Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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For questions about this document, contact the Division of Reproductive, Gastro-Renal, and Urological Devices at 301-796-7030.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Surveillance and Biometrics

Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance identifies content and format for labeling materials for permanent, hysteroscopically-placed tubal implant devices intended for female sterilization. FDA believes this guidance, when finalized, will help to ensure that a woman receives and understands information regarding the benefits and risks of this type of device.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Female sterilization is an elective procedure that permanently prevents a woman from becoming pregnant by disrupting the fallopian tubes and preventing fertilization of an egg following ovulation. As sterilization is intended to be an irreversible procedure, it is only appropriate for women who are certain that they wish to permanently end their ability to conceive naturally. Female sterilization is one of the most common procedures in the United States, with more than

500,000 performed per year.[1] The procedure may be performed immediately following delivery of an infant (post-partum sterilization) or at a time not associated with a recent pregnancy (interval sterilization). For decades, female sterilization has been performed by surgical bilateral tubal ligation (BTL) through a laparotomy, a mini-laparotomy, transvaginal approach or at the time of a cesarean delivery, and, more recently, via laparoscopy. During surgical BTL, the fallopian tubes are cut, or various procedures or medical instruments, such as electrosurgical coagulation, implantable clips or rings, are used to physically block or close the fallopian tubes. Surgical BTL is effective immediately, generally safe, requires little to no patient compliance, and is a highly effective method of permanent sterilization. However, there are certain risks of surgical BTL, including, but not limited to, the risks related to general anesthesia, possible physical injury to local organs (e.g., bowel), and bleeding. Some of these adverse events, although uncommon, may result in hospitalization and/or re-operation.[2]

In addition to surgical BTL, medical devices have been developed to provide alternative, less-invasive methods of female sterilization through the insertion of permanent implants into a woman's fallopian tubes via a hysteroscopic, non-incisional route. The inserted permanent implants are intended to provide sterilization via physical occlusion and/or the elicitation of a local inflammatory/fibrotic response. This type of device may require a "waiting period" in order to accomplish full occlusion. As the number of hysteroscopic sterilizations with such devices has increased, additional information, including reports of adverse events, has accumulated. This information has included reports of hypersensitivity reactions to the implant materials, persistent pain, irregular vaginal bleeding, fallopian tube or uterine perforation, and intra-peritoneal device migration as well as unintended pregnancy. Some instances of adverse events have resulted in surgical intervention, including device removal.

On September 24, 2015, FDA convened its Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to discuss available data regarding benefits, the aforementioned risks, and potential mitigation strategies to prevent or reduce the frequency/severity of the adverse outcomes reported in association with one such device, the Essure System for Permanent Birth Control.[3] The Essure System is the only permanent hysteroscopically-placed tubal implant intended for sterilization that is currently marketed in the United States.

Based on the 2015 Panel meeting, including comments made during the Open Public Hearing portion of the meeting and comments submitted in the associated public docket,[4] FDA believes that some women are not receiving or understanding information regarding the risks and benefits of permanent, hysteroscopically-placed tubal implants that are intended for sterilization. This draft guidance addresses these concerns. In addition, the Agency will continue to monitor

[1] Chan LM, Westhoff CL. Tubal sterilization trends in the United States. Fertility and Sterility, 2010; 94(1): 1-6.
[2] Jamieson DJ, Hillis SD, Duerr A et al.(2000) Complications of interval laparoscopic tubal sterilization: Findings from the United States Collaborative Review of Sterilization. Obstet & Gynecol 96(6): 997-1002.
[3] For more information and meeting materials, see http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm463457.htm.
[4] http://www.regulations.gov/#!docketDetail;D=FDA-2014-N-0736.

information about potential safety risks and take other steps to ensure they are being adequately conveyed to and understood by physicians and patients.

FDA is issuing this draft guidance to enable the public to comment on the proposed language for a boxed warning and patient decision checklist that FDA intends to require as part of the product labeling as described below. FDA believes this information will help to ensure that a woman receives and understands the benefits and risks associated with her contraceptive options so that she can make an informed decision as to whether having a permanent implant placed in her fallopian tubes via a hysteroscopic, non-incisional route is the right choice for her.

