SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AVIBELA levonorgestrel intrauterine delivery system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sterile levonorgestrel-releasing intrauterine system contains 52 mg of levonorgestrel. The initial release of levonorgestrel is approximately 20 micrograms per day. This rate decreases progressively to approximately 8,6 micrograms/day after 6 years. The average *in vivo* release rate of levonorgestrel is approximately 14,3 micrograms/day over a period of 6 years.

Sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Intrauterine delivery system (IUD) consisting of a white reservoir covered with a membrane on the vertical stem of a T-frame; a double blue thread is attached to the eyelet on the T-frame; the vertical stem of the T-frame and the thread are placed in the inserter tube, which is graduated from 5 -12. The thread is located inside along the full length of the inserter and exits out the back end of the handle. The IUD and single-handed inserter are packaged in a thermoformed tray with a lid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

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

4.2 Posology and method of administration

Posology

One unit is inserted into the uterine cavity.

AVIBELA is effective for six years in the indications for contraception and heavy menstrual bleeding. Therefore, it should be removed after 6 years of use.

If the user wishes to continue using the same method, a new system can be inserted at the same 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 she is at risk of pregnancy if she has intercourse in the week prior to removal without use of a backup contraceptive method. 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.

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. AVIBELA can also be inserted immediately after a first trimester abortion. 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.

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 IUD	• insert AVIBELA on the same day the implant or IUD 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.

Special populations

Elderly

AVIBELA has not been studied in elderly women.

Hepatic impairment

AVIBELA is contraindicated in patients with liver tumour or acute or severe liver disease (see section 4.3). AVIBELA has not been studied in women with hepatic impairment.

Method of administration

Instructions for use and handling

AVIBELA is supplied in a tray, sealed with a peel-off lid and is inserted into the uterine cavity with the provided inserter (Figure 1b) by carefully following the insertion instructions. Do not use if the seal of the sterile package is broken or appears compromised. Use strict aseptic techniques throughout the insertion procedure [see section 4.4 – Pelvic infection]. AVIBELA is for single use only.

Figure 1a: Intrauterine contraceptive system (IUD)

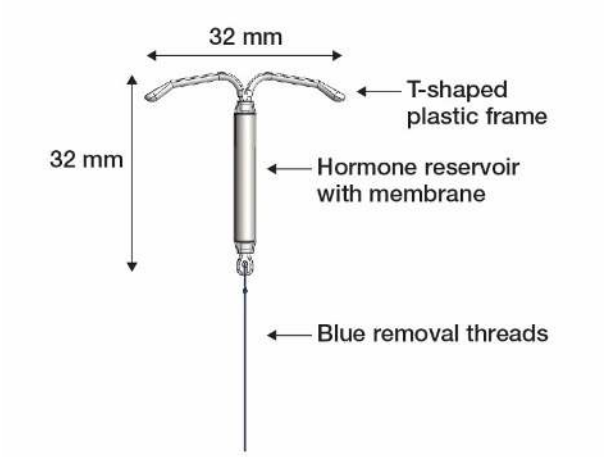
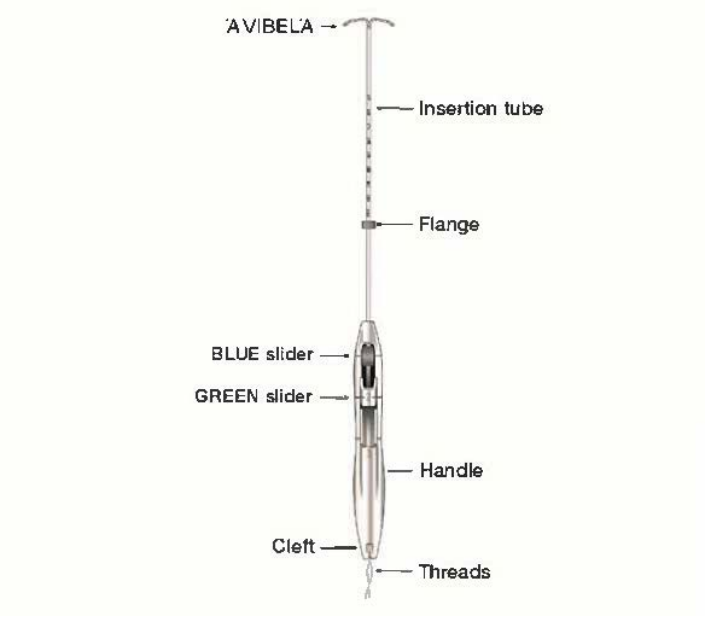


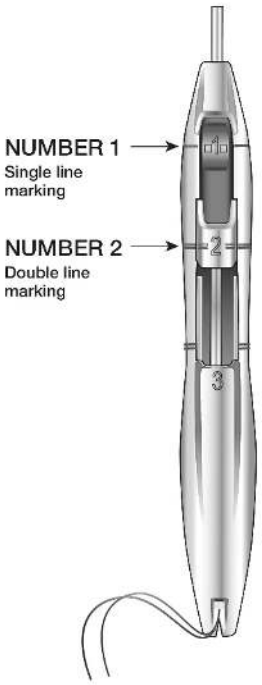
Figure 1b: IUD with Inserter



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

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

Figure 2: Inserter sliders



- The handle of the inserter contains a BLUE slider labelled with the number 1 and a GREEN slider labeled with the number 2 to assist with the insertion process.
- Moving the sliders achieves the positions required to complete the insertion process.

