

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Contraceptive Tubal Occlusion Device and Delivery System

Device Trade Name: Essure™ System

Applicant's Name and Address: Conceptus, Incorporated
1021 Howard Avenue
San Carlos, CA 94070

Premarket Approval Application (PMA) Number: P020014

Date of Panel Recommendation: July 22, 2002

Date of Notice of Approval to Applicant: November 4, 2002

II. INDICATION FOR USE

The Essure™ System is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

III. CONTRAINDICATIONS

The Essure™ System should not be used for

any patient who is

- uncertain about her desire to end fertility;
- for whom only one micro-insert can be placed (including patients with apparent contralateral proximal tubal occlusion and patients with a suspected unicornuate uterus);
- has previously undergone a tubal ligation; or

any patient with any of the following conditions:

- pregnancy or suspected pregnancy;
- delivery or termination of a pregnancy less than 6 weeks before Essure™ micro-insert placement;
- active or recent upper or lower pelvic infection;
- known allergy to contrast media; and
- *known* hypersensitivity to nickel confirmed by skin test. (See Warnings section in labeling regarding *suspected* hypersensitivity to nickel.)

IV. WARNINGS AND PRECAUTIONS

A list of Warnings and Precautions can be found in the device labeling.

V. DEVICE DESCRIPTION

A. Essure™ System Components

The Essure™ System is comprised of the Essure™ micro-insert, a disposable delivery system, and a disposable split introducer.

Essure Micro-Insert

The Essure™ micro-insert is a spring-like device that consists of a stainless steel inner coil, a nickel titanium (Nitinol) expanding outer coil, and polyethelene terephthalate (PET) fibers. The PET fibers are wound in and around the inner coil. The micro-insert, shown below in its wound-down and expanded configurations (Figure 1a and Figure 1b, respectively), is 4 cm in length and 0.8mm in diameter in its wound down configuration. When released from the delivery system, the outer coil expands to 1.5 to 2.0 mm in diameter to anchor the micro-insert in the varied diameters and shapes of the fallopian tube. The spring-like device is intended to provide the necessary anchoring forces during the acute phase of device implantation (3 months post-micro-insert placement), during which time the PET fibers are eliciting tissue in-growth into the coils of the Essure™ micro-insert and around the PET fibers.

Figure 1a
Essure™ Micro-insert:
Shown in its Wound-Down Configuration, Attached to Release Catheter
(NOT TO SCALE)



Figure 1b
Essure™ Micro-insert:
Shown in its Expanded Configuration
(NOT TO SCALE)

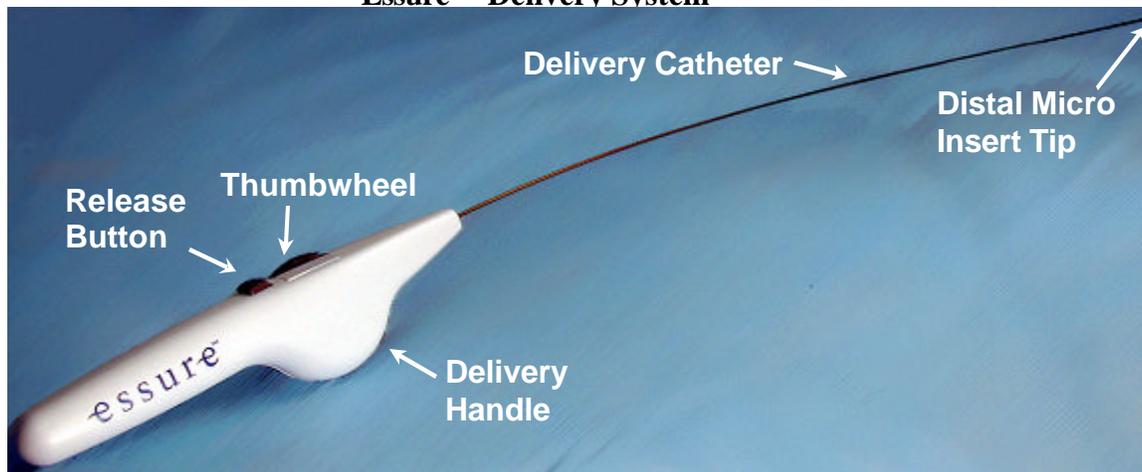


Disposable Delivery System

The disposable delivery system, shown in Figure 2 below, consists of a delivery wire, a release catheter, a delivery catheter and a delivery handle.

NOTE: The delivery wire and the release catheter are not visible in the figure shown below.

Figure 2
Essure™ Delivery System



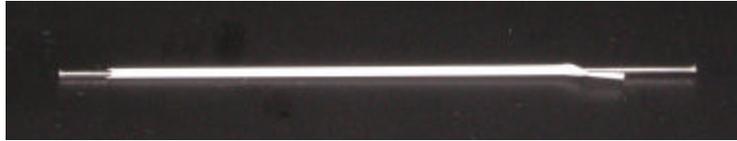
The Essure™ micro-insert is provided attached to the delivery wire, in a wound-down configuration. The delivery wire is composed of a nitinol core wire, which is ground at the distal end to result in a flexible, tapered profile. The device is constrained by the release catheter, which is sheathed by a flexible delivery catheter. A black positioning marker on the delivery catheter aids in proper placement of the device in the fallopian tube.

The delivery handle controls the device delivery and release mechanism. The thumbwheel on the delivery handle retracts both the delivery catheter and the release catheter. The button allows the physician to change the function of the thumbwheel from retracting the delivery catheter to retracting the release catheter. The delivery wire is detached from the micro-insert by rotating the system.

