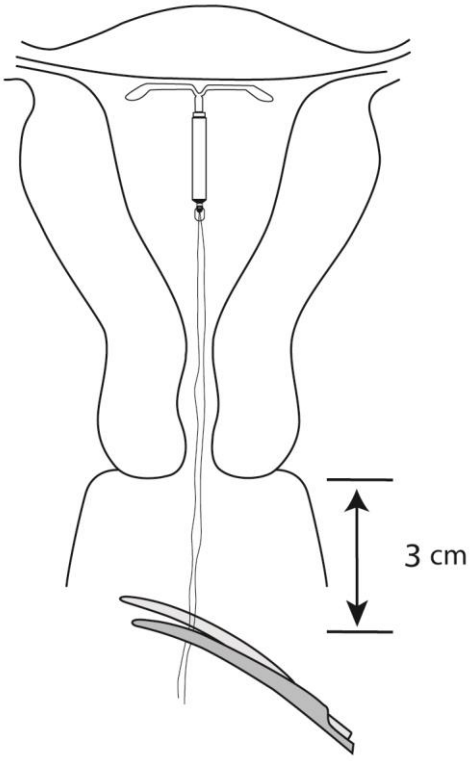
Step 7

- Completely remove the insertion tube.

Step 8

- Use blunt-tipped sharp scissors to cut the IUS threads perpendicular to the thread length, leaving about 3 cm outside of the cervix (Figure 12). *Note: Cutting threads at an angle 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 AVIBELA 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 AVIBELA. A removed AVIBELA must not be re-inserted.

Difficult insertion

- If insertion is difficult because the uterus cannot be appropriately instrumented, the following measures can be considered:
  - 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.
  - 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 perforation.

Patient Counseling and Record-Keeping

- Keep a copy of the consent form and AVIBELA lot number for your records.

- Counsel the patient on what to expect following AVIBELA insertion. Give her the Patient Information Booklet, which includes the website address. Discuss expected bleeding patterns with AVIBELA use. Review the signs and symptoms of expulsion.

- Prescribe analgesics, if indicated.

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.

Removal of AVIBELA

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 contraception method should be started prior to removal of AVIBELA. Counsel your patient that if she has intercourse in the week prior to removal without use of a backup contraceptive method, she is at risk of pregnancy.
- AVIBELA should be removed after 5 years. AVIBELA can be replaced at the time of removal with a new AVIBELA if continued contraceptive protection is desired.

Planning for Removal

- Ensure all needed items for AVIBELA removal are readily available:
    - Gloves
    - Sterile speculum
    - Sterile forceps
    - Additional items that may be required could include:
        - Local anesthetic, needle, and syringe
        - Sterile os finder and/or cervical dilators
        - Ultrasound with abdominal probe
        - Sterile tenaculum
        - Antiseptic solution
        - Sterile 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 AVIBELA, examine the system to ensure that it is intact.

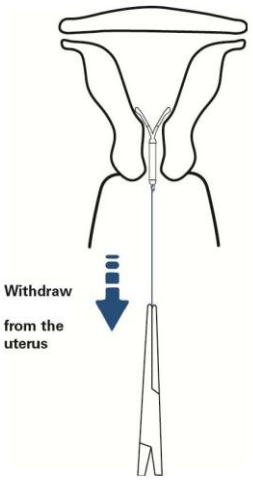
Removal Instructions

- With the patient comfortably in lithotomy position, place a speculum and visualize the cervix.
- When the threads of 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.

- If the threads of AVIBELA are not visible:
  - Determine location of the IUS by ultrasound examination.
  - If the IUS is in the uterine cavity, use long, narrow forceps (e.g., Alligator forceps) to grasp 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.

Figure 13: Removal of AVIBELA



Continuation of Contraception After Removal

- If a patient wishes to continue using AVIBELA or another intrauterine contraceptive, insertion can occur immediately after removal.
- If a patient with regular cycles wants to start a different birth control method, time the removal and initiation of a new method to ensure continuous contraception. Either remove 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 patient 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 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.