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 labelling 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 (STIs)
- check the expiration date on the box before opening it. Do not insert after the expiration date
- visually inspect the packaging 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 pouch
- do not open the packaging to insert AVIBELA if the cervix is unable to be properly visualised, 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 end of 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 IUD.

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 tray, sealed with a peel-off lid
- sterile, blunt-tipped scissors
- additional items that may be useful could include:
  - local anaesthesia, 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, maintain sterility during AVIBELA loading and insertion; do not touch AVIBELA, the inside of the sterile tray, or parts of any sterile instrument that will pierce tissue (e.g., a tenaculum on the cervix) or go into the uterine cavity. If, at any step, there is a need to touch a sterile surface, sterile gloves should be used.

Preparation for insertion

The overall insertion process is conducted in 5 steps.

Step 1 – Preparation of patient for insertion

- with the patient comfortably in lithotomy position, do a bimanual exam to establish the size, shape, and position of the uterus and to evaluate any signs of uterine infection
- gently insert a speculum to visualize the cervix
- thoroughly cleanse the cervix and vagina with antiseptic solution
- administer cervical anaesthetic, 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 packaging 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.

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

Insertion procedure

Step 2 – Opening the sterile AVIBELA packaging

- remove the sealed tray containing AVIBELA from the box
- inspect the sealed tray and do not use the product if the packaging, inserter or IUD is damaged
- lay the tray on a flat surface with the peel-off lid side up
- remove peel-off lid.

Step 3 – Loading AVIBELA into the inserter

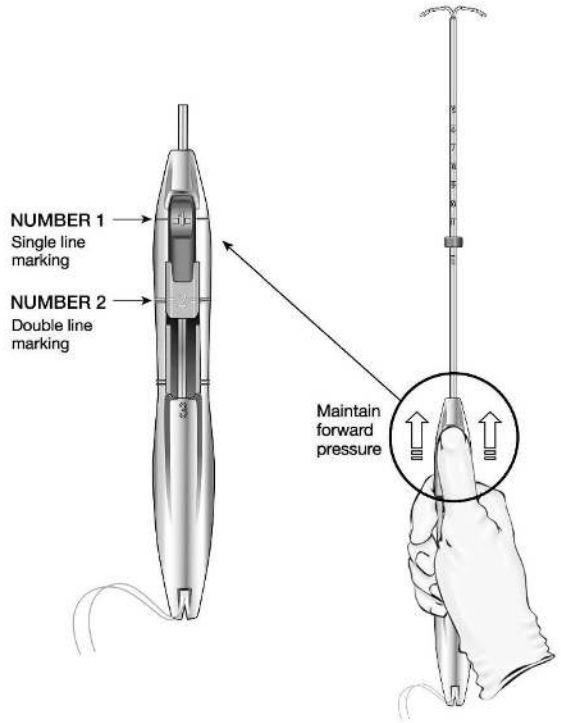
- to remove the inserter from the tray, grasp the handle below the sliders and twist gently (Figure 3)
    - NOTE: Do not attempt to remove the inserter by pulling on the tube.

Figure 3: Removing inserter from tray

- ensure both sliders (labelled 1 and 2) are **fully forward** (Figure 4):
    - the BLUE slider (labelled with the number 1) has a single line marking that will align with the handle's single line marking
    - the GREEN slider (labelled with the number 2) has a double line marking that will align with the handle's double line marking.

- grip the handle keeping your thumb or finger in the groove of the BLUE slider (over the numeral 1) and apply **forward pressure** while ensuring both sliders are **fully forward**

Figure 4: Sliders completely forward for loading AVIBELA



- load AVIBELA into the inserter:
    - ensure the arms of the IUD are horizontal (aligned to the horizontal plane of the handle and flange); adjust the rotation of the IUD as needed using the flat sterile surface of the tray
    - while maintaining **forward pressure** on the BLUE slider, gently pull the threads **straight** back to load AVIBELA into the insertion tube. Ensure even tension is applied to both threads when pulling
    - pull the threads upward or downward to lock the threads into the cleft

at the bottom end of the handle (Figure 5); you must **lock the threads** in the cleft to prevent the IUD from moving out of the top of the insertion tube. Once the threads are locked in the cleft, **stop holding the threads**

- after the IUD is loaded, continue to sustain **forward pressure** on the BLUE slider to maintain a hemispherical dome with the tips of the IUD.

- when correctly loaded, the IUD is completely within the insertion tube with the tips of the arms forming a hemispherical dome at the top of the tube (Figure 6)
- if the IUD is not correctly loaded, ***do not attempt insertion***
- to re-load AVIBELA:
  - pull the BLUE slider back with your thumb until the groove becomes aligned with the GREEN slider to release the IUD
  - manually pull the threads out of the cleft
  - return the BLUE slider to the forward position and repeat the loading steps.

