Essure[®] Device, Clinical Data, and Insertion Procedure

Please see Important Safety Information, including Boxed Warning, on slides 3-8 of this presentation. For important information about Essure[®], please see the accompanying <u>Instructions for Use</u>, including Boxed Warning.

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Indication and Important Safety Information

Indication

• Essure[®] is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

Important Safety Information

WARNING: Some patients implanted with the Essure System for Permanent Birth Control have experienced and/or reported adverse events, including perforation of the uterus and/or fallopian tubes, identification of inserts in the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions. If the device needs to be removed to address such an adverse event, a surgical procedure will be required. This information should be shared with patients considering sterilization with the Essure System for Permanent Birth Control during discussion of the benefits and risks of the device.

IMPORTANT:

- **Caution**: Federal law restricts this device to sale by or on the order of a physician. Device to be used only by physicians who are knowledgeable hysteroscopists; have read and understood the Instructions for Use and Physician Training Manual; and have successfully completed the Essure training program, including preceptoring in placement until competency is established, typically 5 cases.
- The sale and distribution of this device are restricted to users and/or user facilities that provide information to patients about the risks and benefits of this device in the form and manner specified in the approved labeling provided by Bayer.

³

Contraindications

 Essure is contraindicated in patients who are uncertain about ending fertility, can have only one insert placed (including contralateral proximal tubal occlusion or suspected unicornuate uterus), have a known abnormal uterine cavity that makes visualization of the tubal ostia impossible, and/or abnormal tubal anatomy or previous tubal ligation (including failed ligation), are pregnant or suspect pregnancy, delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure, have an active upper or lower genital tract infection, have unexplained vaginal bleeding, have a gynecological malignancy, or have a known allergy to contrast media.

General Warnings

- The Essure procedure should be considered irreversible.
- Pain (acute or persistent) of varying intensity and length of time may occur following Essure placement. This is also more likely to occur in individuals with a history of pain. If device removal is indicated, this will require surgery.

General Warnings (cont'd)

- Patients with known hypersensitivity to nickel, titanium, platinum, stainless steel, and PET (polyethylene terephthalate) fiber or any of the components of the Essure system may experience an allergic reaction to the insert. In addition, some patients may develop an allergy to nickel or other components of the insert following placement. Symptoms reported for this device that may be associated with an allergic reaction include hives, urticaria, rash, angioedema, facial edema and pruritus. Patients should be counseled on the materials contained in the insert prior to the Essure procedure. Currently there is no test that reliably predicts who may develop a hypersensitivity reaction to the materials contained in the insert.
- Patients on immunosuppressive therapy may experience delay or failure of the necessary tissue ingrowth for tubal occlusion. For these patients, physicians must use the modified HSG as the Essure Confirmation Test. Transvaginal ultrasound (TVU) should not be used as the Essure Confirmation Test, as TVU cannot confirm tubal occlusion.

Important Safety Information (cont'd)

Pregnancy Risk

- Pregnancies, including ectopic pregnancies, have been reported among women who have undergone the Essure procedure.
- The patient must use alternative contraception until a satisfactory Essure Confirmation Test is documented. If the Essure inserts are not properly placed or are not in a satisfactory location, then the patient should be advised to not rely on Essure and to use alternative contraception.
- Counsel the patient on the need for the Essure Confirmation Test, the options for the confirmation test including their risks and benefits, and the possibility that the Essure Confirmation Test may be unsatisfactory.
- Effectiveness rates for the Essure procedure are based on patients who had bilateral placement and a satisfactory Essure Confirmation Test.

Procedure Warnings

- Never attempt to advance Essure insert(s) against excessive resistance. If a perforation
 occurs or is suspected, discontinue procedure and monitor the patient for signs and
 symptoms of possible complications related to perforation which may include unusual
 post-operative pain.
- To reduce the risk of hypervolemia, terminate procedure if distension fluid deficit exceeds 1500cc or total hysteroscopic procedure time exceeds 20 minutes. Excess fluid deficit may signal uterine or tubal perforation. If noted, discontinue procedure and evaluate patient for possible perforation.
- Do not attempt hysteroscopic Essure insert removal during the placement procedure unless 18 or more trailing coils are seen inside the uterine cavity due to risk of a fractured insert, fallopian tube perforation, or other injury.
- DO NOT perform the Essure procedure concomitantly with endometrial ablation.

Important Safety Information (cont'd)

MRI Information

 The Essure insert was determined to be MR-conditional according to the terminology specified in the American Society for Testing and Materials (ASTM) International, Designation: F2503-05.

Adverse Events

• The most common (≥10%) adverse events resulting from the placement procedure were cramping, pain, and nausea/vomiting. The most common adverse events (≥3%) in the first year of reliance were back pain, abdominal pain, and dyspareunia.

This product does not protect against HIV infection or other sexually transmitted diseases.

Prescription Only

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Essure[®] Product Overview

Essure Clinical Development Program

- The concept of using the transcervical route to achieve permanent sterilization was first described more than 150 years ago¹
- In 2002, the FDA approved Essure[®] as the first hysteroscopic device for use in women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes²

1. Abbott J. Curr Opin Obstet Gynecol. 2007;19(4):325-330.

^{2.} US Food and Drug Administration. Premarket Approval of Essure. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P020014. Accessed October 20, 2016.