4.3 Contraindications

- Known or suspected pregnancy
- For use as post-coital contraception (emergency contraception)
- Acute pelvic inflammatory disease (PID) or endometritis
- Current lower genital tract infection until infection is controlled
- Infected abortion during the past three months
- Suspected or confirmed uterine or cervical malignancy
- Acute or severe liver disease or liver tumour
- Congenital or acquired abnormality of the uterus including fibroids if they distort the uterine cavity that would be incompatible with correct IUS placement
- Undiagnosed abnormal uterine bleeding
- A previously inserted IUS that has not been removed
- Current, history of, or suspected hormone dependent tumours such as breast cancer (see section 4.4)
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Medical examination
Before insertion, a medical history should be taken. Physical examination should be guided by the medical history and by the contraindications and warnings for use. A bimanual pelvic examination should be performed to establish the orientation of the uterus. Prior to insertion pregnancy should be excluded. Endometrial pathology should be evaluated. Acute genital infection should be excluded clinically. Women should be advised that AVIBELA does not protect against HIV (AIDS) and other sexually transmitted disease (please refer to the section below on pelvic infections). The woman should be re-examined six weeks after insertion and further examinations should be performed where clinically indicated and adapted to the individual woman rather than as routine procedure.

Conditions under which AVIBELA can be used with caution
Should any of the following conditions exist or arise for the first time during treatment, removal of the system should be considered:

- Migraine with aura
- Unusually severe or unusually frequent headache
- Jaundice
- Marked increase of blood pressure
- Conditions associated with increased susceptibility to pelvic infections
- Recent diagnosis of pelvic infections or pelvic inflammatory disease
- Acute malignancies affecting the blood or leukaemias
- Active or previous severe arterial disease, such as stroke or myocardial infarction
- Any current thromboembolic disease
- Recent trophoblastic disease while hCG levels remain persistently elevated

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 patients 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.

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 reduce contraceptive efficacy and result in pregnancy. This may be associated with severe pain and continued bleeding.

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

If perforation is suspected the IUS should be removed as soon as possible, surgery may be required. Delayed detection or removal of 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 and IUD results showed an increased risk of perforation with incidence of 5.6 per 1000 insertions for the entire study cohort in women who were breastfeeding at the time of insertion and who had insertion up to 36 weeks postpartum. These risk factors were independent of the type of IUS/IUD inserted.

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

Pelvic infection:
The risk of pelvic inflammatory disease or endometritis is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Pelvic infection may have serious consequences as it may impair fertility and increase the risk of ectopic pregnancy. As with other gynaecological or surgical procedures, severe infection or sepsis (including group A streptococcal sepsis) can occur following IUS insertion, although this is extremely rare.

For women using AVIBELA with symptoms and signs suggestive of pelvic infection, appropriate antibiotics should be started. There is no need to remove AVIBELA unless the symptoms fail to resolve within the following 72 hours or unless the women wishes AVIBELA to be removed. Removal of AVIBELA should be considered if the woman experiences recurrent endometritis or pelvic infection, or if an acute infection is severe.

Complications leading to failure
Expulsion:
Symptoms of the partial or complete expulsion of any IUS may include bleeding or pain. However, a system can be expelled from the uterine cavity without the woman noticing it. Partial expulsion may decrease the effectiveness of AVIBELA. As the device decreases menstrual flow, increase of menstrual flow may be indicative of an expulsion. A displaced AVIBELA should be removed and a new system inserted. The woman should be advised how to check the threads of AVIBELA.

Lost threads:
If the retrieval threads are not visible at the cervix on follow-up examination, first exclude pregnancy.
If pregnancy has been excluded, the threads may usually be located by gently probing with a suitable instrument. If they cannot be found, they may have broken off, withdrawn into the uterus, or the device may have been expelled. Ultrasound or X-ray may be used to locate the IUS.

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 irregularities
Use of AVIBELA can alter the menstrual bleeding pattern and may result in spotting, irregular bleeding, heavy bleeding, oligomenorrhea or amenorrhea.

Increased menstrual flow or unexplained bleeding, especially with increased cramping, may be indicative of expulsion and clinical evaluation should be performed as indicated. 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.

Other risks during use
Ectopic pregnancy:
The absolute risk of ectopic pregnancy in users of levonorgestrel IUS is low. However, when a woman becomes pregnant with AVIBELA in situ, the relative likelihood of ectopic pregnancy is increased. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts bleeding.

The incidence of ectopic pregnancy in the clinical trial of contraception with AVIBELA, which excluded women with a history of ectopic pregnancy who did not have a subsequent intrauterine pregnancy, was approximately 0.1% for the first year of use. The risk of ectopic pregnancy in women who have a history of ectopic pregnancy and use AVIBELA 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.