Figure 5: Locking the threads in cleft

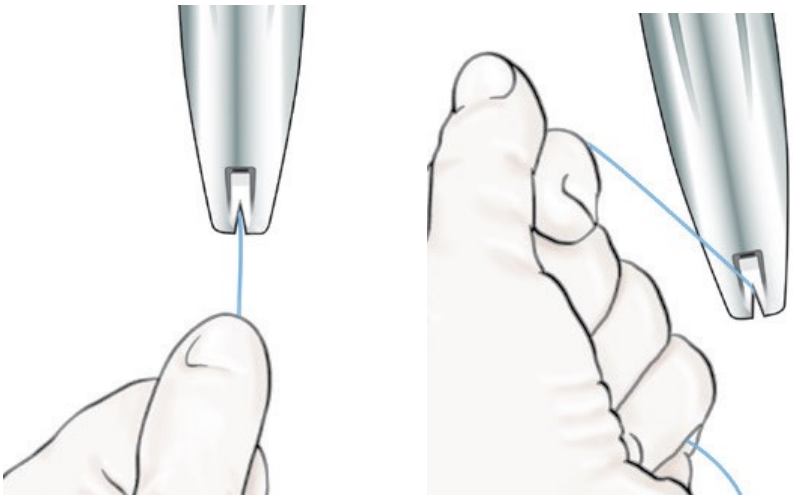


Figure 6: Close-up of hemispherical dome at tip of tube

- adjust the flange to the measured uterine depth based on sounding. To adjust, place the flat side of the flange in the tray notch (Figure 7) or against a sterile edge inside of the tray. Slide the insertion tube as necessary to move the flange to the correct measurement. Ensure the flat sides of the flange are in the same horizontal plane as the handle. If, at any step, there is a need to touch the flange or another sterile surface, sterile gloves should be used

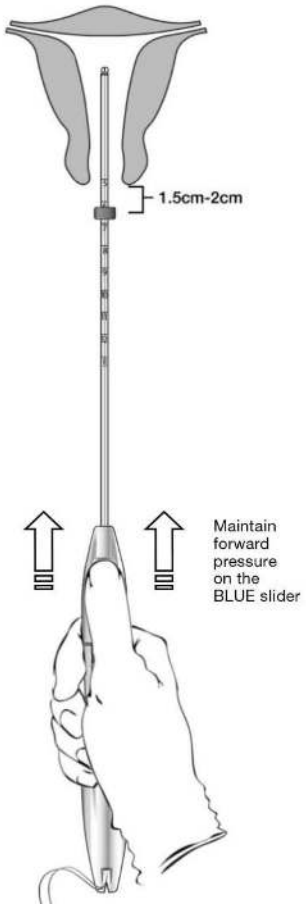
Figure 7: Adjusting the flange

- if an adjustment to the curvature of the insertion tube is required to accommodate the anatomical orientation of the uterus, you may bend or straighten the insertion tube, but do not touch above the flange unless using sterile gloves. When bending the tube, avoid sharp bends to prevent kinking
- once the flange has been properly positioned, avoid contact with flange against objects that can change its position (e.g. tray, speculum, tenaculum, etc.).

Step 4 – Inserting AVIBELA into the uterus

- apply gentle traction on the tenaculum and continue to apply **forward pressure** on the BLUE slider while inserting the loaded insertion tube through the cervical os. Advance the tube until the upper edge of the flange is 1,5-2 cm from the external cervical os (Figure 8). Maintain forward pressure on the BLUE slider throughout the insertion process.
    - DO NOT advance flange to the cervix at this time
    - DO NOT force the inserter. If necessary, dilate the cervical canal.

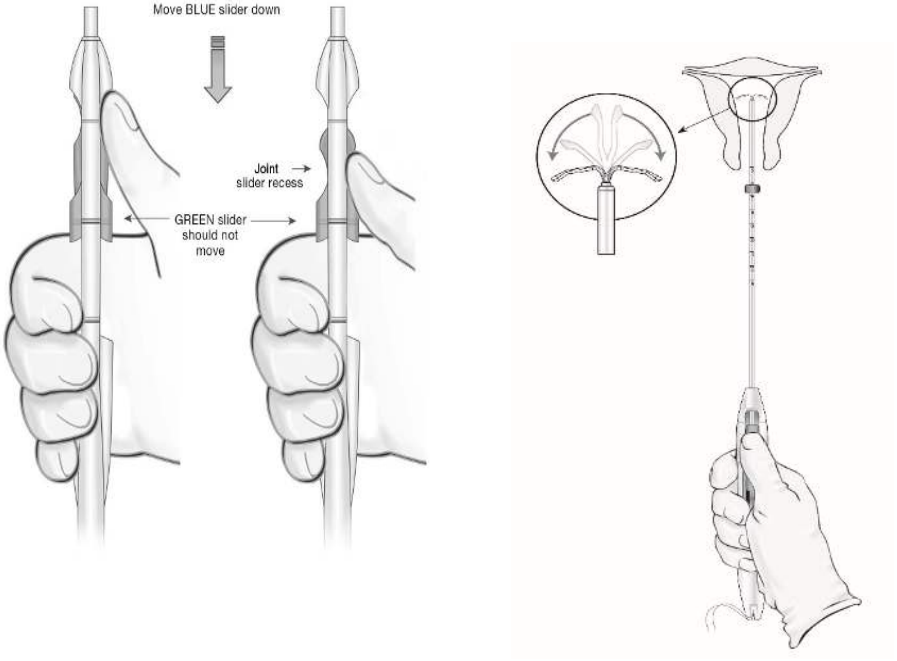
Figure 8: Advancing insertion tube until flange is 1,5 - 2 cm from the external cervix