The Essure[®] Insert Design



- Each Essure[®] insert includes:
 - A nitinol (nickel-titanium alloy) outer coil
 - A stainless steel inner coil wrapped with polyethylene terephthalate (PET) fibers
 - 2 platinum marker bands
 - Silver-tin solder
- Inserts are visible by x-ray, ultrasound, and MRI



Essure [Instructions for Use] ..

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The Essure[®] Insert Design (cont'd)

 In the wound-down configuration (attached to the delivery system), an Essure[®] insert measures approximately 4 cm in length and 0.8 mm in diameter



• When released (detached from the delivery system), the outer coil expands up to 2.0 mm in diameter, conforming itself to the varied diameters and shapes of the fallopian tube



These images are not to scale.

Essure [Instructions for Use].

Essure[®]: Insert Placement

- Under hysteroscopic visualization, the Essure[®] inserts are delivered by the physician to the proximal section of the fallopian tube lumen using the delivery system
- Ideal placement:
 - Insert spans serosal uterotubal junction (SUTJ) as viewed on TVU, OR



- Insert spans the uterotubal junction (UTJ) as visualized in on modified HSG
- In this location, the insert is:
 - Distal enough to avoid expulsion
 - Proximal enough to visualize trailing coils in the uterine cavity

Essure [Instructions for Use].

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Essure®: Mechanism of Action

Dynamic anchoring

- The insert is a dynamic and flexible springlike device
- The outer coil expands upon deployment, conforming to and pushing against the fallopian tube wall, acutely anchoring the insert in the lumen of the fallopian tube

Tubal occlusion and tissue in-growth



- Tubal occlusion is attributed to the space-filling design of the device and benign tissue response elicited by PET fibers
- PET fibers cause tissue in-growth into and around insert, facilitating insert retention, and resulting in tubal occlusion and contraception

Essure [Instructions for Use].

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Tissue Response to PET Fibers

Local immediate inflammatory response¹

• Characterized by macrophages, fibroblasts, foreign body giant cells, and plasma cells

Moderate foreign body inflammatory reaction^{1,2}

- Elicited by PET fibers
- Peaks between 2 and 3 weeks
- Resolution of the inflammatory response during the subsequent 10 weeks



Tissue reaction to Essure® after 13 weeks

- Extensive fibrosis results
 - Occluding tubes
 - Anchoring insert



Normal tubal architecture distal to insert

- 1. Valle RF, Carignan CS, Wright TC; STOP Prehysterectomy Investigation Group. Fertil Steril. 2001;76(5):974-980.
- 2. Perez-Medina T, Font EC. Diagnostic and Operative Hysteroscopy. 2nd ed. New Delhi, India: Jaypee Brothers Medical Publishers; 2011.
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Essure[®] Clinical Trials

Essure[®] Clinical Development Overview

- 2 clinical trials were conducted to demonstrate the safety and effectiveness of the Essure[®] system in providing permanent contraception prior to marketing¹
 - Phase II trial
 - Pivotal trial
 - Both trials used the modified HSG only as the Essure Confirmation Test^{2,3}
- A third trial (ESSTVU) was conducted to evaluate the effectiveness of the Essure procedure when using the TVU/HSG Confirmation Test Algorithm¹

1. Essure [Instructions for Use].

- 2. Kerin JF, Cooper JM, Price T, et al. *Hum Reprod*. 2003;18(6):1223-1230.
- 3. Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Obstet Gynecol. 2003;102(1):59-67.

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Reliance Rate: Definitions from Phase II Trial and Pivotal Trial

When a modified hysterosalpingogram is used as the confirmation test

Reliance^{1,2}

 Ability to discontinue alternative birth control and rely on Essure[®] for birth control after 3-month Essure Confirmation Test verified proper insert location and bilateral tubal occlusion

Reliance rate in women with successful bilateral placement after first for second attempt^{1,2}

• Number of women who were able to rely on Essure[®] for birth control divided by the number of women with bilateral insert placement

ITT reliance rate²

- Reliance rate among ALL enrolled women, including those in whom placement was unsuccessful, who had unilateral placement, and those in whom placement was not attempted
- 1. Kerin JF, Cooper JM, Price T, et al. *Hum Reprod*. 2003;18(6):1223-1230.
- 2. Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Obstet Gynecol. 2003;102(1):59-67

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Clinical Trial Summary: Phase II Trial and Pivotal Trial

Overview	Demographics	Bilateral placement rates	Reliance rates
Phase II trial¹ Prospective, multi- center, single-arm, nonrandomized,	 Phase II trial² N=269 Placement attempted= 227 	 Phase II trial² Placement rate among attempts: 200/227 (88.1%) 	 Phase II trial² Bilateral placement reliance rate: 194/200 (97.0%)
international study	• Mean age: 35 years	 Pivotal trial³ Placement rate among 	Pivotal trial ³
Pivotal trial¹ Prospective, multi- center, single-arm, nonrandomized, international study using the CREST study as a qualitative benchmark	 Pivotal trial³ N=518 Placement attempted= 507 Mean age: 32 years Combined¹ Mean gravidity: 2.91 (0-11) Mean parity: 2.23 (0-6) Mean BMI: 27 kg/m² (16-57) 	attempts: 464/507 (91.5%)	• Bilateral placement reliance rate: 449/464 (96.8%)

- 1. Essure [Instructions for Use].
- 2. Kerin JF, Cooper JM, Price T, et al. Hum Reprod. 2003;18(6):1223-1230.
- 3. Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Obstet Gynecol. 2003;102(1):59-67.

