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Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization

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Guidance for Industry and Food and Drug Administration Staff

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

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Food and Drug Administration
Center for Devices and Radiological Health
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Office of Surveillance and Biometrics

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Preface

Public Comment

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Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization

Guidance for Industry and Food and Drug Administration Staff

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

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 appropriate only 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, a 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, is 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, adverse events 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 suspected hypersensitivity reactions to the implant materials, persistent pain, irregular vaginal bleeding, fallopian tube or uterine perforation, the identification of inserts in the pelvic cavity, and 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]

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 guidance addresses these concerns by identifying labeling components, namely a boxed warning and patient decision checklist, which FDA intends to require as part of the labeling for these devices. FDA believes this will help to ensure a woman receives and understands the benefits

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[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] *See id*.

and risks associated with her contraceptive options so that she can make an informed decision as to whether a permanent hysteroscopically-placed tubal implant intended for sterilization is the right choice for her.

III. Scope

This guidance identifies the content and format of certain labeling components 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. 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 as part of a premarket approval application (PMA) for permanent hysteroscopically-placed tubal implants intended for sterilization (or a PMA supplement for already marketed devices). 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]

IV. Labeling Components

This section contains the content and format 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

[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.

FDA believes that a boxed warning should be part of labeling 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, use, and/or removal procedure, including those noted in clinical trials, as well as those reported in other device use experience.
- Include a statement noting that these risks should be conveyed to the patient during the 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 document. 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 and marked.

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 deciding 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 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 topic grouping in the body of the checklist (e.g., items related to birth control options, items related to long-term risks of the device) should be accompanied by a line for the patient to initial her acknowledgment and understanding of that information.

At the end, the checklist should include a section that 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 a signature line for the patient. At the end of the checklist there should also be a section that confirms that the physician discussed the benefits and risks of the device, as set forth in the patient decision checklist, with the patient. This should be followed by a signature line for the physician.

The FDA recommends that a copy of the patient decision checklist 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 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.

Appendix B: Patient Decision Checklist Example

To the patient considering the Essure System for Permanent Birth Control ("Essure"):
The review and completion of this document is a critical step in helping you decide whether or not to have Essure implanted. You should carefully consider the benefits and risks associated with the device before you make that decision. After reviewing the information in this brochure, please read and discuss the items in this checklist with your doctor. You should not initial or sign the document, and should not undergo the procedure, if you do not understand each of the elements listed below.

Birth Control Options

I understand that Essure is a permanent form of birth control (referred to as "sterilization"). I understand that sterilization must be considered permanent and not reversible.

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

I am aware that there are highly effective methods of birth control which are not permanent and which may allow me to become pregnant when stopped.

Patient Initials _____

Requirements for Essure Placement and Reliance
I understand that I am not a candidate for Essure 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.

Essure works as intended only when the devices are successfully placed in both fallopian tubes. I understand that if this is not possible in my case, I may need to undergo a repeat attempt at Essure placement or consider a different form of birth control.

I understand that the placement procedure is only the first step in relying on Essure for birth control. After placement I must:

- Use an alternative form of birth control until my doctor tells me I can stop (typically for 3 months).
- Schedule and undergo a confirmation test after three months to determine whether I may rely on Essure. I understand that payment for this test may or may not be covered by my insurance company.

I understand that a satisfactory confirmation test is needed before I can rely on Essure alone. I also understand that after the confirmation test my doctor may inform me that I may not be able to rely on Essure. If this occurs, I will have to use an alternative form of contraception.

I understand that based on clinical studies, approximately 8% of women who undergo attempts at Essure placement are not able to rely on the device for contraception.

Patient Initials _____

Pregnancy Risks

I understand that no form of birth control is 100% effective. Even if my doctor tells me I am able to rely on Essure, there is still a small chance that I may become pregnant. Based on clinical studies, the chance of unintended pregnancy for women who have been told they can rely on Essure is less than 1% at 5 years.

I understand that the risks of Essure on a developing fetus have not been established. If I become pregnant with Essure, there may be an increased risk for the pregnancy to occur outside of the uterus ("ectopic pregnancy"). This may result in serious and even life-threatening complications. I understand that after Essure placement, I should contact my doctor immediately if I think I may be pregnant.

Patient Initials _____

What to Expect During the Procedure and the Days Afterwards

I understand that in clinical studies supporting device approval, the following events were reported to occur during the Essure placement procedure and/or in the hours or days following placement:

- 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 worsening of any of the events listed above or I continue to have the symptoms 1 week after placement, I understand that I should contact my doctor.

Patient Initials _____

Long-Term Risks

I understand that some women may experience continued pain or develop new pain after Essure placement. I understand that I should contact my doctor if abdominal, pelvic or back pain continues for more than 1 week after placement or if I develop the onset of new pain more than 1 week after placement.

I understand that the Essure implants contain 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 reactions to the device following implantation and have signs or symptoms such as rash and itching. This may occur even if there is 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.

I understand that persistent or new pain, and/or allergic reaction may be a sign of an Essure-related problem which might require further evaluation and treatment, including possibly the need to have the devices removed by surgery.

I recognize that other symptoms have been reported to FDA by women implanted with Essure, although they were not seen in the clinical trials supporting Essure approval. The more common symptoms reported include headache, fatigue, weight changes, hair loss and mood changes such as depression. It is unknown if these symptoms are related to Essure or not.

I understand that because Essure contains metals, I should tell all my doctors that I have the device before getting an MRI.

I understand that there is a small possibility that the device could poke through the wall of the uterus or fallopian tubes ("perforation"), and/or move to other locations in the abdomen or pelvis ("migration"). The rate of perforation in studies has ranged from 1% to 4%. The rate for device migration into the abdomen or pelvis has not been determined but its occurrence is uncommon.

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.

I understand that should my doctor and I decide that Essure should be removed after placement, a surgical procedure will be required. In complicated cases, my doctor 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: I acknowledge that I have received and read the Essure Patient Information Brochure, and that I have had time to discuss the items in it and in this document with my doctor. 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 birth control are available.

_____
Patient Signature and Date

Physician: I acknowledge that I have discussed with the patient the benefits and risks of Essure as described in the Essure System Patient Information Brochure as well as this document. I have also explained the benefits and risks of other birth control 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