Split Introducer

The split introducer (Figure 3 below) is placed into the sealing cap of the working channel of the hysteroscope, and is intended to help protect the Essure™ micro-insert as it is being passed through the sealing cap of the hysteroscope working channel.

Figure 3
Split Introducer
(NOT TO SCALE)

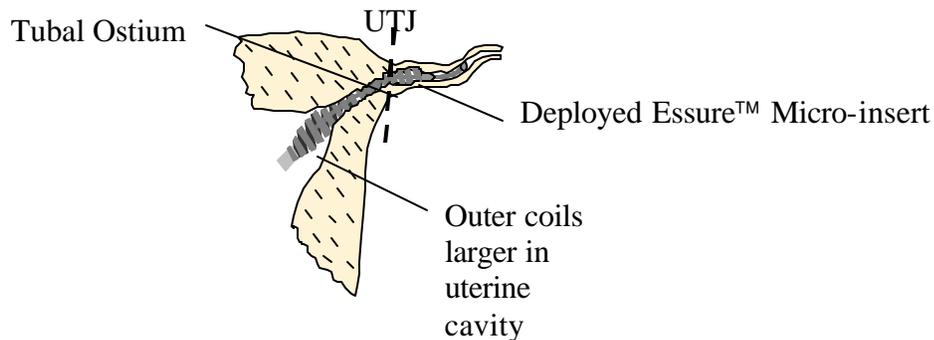


B. Mechanism of Action

1. Placement at Utero-Tubal Junction (UTJ)

The Essure™ micro-insert is intended for placement into the fallopian tube with the implant portion of the device spanning the utero-tubal junction (UTJ). For purposes of micro-insert placement, the UTJ is defined as the portion of the fallopian tube, just as it enters the uterus. (Refer to Figure 4 below for graphic representation of UTJ.) Placement at the UTJ is expected to aid in anchoring since it most consistently represents the narrowest portion of the fallopian tube. Expulsion of the Essure™ micro-insert has occurred when micro-insert placement was too proximal. If the device is placed without any trailing portion of the device in the uterus, then direct visualization of device location is not possible.

Figure 4: Optimal Essure™ Micro-insert Placement



2. Tissue In-Growth

The effectiveness of the Essure™ micro-insert in preventing pregnancy is believed to be due to a combination of the space-filling design of the device and a local, occlusive, benign tissue response to the PET fibers. The tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibers. It is believed that the tissue in-growth into the device caused by the PET fibers results in both device retention and pregnancy prevention.

3. Permanency of Tubal Occlusion (and Sterilization)

The long-term nature of the tissue response to the Essure™ micro-insert is not known. The majority of the clinical data regarding PET in the fallopian tube is based on 12-24 months of implantation, with little data at 36 months. Therefore, beyond 24 months, the nature of the cellular/fibrotic response and the ability of the response and the device to maintain occlusion are not known.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The following alternative practices or procedures are currently available for permanent female sterilization.

- Hysterectomy
- Salpingectomy
- Tubal Ligation
- Tubal Fulguration
- Application of clips, and

The permanent male method is vasectomy.

VII. MARKETING HISTORY

The Essure™ System is currently commercially available in the following countries: Australia, Austria, Belgium, Canada, Denmark, Finland, Germany, Holland, Indonesia, Italy, Norway, Portugal, Singapore, Spain, Sweden, Switzerland, Turkey, and the U.K. CE Mark was granted by TÜV in February, 2001, and a Medical Device License was granted by Health Canada in November, 2001. The Essure™ System has not been withdrawn from marketing for any reason relating to safety and effectiveness.

VIII. OBSERVED AND POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Between November of 1998 and June of 2001, a total of 745 women underwent an Essure™ placement procedure in two separate clinical investigations to evaluate the safety and effectiveness of the Essure™ System (227 in the Phase II study and 518 women in the Pivotal trial¹). Some women underwent more than one procedure if successful bilateral placement was not achieved in the initial procedure.

¹ In the Pivotal trial, 657 women initially enrolled in the study. Ninety-nine women subsequently changed their mind about participating. Twenty-three women were subsequently terminated because they did not meet the inclusion criteria, and 17 failed the screening tests. Therefore, 518 underwent the Essure placement procedure. There were a total of 13 women who were lost-to-follow-up in the Pivotal trial.

A. Observed Adverse Events

Table 1 below presents adverse or other events for patients that delayed or prevented reliance on Essure™ for contraception in the Phase II Study. Four of the six perforations occurred with use of the since-discontinued Support Catheter.

Table 1

Phase II Study -- Adverse or other events that delayed or prevented reliance on Essure™ for contraception

Event	Number	Percent
Perforation	6/206	2.9%
Expulsion	1/206	0.5%
Other unsatisfactory micro-insert location	1/206	0.5%
<i>Initial</i> tubal patency	7/200	3.5%*

* Tubal patency was demonstrated in seven women at the 3-month HSG, but all seven women were shown to have tubal occlusion at a repeat hysterosalpingogram (HSG) performed 6 months after Essure™ placement.

Table 2 below presents adverse or other events for patients that delayed or prevented reliance on Essure™ for contraception in the Pivotal Study. These were primarily micro-insert expulsions following unsatisfactory placement.

Table 2

Pivotal Study - Adverse or other events in Pivotal Study that delayed or prevented reliance on Essure™ for contraception

Event	Number	Percent
Expulsion	14/476	2.9%*
Perforation	5/476	1.1%
Other unsatisfactory micro-insert location	3/476	0.6%
<i>Initial</i> tubal patency	16/456	3.5%**

* Fourteen women experienced an expulsion, however nine of these 14 women chose to undergo a second micro-insert placement procedure, which was successful in all nine cases.

