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VI. RISK/BENEFIT

DRAFT PREPARED BY CYTYC;
NOT YET REVIEWED BY FDA

Current Medical Need for and Risks and Benefits of the Adiana Transcervical Sterilization System

This document is intended to provide a brief description of the current need for new, safe, and highly effective contraceptive options, and to discuss the risks and benefits associated with the Adiana System.

Problems of Unintended Pregnancies, and Maternal Mortalities and Morbidities

In the United States, the average age for initiation of sexual activity is 17.[1] Women, on average, marry and deliver their first child by the age of 25, and achieve their desired family size of two children by the age of 31.[2,3] Taking this into account, the average American woman spends nearly three decades avoiding pregnancy despite continued sexual activity. As such, an estimated 43 million women are of reproductive age, at risk for unintended pregnancy, and in need of an effective contraceptive method.[4] It therefore is not surprising that the Centers for Disease Control and Prevention (CDC) cited family planning among the 10 most significant achievements for US public health in the 20th century.

In the year 2001 alone, there were 6.1 million pregnancies recorded in the US, and 49% of these were considered unintended.[5] It has been estimated that over half of all unplanned pregnancies end in abortion.[6] It also has been reported that just over half of all

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[1] The Guttmacher Report on Public Policy. December 2003, Volume 6, Number 5
[2] www.census.gov/population/www/socdemo/fertility/mar-fert-slides.html accessed October 23, 2007
[3] http://www.cdc.gov/mmwR/preview/mmwrhtml/mm5419a5.htm accessed October 23, 2007
[4] Mosher WD et al. Use of contraception and use of family planning services in the United States: 1982-2002, Advance Data from Vital and Health Statistics, No. 350. 2004.
[5] Finer LB and Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001, Perspectives on Sexual and Reproductive Health, 2006, 38:90-96.
[6] http://www.cdc.gov/nchs/data/series/sr_23/sr23_025.pdf accessed October 20, 2007

pregnancies occurred because of a failure to use adequate contraception.[7] For sexually active women whose intention is pregnancy prevention, failure to use a contraceptive method is in part the result of an access problem, i.e., a failure to overcome difficult economic and structural situations. However, studies indicate that dissatisfaction with various prevention methods also contribute to the high rate of unintended pregnancies, as patients perceive some methods to be undesirable and compliance with others to be overly complex. Although married women often report lower rates of contraceptive failure, unintended pregnancy, and abortion than do single women, the most recent data indicates that nearly one million married US women experience an unintended pregnancy each year and that the majority of those who choose to abort were practicing contraception but used their chosen method(s) inconsistently.[8] Thus, to prevent undesired pregnancies, the availability of contraceptive methods that are safe, effective, acceptable to patients, and easily complied with is critical. Further, because patient perceptions and needs vary, it is important for women to have a wide range of contraceptive options; studies conducted in geographic locations where choices are limited have consistently confirmed the benefit of having additional methods made available to both current and new contraceptive users.[9]

It is important to understand that the risks of unintended pregnancy are multi-factorial and go far beyond questions of unexpectedness and concerns related to abortion. Specifically, undesired and unplanned pregnancies can lead to inadequate prenatal care, poor birth spacing, conception prior to the emotional and financial stability that often comes with adulthood, and/or the health risks associated with conception at an advanced maternal age. Each of these factors possesses substantial risks for the mother, her fetus, and eventually, her newborn.[10] In fact, it has been reported that the likelihood of preterm delivery, premature rupture of membranes, and delivery of a low birth weight infant all

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[7] Finer LB and Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001, Perspectives on Sexual and Reproductive Health, 2006, 38:90-96.
[8] Henshaw SK, Unintended pregnancy in the United States, *Family Planning Perspectives,* 1998, 30(1):24-29 & 46.
[9] Ross, J., Stover J, and. Adelaja D, *Profiles for Family Planning and Reproductive Health Programs: 116 Countries*. Second Edition. Futures Group, 2004.
[10] The Guttmacher Report on Public Policy. December 2003, Volume 6, Number 5

increase when pregnancies are unintended rather than intended or mistimed.[11] Further, the CDC's Morbidity and Mortality Weekly Report (MMWR) indicates that women who have live births associated with an unintended pregnancy are more likely to have delayed the start of prenatal care, maintained poor nutrition during pregnancy, and used alcohol while pregnant.[12] Thus, the health-related impacts extend beyond the immediate choices of how to deal with an unintended pregnancy.