- using your thumb or finger, gently slide only the BLUE slider back. You will feel slight resistance initially to move the BLUE slider out of its starting position. Continue to move the BLUE slider back until you feel slight resistance again as the BLUE and GREEN sliders will merge together to form a joint slider recess. Do not move the BLUE slider any more than is necessary to create the recess. Maintain the GREEN slider so that the double line markings on the slider and the insertion handle remain aligned (Figure 9). This will allow the IUD arms to

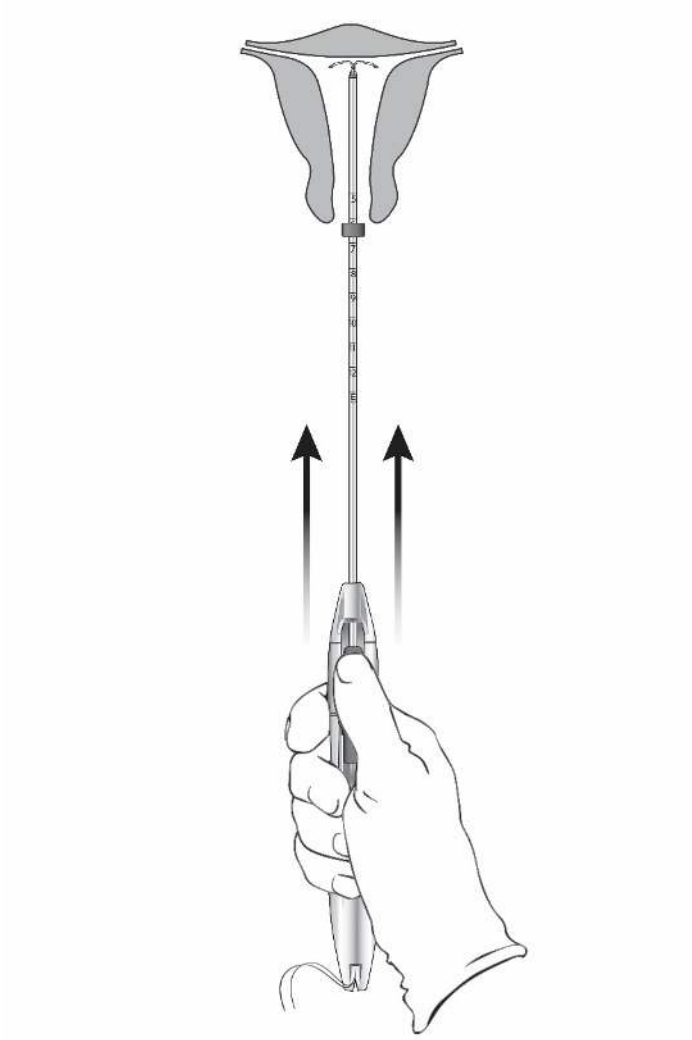
open in the lower uterine segment**.** Do not pull the sliders back any further as this could result in premature release of the IUD at the incorrect location

Figure 9: Releasing and Opening the Arms of the IUD



- wait 10 -15 seconds to allow for the arms of the IUD to fully open
- without moving the sliders, advance the inserter until the flange touches the cervix. If fundal resistance is encountered, do not continue to advance. AVIBELA is now in the fundal position (Figure 10)
- note: Fundal position is important to prevent expulsions.

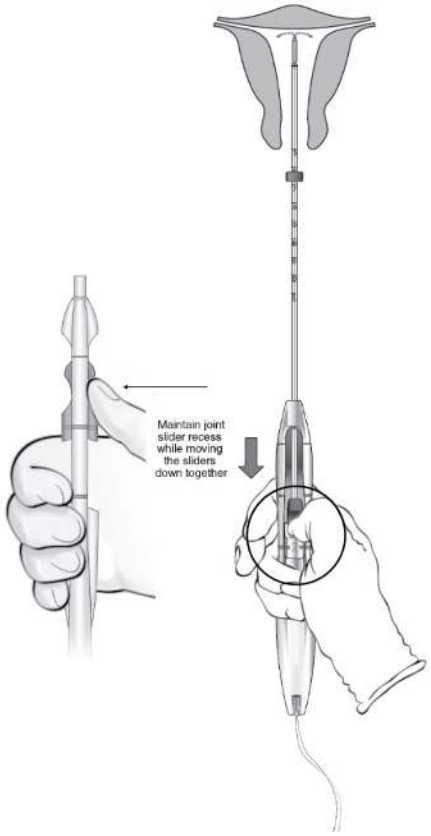
Figure 10: Move AVIBELA into the fundal position



Step 5 – Releasing AVIBELA and procedure completion

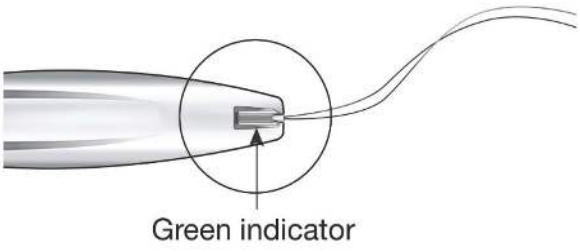
While holding the inserter steady and maintaining its position relative to the cervix, move **both** sliders (BLUE and GREEN) together while maintaining the joint slider recess down toward the number 3 on the handle (Figure 11) until a click is heard and the GREEN indicator at the bottom of the handle is visible, signifying deployment (Figure 12).