** Tubal patency was demonstrated in 16 women at the 3-month HSG, but all 16 women were shown to have tubal occlusion at a repeat HSG performed 6-7 months after Essure™ placement

Table 3 shows adverse events or side effects reported as a result of the hysteroscopic placement procedure in the Phase II Study.

Table 3

Phase II Study - Adverse events reported on day of placement procedure (n=233procedures)

Event	Number	Percent
Band Detachment*	3	1.3%
Vaso-vagal response	2	0.9%
Pain	2	0.9%

* Band detachment occurs when the platinum band of the outer coil of the micro-insert breaks off during placement. This band holds the outer coil in a wound-down configuration.

Table 4 shows adverse events or side effects reported as a result of the hysteroscopic placement procedure in the Pivotal Study.

Table 4

Pivotal Study - Adverse events and side effects reported on day of placement procedure (n=544 procedures)

Event	Number	Percent
Cramping	161	29.6%
Pain	70	12.9%
Nausea/vomiting	59	10.8%
Dizziness/light headed	48	8.8%
Bleeding/spotting	37	6.8%
Vaso-vagal response/fainting	7	1.3%
Hypervolemia	2	0.4%
Band Detachment	2	0.4%
Other*	16	2.9%

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

Adverse events on the day of the placement procedure were reported for 16 (3%) women in the Pivotal Study. All events were resolved prior to the woman being discharged, except for one woman who required overnight observation following an adverse reaction to pain medication. Day of procedure events included the following, all of which occurred in <1% of cases: vomiting, vasovagal response,

hypervolemia, band detachment, excessive vaginal bleeding, and “other” (skin itching, bloating, loss of appetite, and reaction to saline used for distension).

The majority of women in *both* the Phase II Study and the Pivotal Study experienced mild to moderate pain during and immediately following the procedure, and the majority of women experienced spotting for an average of 3 days after the procedure. Pain was managed in every case with oral non-steroidal anti-inflammatory drugs (NSAIDs) or oral narcotic pain reliever.

Table 5 summarizes all adverse events in the Pivotal Study reported to be at least “possibly” related to the Essure™ micro-insert or micro-insert placement procedure during the first year of reliance on Essure™ (up to approx. 15 months post-procedure).

The most frequently reported adverse events in the first year that did not prevent women from relying on Essure™, but were rated by the Investigator as at least “possibly” related to Essure™ were back pain (9.0%), and abdominal pain/cramps (3.8%), and dyspareunia (3.6%). All other events occurred in less than 3% of women.

Table 5
Pivotal Trial
Adverse Events by Body Systems, First Year of Reliance^{1,2}
(N=476 patients implanted with at least one device)

Adverse Events by Body System	Number	Percentage
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8
Gas/bloating	6	1.3
Musculo-skeletal:		
Back pain/low back pain	43	9.0
Arm/leg pain	4	0.8
Nervous/Psychiatric:		
Headache	12	2.5
Premenstrual Syndrome	4	0.8
Genitourinary:		
Dysmenorrhea/menstrual cramps (severe)	14	2.9
Pelvic/lower abdominal pain (severe)	12	2.5
Persistent increase in menstrual flow ³	9	1.9
Vaginal discharge/vaginal infection	7	1.5
Abnormal bleeding - timing not specified (severe)	9	1.9
Menorrhagia/prolonged menses (severe)	5	1.1
Dyspareunia	17	3.6
Pain/discomfort - uncharacterized:	14	2.9

¹ Only events occurring in $\geq 0.5\%$ are reported.

² The percentages presented reflect the number of *events* in the numerator and the number of *women in the trial wearing at least one micro-insert* in the denominator. While a woman reporting numerous episodes of the same event is represented in the numerator as multiple reports of that event, she is represented in

the denominator only once. Consequently, in some cases these percentages over-represent the percentage of women who have experienced that event.

³ Eight women reported persistent *decrease* in menstrual flow.

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

B. Potential Adverse Events Not Observed in Clinical Studies

The following adverse events were not experienced by women who participated in clinical studies evaluating the Essure™ System but are still possible:

- pregnancy, including ectopic pregnancy, in women relying on Essure™ device*;
- perforation of internal bodily structures other than the uterus and fallopian tube;
- adnexal infection/salpingitis;
- adverse events associated with the hysterosalpingogram (HSG) or x-rays;
- the effect of future medical procedures that involve the uterus or fallopian tubes on the ability of the Essure™ micro-insert to provide protection against pregnancy;
- adverse events associated with surgery attempting to reverse the Essure™ procedure, as well as adverse events associated with pregnancy following a reversal procedure or an *in vitro* fertilization (IVF) procedure; and
- adverse events associated with gynecologic surgical procedures (e.g., endometrial ablation).

* In the Phase II Study, one woman who received a prior device design that was discontinued in 1998 (the Beta design of the STOP device) became pregnant after nearly two years of reliance on Essure™ for contraception. That pregnancy is not included in the effectiveness rate calculations, since that device design was not subject of the PMA that supported approval of the Essure™ System.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Preclinical studies included several iterations of testing that began with concept testing on an early model of the system. This led to feasibility testing on the next generation system, culminating in verification testing on the final Essure™ System.

A summary of these iterative tests are provided below:

1. Concept Testing of the Essure™ System

Concept testing was performed in the initial design evaluation with the objective being to help design the Essure™ System for optimal safety and performance. Concept testing consisted of: evaluation of navigation and deployment in pig fallopian tubes and varying fixtures; tensile testing of raw materials, solder bonds and subassemblies; initial tip fatigue evaluation;

release mechanism testing; delivery wire release testing; handle process evaluation; torque evaluation; Initial corrosion analysis; and, fibering evaluation.