In the US, more than 10,000 women give birth each day, and 2-3 women die from a pregnancy related complication. According to the MMWR, the most frequent causes for pregnancy-related deaths in the US are:

- Embolism (20%);
- Hemorrhage (17%); and
- Pregnancy induced hypertension (16%).

In addition to these causes, other reasons for death include cardiovascular, pulmonary, and neurological/neurovascular conditions.[13] As a separate but related issue, it also has been observed that women increasingly are becoming pregnant later in life and that pregnancy-related death rates are known to increase significantly in women over the age of 35.[14]

Within the general US population, approximately 2 pregnancies per 100 occur outside of the uterus and are diagnosed as ectopic.[15] Although the incidence of ectopic pregnancy has increased from a low of 4.5 per 1000 pregnancies to 19.7 per 1000 (as of 1992),[16] the case fatality rates have been decreasing; between 1979 and 1986, 13% of maternal deaths were attributed to ectopic pregnancy[17] compared to 9% in 1992[18] and 6% in 1999.[19] Accounting for the rise in ectopic pregnancy rate is difficult, however, due to several

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[11] Mohllajee AP, Curtis KM, Morrow B, Marchbanks PA. Pregnancy intention and its relationship to birth and maternal outcomes. Obstet Gynecol 2007;109:678-86
[12] http://www.cdc.gov/mmwr/PDF/ss/ss5509.pdf accessed October 23, 2007
[13] http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5202a1.htm accessed October 21, 2007
[14] http://www.cdc.gov/nccdphp/publications/aag/pdf/drh.pdf accessed October 20, 2007
[15] MMWR 1995;44(03):46-8)
[16] Ectopic Pregnancy- United States, 1990-1992. JAMA. 1995;273:533
[17] MMWR 1992;41:591-594
[18] JAMA, 1995 op. cit.
[19] MMWR 2003; 52 No SS2;1

factors. Specifically, accurate diagnosis has increased due to the availability of improved diagnostic tools (e.g., more widely available, highly sensitive, rapid, quantitative pregnancy tests, and high resolution transvaginal ultrasound [TVUS]), there has been an increase in several population-based risk factors (e.g., sexually transmitted infections), and Assisted Reproductive Technology (ART) is increasingly available. (Note that ART explicitly carries an increased risk of ectopic pregnancy.)

In addition to maternal mortality, morbidity associated with pregnancy is significant, although more difficult to monitor. The most useful morbidity measure is the number of non-delivery related hospitalizations per pregnant woman. While the overall rate of admissions has declined from 22.2% in 1992 to 16.7% in 1998, these figures do not reflect the outpatient treatments that may have occurred in lieu of an admission. The CDC, therefore, indicates that this apparent decrease should not be construed to mean that maternal morbidity has decreased, but rather that more complete data cannot be obtained. General categories of maternal morbidity, however, are known to include hemorrhage, ectopic pregnancy, pregnancy-induced hypertension, infection, and depression.[20]

While the potential risks of pregnancy generally are outweighed by the benefits when the pregnancy is desired, the possible mortality and morbidity outcomes are substantially more concerning in cases of unintended pregnancy. Additionally, the risks to the woman (especially younger and older mothers), the fetus, and eventually, the newborn infant that arise from an unintended pregnancy can lead to long-term health impacts. While the financial burden on the healthcare system associated with unintended pregnancies is beyond the scope of this document, there clearly are implications there as well. Given that safe and effective contraception methods can reduce the number of unintended pregnancies, abortions, and pregnancy-related health concerns, it is critical to provide women with acceptable options that also make compliance relatively simple.