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Clinical Trial Summary: ESSTVU

Overview	Demographics	Bilateral placement rates	Reliance rates
Prospective, multi- center, single-arm, nonrandomized international study to evaluate the effectiveness of Essure [®] when the TVU/HSG Confirmation Test algorithm is used for confirmation testing	 N=620 enrolled Procedure initiated= 597 Placement attempted= 594 Mean age: 34 years Mean BMI: 27.5 kg/m² 	 Bilateral placement rate after first or second attempt: 582/597 (97%)* 	 Reliance rate in women who had procedure initiated: 547[†]/597 (92%) Reliance rate in women with successful bilateral placement after first or second attempt: 547[†]/582 (94%)

*Excludes 15/597 subjects with no insert placement attempt 3/597(0.5%) and nonbilateral placement after 1 or 2 procedures 12/597 (2.0%).

[†]Excludes 50/597 subjects who were unable to rely for the following reasons: No insert placement attempt 3/597 (0.5%), nonbilateral placement after 1 or 2 procedure 12/597 (2.0%), incomplete or no confirmation testing (28/597; 4.7%); unsatisfactory device location/occlusion identified at confirmation testing (perforation, expulsion, distal placement, proximal placement) (7/597; 1.2%).

Essure [Instructions for Use].

Summary of Insert Reliance Rates

Outcome	Number	Percentage
Phase II & Pivotal trials bilateral* reliance rates [†] Among women with bilateral placement	643/664	97%
ESSTVU trial bilateral* reliance rate	547/582	94%
ESSTVU trial intent-to-treat reliance rate [‡]	547/597	92%

*The reliance rate is the number of women who relied on Essure[®] for contraception divided by the number of women with bilateral insert placement. †In the Phase II trial, the following adverse events prevented reliance: perforation (7/206; 3.4%, including 1 patient who relied for 31 months before laparotomy and cornual resection due to pain, the other 6 never replied); expulsion (1/206; 0.5%); unsatisfactory insert location (1/206; 0.5%); Initial tubal patency (7/200; 3.5%) was found at the 3-month Essure Confirmation Test using a modified HSG; however, all had tubal occlusion at a 6-month repeat Essure Confirmation Test using a modified HSG. In the Pivotal trial, the following adverse events prevented reliance: perforation (5/476; 1.1%); expulsion (14/476; 2.9%, 9 out of the 14 underwent a successful second placement procedure; unsatisfactory insert location (3/476; 0.6%); initial tubal patency (16/456; 3.5%) was found at the 3-month Essure Confirmation Test using a modified HSG; however, all had tubal occlusion at a 6- or 7-month repeat Essure Confirmation Test using a modified HSG. ‡In the ESTVU trial, the following prevented reliance: nonbilateral placement after 1 or 2 procedures (15/597; 2.5%), did not have confirmation testing (23/597; 3.9%) (ie, lost to follow up [15]; excessive length of time since procedure [1]; no longer at risk for pregnancy [1]; voluntary withdrawal [6]); expulsion (2/597; 0.34%); expulsion or unsatisfactory placement (1/597; 0.17%); expulsion on TVU and unsatisfactory placement on HSG (1/597; 0.17%); unsatisfactory placement and unsatisfactory occlusion (both TVU and HSG) (3/597; 0.50%); unable to tolerate HSG (narrow vagina) (1/597; 0.17%); TVU unsatisfactory and unsatisfactory placement on HSG (1/597; 0.17%); no longer at risk for pregnancy (1/597; 0.17%); lost to follow-up (2/597; 0.34%).

Essure [Instructions for Use].

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Procedure and Recovery Time

- Procedure time¹
 - The average total procedure time is 36 minutes
- Following the procedure¹:
 - Most women are able to leave the doctor's office about 45 minutes after the procedure is completed
 - Most women return to normal activities within 1 or 2 days
- In the pivotal trial, 14 of 20 investigators had no prior experience with the inserts²

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The sale and distribution of this device are restricted to users and/or user facilities that provide information to patients about the risks and benefits of this device in the form and manner specified in the approved labeling provided by Bayer.

- 1. Data on file, Bayer HealthCare Pharmaceuticals Inc.
- 2. Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Obstet Gynecol. 2003;102(1):59-67.
- 3. Essure [Instructions for Use].
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Phase II and Pivotal Trial: Adverse Events on the Day of the Procedure

Adverse event/ side effect	Phase II Trial n (%) (N=233 procedures)	Pivotal Trial n (%) (N=544 procedures)
Cramping	*	161 (29.6%)
Pain	2 (0.9%)	70 (12.9%)
Nausea/vomiting	*	59 (10.8%)
Dizziness/light headed	*	48 (8.8%)
Bleeding/spotting	*	37 (6.8%)
Other	*	16 (2.9%)†
Vasovagal response	2 (0.9%)	7 (1.3%)
Hypervolemia	*	2 (0.4%)
Band detachment	3 (1.3%)	2 (0.4%)

*Data not collected.

[†]Includes: ache (3), hot/hot flashes (2), shakiness (2), uncomfortable (1), weak (1), profuse perspiration (1), bowel pain (1), sleepiness (1), skin itching (1), loss of appetite (1), bloating (1), allergic reaction to saline used for distension (1).