2. Feasibility Testing of the Essure™ System

Feasibility testing was conducted to evaluate product consistency in meeting design input specifications. The feasibility testing included the following: positioning marker evaluation; catheter tip integrity testing; fiber configuration testing; tracking and retraction evaluation in multiple orientations; tensile testing of subassemblies; handle functional testing; nitinol flux evaluation, and corrosion/leaching evaluation.

3. Verification Testing of the Essure System

Verification activities included worst-case (tolerance) analysis, FMEA review, packaging integrity, clinical testing, biocompatibility, bioburden, as well as comparisons to previous designs/products using multiple methods such as testing, inspection, and technical analysis.

The design and process verification testing for the Essure™ System consists of

- tensile strength testing to evaluate bonds between components in the delivery system and micro-insert, as well as to evaluate several raw materials;
- functional testing to evaluate selected steps at the sub-system level;
- environmental cycle testing to show functionality after exposure to environmental and aging conditions;
- tracking force testing to establish worst-case compression and verify tracking characteristics in the fallopian tube;
- flexibility testing to assess the delivery catheter for longitudinal and axial bend-ability;
- anchoring testing to establish the anchoring strength of the micro-insert in a fallopian tube simulation under various dynamic forces;
- raw material specification verification;
- chemical analysis of the etched nitinol material to determine worst-case nickel leaching;
- corrosion analysis of the Essure™ Micro-insert; and
- testing to ensure compatibility with MR imaging. (See labeling for additional precaution.)

4. Biocompatibility

The Essure™ System has undergone extensive biocompatibility testing. The following studies were conducted:

Body Contact	Contact Duration	Biologic Tests Conducted
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Body Contact		Contact Duration	Biologic Tests Conducted
Delivery System	Surface Device with Tissue Contact	A- Limited (<24 hrs)	1. Cytotoxicity 2. Sensitization 3. Irritation
Micro-insert	Implant Device with Tissue Contact	C- Permanent (>30 days)	1. Cytotoxicity 2. Sensitization 3. Genotoxicity 4. Implantation 5. Irritation 6. <i>In Vivo</i> Mutagenicity 7. Sub Chronic Toxicity 8. Acute Systemic Toxicity

Extracts prepared from the Micro-insert did not exhibit any detectable toxicity during biocompatibility testing. Muscle implantation studies of the Micro-insert in rabbits demonstrated an inflammatory response consistent with the desired *in vivo* reactions to polyethylene terephthalate (PET) fiber.

Polar and non-polar extracts of the Essure™ Micro-insert did not elicit any evidence of *in vitro* cytotoxicity or *in vivo* delayed dermal contact sensitization. Similarly, extracts of the Essure™ Micro-insert did not elicit vaginal irritation or any evidence of acute or sub-chronic systemic toxicity. In addition, evaluations of genotoxicity (bacterial reverse mutation, mouse lymphoma, mouse bone marrow micronucleus test and chromosomal aberrations tests) did not reveal any mutagenic or genotoxic effect of the Essure™ Micro-insert. Implantation of either one or three Essure™ micro-inserts into female double transgenic mice resulted in no adverse toxicological effects and no increase in gene mutations at the site of implantation. Lastly, the implantation of the Essure™ micro-insert in the paravertebral muscle of rabbits over a 26-week implantation period demonstrated that the Essure™ micro-insert was not systemically or locally toxic.

Extensive biocompatibility testing of the Essure™ micro-insert and delivery system has been conducted and the data support the biocompatibility of the entire system. In addition, the data obtained from the biocompatibility testing of Essure™ are consistent with the long history of safe use of the biomaterials contained in the Essure™ micro-insert and the well-characterized *in vivo* response to PET materials in other organ systems.

B. Other Animal Studies

Three separate rabbit studies were performed during the initial stages of development of the Essure™ micro-insert. These studies evaluated the performance of early device designs. These studies provided early

proof-of-concept and effectiveness data and supported the feasibility of the device concept.

C. Sterilization

The Essure™ device is provided sterile and for single use only. The sterilization method used for the Essure™ device is 100% ethylene oxide (EO). The sterility assurance level is 10^{-6} . The standard used to validate the sterilization method is ANSI/AAMI/ISO 11135-1994 Medical Devices, validation and routine control of ethylene oxide sterilization.

D. Shelf-Life Testing

Conceptus conducted shelf-life studies to establish and support expiration dating for the Essure™ System. These studies include an Environmental Conditioning and Package Performance (Shipping) study, and a Real Time Aging study. The shelf-life tests performed for the package and cytotoxicity are ASTM D4169, ASTM E515, ASTM F88 and NAMSA protocol V14. Real-time aging studies were used to establish a nine-month shelf-life.

X. CLINICAL STUDIES

A. Early Clinical Studies

1. Peri-hysterectomy study – 99 subjects

The specific objectives of the study were to

- evaluate new micro-insert placement techniques and delivery systems; and
- assess acute tubal occlusion immediately after micro-insert placement.

This study was a single-arm, prospective, non-randomized, non-controlled, multi-center, international study to test the placement feasibility of various micro-insert designs and design iterations. Clinical variables that were evaluated included:

- ability to cannulate the fallopian tube;
- ability to release the micro-insert;
- ability to remove the guidewire catheter system;
- immediate tubal occlusion (as demonstrated by non-patent tubes under chromopertubation); and
- acute retention of the micro-insert (evaluated by the tug test).

The patient population consisted of women who were scheduled to undergo a hysterectomy, who met the inclusion and exclusion criteria, and who were willing to prolong the operative time of their hysterectomy

procedure in order to have micro-inserts placed while under anesthesia (general or regional).