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[20] http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/ManageCare.htm accessed October 23, 2007

Contraceptive Solutions

The results of The National Survey of Family Growth[21] repetitively underscore the ongoing problem of unintended pregnancy, abortion, and discontinuation of contraceptive methods due to method-related side-effects or health impacts. These findings appear static, having failed to change significantly between the 1995 and 2002 surveys. Additionally, a significant unmet need in the field of contraception has been recognized in the past by the FDA, the Institute of Medicine, and the United States Agency for International Development (a long time investor in research and development of transcervical sterilization methods).

By nature, however, no contraceptive method is perfect for all women. Weighing the balance between efficacy rates, ease of compliance/use, and safety profiles represent the individual choices that women, men, and couples make throughout their reproductive lives. These choices are not straightforward as they involve pregnancy prevention options that range from temporary to permanent, hormonal to non-hormonal, highly efficacious and non-user dependent to moderately efficacious and user-dependent, female controlled to male controlled, and protective to not protective against sexually transmitted infections. When determining, on a population basis, adequate efficacy in particular, but also risk related to safety and side effects, comparability of all methods should be considered, especially when each method has individual advantages that could make it a more likely choice over no choice at all.

Reversible pregnancy prevention options are widely available, but rely on patient compliance and have varying failure rates. For example, it has been reported that contraceptive failure occurs in the first year of use for 80 per 1,000 women who rely on oral contraceptives, 150 per 1,000 women who rely on the male condom, and 30 per 1,000 women who use injectable methods. Alternatively, the less user-dependent IUDs

[21] http://www.cdc.gov/nchs/data/series/sr_23/sr23_025.pdf accessed October 20, 2007

are more highly effective with first year failure rates of less that 10 per 1,000 women,[22] but currently are utilized only by 1-2% of all contraceptive users in the US.[23]

While reversible solutions are utilized extensively, sterilization continues to be the most commonly used method in the US with 15 million women relying on either female or male sterilization.[24] In fact, approximately 700,000 tubal sterilizations[25] and 500,000 vasectomies[26] are performed in the US annually; of all women aged 15 to 44 who used contraceptive methods in 2002, female sterilization accounted for 27% and male sterilization accounted for 9.2% of method use (these proportions have remained largely unchanged since 1995).

Prior to the mid-1970's when laparoscopic sterilization was introduced, vasectomies were far more popular than female sterilizations in the US because of the risks associated with abdominal surgery. The advent of laparoscopic technology, however, marked a shift in thinking about female sterilization as a contraceptive option because barriers of both access and safety were markedly reduced. Over the years, as training in laparoscopy has expanded, the number of providers who can perform sterilization as an "interval" procedure has increased such that half of all female sterilizations in the US today are performed as interval procedures.

The consistent preference toward sterilization, including traditional transabdominal procedures, is based on perceived efficacy and safety. In terms of the former, sterilization's efficacy rate is clearly superior to short-term, user-dependent, reversible methods. In regard to safety, the mortality rate from transabdominal sterilization in the US has been estimated at 1-4 deaths per 100,000 procedures. It should be noted, however,

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[22] http://www.contraceptivetechnology.org/table.html
[23] http://www.guttmacher.org/pubs/fb_contr_use.html
[24] Mosher W, Martinez G, Chandra A, Abma J, Willson S. Use of contraception and use of family planning services in the United States:1982–2002. Advance data from vital and health statistics; no 350. Hyattsville, Maryland: National Center for Health Statistics. 2004.
[25] MacKay AP, Kieke BA Jr, Koonin LM, Beattie K. Tubal sterilization in the United States, 1994–1996. Fam Plann Perspect 2001;33:161–5.
[26] Magnani RJ, Haws JM, Morgan GT, Gargiullo PM, Pollack AE, Koonin LM. Vasectomy in the United States, 1991 and 1995. Am J Public Health 1999;89:92–4.