Essure [Instructions for Use] ..

Pivotal Trial: Adverse Events: First Year of Reliance (N=476 patients with at least 1 insert)

Adverse events (≥0.5%) by body system	n (%)
Abdominal Abdominal pain/abdominal cramps Gas/bloating 	18 (3.8%) 6 (1.3%)
Musculoskeletal • Back pain/low back pain • Arm/leg pain	43 (9.0%) 4 (0.8%)
 Nervous/psychiatric Headache Premenstrual syndrome 	12 (2.5%) 4 (0.8%)
 Genitourinary Dysmenorrhea/menstrual cramps (severe) Pelvic/lower abdominal pain (severe) Persistent increase in menstrual flow Vaginal discharge/vaginal infection Abnormal bleeding—timing not specified (severe) Menorrhagia/prolonged menses (severe) Dyspareunia 	14 (2.9%) 12 (2.5%) 9 (1.9%)* 7 (1.5%) 9 (1.9%) 5 (1.1%) 17 (3.6%)
Pain/discomfort—uncharacterized	14 (2.9%)

*Eight women reported persistent decrease in menstrual flow.

In the Phase II trial, 12/206 (5.8%) women with ≥1 insert reported episodes of period pain, ovulatory pain, or changes in menstrual function.

Essure [Instructions for Use].

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Pivotal Trial: Procedural Pain and Management

- 65% of 518 patients rated the pain during procedure as either mild or none
 - 4% rated the average procedural pain as severe
- In 84% of 544 procedures, patients received preoperative NSAIDs

Predominant anesthesia used:

• 93% of procedures used local anesthesia, with or without IV sedation



Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Obstet Gynecol. 2003;102(1):59-67.

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Pivotal Trial: Tolerability and Recovery



- 88% of patients rated tolerance of the placement procedure as good, very good, or excellent
- 75% required no pain medication in the recovery room
 - 72% did not request analgesia prescription at discharge

Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Obstet Gynecol. 2003;102(1):59-67.

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Post-procedure Bleeding and Return to Normal Activities

- Post-procedure bleeding¹
 - The majority of patients experienced spotting for an average of 3 days after the procedure
- Return to normal activities²
 - More than 75% of women undergoing the Essure procedure return to normal activities within 2 days

- 1. Essure [Instructions for Use].
- 2. Data on file, Bayer HealthCare Pharmaceuticals Inc.
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Please see Important Safety Information, including Boxed Warning, on slides 3-8 of this presentation. For important information about Essure[®], please see the accompanying <u>Instructions for Use</u>, including Boxed Warning.

Essure Instructions for Use Section IX: Summary of Pregnancies Reported in Commercial Use of Essure[®]

Potential contributing factor	US n (%)	Ex-US* n (%)	Total n (%)
Patient noncompliance (eg, failure to use alternative contraception or return for Essure Confirmation Test)	213 (32%)	16 (18%)	229 (31%)
Perforation ^{†‡}	91 (14%)	4 (5%)	95 (13%)
Unsatisfactory placement [†]	32 (5%)	13 (15%)	45 (6%)
Physician noncompliance	22 (3%)	13 (15%)	35 (5%)
Pregnant at time of placement (luteal)	26 (4%)	6 (7%)	32 (4%)
Inadequate confirmation test [†]	28 (4%)	0	28 (4%)
Expulsion [†]	20 (3%)	4 (5%)	24 (3%)
Tubal patency [†]	19 (3%)	1 (1%)	20 (3%)
Insufficient information	209 (32%)	31 (35%)	240 (32%)
Total	660	88	748§

*Outside of the United States, during this reporting period, the Essure Confirmation Test may have been an x-ray or TVU; device location alone, not occlusion, is primarily used to determine whether the patient may rely on Essure[®] for birth control. [†]Most pregnancies are due to misinterpreted Essure Confirmation Tests where occlusion is seen but insert is not properly located. [‡]Causal association cannot be established between perforation and pregnancy. [§]497,306 kits were sold worldwide from 2001 to 2010.

Essure [Instructions for Use].

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The Essure[®] Insert Placement Procedure

Important Information Regarding the Essure Procedure

Refer to the Essure Physician Training Manual for detailed information not included in this presentation or not included in the Essure[®] Instructions for Use.

The Essure procedure should only be performed by knowledgeable hysteroscopists who have completed the Essure training program, including preceptoring in placement until competency is established, typically 5 cases.

The sale and distribution of Essure[®] are restricted to users and/or user facilities that provide information to patients about the risks and benefits of this device in the form and manner specified in the approved labeling provided by Bayer.

The directions for the use of Essure[®] will be reviewed in these categories:

- Considerations prior to the Essure[®] procedure
- Essure setup
- The Essure placement procedure
- Assessment after Essure[®] insert deployment
- Post-procedure instructions and patient follow-up requirements

Essure [Instructions for Use].

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Considerations Prior to the Essure Procedure

- Have appropriate equipment, medication, staff, and training in place to handle emergency situations such as vasovagal response. Adequate visualization of the uterine anatomy and tubal ostia is required
- Timing of the procedure to the early proliferative phase of the menstrual cycle should:
 - Enhance visualization of the uterine cavity and fallopian tube ostia
 - Decrease potential for insert placement in a patient with an undiagnosed pregnancy
- Women with menstrual cycles shorter than 28 days should undergo careful ovulationday calculations
- Insert placement should not be performed during menstruation
- Pretreatment of the patient with medications that suppress endometrial proliferation may enhance visualization and scheduling flexibility

Essure [Instructions for Use].