Ovarian cysts:
Since the contraceptive effect of levonorgestrel IUS is mainly due to its local effect, ovulatory cycles with follicular rupture usually occur in women of fertile age. Sometimes atresia of the follicle is delayed and folliculogenesis may continue. Most ovarian cysts that occur during use of levonorgestrel-releasing IUS's are asymptomatic and disappear spontaneously during two to three months of observation. Ovarian cysts that cause clinical symptoms can result in pelvic or abdominal pain or dyspareunia. In a clinical trial of AVIBELA that enrolled 280 women presenting with heavy menstrual bleeding of which 141 received AVIBELA, ovarian cyst (symptomatic and asymptomatic) was reported in 9.9% of patients within 12 months of insertion. In a clinical trial of AVIBELA which enrolled 1,751 subjects, symptomatic ovarian cysts occurred in approximately 4.5% of subjects using AVIBELA, and 0.3% of subjects discontinued use of AVIBELA because of an ovarian cyst.

It is recommended to 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 AVIBELA.

Breast cancer:
Women 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 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.

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
The use of AVIBELA during an existing or suspected pregnancy is contraindicated (see section 4.3). In case of an accidental pregnancy with AVIBELA *in situ* (see section 5: pharmacological properties), advise a woman of the increased risks for pregnancy complications, including miscarriage, premature labor, premature delivery, infection and sepsis. Ectopic pregnancy should be excluded (see section 4.4) and removal of the system should be considered. Removal of AVIBELA or probing of the uterus may result in spontaneous abortion. Should these procedures not be possible or if the woman wishes to continue the pregnancy, the woman should be informed about these risks, and accordingly, such pregnancies should be closely monitored. The woman should be instructed to report all symptoms that suggest complications of the pregnancy, like cramping abdominal pain with fever.

Local exposure to levonorgestrel
Clinical experience of the outcomes of pregnancies with levonorgestrel IUS *in situ* is limited. However, to date, there is no evidence of birth defects caused by local levonorgestrel IUS use in cases where pregnancy continues to term with the IUS in place.

Breastfeeding
Levonorgestrel is excreted in very small quantities in breast milk after use in levonorgestrel IUS. Since no risk for the child is expected, breastfeeding can be continued during use of AVIBELA.

Fertility
The use of levonorgestrel IUS has not been demonstrated to alter the course of female fertility after removal of the IUS. In the clinical trial of women using AVIBELA for contraception, the 97% of women had a rapid return of menses within 3 months of IUS removal and 83% of women who attempted to become pregnant were successful within a year.

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

Undesirable effects are more common during the first months after the insertion, and generally subside during prolonged use.

Contraception Clinical Trial

In a large clinical trial of 1,751 women using AVIBELA for contraception, the most common adverse reactions during the contraception clinical trial (occurring in ≥ 10% of users) include vaginal bacterial infections, vulvovaginal mycotic infections, and acne.

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

Organ System	**Very common >1/10**	**Common: ≥1/100 to <1/10**	**Uncommon: ≥1/1000 to <1/100**	**Rare: ≥1/10000 to <1/1000**
Infections and infestations	Vaginal bacterial infections Vulvovaginal mycotic infections		Pelvic inflammatory disease Endometritis	
Gastrointestinal disorders		Abdominal pain/discomfort Abdominal distension Nausea or vomiting Weight increased Back pain		
Injury, poisoning and procedural complications		Intrauterine contraceptive device expelled Procedural pain Procedural bleeding	Perforation	
Nervous system disorders		Headache Migraine Presyncope	Syncope	
Pregnancy, puerperium and perinatal conditions			Ectopic pregnancy	
Psychiatric disorders		Depression Mood changes Anxiety	Exacerbation of bipolar disorder	Suicidality

Reproductive system and breast disorders		Dysmenorrhea Dyspareunia Breast tenderness/pain Pelvic discomfort/pain Uterine spasm Vaginal discharge	Ovarian cysts	
Skin and subcutaneous tissue disorders	Acne			

Heavy Menstrual Bleeding Clinical Trial

A multiple center randomized parallel group single blind clinical trial has been conducted to assess the therapeutic equivalence of AVIBELA and reference product MIRENA in patients with heavy menstrual bleeding. A total 280 patients were randomized, of which 141 patients using AVIBELA.

The table below reports adverse reactions assessed as related to the drug by investigator, by MedDRA system organ class (MedDRA SOCs).