III. Scope

This draft guidance is about the content and format of labeling for permanent, hysteroscopically-placed tubal implants that are intended for sterilization. The guidance applies to all devices of this type, regardless of the insert material composition, location of intended implantation, or exact method of delivery. It is being issued in response to information provided to FDA, including at the 2015 Panel meeting and in the associated public docket, that some women are not receiving or understanding information regarding the risks and benefits of this type of device, including those associated with device implantation and removal. Medical devices used during surgical BTL procedures (e.g., cautery devices, rings, clips) are outside the scope of this guidance.

The guidance is not intended to include a complete listing of all labeling components for permanent, hysteroscopically-placed tubal implants intended for sterilization. Rather, this guidance specifically focuses on inclusion of a boxed warning and patient decision checklist in the product labeling. Accurate product labeling and effective messaging of that labeling is important to make device users and patients aware of the risks associated with permanent, hysteroscopically-placed tubal implants intended for sterilization. FDA believes that a boxed warning and a patient decision checklist as described in this guidance should be included in labeling under sections 502(a), 201(n), and 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA intends to require such labeling information as part of a premarket approval (PMA), and intends to work with manufacturers, including of already marketed products, through the PMA and PMA supplement process. We have determined that a boxed warning and a patient decision checklist are particularly effective means of communicating this information to patients. This guidance should be used as a complement to FDA's "Guidance on Medical Device Patient Labeling" (which describes FDA's current thinking on making medical device patient labeling understandable to and usable by patients), existing regulations, and other relevant guidance documents containing additional labeling recommendations.[5] FDA requests comment on the wording and content of the recommended boxed warning and patient decision checklist.

[5] We note that a device is misbranded if its labeling is false or misleading in any particular (section 502(a) of the FD&C Act) or, if applicable, its labeling does not provide adequate warnings (section 502(f)(2) of the FD&C Act). Under section 301(a) of the FD&C Act, it is a prohibited act to introduce or deliver for introduction into interstate commerce any device that is misbranded.

IV. Labeling Components

This section contains the wording and content FDA believes should be included in a boxed warning and patient decision checklist in the product labeling of permanent, hysteroscopically-placed tubal implants intended for sterilization. The specific examples referenced in the appendices are written to address the currently marketed device of this type.

A. Boxed Warning

FDA believes that a boxed warning should be part of physician and patient labeling materials for a permanent, hysteroscopically-placed tubal implant for sterilization and should:

- Note the types of significant and/or common adverse events that may be associated with the device and its insertion and/or removal procedures, including those noted in clinical trials, as well as those reported in device use experience.
- Include a statement noting that these risks should be conveyed to the patient during the woman's decision-making process.

An example of a boxed warning that follows this guidance is provided in **Appendix A**.

B. Patient Decision Checklist

In addition to the boxed warning, FDA also believes that a patient decision checklist highlighting key risk and benefit information should be included at the end of the patient labeling brochure. The checklist is intended to be reviewed and signed by the patient and physician, and should be printed in a fashion where it can be easily separated from the remainder of the patient information brochure, and upon which pen markings can be permanently made.

The introduction for the checklist should include a description of the purpose and importance of the checklist, as well as instructions to the patient on how to review and complete the document prior to her decision whether to undergo the permanent implant procedure.

The body of the checklist should include key items related to the device, its use, and its safety and effectiveness. Items that should be addressed include the following:

- notification of the permanent (and if applicable, irreversible) nature of sterilization in general, and the implant more specifically;
- recognition of available alternative contraceptive modalities and their safety and effectiveness;
- situations in which the device should not be used or implanted (e.g., contraindications);
- steps, if any, that will need to be followed before the implant can be relied upon for contraception, and the importance of compliance with those steps;

- information on effectiveness and chances for unintended pregnancy and ectopic pregnancy, including a statement that no contraceptive device is 100% effective;
- significant and/or common adverse events, including patient-reported outcomes, which may occur during or immediately following device placement;
- clinically significant longer-term adverse events or outcomes that have been reported in clinical trials or via other device use experience – including significant events that may persist from the time of implantation and those that may appear for the first time later after implantation;
- a brief discussion of the types of signs, symptoms or events that may represent device-related complications for which the patient should seek prompt evaluation;
- a disclosure of the device materials and any risks that may be associated with them, including allergy/hypersensitivity and Magnetic Resonance Imaging (MRI) safety information, if applicable; and
- information related to device removal and/or reversal (e.g., reasons for removal, techniques, outcomes).

Where applicable, and if known (e.g., based on clinical trial results), probabilities or rates of events should be included within the individual checklist items. The source of the probabilities or rates of events should be identified.