Figure 11: Releasing AVIBELA from the inserter tube



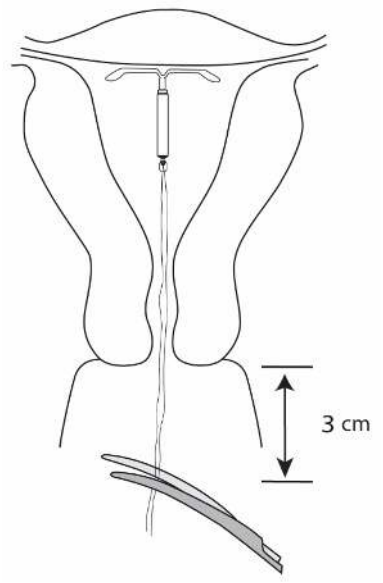
- look at the cleft to ensure the threads were properly released (Figure 12); if not released or if a click is not heard, grasp the threads and gently pull the threads out of the cleft

Figure 12: Green indicator visible and threads released from cleft



- withdraw the inserter from the uterus
- use blunt-tipped sharp scissors to cut the IUD threads perpendicular to the thread length, leaving about 3 cm outside of the cervix (Figure 13). *Note: Do not cut threads at an angle as this may leave sharp ends*
- do not apply tension or pull on the threads when cutting to prevent displacing the IUD.

Figure 13: 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 IUD is not in the correct position:

- check insertion with an ultrasound or other appropriate radiologic test
- if incorrect insertion is suspected, remove AVIBELA. Do not reinsert the same AVIBELA IUD after removal.

Difficult insertion

- if insertion is difficult because the uterus cannot be appropriately instrumented, the following measures can be considered:
    - use of cervical anaesthesia 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

- counsel the patient on what to expect following AVIBELA insertion. Review the signs and symptoms of expulsion
- prescribe analgesics, if indicated.

Patient follow-up

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

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 she is at risk of pregnancy if she has intercourse in the week prior to removal without use of a backup contraceptive method
- AVIBELA should be removed after 6 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 anaesthetic, 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 patients with a predisposition to these conditions
- after removal of AVIBELA, examine the system to ensure that it is intact.

Removal instructions

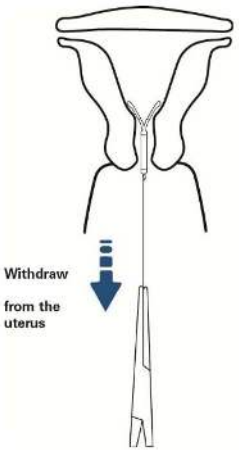
- with the patient comfortably in lithotomy position, place a speculum and visualise the cervix
- when the threads of AVIBELA are visible:
    - remove the IUD by applying traction on the threads with forceps (Figure 14)
    - the arms of the device will fold upward as it is withdrawn from the uterus
    - if the IUD cannot be removed with traction on the threads, perform an ultrasound examination to confirm location of the IUD, including assessment for partial or total perforation. If the IUD is in the uterus, use a long, narrow forceps to grasp

AVIBELA. Consider use of a tenaculum, cervical anaesthesia, 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 IUD by ultrasound examination
  - if the IUD 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 IUD is not in the uterine cavity, consider an abdominal x-ray or CT scan to evaluate if the IUD is in the abdominal cavity. Consider laparoscopic evaluation for removal, as clinically indicated
  - after removal, examine the system to ensure it is intact.

Figure 14: 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

AVIBELA is contraindicated in the following conditions:

- hypersensitivity to levonorgestrel or to any of the ingredients of AVIBELA listed in section 6.1
- known or suspected pregnancy
- lower genital tract infection
- current or recurrent pelvic inflammatory disease or conditions associated with increased risk of pelvic infections, including gonorrhoea and other sexually transmitted infections
- postpartum endometritis
- infected abortion during the past three months

- acute cervicitis or vaginitis
- cervical dysplasia or neoplasm
- uterine or cervical malignancy
- progestogen-dependent tumours, known or suspected breast cancer or other hormone-sensitive cancer, now or in the past (see section 4.4)
- undiagnosed abnormal uterine bleeding
- congenital or acquired uterine anomaly including fibroids which would interfere with insertion and/or retention of the intrauterine system i.e. if they distort the uterine cavity
- acute or severe liver disease or liver tumour
- a previously inserted IUD that has not been removed
- conditions associated with increased susceptibility to infections
- acute malignancies affecting the blood or leukaemia except when in remission recent trophoblastic disease while human chorionic gonadotropin (hCG) levels remain elevated.

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 IUD for contraception and/or heavy menstrual bleeding.