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Considerations Prior to the Essure Procedure (cont'd)

- Administer a pregnancy test within 24 hours prior to or immediately preceding the insert placement procedure
- Patient comfort
 - Administration of a nonsteroidal anti-inflammatory drug (NSAID) should be considered 1-2 hours before the scheduled insert placement procedure, if appropriate for the patient
 - Local anesthesia is the preferred method for the placement of the inserts. A
 paracervical block may be administered. Risks and benefits associated with the
 planned anesthesia should be discussed prior to performing the procedure
 - An anxiolytic agent may also be administered to prevent or reduce discomfort if needed

Essure [Instructions for Use].

Considerations Prior to the Essure Procedure (cont'd)

- Essure[®] inserts may be placed with an intrauterine device (IUD) in the uterine cavity
- In some cases, the IUD may need to be removed to complete the placement procedure, and the patient must use alternative contraception until a satisfactory Essure Confirmation Test is documented
- While highly unlikely, there is a theoretical risk of dislodgement of an Essure[®] insert at the time of IUD removal

Essure [Instructions for Use]

Reminders

- Essure placement can be performed in an outpatient or ambulatory setting¹
- Utilize eye protection as back splash of hysteroscopic distention fluid (saline) into face can occur¹
- The Essure procedure should be supported by knowledgeable and qualified support staff²
- In addition to passing sterile instruments to physician, a sterile assistant may help insert DryFlow[™] introducer and Essure delivery system through the sealing cap of the hysteroscope working channel while the physician manipulates the hysteroscope to maintain visualization of the tubal ostia²

Refer to the Essure[®] Instructions for Use and Clinical Resource/Physician Training Manual for a complete list of equipment and supplies

- 1. Essure [Instructions for Use].
- 2. Data on file, Bayer HealthCare Pharmaceuticals Inc.

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Hysteroscopy equipment

- 12- or 30-degree scope with ≥5 French operating channel
- Sterile sealing cap for instrument port
- Monitor

Distension media

• 0.9% sterile saline, preferably 3L bag

Data on file, Bayer HealthCare Pharmaceuticals Inc.

Essure[®] Setup (cont'd)

Essure[®] kit

- Includes¹:
 - 2 Essure[®] systems
 - 2 DryFlow[™] Introducers
 - 1 Instructions for Use (IFU)
 - 1 Patient Identification Card
- Only open and place on the tray after bilateral ostia are visualized²
- Have a backup kit available²

1. Essure [Instructions for Use].

2. Data on file, Bayer HealthCare Pharmaceuticals Inc.

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Essure Delivery System



Essure [Instructions for Use].

Risks Associated with the Essure[®] Insert Placement Procedure

- Possible adverse events that have been reported within 24 hours following the Essure placement procedure include: nausea/vomiting, dizziness/lightheadedness, vasovagal response/syncope, pain, dysmenorrhea, uterine bleeding/spotting, infection, fluid overload, anesthetic complications, detachment difficulties, and unsatisfactory insert location
- Anesthesia
 - Local anesthesia, oral analgesia/sedation, regional anesthesia (i.e., spinal, epidural), oral or conscious (intravenous) sedation, or general anesthesia may be administered to the patient to prevent or reduce discomfort. Regardless of the type of anesthesia, patients may not be able to resume normal activities for 12-24 hours following the procedure. Risks and benefits associated with the planned anesthesia should be discussed prior to performing the procedure
 - Serious reactions to anesthesia, including general anesthesia and paracervical block, have been reported. Risks and benefits associated with the planned anesthesia should be discussed prior to performing the procedure

Essure [Instructions for Use].

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Risks Associated with the Essure[®] Insert Placement Procedure (cont'd)

- Intra-operative and post-operative symptoms
 - Pain, cramping, vaginal bleeding, nausea/vomiting, and dizziness, lightheadedness, and vasovagal response may occur during and following the insert placement procedure. Typically, these incidents are tolerable, transient, and successfully treated with medication
- Device properties and deployment
 - Bending of the insert tip or catheter, breakage of the catheter during attempted insertion, and difficulty in deployment or detachment may occur, especially in tubal ostia that are more laterally located or in cases of tubal spasm
- Unsatisfactory insert location
 - Any insert that is not satisfactorily located within the fallopian tube can NOT be relied on for effective contraception. Unusual pain or uterine bleeding after the placement procedure should prompt investigation of an unsatisfactory insert location

Essure [Instructions for Use].

Risks Associated with the Essure® Insert Placement Procedure (cont'd)

- Unsatisfactory insert location (cont'd)
 - There is a risk of uterine perforation by the hysteroscope, Essure[®] system or other instruments used during the procedure with possible injury to the bowel, bladder, and major blood vessels. Depending on symptomatology, surgical intervention at the time of placement or shortly thereafter may be required; however, for asymptomatic perforations, intervention may not be necessary. To reduce the risk of uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation
 - There is a risk of perforation or dissection of the fallopian tube or uterine cornua. Bleeding and scarring may result from such a perforation or dissection; however, treatment is typically not required
 - There is a risk of perforation of internal bodily structures other than the uterus and fallopian tube for inserts located outside the fallopian tube and uterus
 - Additional imaging may be required to identify the location of the inserts. Removal of an unsatisfactorily located insert (perforation, embedment, migration expulsion, proximal or distal fallopian tube placement, or within the peritoneal cavity) may require surgery

Essure [Instructions for Use].