The study demonstrated the feasibility of the micro-insert to be reliably and safely placed in the fallopian tube at a reasonably high rate for this patient population. The system was shown to be able to access 80% of tubes bilaterally and 6% unilaterally, despite preexisting uterine pathology. An Essure™ micro-insert was placed bilaterally in 73% of participants and unilaterally in 13% of participants. Overall, a micro-insert was placed in 96% of the tubes that could be accessed. The micro-insert also showed its ability to acutely anchor in the fallopian tube, as demonstrated by a “tug test,” in 95% of micro-inserts tested. The placement procedure and micro-insert were shown to be safe with only three adverse events (3%) reported, none of which had clinical sequelae. Immediate occlusion of the fallopian tube was demonstrated in 82% of tubes tested, using chromopertubation.

2. Prehysterectomy study – 63 subjects

The objectives of the Pre-hysterectomy study were to evaluate

- placement of the micro-insert in the proximal portion of the fallopian tube, ideally so that the outer coil spans the uterotubal junction (UTJ);
- detachment of the micro-insert from the delivery wire;
- the woman’s tolerance of and recovery from the micro-insert placement procedure;
- micro-insert stability within the fallopian tube until the hysterectomy;
- tubal occlusion within 24 hours to 12 weeks of micro-insert placement (as demonstrated by non-patent tubes under hysterosalpingogram (HSG);
- the local tissue response to the micro-insert; and
- the effect of fiber on the ability of the micro-insert to create a local tissue response.

Participants were women with benign conditions scheduled for hysterectomy and who were willing to undergo Essure™ micro-insert placement and wear the micro-inserts from 24 hours to 12 weeks prior to hysterectomy.

Fifty-four women (54/63, 86%) were implanted with at least one Essure™ micro-insert, 46 bilateral and 8 unilateral. They were to be followed from 24 hours to 12 weeks, however, several were seen at 16 weeks with one outlier case at 30 weeks, to the time of their hysterectomy. Within 72 hours prior to the hysterectomy, they underwent an HSG to determine tubal occlusion. Following hysterectomy, the uterus was x-rayed and micro-insert location evaluated, the uterus was bivalved and examined for gross pathologic findings, and the tubes were removed and histologically

evaluated. During the time of micro-insert wearing, women recorded any side effects they experienced on a daily log.

The procedure was found to be safe with minimal post-procedure discomfort and sequelae and minimal adverse events. The short-term wearing of the micro-insert was also found to be acceptable, with no side effects reported in the participant diaries.

While 3 perforations were noted at the time of hysterectomy, 2 were with the since-discontinued support catheter (no longer part of the Essure™ System). Women who experienced the perforations reported no discomfort or difference in tolerance to the micro-inserts from women without perforation.

The local, occlusive, benign tissue response demonstrated by histological evaluation of the specimens supports the theorized mechanism of action. The acute inflammatory response and low level chronic inflammatory response is consistent with other devices that have used PET fibers. The reaction is confined, however, to the area immediately adjacent to the micro-insert and does not extend beyond the tubal wall. Also, immediately distal to the micro-insert, the tube resumes its normal appearance.

This study demonstrated that the tissue in-growth reaction is predictable, occurred in all specimens containing fibered section of the micro-insert, was localized to the micro-insert, and did not result in adverse clinical sequelae.

B. Clinical Studies on Safety and Effectiveness

Description of Clinical Effectiveness Studies

The PMA included data from two clinical effectiveness studies: (i) a 'Phase II Study' and (ii) a 'Pivotal Study'. A total of 745 women underwent the Essure™ procedure in these two trials, including 632 women with successful bilateral placement and at least one year of safety and effectiveness follow-up. (An additional five women have been followed who are relying on only a single device.)

Purpose of the Study, Study Design, Primary Endpoints

Conceptus conducted the two clinical trials (Phase II Study and Pivotal Study) to demonstrate the safety and effectiveness of the Essure™ System in providing permanent contraception. For both studies, all study participants were screened for eligibility to participate in the clinical study. A complete medical history was obtained. A physical examination, a pelvic examination and required laboratory tests (including a pregnancy test) were conducted.

An Essure™ device placement procedure was attempted on each fallopian tube. A pelvic x-ray was performed within 24 hours following device placement to serve as a baseline evaluation of device location. Participants were instructed to use either a barrier contraceptive method or oral contraceptives for the first 3 months following the device placement procedure. In both studies, reliance on the Essure™ System for permanent contraception began only after HSG confirmation (three-months post-procedure) that the fallopian tubes were no longer patent. Because of the similarity of the Phase II Study and Pivotal Study, contraceptive effectiveness results from the two studies were combined using Bayesian statistics.

1. Phase II Study of Safety and Effectiveness

The Phase II study was a prospective, multi-center, single-arm, non-randomized, international study of women seeking permanent contraception.

The objectives of the Phase II Study were to evaluate

- the woman's tolerance of, and recovery from, micro-insert placement;
- the safety of the micro-insert placement procedure;
- the woman's tolerance of the implanted micro-inserts;
- the long-term safety and stability of the implanted micro-inserts; and
- the effectiveness of the micro-inserts in preventing pregnancy.

All women filled out a questionnaire one week after micro-insert placement, documenting any bleeding, discomfort or other symptoms they experienced following the procedure. They were also asked about their perceptions of the placement procedure. Women then kept diaries for 6 months detailing menstrual and sexual activity, as well as accompanying symptoms.

During the first three months following micro-insert placement, women were required to use an alternative form of contraception. This alternative contraception period was to allow adequate time for the tissue in-growth process to occlude the fallopian tube. Women could choose a barrier method or oral contraceptives for their alternative contraception.