Before insertion, the woman must be informed of the benefits and risks of AVIBELA. Exclude underlying endometrial pathology (e.g., polyps or cancer) prior

to the insertion of AVIBELA in women 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 women with uterine bleeding of unknown aetiology. Exclude underlying congenital or acquired uterine anomalies, including fibroids, that distort the uterine cavity and would be incompatible with correct IUD placement.

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

Assess whether the woman is at increased risk of infection (e.g. leukaemia, acquired immune deficiency syndrome [AIDS], intravenous [IV] substance abuse), or has a history of pelvic inflammatory disease (PID) unless there has been a subsequent intrauterine pregnancy. AVIBELA does not protect against human immunodeficiency virus (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 IUD if any of them arise during use: migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischaemia
- exceptionally severe or frequent headache
- marked increase of blood pressure
- severe arterial disease such as stroke or myocardial infarction
- coagulopathy or use of anticoagulants.

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

- uterine or cervical malignancy

- jaundice.

Vascular effects

In women using progestogen-only pills some recent epidemiological studies indicated that there may be a slightly increased risk of venous thromboembolism, but the results were statistically not significant. However, appropriate diagnostic and therapeutic measures should be undertaken immediately if there are symptoms or signs of thrombosis. Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; “acute” abdomen. Symptoms or signs indicating retinal thrombosis are: unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions.

There is no consensus about the possible role of progestogens in patients with varicose veins and superficial thrombophlebitis in the causation of venous thromboembolism.

Cardiac effects

AVIBELA may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis. Antibiotic prophylaxis should be administered to these women when inserting or removing the intrauterine

system.

Syncope or bradycardia may occur in some women during insertion or removal of an intrauterine system. In the event of early signs of a vasovagal attack, insertion may need to be abandoned or the system removed.

Blood glucose effects

Low-dose levonorgestrel may affect glucose tolerance, and the blood glucose concentration should be monitored in diabetic users of AVIBELA.

Bleeding irregularities

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

In the AVIBELA contraception clinical trial, amenorrhea developed in approximately 19 % of AVIBELA users by the end of the first year of use, 27 % by the end of the second year of use, 37 % by the end of the third year of use, 37 % by the end of the fourth year of use, 40 % by the end of the fifth year of use, and 40 % by the end of the sixth year of use. In the trial, 2,3 % of AVIBELA subjects discontinued due to bleeding complaints.

In the AVIBELA contraception clinical trial, 537 of 538 (99,8%) women evaluated experienced menses after AVIBELA removal. This excludes fourteen women who became pregnant (9 women), had a hysterectomy (3 women), were considered menopausal after removal (1 woman), or had ovulatory dysfunction (1 woman).

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 amenorrhoeic women unless indicated, for example, by other signs of pregnancy or by pelvic pain.

Pelvic infection

Insertion of AVIBELA is contraindicated in the presence of known or suspected pelvic inflammatory disease (PID) or endometritis or a history of PID unless there has been a subsequent intrauterine pregnancy (see section 4.4). It is contraindicated in patients 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. IUDs 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.

In the contraception clinical trial with AVIBELA, pelvic infection was diagnosed in 0,8 % of women. Pelvic infection was diagnosed as PID in 0,5 % of women and as endometritis in 0,3 % of women. Infections occurred following variable duration-of-use. One woman diagnosed with PID and two women 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 IUD removal. Women who use AVIBELA should be counselled 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.

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 women who have multiple sexual partners, and for women whose sexual partner(s) have multiple sexual partners. Women who have had PID or endometritis are at increased risk for a recurrence or re-infection. Other risk factors for these infections include leukaemia, acquired immune deficiency syndrome (AIDS), and illicit intravenous substance use.

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

Following a diagnosis of PID or endometritis, or suspected PID or endometritis, perform appropriate testing for sexually transmitted infection and initiate antibiotic therapy promptly. AVIBELA does not need to be removed immediately if the woman needs ongoing contraception. In the AVIBELA contraception clinical trial, 12 of the 14 women who developed PID or endometritis were successfully treated without removal of AVIBELA (one of the 14 women developed PID 30 days after removal). Reassess the woman in 48-72 hours. If no clinical improvement occurs, continue antibiotics and consider removal of AVIBELA. If the woman wants to discontinue use, remove AVIBELA after antibiotics have been started to avoid the potential risk for bacterial spread resulting from the removal procedure.

Actinomycosis has been associated with IUD use. Symptomatic women with known actinomycosis infection should have AVIBELA removed and receive antibiotics. *Actinomycetes* can be found in the genital tract cultures in healthy women without IUDs. The significance of *actinomyces*-like organisms on a Pap test in an asymptomatic IUD 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.

Expulsion

Partial or complete expulsion of AVIBELA may occur, resulting in the loss of contraceptive protection. In the contraception clinical trial with AVIBELA, an overall expulsion rate of 4,0 % over 6 years was reported, with a rate of 2,2 % in nulliparous women and 6,2 % in parous women. The majority (73,5 %) occur in the

first 12 months, with 25,0 % occurring in the first three months and 44,1 % in the first six months, cumulatively. 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 of 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 may be increased when the uterus is not completely involuted at the time of insertion. Delay AVIBELA insertion a minimum of 4 weeks or until uterine involution is complete following a delivery or a second trimester abortion.