that most deaths are associated with either traumatic abdominal entry or anesthesia complications.[27] As reported in the 1996 US Collaborative Review of Sterilization Trial (CREST)—a large, CDC-sponsored, prospective, multicenter, observational study of over 10,000 women who were followed for up to 14 years—no procedure related deaths were reported among the 9,475 women who underwent interval laparoscopic tubal ligation.[28] The major complications from transabdominal tubal sterilizations generally are considered uncommon, but not rare. Overall, complication rates for tubal sterilization are estimated to be 0.9-1.6 per 100 procedures.[29] The types of complications tend to vary by type of surgical procedure conducted and specific anesthesia administered. Intraoperative complications include damage to bowel, bladder, or major vessels. Laparotomy and/or blood transfusion may be required to manage these rare events. Postoperative complications include wound infection and possible prolonged pelvic/abdominal pain. Risk factors for complications include previous abdominal or pelvic surgery, obesity, and diabetes[30]

Although pregnancy following sterilization generally is uncommon, there is an increased risk that the pregnancy, if it occurs, will be ectopic. As reported in the CREST study, the 10-year cumulative probability of ectopic pregnancy for all methods of tubal sterilization (including unipolar, bipolar, Hulka Clip, Falope Ring, and partial salpingectomy) was 7.3 per 1000 procedures; the CREST study used cumulative life table probabilities and proportional hazards analysis to determine this estimate. It should be noted, however, that rates varied significantly with age and method but, depending upon the procedure, 15-65% of post-sterilization failures were ectopic.[31] Bipolar tubal coagulation is the most common tubal sterilization method used in the US and may carry the highest associated risk of failure and ectopic pregnancy due to recanalization or uteroperitoneal fistula formation. While the CREST study had a 42% lost to follow-up rate 8-14 years post-

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[27] Peterson HB, DeStefano F, Rubin GL, Greenspan JR, Lee NC, Ory HW. Deaths attributable to tubal sterilization in the United States, 1977-81. Am J Obstet Gynecol 1983;146:131-6.
[28] Jamieson DJ, Hillis SD, Duerr A, Marchbanks PA, Costello C, Peterson HB. Complications of interval laparoscopic tubal sterilization: findings from the United States Collaborative Review of Sterilization. Obstet Gynecol 2000;96:997-1002.
[29] Ibid.
[30] Ibid.
[31] Peterson HB. et al. The risk of ectopic pregnancy after sterilization. N Engl J Med 1997;336:762-7

procedure, of the women who reported pregnancies, 47/143 were reported to be ectopic (only one was ovarian); this equates to 32.9%. Overall, the results of the CREST study indicate that there is an ectopic pregnancy risk associated with any kind of tubal manipulation.

In addition to reviewing safety, the CREST study concluded that although tubal sterilization is highly effective, the risk of sterilization failure is substantially higher than had been reported previously. Analysis of the CREST data found a pregnancy rate at year one that ranged from 0 to 24.1 per 100,000 women; the rate varied significantly by method of tubal occlusion and age. It further was noted that the risk of sterilization failure persisted for years after completing the procedures.[32] Overall, the lowest reported failure rates were in women over 34 years of age who underwent post-partum partial salpingectomy or unipolar coagulation.[33] (Safety and efficacy comparisons between these two methods and other laparoscopic or transcervical sterilization techniques are not considerations, however, as the salpingectomy method is delivered exclusively in the immediate post-partum period [i.e., it is not an interval procedure] and unipolar coagulation is rarely used in the US due to safety concerns.) The results of the CREST study therefore indicated that additional sterilization techniques were needed.