At three months post-procedure, women underwent an HSG and an ultrasound or an HSG alone to determine micro-insert position and retention, and to evaluate occlusion of the fallopian tubes. If the micro-inserts were in a satisfactory location, women were advised to discontinue alternative contraception and rely on the micro-inserts for contraception. Women were then followed at the 6, 12, and 18-month post-procedure time points, and 24 months after discontinuation of alternative contraception. The study was amended to also include follow-up at 3, 4, and 5 years after discontinuation of alternative contraception.

Less than 1% of women experienced an adverse event on the day of the procedure. Adverse events experienced after the day of the procedure that prevented reliance on Essure™ occurred in less than 4% of women.

The primary adverse event experienced was perforation (2.9%). Of the six perforations, four (67%) occurred with women where the since-discontinued support catheter was used. The support catheter was discontinued prior to commencement of the Pivotal Trial, and the perforation rate in the Pivotal Trial was approximately 1%.

The long-term tolerance to wearing the Essure™ micro-inserts was found to be “good” to “excellent” in 99% of women who have been followed-up for up to 2 years.

None of the women in the Phase II Study became pregnant while relying on the final version of the micro-insert. One woman relying on an earlier version of the micro-insert did become pregnant.

2. Pivotal Study of Safety and Effectiveness

The Pivotal Study was a prospective, multi-center, single-arm, non-randomized, international study of women seeking permanent contraception. This study was conducted in the U.S., Europe, and Australia. The targeted study population was 400 women in whom bilateral micro-insert placement was achieved. The study used findings from the U.S. Collaborative Review of Sterilization (CREST study) as a qualitative benchmark (Ref. 1).

Primary endpoints for the Pivotal Study included

- pregnancy (after HSG confirmation of occlusion);
- safety of device placement procedure; and
- safety of device wearing.

Secondary endpoints of the Pivotal Study included

- participant satisfaction with device placement procedure;
- participant satisfaction with device wearing;
- bilateral device placement rate; and
- data for development of clinical patient profile for appropriate Essure™ candidates.

The Pivotal Study had two phases: 1) the Post-Device (micro-insert) Placement (PDP) phase, and 2) the Post-Alternative Contraception (PAC) phase. The PDP phase was the time period between micro-insert placement and the 3-month visit, during which women were instructed to rely on alternative contraception. At the 3-month visit, an HSG and a scout film x-ray were performed to evaluate micro-insert location and occlusion. If both were

satisfactory, women were instructed to discontinue alternative contraception, thus entering the PAC phase of the study, during which they relied solely on Essure™ for contraception. If the HSG was not satisfactory, then, depending on the circumstances, women were instructed to either seek alternative contraception or remain in the PDP phase until a second HSG or micro-insert placement procedure was performed. The visits in the study are described as follows:

Micro-insert Placement

Women underwent the micro-insert placement with typically either local anesthesia alone or with IV sedation. Following the placement procedure women completed a questionnaire on pain assessment and satisfaction.

One-Week

During the first week after the procedure, women were asked to complete a series of questionnaires to evaluate recovery and satisfaction. In addition, there was a phone visit at the one-week time point that served to remind women of the need for alternative contraception, and to assess any adverse events.

3-Month Post-Device Placement (PDP) Visit

Women were then seen at the 3-month post-device placement follow-up visit.

This visit included

- pelvic exam;
- pregnancy test;
- verification of partner fertility and coital activity;
- questions on satisfaction, adverse events, concomitant medications, etc.; and
- HSG to evaluate micro-insert location and tubal occlusion.

Post-Alternative Contraception (PAC) Phase

Phone follow-up visits were scheduled for 3, 6 and 18 months of reliance on the micro-inserts for contraception. The phone visits include questions on

- verification of coital activity, sole reliance on Essure™, and partner fertility;
- satisfaction/comfort;
- plans for intrauterine procedures or extirpative surgery of reproductive organs; and
- adverse events or unusual symptoms.

Office follow-up visits were scheduled for years 1, 2, 3, 4 and 5. The office visits included

- pelvic exam (at years 1, 2, and 5);
- pregnancy test (at years 1, 2, and 5);
- x-ray verification of micro-insert retention (at years 1, 2, and 5);
- verification of coital activity, sole reliance on Essure™, and partner fertility;
- questions regarding comfort and overall satisfaction;
- questions regarding any plans for intrauterine procedures or extirpative surgery of reproductive organs; and
- adverse events or unusual symptoms.

3. Effectiveness Results for Phase II and Pivotal Studies

Of the 632 women enrolled in the two clinical effectiveness trials (with bilateral micro-insert placement) and who relied on the Essure™ System for contraception for 12 to 24 months, no (zero) pregnancies have been reported. Of the 632 women, all have been followed for 12 months, 197 have been followed for 24 months, and 34 have been followed for 36 months. Adverse events that were reported in the clinical studies are discussed in Section VIII B.

Placement Rates

Of the 518 women who underwent hysteroscopy, bilateral placement was achieved in 446/518 (86%) after the first procedure and 464/518 (90%) after a second procedure. Of the 54 women for whom bilateral placement was never achieved, 11 did not undergo a placement attempt micro-insert placement because the tubal ostia could not be visualized. In addition, two women were found to have a unicornuate uterus (both of whom received unilateral placement with Essure™). Also, of women who never achieved bilateral placement and who also underwent a follow-up HSG, 15/18 (83%) were diagnosed with proximal tubal occlusion (PTO).

Reliance Rates

Of the 464 women with bilateral placement, 449 (97%) were ultimately able to rely on Essure™ for contraception. Inability to rely on Essure™ for contraception was due to expulsion, perforation, other unsatisfactory micro-insert location, or loss-to-follow-up.

Table 6 presents the placement and reliance rates for the Phase II Study and Pivotal Study.