Each separate item in the body of the checklist should be accompanied by a line for the patient to initial her acknowledgment and understanding of that individual piece of information.

At the end, the checklist should include a section that summarizes the importance of the information and confirms that the patient has read and understood the material and has had the opportunity to satisfactorily discuss and ask questions of her physician. This should be followed by signature lines for both the patient and physician.

The FDA recommends that the original signed copy be retained by the physician in the patient records, and that a copy be provided to the patient. The FDA also encourages device manufacturers to develop a plan to audit (and if appropriate, institute steps to improve) the distribution and signing of the checklists as a component of the patient decision-making process, and to periodically update the checklist as additional data is collected with post-market experience.

Appendix B provides an example of a Patient Decision Checklist that follows this guidance.

Appendix A: Boxed Warning Example

WARNING: Some patients implanted with the Essure System for Permanent Birth Control have reported adverse events, including perforation of the uterus and/or fallopian tubes, intra-abdominal or pelvic device migration, persistent pain, and allergy or hypersensitivity reactions. Some of these reported events resulted in device removal that required abdominal surgery. This information should be shared with patients considering sterilization with the Essure device during discussion of the benefits and risks of the device.

Appendix B: Patient Decision Checklist Example

To the patient considering implantation of the Essure System for Permanent Birth Control:
The review and completion of this form is a critical step in helping you decide whether to have the Essure System procedure and implants. You should carefully consider the benefits and risks associated with the device before you make that decision. This form lists important risks, including those known or reported to be associated with the use of the device based on information from clinical trials, scientific literature, and reports from women who have undergone device placement.

After reviewing the Essure Patient Information Brochure, please read and discuss this document carefully in consultation with your physician. You should place your initials in the location provided next to each item to indicate that you have read and understood that item. Your full signature at the end of this document means that you have read the materials, that your physician has answered all questions to your satisfaction, and that you understand all statements listed below. You should not sign the form, and should not undergo the procedure, if you do not understand each of the elements listed below.

_____

I understand that the Essure System is a permanent form of birth control (referred to as "sterilization") and that by electing to have the Essure device implanted in my fallopian tubes, I am deciding to permanently end my ability to become pregnant. I understand that sterilization must be considered permanent and not reversible.

Patient Initials _____

I am aware that there are temporary, highly effective methods of birth control that are available, which may allow me to bear a child in the future.

Patient Initials _____

I was told about other alternative permanent sterilization procedures, such as bilateral tubal ligation ("getting tubes tied"), and their benefits and risks.

Patient Initials _____

I understand that I am not a candidate for the Essure System if:

- I am uncertain about ending my fertility.
- I have had a tubal ligation procedure ("tubes tied").
- I cannot have two inserts placed due to my anatomy.
- I am pregnant or suspect that I may be pregnant.
- I have delivered or terminated a pregnancy within the last 6 weeks.
- I have had a pelvic infection within six weeks prior to the date of the scheduled implantation.
- I have a known allergy to contrast dye used during x-ray procedures.

Patient Initials _____

I understand that successful placement of the Essure devices into both fallopian tubes may not be possible in some women. If that is the case with me, I may need to undergo a repeat attempt at Essure device placement or consider a different form of birth control, because the system works only when both Essure devices are successfully implanted.

Patient Initials _____

I understand that having the insert procedure is only the first step in the process of the Essure System and that I must:

- Use an alternative form of contraception (e.g., intrauterine device (IUD), birth control pill or implant) until my physician tells me I can stop (typically for 3 months, but possibly longer).
- Schedule and undergo the confirmation test recommended by my physician after three months to ensure that my inserted Essure devices are in the proper location and that the fallopian tubes are blocked. I understand that this is a critical part of the Essure System procedure and sterilization process, and that payment for this test may or may not be covered by my insurance company.

Patient Initials _____

I understand that even after the confirmation test, my physician may inform me that I may not be able to rely on the Essure System for permanent contraception. If this occurs, I will have to use an alternative form of contraception. In a recent study with the Essure device, over 90% of women who underwent attempts at device placement were able to rely on the device for contraception.

Patient Initials _____

I understand that no form of birth control is 100% effective and that even if my physician tells me I am able to rely on the Essure System, there is still the small possibility that I may become pregnant. Based on currently available data, the chance of unintended pregnancy for women whose confirmation tests indicate that the devices have been successfully placed and the fallopian tubes have been blocked is less than 1%.