In December 2002, the FDA approved Essure™ as the first transcervical sterilization device. This represented the next major shift in sterilization technology as the Essure™ micro-insert can be placed in an out-patient or office surgery setting using a paracervical block with or without IV sedation. This eliminates the need for abdominal entry and general anesthesia. The micro-insert is comprised of a stainless steel inner coil and a nickel titanium alloy outer coil. The device is 4 cm in length and 0.8 mm in diameter prior to release from the insertion catheter. Following release, it expands to 1.5 to 2.0 mm in diameter, and, as it attaches to the fallopian tube across the utero-tubal junction; 5-10 mm of the micro-insert (the equivalent of 3-8 coils) are left trailing into the uterus. Safety

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[32] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol 1996;174:1161–8;discussion 1168–70.
[33] Ibid.

concerns related to Essure™ include allergic reaction to the metal foreign body (nickel), extension of the device into the uterine cavity, expulsions and migrations, and potential difficulty with removal. While the Essure™ method represents an advance in sterilization technology, these concerns suggest that there continues to be a need for technology innovation to minimize device risks and potential side effects.

The Adiana System: Risks and Benefits

The Adiana Transcervical Sterilization System (Adiana System) is intended to provide a safe and effective means of permanent contraception for women. Because it is placed transcervically, there are few medical contraindications associated with its use. A brief discussion of the risks and benefits of the Adiana System is provided below. Overall, however, the Adiana System:

- Is comprised of a safe, biomaterial device that does not contain metal or hormones and has an understood mechanism of action which does not rely on long term chronic inflammation;
- Avoids the risks associated with intra-abdominal entry and general anesthesia;
- Leaves nothing in the uterus;
- Includes only a low, procedure-related risk that is associated with hysteroscopy;
- Has efficacy which is comparable to the outcomes reported in the CREST study for the first two years of reliance;
- Has risks that are associated only with the low potential for pregnancy and the possibility of ectopic pregnancy that is present in all female sterilization methods;
- Offers advantages over other available methods;
- Provides a much needed option for women.

Device Safety: Mechanism of Action

The Adiana Matrix is a 3.5 mm, non-absorbable, biomaterial that consists of a fully cured silicone elastomer containing no hormones or metal; the matrix has a long history of use in various implant applications. It is designed to lie completely within the intramural portion of the tube and to provide a permanent scaffold that allows for "space filling"

occlusive tissue in-growth. No portion of the device remains in the uterine cavity. Histological evaluation of eight specimens following elective hysterectomy at an average of 3.1 years of wearing consistently showed complete occlusion of the fallopian tube. with tissue in-growth into the porous luminal implant consistent with a biocompatible implant response.

Procedure Safety

The Adiana System consists of a unique three step procedure: hysteroscopy with bilateral tubal cannulation; low-power radio frequency treatment of the tubal endothelium and matrix placement at the site; and follow-up confirmatory hysterosalpingogram (HSG) to confirm tubal blockage at three months. In-growth is stimulated following application of very low power (<3 Watts) radio frequency energy to the intramural portion of the fallopian tube for 60 seconds prior to Matrix placement. Because of the low energy level used for the superficial thermal lesion, complications from thermal injury were not reported in a large, multicenter, prospective clinical trial (the **E**valuation of the **A**diana system for transcervical **S**terilization using **E**lectrothermal energy, or, EASE.

The EASE study indicates that the Adiana procedure has a high degree of safety because of its simplicity and ease of use; the only recognized significant risk is associated with hysteroscopy. Additionally, the procedure duration averaged less than 12 minutes in the clinical trial. Of 645 intent-to-treat patients, 611 (95%) had successful bilateral device placement, and only 34 (5%) underwent hysteroscopy with failure to place the device, 29/34 secondary to anatomic variability. There were no uterine or tubal perforations or surgical interventions related to the device placement procedure. Additionally, there were no post-procedure infections/salpingitis, and no adverse events associated with the HSG procedure. There was one procedure-related, serious adverse event (hypervolemia/hyponatremia) associated with hysteroscopy. (Note that hypervolemia/hyponatremia is recognized as a possible complication of hysteroscopy.). In this particular instance, the single complication was treated conservatively without hospital admission and without any residual negative outcome; see the PMA Clinical Report, pages 271 and 291.)