Table 6
Micro-insert Placement and Reliance Rates

Outcome	Phase II N=227		Pivotal N=518	
	Number	Percent	Number	Percent
Bilateral Placement*: <i>After one procedure</i>	196/227	86%	446/518**	86%
Bilateral Placement*: <i>After two procedures</i>	200/227	88%	464/518**	90%
Reliance Rate***: <i>Among women with bilateral placement</i>	194/200	97%	449/464	97%

* The placement rates presented here are based on data from the Essure™ clinical trials. Data on the placement rates in the commercial setting are being gathered in a post-approval study. As updated data regarding placement rates are included in the product labeling, they will also be posted on the Conceptus website: www.Essure.com

** Of the 54 women for whom bilateral placement was never achieved, 11 did not undergo a placement attempt micro-insert placement because the tubal ostia could not be visualized. In addition, two women were found to have a unicornuate uterus (both of whom received unilateral placement with Essure™). Also, of women who never achieved bilateral placement and who also underwent a follow-up HSG, 15/18 (83%) were diagnosed with proximal tubal occlusion (PTO).

***The reliance rate is the number of women who were able to rely on Essure™ for birth control (i.e., the 3-month HSG indicated correct location and bilateral occlusion) divided by the number of women with successful bilateral micro-insert placement. Note: Three of the 449 in the Pivotal Study decided to rely on Essure™ without the recommended 3-month HSG and visit.

Tables 7 presents the principal contraceptive effectiveness rates for the Phase II Study, Pivotal Study, and combined, as of October 2002.

Table 7
Effectiveness Results as of October, 2002

Cumulative Failure Rates	Phase II N=193	Pivotal Trial N=439	Both Trials Combined N=632
One-Year*	0%** (95% CI 0 – 1.53%) (Adj 95% CI 0-2.19%***)	0%** (95% CI 0 – 0.68%) (Adj 95% CI 0 – 0.78%***)	0%** (95% CI 0 – 0.47%) (Adj 95% CI 0 – 0.57%***)
	Phase II N=181	Pivotal Trial N=16	Both Trials Combined N=197
Two-Year*	0%** (95% CI 0 – 1.54%) (Adj 95% CI 0 – 2.36%***)	0%** (95% CI 0 – 0.86%) (Adj 95% CI 0 – 0.93%***)	0%** (95% CI 0 – 0.55%) (Adj 95% CI 0 – 0.67%***)

- * While the one- and two-year effectiveness rates for Essure™ compare quite favorably to the effectiveness rate for other methods of tubal sterilization at these time points, longer-term data on Essure™ are not available and may not compare favorably to other methods once these data are obtained. Follow-up of the women in both the Phase II and Pivotal trials is ongoing, and will continue to 5 years of follow-up. As updated data regarding longer-term failure rates are included in the product labeling, they will also be posted on the Conceptus website: www.Essure.com.
- ** Although the effectiveness rate established in the clinical trials of Essure™ was 100%, no method of contraception is 100% effective, and pregnancies are expected to occur in the commercial setting.
- *** Adjustment using indirect method (CDC CREST study population, Ref. 1) based on the three age groups given in Table 8.

4. Patient Demographics for Phase II and Pivotal Studies

The population of the two studies combined consisted of 664 women in whom bilateral device placement was achieved after one or more attempts (200 in the Phase II study and 464 in the Pivotal trial). All study participants were between 21 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had at least one live birth, had regular, cyclical menses and were able and willing to use alternative contraception for the first three months following Essure™ micro-insert placement.

Tables 8 and 9 present age distribution and other patient demographics.

Table 8
Age Distribution

Study	<28 years old	28-33 years old	=34 years old
Phase II (mean age: 35)	7%	23%	70%
Pivotal Trial (mean age: 32)	17%	47%	36%

Table 9
Patient Demographics

	Phase II N=227	Pivotal Trial N=518
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Race	Not collected	
White/Caucasian		428
Latin		31
Black		24
Other		9
Gravidity	Mean=2.6 (0-10.0)	Mean=3.03 (1.0-11.0)
Parity	Mean=2.2 (0-5.0)	Mean=2.26 (1.0-6.0)
Body Mass Index (BMI) (kg/m²)	Mean=26 (17-57)	Mean= 27(16-52)

5. Other Results from Pivotal Study

Adverse Event Rate

Adverse events observed in the pivotal trial are discussed in Section VIII.

Patient Satisfaction/Comfort

Women in the study consistently rated their overall satisfaction and comfort in wearing the Micro-inserts as very high. At all study visits after the One-Week phone visit, 99% of women rated their comfort with wearing Essure as “good” to “excellent”. At all study visits, at least 98% of women rated their overall satisfaction as somewhat to very satisfied (this included women who were not able to rely on Essure).

Luteal Phase Pregnancies

There were 4 luteal phase pregnancies reported in the Pivotal Trial (pregnancies occurring prior to Essure™ micro-insert placement but not detected on the day of placement). None of these 4 women became pregnant while relying on Essure™ for contraception. Three of the pregnancies in these four women were terminated and one ended in a spontaneous miscarriage. Each of the four women was subsequently able to rely on Essure™ for contraception and has not reported a pregnancy while relying on Essure™.

XI. CONCLUSIONS DRAWN FROM STUDIES

In vitro assays, acute and sub-chronic animal studies revealed no evidence of local or systemic toxicity, or undesirable tissue response. Results of *in-vitro* cytotoxicity testing were negative. Results of a 12-week *in-vivo* mutagenicity study in female double transgenic mice resulted in no adverse toxicological effects and no increase in gene mutations at the site of implantation. Results of a 26-week toxicity study in rabbits showed no adverse local device effects or systemic toxicity. An *in-vitro* study of the safety and compatibility of the Essure™ micro-insert with MRI showed that the device is safe at 1.5 tesla, though localized MR image artifact (within the pelvis) is likely.