Patient Initials _____

I understand that the risks of the Essure device on a developing fetus during pregnancy have not been established. I also understand that I may be at increased risk for a pregnancy occurring outside of the uterus (“ectopic pregnancy”), which may result in serious and even life-threatening complications. I understand that I should contact my physician immediately if there are any indications I may be pregnant.

Patient Initials _____

I understand the following events were reported to occur during the Essure procedure and/or in the hours or days following insertion. The rates included below in parentheses were reported during the original Essure System studies:

- Cramping (Reported in up to 30% of procedures)
- Mild to moderate pain (Up to 9-10%) or moderate pain (Up to 13%)
- Nausea/Vomiting (Up to 11%)
- Dizziness/Lightheadedness (Up to 9%)
- Vaginal bleeding (Up to 7%)

If I experience any of these events listed above, and they persist or worsen in the days to weeks following implantation, I understand that I should promptly consult my physician as they may be a sign of an Essure-related problem that needs prompt attention.

Patient Initials _____

I understand that following Essure System placement, some women may experience adverse events including persistent pain, device puncture of the uterus and/or fallopian tubes (“perforation”), or movement of the device into the abdomen or pelvis (“intra-peritoneal migration”). There have also been reports of allergy or hypersensitivity reactions in some women.

I understand that if I experience any of the following, I should contact my physician:

- Abdominal, pelvic or back pain that develops or persists more than 1 week following insertion. Data suggest that for those women who do experience pain during and/or immediately after the procedure, most will have their symptoms resolve within a few days, and 99% will have their symptoms resolve within 1 week.
- Signs or symptoms consistent with an allergic or hypersensitivity reaction. These may include persistent changes in my skin (rash, itching) but may also include other persistent symptoms such as chest pain, palpitations, breathing difficulties or wheezing, and intestinal discomfort such as nausea, diarrhea, and vomiting. These types of events, although not reported in the clinical trials supporting device approval, have been reported by women implanted with the Essure System.
- Other signs or symptoms that continue or recur including joint or muscle pain, muscle weakness, excessive fatigue, hair loss, weight changes, and mood changes. These types of events, although not reported in the clinical trials supporting device approval, have been reported to FDA by women implanted with the Essure System.

I understand that these <u>may</u> be signs of an Essure-related problem, which may require prompt evaluation and intervention, including possibly the need for Essure device removal by surgery.

Patient Initials _____

The Essure System contains metals including nickel, titanium, iron, chromium, and tin, as well as a material called polyethylene terephthalate (PET). I understand that some women may develop allergic or hypersensitivity reactions to the device following implantation, even if they have no prior history of sensitivity to those materials. I also understand that there is no reliable test to predict ahead of time who may develop a reaction to the device.

Patient Initials _____

I understand that in some patients, the Essure device can move after placement. I understand there is a possibility that the device could poke through the wall of the uterus or fallopian tubes ("perforation"), and/or travel to other locations in the abdomen or pelvis ("migration"). The rate of perforation in the original Essure System study and several subsequent studies was 1% or less. However, some studies have reported rates up to 3-4%. The rate for device migration into the abdomen or pelvis has not been determined. However, reports of such movement have been rare. I understand that should one of these events occur, the device may become ineffective in preventing pregnancy and may lead to serious adverse events such as bleeding or bowel damage, which may require surgery to address.

Patient Initials _____

I understand that should my physician and I decide that the Essure System should be removed after placement, I will require a surgical procedure and in complicated cases, my physician may recommend a hysterectomy (removal of the entire uterus). I also understand that device removal may not be covered by my insurance company.

Patient Initials _____

CONFIRMATION OF DISCUSSION OF RISKS

Patient: With my signature below, I acknowledge that I have received and read the Essure System for Permanent Birth Control Patient Information Brochure, and that I have had ample time to discuss the items contained within it and on this form with my physician. I have had the opportunity to ask questions and understand the benefits and risks of the device and procedure, and understand that alternative methods of contraception are available. I voluntarily choose to proceed with placement of the Essure device.

_____

Patient Signature and Date

Physician: With my signature below, I acknowledge that I have discussed the benefits and risks of the Essure device and procedure as described in the Essure System for Permanent Birth Control Patient Information Brochure as well as this document. I have also explained the benefits and risks of other contraceptive methods. Should device removal become necessary, I may perform the removal myself, or provide a referral to a physician who is willing and able to perform device removals. I have encouraged the patient to ask questions, and I have addressed all questions.

_____

Physician Signature and Date