Risks Associated with the Essure[®] Insert Placement Procedure (cont'd)

- Infection
 - As with all hysteroscopic procedures, insert placement can cause an infection. An infection could cause damage to the uterus, fallopian tubes, or pelvic structures, which may require antibiotic therapy, or rarely, hospitalization or surgery, including hysterectomy
- Fluid overload
 - There is a minimal risk of excess fluid absorption of the physiologic saline fluid, used for distention of the uterus, to perform the hysteroscopic procedure

Essure [Instructions for Use].

Step 1

- The Essure[®] insert placement procedure can be performed in an outpatient or ambulatory setting.
 - Use universal precautions and sterile technique

Step 2

• Check all equipment for damage; ensure that there are no missing parts

Step 3

• Place the patient in the lithotomy position

Step 4

• Introduce a speculum to allow cervical access. Prep cervix with Betadine or another antibacterial solution according to standard practice. Vaginoscopy may also be used to access the uterine cavity

Essure [Instructions for Use].

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Step 4: Accessing the Uterine Cavity

Traditional approach

- Involves the use of speculum and tenaculum to facilitate the entry of the scope through the cervix¹
- Pain during hysteroscopy may be due to placement of the speculum, use of a tenaculum, passage of the scope through the cervix, and uterine distension^{1,2}
 - Eliminating some of these steps may decrease discomfort accompanying the hysteroscopy procedure

1. Bettocchi S, Selvaggi L. J Am Assoc Gynecol Laparosc. 1997;4(2):255-258.

2. Allen RH, Micks E, Edelman A. Obstet Gynecol Clin North Am. 2013;40(4):625-645.

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Vaginoscopic approach

- Eliminates need for speculum/tenaculum—2 sources of patient discomfort^{1,2}
- Is an alternative for uterine access during hysteroscopic techniques³
- Randomized, controlled trial comparing the Essure procedure using vaginoscopy vs traditional hysteroscopy⁴
 - Vaginoscopy was successful in 93%; the first attempt bilateral placement rate was 95% in both groups
 - No difference in pain scores, but shorter time for treatment completion with vaginoscopy (9 vs 16 minutes)

1. Allen RH, Micks E, Edelman A. Obstet Gynecol Clin North Am. 2013;40(4):625-645.

- 2. Emanuel MH. Best Pract Res Clin Obstet Gynaecol. 2013;27(3):421-429.
- 3. Cooper NA, Smith P, Khan KS, Clark TJ. BJOG. 2010;117(5):532-539.
- 4. Chapa HO, Venegas G. J Reprod Med. 2015;60(1-2):43-47.

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Step 5

Administer anesthesia as needed

Step 6

- Insert sterile hysteroscope, with camera and operating channel (≥5 French), through cervix into uterine cavity
- Do not perform cervical dilation unless necessary; if necessary, dilate only enough for hysteroscope insertion
- In order to prevent uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilation

Step 7

- Distend uterus with physiologic saline solution through the working channel of the hysteroscope
- It is strongly recommended that the saline solution be prewarmed to body temperature and introduced under gravity feed to minimize spasm of the fallopian tubes
- Maintain uterine distension throughout the procedure for optimal visualization
- Monitor fluids to reduce the risk of hypervolemia; terminate procedure if fluid deficit exceeds 1500cc
 or hysteroscopic time exceeds 20 minutes

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Step 8

- Identify and assess hysteroscopically both tubal ostia prior to insert placement. Do not attempt
 placement in one tubal ostium unless both tubes are accessible
 - Unusual uterine anatomy may make it difficult to place Essure[®] inserts

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Step 9

- Once the fallopian tube ostia have been identified, insert introducer through sealing cap on operating channel of hysteroscope. Use an introducer to avoid insert tip damage
- Operating channel stopcock should remain in open position
 - Device and/or introducer can be damaged if stopcock closes on either device
- Place Essure delivery system through introducer and advance through operating channel of hysteroscope

PROCEDURE WARNING AND PRECAUTION

 At this point in the procedure, both tubal ostia should be identified and assessed hysteroscopically prior to proceeding to the Essure[®] insert placement. No attempt should be made to place an insert in 1 tubal ostium unless both tubes are accessible





Never attempt to resterilize the Essure[®] system as it is single use only. Resterilization may adversely affect device function or cause the patient injury. Do not use if the sterile package is open or damaged. Do not use if the insert damaged.

Essure [Instructions for Use].

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Step 10

- Insert delivery catheter through introducer; avoid bending the insert tip¹
- Under direct visualization, advance catheter through operating channel into the proximal fallopian tube with gentle, constant forward movement to prevent tubal spasm¹
- The Essure delivery system is designed with a 15-degree angle at the tip to facilitate placement within the fallopian tube



- When advancing the catheter, direct the tip laterally following the contour of the fallopian tube
 - This should facilitate advancement of the catheter under direct visualization without undue resistance
- Proper alignment of the delivery catheter with the tubal lumen is suggested by the ability to advance the catheter under direct visualization without undue resistance²

- 1. Essure [Instructions for Use].
- 2. Data on file, Bayer HealthCare Pharmaceuticals Inc.