The human clinical data provide a reasonable assurance based on valid scientific evidence that the Essure™ System has been shown to be safe, acceptable to women, and effective, with age-adjusted one- and two-year cumulative probabilities of failure (pregnancy) of 0% (95% CI 0.00-0.57%) and 0% (95% CI 0.00-0.67%), respectively.

XII. RISK/BENEFIT ANALYSIS

A. Risks

The most significant risk with the Essure™ System noted in the Pivotal Study was the inability to rely on the Micro-inserts for contraception, due either to inability to achieve bilateral placement initially (14%), or misplacement of the micro-inserts which resulted, in turn, in perforation, proximal placement leading to expulsion, or other unsatisfactory micro-insert location (initially 4.5%, ultimately 2.6%).

In addition, data from these two clinical effectiveness studies are based on only 1-year and 2-year follow-up. The risks of long term implantation are unknown. This is of special significance with respect to pregnancy, including ectopic pregnancy.

B. Benefits

The Essure™ System provides permanent birth control without invasive surgery or general anesthesia, and their associated risks.

The majority of women returned to normal activities within one day or less after the procedure. The vast majority of women rated their comfort with wearing the Micro-inserts at one-week as “good” to “excellent”. The vast majority of women rated their overall satisfaction with the Essure™ System as “very satisfied”.

In addition to the above benefits, none of the women in the Essure clinical trials became pregnant while relying on Essure for contraception.

Essure does not contain drugs or hormones.

XIII. PANEL RECOMMENDATIONS

On July 22, 2002, the Obstetrics and Gynecology Devices Advisory Panel met and recommended approval of the PMA for the Essure™ System with the following conditions:

1. Conceptus will continue to follow all study subjects from the Phase II Study and Pivotal Study for at least five (5) years;

2. Conceptus will conduct a postapproval study to evaluate bilateral placement for newly trained physicians;
3. A 3-month HSG after device placement should remain the method for confirming proper device location and tubal occlusion;
4. Conceptus will institute a clinical training plan, with the following stipulations:
 - Statement of physician qualifications, “knowledgeable hysteroscopist”
 - Minimum number of cases performed under preceptor supervision to achieve competency
5. Labeling should address the following:

Professional Labeling

- Clear and prominent information on the lack of long-term data and unknown failure rate beyond two years;
- 14% failure to achieve bilateral placement of devices during the first attempt (i.e., 1st surgical procedure);
- Information on back-up plan in the event that one or both devices cannot be satisfactorily placed;
- Placement of micro-inserts should be performed during the early proliferative phase of the menstrual cycle in order to decrease the potential for micro-insert placement in a patient with an undiagnosed (luteal phase) pregnancy and to enhance visualization of the fallopian tube. In women with menstrual cycles shorter than 28 days, the day of ovulation must be carefully calculated to reduce the potential of a luteal phase pregnancy. Device placement should NOT be performed during menses;
- Information on the relationship between age, regret, and patient selection and the correlation between patient age and changing her mind;
- The Essure™ System should be considered irreversible;
- Information on the recommended duration of the placement procedure and limit of 1,500 ml of saline for fluid deficit during the hysteroscopic procedure;
- Success rate (failure rate), explain carefully; give qualifications and limitations
- Electrosurgery should be avoided in procedures undertaken on the uterine cornua and proximal fallopian tubes without either hysteroscopic visualization of the micro-inserts, or visualization of the proximal portion of the fallopian tube via open surgical procedures or laparoscopy
- Inform the physician that there is a theoretical increased risk of ectopic pregnancy in patients with the Essure™ micro-inserts, should they become pregnant, since this increased risk exists for incisional methods of tubal ligation.

Patient Labeling

- Provide carefully worded description of expected success (limitations on follow-up, etc.);
- The patient should be clearly informed that the Essure procedure is permanent and there is no data to support its reversibility;
- Include warning about risks of certain kinds of future surgical procedures, e.g., electrosurgical;

- recommendations on what patients should do in the event of a missed period. There is a theoretical increased risk of ectopic pregnancy in patients with the Essure™ System micro-inserts, should they become pregnant, since this increased risk exists for incisional methods of tubal ligation.

XIV. CDRH DECISION

CDRH granted this PMA an expedited review because it offers significant advantages over existing approved alternatives for permanent birth control. Namely, the Essure™ System is delivered hysteroscopically without general anesthesia or an abdominal incision.

CDRH concurred with the Panel's recommendations, and Conceptus adequately addressed all issues raised by the panel. CDRH found the Essure™ System to be safe and effective for permanent birth control. In reaching this conclusion, CDRH considered long-term effectiveness data on alternative methods, especially data from CDC's U.S. Collaborative Review of Sterilization (Ref. 1).

As a condition of approval, Conceptus agreed to conduct a post-approval study in order to gather long-term safety and effectiveness data, with 5-year follow up on all patients from the Phase II and Pivotal studies. In addition, Conceptus also agreed to conduct a post-approval study to evaluate the bilateral placement rate for newly trained physicians. This study is intended to document the bilateral placement rate for newly trained physicians (800 patients, 40 physicians, first 20 attempts). These data will be used to evaluate the training procedures and to update labeling.

FDA inspected Conceptus' manufacturing facilities and determined them to be in compliance with the Quality System Regulation (21 CFR 820).

CDRH issued an approval order on November 4, 2002.

Reference 1 – Peterson et al., *Am J Obstet Gynecol*, 1996, 174(4), 1161-1170

XV. APPROVAL SPECIFICATIONS

Direction for use: See the Device Labeling.

Hazards to Health from Use of the Device: See Indication, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.