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 IUD 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 IUD the incidence of uterine perforation was reported as 6,3 per 1000 insertions for lactating women, compared to 1,0 per 1000 insertions for non-lactating women.

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.

Ectopic pregnancy

The absolute risk of ectopic pregnancy in users of levonorgestrel IUD is low. However, when a woman becomes pregnant with AVIBELA *in situ*, the relative likelihood of ectopic pregnancy is increased. Approximately half of pregnancies that occur with AVIBELA in place are likely to be ectopic. 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. If an ectopic pregnancy is confirmed, AVIBELA should be removed.

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 0,12 per 100 women-years. 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.

Women 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).

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 the cervical canal 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 IUD.

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.

Ovarian cysts/enlarged ovarian follicles/delayed follicular atresia

Since the contraceptive effect of AVIBELA 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 IUDs 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. Symptomatic ovarian cysts occurred in 4,5 % of subjects using AVIBELA over the

course of 6 years, 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 post-marketing experience with another LNG-releasing IUD. Observational studies have not provided consistent evidence of an increased risk of breast cancer with use of an LNG-releasing IUD.

Other

AVIBELA is not the method of first choice for postmenopausal women with advanced uterine atrophy.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst using AVIBELA.

4.5 Interaction with other medicines and other forms of interaction

The effect of hormonal contraceptives may be impaired by medicines which induce liver enzymes which may result in increased clearance of sex hormones.

Substances increasing the clearance of levonorgestrel include primidone, barbiturates, phenytoin, carbamazepine, rifampicin and oxcarbazepine, topiramate, felbamate, griseofulvin, rifabutin, nevirapine, efavirenz and products containing St. John's wort. The influence of these medicines on the contraceptive efficacy of AVIBELA has not been studied but is not believed to be of major importance due to the mainly local mechanisms of contraceptive action. No drug-drug interaction studies have been conducted with AVIBELA.

The 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). If the woman becomes pregnant with AVIBELA *in situ* (see section 5), advise a woman of the increased risks for pregnancy complications, including miscarriage, premature labour, 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. Prenatal care should include counselling about these risks and that she should report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of

fluid, or any other symptom that suggests complications of the pregnancy.

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

Breastfeeding

Levonorgestrel has been identified in the breast milk of lactating women using IUDs. The quantity and quality of breast milk are however not affected. About 0,1 % of the levonorgestrel dose passes into the breast milk in nursing mothers.

Fertility

The use of AVIBELA does not alter the course of future fertility. Upon removal of the AVIBELA, women usually return to their normal fertility (see section 4.4). In the clinical trial of women using AVIBELA for contraception, 99,8 % of women had a rapid return of menses after IUD removal. This excludes fourteen women who became pregnant (9 women), had a hysterectomy (3 women), were considered menopausal after removal (1 woman), or had ovulatory dysfunction (1 woman). Of 191 women who desired pregnancy after study discontinuation, 79 % conceived within 6 months after removal of AVIBELA, and 85 % conceived within 12 months after removal of AVIBELA.

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

a. Summary of the safety profile

Side-effects are more common during the first months after the insertion and subside during prolonged use. Very common undesirable effects (occurring in more than 10 % of users) include vaginal bacterial infections, vulvovaginal mycotic infections, nausea or vomiting, and acne.

b. Tabulated list of adverse effects

The table below reports adverse reactions assessed as related to 52 mg levonorgestrel intrauterine delivery system by investigator, by MedDRA system organ class (MedDRA SOCs).

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	
Psychiatric disorders		Anxiety, depression, mood changes, insomnia, libido decreased	Exacerbation of bipolar disorder	Suicidality
Nervous system disorders		Headache, migraine, presyncope, dizziness, syncope		
Gastrointestinal disorders		Abdominal pain/discomfort, abdominal distension,		

		constipation, dyspepsia, diarrhoea, vomiting		
Skin and subcutaneous tissue disorders	Acne	Alopecia		Greasy hair, hirsuitism
Musculoskeletal and connective tissue disorders		Back pain, pain in extremity		
Pregnancy, puerperium and perinatal conditions			Ectopic pregnancy	
Reproductive system and breast disorders	Uterine/ vaginal bleeding including spotting, oligomenorrhea, amenorrhea, menstrual cycle prolonged	Ovarian cysts, dysmenorrhoea, breast tenderness/pain, pelvic discomfort/pain, uterine spasm, vaginal discharge, vulvovaginal dryness/ discomfort, ovarian cyst, menorrhagia, coital bleeding, vaginal odour, vaginal haemorrhage, bleeding menstrual heavy	Parametritis, pelvic pain, salpingo-oophoritis, polymenorrhoea	
General disorders and Administration site conditions			Oedema abdomen, peripheral oedema	
Investigations		Weight increase, ultrasound ovary abnormal		
Injury, poisoning and procedural complications	Procedural bleeding	Intrauterine contraceptive device expelled, intrauterine contraceptive device migration, procedural pain	Perforation	

Cases of sepsis (including group A streptococcal sepsis) have been reported

following insertions with hormonal IUDs (see section 4.4).

a. Description of selected adverse reactions

Changes in menstrual bleeding

The most common adverse effect of IUDs, like AVIBELA, is a change in menstrual bleeding patterns. The changes may include spotting, shorter or longer menstrual periods, irregular bleeding, oligomenorrhoea, amenorrhoea, heavy flow, back pain and dysmenorrhoea. The average number of spotting days decreased gradually during the first six months of use.