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Step 10 (cont'd)

- Do not attempt to advance the delivery system if excessive resistance is encountered
- If tubal spasm is suspected, move hysteroscope closer to tubal ostium
 - Apply gentle, constant forward pressure on delivery catheter and wait. Repeatedly removing/attempting to recannulate may irritate the tube



- It may take more than a minute for a spasm to resolve and the catheter to advance
- If excessive resistance occurs (ie, catheter does not advance, bends, or flexes excessively), or several minutes have passed, terminate the procedure to avoid perforation or placement into a false passage

PROCEDURE WARNING AND PRECAUTION

• When introducing the Essure[®] insert into the fallopian tube, never advance the insert against excessive resistance. Do not advance the Essure[®] system if the patient is experiencing excessive pain or discomfort

Essure [Instructions for Use].

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Step 10 (cont'd)

- Resistance to advancement apparent in 2 ways:
 - Black marker on the outside surface of catheter is seen not to advance forward toward the tubal ostium
 - Delivery catheter bends or flexes excessively, preventing physician from applying forward pressure on the catheter assembly
- When resistance to forward motion of catheter is observed:
 - No further attempts should be made to place insert in order to avoid possibility of uterine or tubal perforation or inadvertently placing insert in uterine muscle rather than within the tubal lumen



Essure [Instructions for Use].

Step 11

- Advance delivery system until black positioning marker on the delivery catheter reaches the fallopian tube ostium
- Visual marker indicates that the Essure[®] insert is spanning the distal intramural to proximal isthmic segments of the fallopian tube, with the outer coil spanning the uterotubal junction

This is the ideal placement for the Essure[®] insert.



Advance until black positioning marker at tubal ostium, indicating proper position.

Essure [Instructions for Use].

Step 12

• If the tube is blocked or the catheter cannot be advanced to the positioning marker, the procedure should be terminated

If the insert placement is not successful after 10 minutes of attempted cannulation per tube, the procedure should be terminated.

Essure [Instructions for Use].

PROCEDURE WARNING AND PRECAUTION

- To reduce risk of hypervolemia, terminate procedure if distension fluid deficit exceeds 1500cc or total hysteroscopic procedure time (scope in-scope out) exceeds 20 minutes. Excess fluid deficit may signal uterine or tubal perforation. If noted, discontinue procedure and evaluate patient for possible perforation
- Never attempt to advance Essure[®] insert(s) against excessive resistance. If a perforation occurs or is suspected, discontinue the procedure and monitor the patient for signs and symptoms of possible complications related to perforation, which may include unusual postoperative pain
 - If unusual postoperative pain occurs, imaging to localize the insert should be performed prior to the 3-month confirmation test
- A small percentage, 1.8% (12/682), of women in Essure[®] clinical trials, were identified as having device-related perforations. Retrieval of perforating inserts, if necessary, will require surgical removal
- A false-positive modified HSG and pregnancy have been associated with tubal perforation by the insert in the literature; evaluate the Essure Confirmation Test for perforation if excessive resistance is experienced during procedure
- Do not continue to advance the Essure[®] system once the end of the black positioning marker on the catheter has reached the tubal ostium. Advancement beyond this point could result in unsatisfactory insert placement or tubal/uterine perforation
- If breakage of any component (eg, catheter or insert) occurs during placement, all fragments should be removed, if possible, and appropriate based on the physician's judgement

Essure [Instructions for Use].

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Step 13

- Stabilize the delivery system handle against the hysteroscope to prevent inadvertent forward movement
- To do so, first stabilize the handle of the Essure[®] insert against the hysteroscope camera or some other fixed object to prevent inadvertent forward movement of the Essure[®] system during retraction of the delivery catheter



Before proceeding with the Essure procedure, recall that 2 distinct operations will take place:

- 1. Retraction
 - <u>Retraction</u> of the delivery catheter away from insert, prior to actual detachment of the insert
 - Full retraction is accomplished by rotating the thumbwheel to the point where you cannot rotate it any further

2. Detachment

- Actual <u>detachment</u> is accomplished after retraction by pressing the handle button, then continuing to rotate the thumbwheel
- Only after detachment of the insert has occurred can you <u>remove</u> the delivery system

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Step 14

 Being certain that the black positioning marker is at the fallopian tube ostium, rotate thumbwheel on handle toward you so that the wheel no longer rotates



- Delivery catheter and black positioning marker will move away from the tubal ostium and disappear into the operating channel
- Withdrawal of the delivery catheter exposes the wound-down insert
- ≈1 cm of the insert (wound-down coils) should appear trailing into the uterus when the delivery catheter is withdrawn



Essure [Instructions for Use].

Step 15

- Stop and check proper positioning
 - Confirm placement of the gold marker band just outside of the ostium
 - Confirm visualization of the distal tip of the green release catheter



Visualize the gold band at the ostium and green release catheter

It is very important that the gold band is not inside of the tube at the time of deployment. If the gold band is not visible, do not deploy. Move the delivery catheter toward you until the gold band is visible.

If more than 1 cm of the insert is visible in the uterus, the insert should be repositioned by moving the entire system further into the tube, if possible.