Organ system	Undesirable effects			
	Very common: ≥1/10	**Common: ≥1/100 to <1/10**	**Uncommon: ≥1/1000 to <1/100**	**Rare: ≥1/10000 to <1/1000**
Gastrointestinal disorders		Abdominal pain		
General disorders and Administration site conditions			Oedema abdomen Peripheral oedema	
Injury, poisoning and procedural complications		Intrauterine contraceptive device expelled Intrauterine contraceptive device migration Procedural pain		
Investigations		Weight increase Ultrasound ovary abnormal		
Musculoskeletal and connective tissue disorders				
Nervous system disorders		Headache		
Psychiatric disorders			Depression	
Reproductive system and breast disorders	Uterine/vaginal bleeding including spotting, oligomenorrhea, amenorrhea, menstrual cycle prolonged	Ovarian cysts Dysmenorrhoea Breast tenderness Bleeding menstrual heavy	Parametritis Pelvic pain Salpingo-oophoritis Polymenorrhoea	

Cases of sepsis (including group A streptococcal sepsis) have been reported following insertions with other hormonal IUSs (see section 4.4).

The following adverse reactions have been reported in connection with the insertion or removal procedure of AVIBELA: pain, bleeding, and insertion-related vasovagal reaction with dizziness or syncope (see section 4.4). The procedure may also precipitate a seizure in patients with epilepsy.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse drug event (ADE) means any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction (ADR) means a response to a medicine which is noxious (harmful) and unintended, and which occurs at doses normally used in man.

Postmarketing Experience

Hypersensitivity, including rash urticarial and angioedema
Increased blood pressure
Device breakage

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The primary local mechanism by which levonorgestrel continuously released in the uterus provides contraception has not been conclusively demonstrated; however, it is largely accepted that the contraceptive mechanism of action of the AVIBELA is based mainly on hormonal effects producing the following changes:

- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Prevention of proliferation of the endometrium
- Suppression of ovulation in some women.

The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.

In heavy menstrual bleeding, prevention of proliferation of the endometrium is the probable mechanism of action of AVIBELA in reducing blood loss.

Clinical Efficacy

Contraception Trial
When placed according to the insertion instructions, AVIBELA offers contraceptive protection which does not appear to vary by parity, race or body mass index. Contraceptive efficacy of AVIBELA was investigated in a large clinical trial. The cumulative pregnancy rate calculated as the Pearl Index (PI) in women aged 16 to 35 years, inclusive, was 0.15 (95% CI: 0.02, 0.55) at the end of year 1 and 0.20 (95% CI: 0.09, 0.37) at the end of year 5.

In the clinical trial of AVIBELA evaluating contraception, during the first three to six months of 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. Amenorrhea develops in approximately 19% of AVIBELA users by the end of the first year of use, in 27% by the end of the second year of use, in 37% by the end of the third year of use, 37% by the end of the fourth year of use, and 42% by the end of the fifth year of use.

Following removal of AVIBELA, 487 of 48 (99.8%) of women evaluated in the contraception study experienced menses after removal of AVIBELA.

Heavy Menstrual Bleeding Trial
In the clinical trial evaluating women 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 women 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. Heavy menstrual bleeding caused by submucosal fibroids may respond less favourably. Reduced bleeding promotes an increase of blood haemoglobin in patients with heavy menstrual bleeding.

5.2 Pharmacokinetic properties

The initial *in vivo* release of 19.5 µg/day levonorgestrel from AVIBELA decreases to 17.0 µg/day during the first year and 9.8 µg/day during the fifth year. Levonorgestrel is delivered directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 113 ± 50 pg/mL after 5 years) resulting in only minor systemic effects.

The pharmacokinetics of levonorgestrel itself have been extensively investigated and reported in the literature. Levonorgestrel is extensively metabolized to a large number of inactive metabolites which are excreted in the urine and faeces. The elimination half-life of levonorgestrel has been estimated to be approximately 20 hours although there are marked differences in metabolic clearance rates among individuals resulting in some studies reporting half-life values ranging from 9 to 80 hours. Levonorgestrel in the plasma is extensively bound to circulating proteins (mainly sex hormone binding globulin [SHBG]).

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

Polydimethylsiloxane elastomer
Polydimethylsiloxane tubing
Polyethylene T-frame with 20-24% barium sulphate
Polypropylene thread
Copper phthalocyanine blue

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package. Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

AVIBELA IUS with the inserter device is packaged together with an inserter in a peelable pouch, and is available in a carton of one sterile unit.

AVIBELA is supplied sterile. AVIBELA 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.

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 pouch can be handled as household waste.

AVIBELA is not for resale or redistribution.

The name and address of holder of Product Licence

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