Combination with estrogen replacement therapy

When used in combination with estrogen replacement therapy, perimenopausal users of AVIBELA may experience spotting and irregular bleeding during the first months of the treatment. A non-bleeding pattern gradually develops in most women during the first year.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Not applicable

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 32.9 Other – Intrauterine devices

ATC code: G02BA03

Pharmacological classification: Plastic IUD with progestogen

Pharmacological action

Levonorgestrel is a progestogen with anti-estrogenic activity. The contraceptive and therapeutic effects of levonorgestrel are mainly based on local progestogenic effects in the uterine cavity. Levonorgestrel has an antiproliferative effect on the endometrium and it inhibits the endometrial synthesis of estrogen receptors, making the endometrium insensitive to the circulating estradiol. Morphological changes of the endometrium and a weak local foreign body reaction are observed. Thickening of the cervical mucous prevents passage of the sperm through the cervical canal, and the changes in the uterus and the ovarian tubes inhibit sperm mobility and function, preventing fertilisation. Ovulation is inhibited in some women.

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 pregnancy rate calculated as the Pearl Index (PI) in women aged 16 - 35 years, inclusive, was the primary efficacy endpoint used to assess contraceptive reliability. The PI was calculated based on 28-day equivalent exposure cycles; evaluable cycles excluded those in which back-up contraception was used unless a pregnancy occurred in that cycle. The Year 1 PI was based on two pregnancies and the cumulative 6-year pregnancy rate was calculated by the life table method, based on a total of nine pregnancies that occurred after the onset of treatment and within 7 days after AVIBELA removal or expulsion. The cumulative pregnancy rate was 0,14 (95 % CI: 0,04; 0,57) at the end of Year 1 and the Life Table pregnancy rate was 0,87 (95 % CI: 0,44; 1,70) at the end of Year 6.

In the clinical trial of AVIBELA evaluating contraception, during the first 3 - 6 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, 27 % by the end of the second year of use, 37 % by the end of the third year of use, 37 % by the end of the fourth year of use, 40 % by the end of the fifth year of use, and 40 % by the end of the sixth year of use.

Following removal of AVIBELA, 99,87 % of women evaluated in the contraception study experience menses within 3 months. Of 191 women who desired pregnancy after study discontinuation, 79 % conceived within 6 months after removal of AVIBELA, and 85 % conceived within 12 months 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 - 6 months of treatment. The volume of menstrual bleeding was decreased by 88 % in women with heavy menstrual bleeding by the end of 3 months of use and 82 % reduction was sustained for the duration of the study (12 months), with 15 % becoming amenorrhoeic 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

Absorption:

The pharmacokinetics of levonorgestrel itself have been extensively studied and reported in the literature. Orally administered levonorgestrel is rapidly and completely absorbed and the absolute bioavailability is about 90 %.

Distribution:

The initial in vivo release rate is 20,1 micrograms/day and decreases to 17,5

micrograms/day at 1 year, 15,2 micrograms/day at 2 years, 13,2 micrograms/day at 3 years, 11,4 micrograms/day at 4 years, 9,9 micrograms/day at 5 years, and 8,6 micrograms/day at 6 years. Levonorgestrel is delivered directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 93 ± 45 pg/mL after 6 years) resulting in only minor systemic effects.

Levonorgestrel is bound to serum albumin and to sex hormone-binding globulin (SHBG). The relative distribution (free, albumin-bound, SHBG-bound) depends on the SHBG concentration in the serum. Only about 2,5 % of the total serum drug levels are present as free steroid, but 47,5 % and 50 % are bound to SHBG and albumin, respectively. For levonorgestrel, a mean volume of distribution of approximately 137 litres and a metabolic clearance rate from serum of about 5,7 L/h were reported.

Biotransformation:

A terminal half-life of levonorgestrel in serum in the range of about 14 - 20 hours can be observed after single dose administration.

Elimination:

Levonorgestrel is excreted as metabolites at about equal proportions with urine and faeces. The metabolites have only weak or no pharmacological activity.
About 0,1% of the maternal dose of levonorgestrel can be transferred via milk to the infant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Reservoir of the IUD

Silicone base

Tetra-n-propyl silicate

Stannous octoate

T-frame

Low density polyethylene (LDPE)

Barium sulphate

Polydimethylsiloxane (PDMS) membrane

Polypropylene thread dyed with Phthalocyaninato (2-) copper

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store at or below 30 °C

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

6.5 Nature and contents of container

The AVIBELA device is supplied partially preloaded within the single-handed inserter (a

single-use, disposable, sterile insertion system) and packaged in a clear plastic tray with lid. AVIBELA is available in a carton of one sterile unit.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

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 tray can be handled as household waste.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

56/32.9/1048

9. DATE OF FIRST AUTHORISATION

18 March 2025