Essure [Instructions for Use].

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Step 16

• Press the button on the delivery handle; this enables the thumbwheel to be rotated further for insert deployment

NOTE: DO NOT PRESS BUTTON until the delivery system is in the correct position for insert placement



Press the button to enable the thumbwheel to rotate again.

Essure [Instructions for Use].



PROCEDURE WARNING AND PRECAUTION

- Each fallopian tube should only contain 1 insert. If a physician suspects that the device has not deployed (eg, sees no trailing coils), the physician must verify by inspection of the delivery system that deployment has not occurred. If the physician suspects or is uncertain that deployment has occurred, imaging (eg, x-ray or TVU) may be used to identify the presence of an insert in the tube or elsewhere in the body
- If the physician verifies that the tube does not contain an insert, a second placement attempt may be performed

Essure [Instructions for Use].

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Step 18

• Repeat the procedure in the contralateral fallopian tube

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Assessment After Essure[®] Insert Deployment

- The position of the deployed Essure[®] insert will be assessed under hysteroscopic visualization
- Inserts showing 0-17 trailing coils should be left in place and evaluated via the Essure Confirmation Test
- Ideally, 3-8 expanded outer coils should be trailing into the uterine cavity
- If dissatisfied with the insert placement based on the hysteroscopic view, and if there are fewer than 18 trailing coils, the inserts should be left in place and assessed during the Essure Confirmation Test
- In cases of suspected perforation, monitor the patient for signs and symptoms of possible complications related to perforation, which may include unusual postoperative pain
 - If unusual post-operative pain occurs, imaging to localize the insert should be performed prior to the 3-month confirmation test
- If no trailing coils are visible, examine the delivery system upon removal from the hysteroscope
 - Appearance of a deployed versus a nondeployed delivery system is shown here



Ideal placement of insert



If the insert was inadvertently deployed in the uterine cavity and not in the tube, remove the device from the uterus and attempt another placement.

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WARNING: Do not attempt insert removal hysteroscopically unless 18 or more coils of the Essure[®] insert are trailing into the uterine cavity.

- An attempted removal of inserts having fewer than 18 trailing coils may cause the insert to fracture or injure the patient
- If 18 or more coils are trailing into the uterine cavity, the removal should be attempted immediately during the placement attempt
- Removal of the inserts may not be possible

If the insert removal is indicated, perform removal immediately after failed placement, as follows:

- 1. As necessary, administer analgesia/anesthesia to reduce or prevent patient discomfort
- 2. Introduce a grasping instrument through the hysteroscope-operating channel
- 3. Grasp both the outer and inner coils of the insert together
- 4. Withdraw the grasping instrument and hysteroscope simultaneously; the insert may stretch or elongate. Do not pull the insert through the operating channel

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If the insert removal is successful, repeat the Essure[®] insert placement procedure.

If the removal is not accomplished, leave the insert in place

- If the insert is not completely removed, do not place additional inserts
- Take a diagnostic x-ray to determine if the insert fragment remains in the patient

If the fragment remains, refer to the INSERT REMOVAL section of the Essure IFU.

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Assessment After Essure[®] Insert Deployment (cont'd)

- Document procedural concerns. This information should be reviewed when performing the Essure Confirmation Test
- Note possible perforations due to:
 - Excessive or sudden loss of resistance;
 - Inability to visualize coils;
 - Problems with identification of tubal ostium;
 - Poor distension;
 - Poor illumination; or
 - Poor visualization secondary to endometrial debris

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Assessment After Essure[®] Insert Deployment (cont'd)

- Ensure that the patient uses alternative contraception until the Essure Confirmation Test
 - Counsel patients regarding the risk of pregnancy (including ectopic pregnancy) attributable to noncompliance during all of the steps of the Essure procedure
- Schedule the patient for an Essure Confirmation Test 3 months following the procedure to evaluate insert location (TVU), or location and occlusion (modified HSG) of the fallopian tubes
- Provide the patient with the Patient Identification Card and instruct her to show it to her physicians
- Send back the Essure Insert Information Card as acknowledgement that the Patient-Doctor Discussion Checklist-Acceptance of Risk and Informed Decision Acknowledgement, was reviewed with the patient.

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Management of Cases with Unsuccessful Insert Placement During the Initial Procedure

- Placement may not be achieved due to conditions such as temporary difficulty with visualization, which could be satisfactorily managed prior to a second attempt
- The patient should be informed that her permanent contraception has not been successful and should continue to use an alternative contraception
- Counsel the patient on undergoing a second procedure, especially if unilateral placement was achieved
 - In the Pivotal trial, 83% of those who underwent a second procedure achieved bilateral placement

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Management of Cases with Unsuccessful Insert Placement During the Initial Procedure (cont'd)

- Before a second placement attempt, determine tubal patency by modified HSG, which can be scheduled after the patient's next menses
 - If patency is documented, a second attempt may be performed
 - If a second attempt fails, success with subsequent attempts is unlikely
- If one insert is left in vivo, counsel the patient not to rely on the insert for contraception
 - Do not remove a unilaterally placed insert unless the patient experiences an adverse event(s) due to its presence
- If the patient chooses laparoscopic sterilization, clip or coagulate both fallopian tubes distal or proximal to the insert. Do not perform clipping or coagulation adjacent to or over the insert

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