Wearing Safety

Because the Adiana Matrix is biocompatible and well tested as a material for long term use, safety concerns beyond those associated with the procedure are specific to side effects or adverse events considered related to the device as well as to the risk associated with pregnancy prevention failure. It should be noted that the Adiana device is placed into the intramural portion of the tube and therefore no part remains in the uterine cavity. This further contributes to the long term wearing safety of the device. Additionally, no adverse implant reactions and no device removals occurred during wearing of the Adiana Matrix in the EASE trial.

Short Term Side Effects

Manipulation of the cervical os, uterine cavity, and fallopian tube resulted in expected reports of post-procedure cramping and vaginal spotting; and less frequent reports of temporary bleeding, pelvic pain, nausea and/or vomiting, back pain, headache, vaginal discharge, or dysuria. The rates of these events were considered comparable to rates in published literature and despite these minor, short term side-effects, the majority of women reported that the procedure was well tolerated and that discomfort was as expected.[34] All immediate side effects, with the exception of back pain, resolved within a mean time of three days post-procedure; back pain had a mean duration of nine days, a rate also described in the literature following use of the lithotomy position for gynecologic procedures[35, 36] (see the PMA Clinical Report, page 264).

Long term Side Effects

Analysis of longer term side effects related to gynecologic complaints such as bleeding, spotting, and cramping/dysmenorrhea suggests that the incidence of complaints conforms to rates reported in the general population as well as the post-sterilization population (see

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[34] http://www.emedicine.com/med/topic3314.htm accessed October 23, 2007

[35] Clarke AM, Stillwell S, Paterson ME, Getty CJ. Role of the surgical position in the development of postoperative low back pain. J Spinal Disord. 1993 Jun;6(3):238-41.

[36] Hirabayashi Y, Igarashi T, Suzuki H, Fukuda H, et al. Mechanical effects of leg position on vertebral structures examined by magnetic resonance imaging . Reg Anesth Pain Med. 2002; 27(4):429-32.

the PMA Clinical Report, pages 266-268). To date, there have been no requests for removal of the Adiana Matrix.

In the Ease study, 48.2% of the intent-to-treat patients used hormonal contraception prior to sterilization, increasing their likelihood of menstrual change following transition to a non-hormonal method. Review by the Data Safety Monitoring Board (DSMB) confirmed that trial rates for changes in menstruation post-relying in the intent-to-treat population could not be considered outside of a normal variation in range.

This similarly was true during the follow-up period for the incidence of hysterectomy in the EASE study population. Of 625 patients who had devices placed, there have been 10 reported hysterectomies over the course of the trial to date. Of these, seven cases are considered serious adverse events based on criteria established in the protocol for the EASE study (i.e., overnight hospitalization). The remaining three cases are considered non-serious adverse events (i.e., uncomplicated out-patient procedures). Seven of the ten cases had menorrhagia as the primary indication; two cases had complaints of dysmenorrhea or pelvic pain as the primary indication; and the final case had a pre-cancerous lesion of the cervix as the primary indication. In addition, for one of the cases, medical treatment of multiple sclerosis was considered the cause of menorrhagia. During the limited follow-up of the EASE study cohort, the rate of hysterectomy in the device wearing population at the data close point (March 1, 2007) was 1.6%. During the limited follow-up of the EASE study cohort, the rate of hysterectomy in the device wearing population at the data close point (March 1, 2007) was 1.6%, which is comparable to rates in the published literature. [37, 38] The DSMB reviewed all study cases and supported the conclusion that the rate is consistent with the current literature (see the PMA Clinical Report, pages 302-303).

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[37] Goldhaber, M. K., M. A. Armstrong, et al. (1993). "Long-Term Risk of Hysterectomy among 80,007 Sterilized and Comparison Women at Kaiser Permanente, 1971-1987." American Journal of Epidemiology 138(7): 508-521.l.

[38] Hillis, S. D., P. A. Marchbanks, et al. (1998). "Higher hysterectomy risk for sterilized than nonsterilized women: findings from the U.S. Collaborative Review of Sterilization. The U.S. Collaborative Review of Sterilization Working Group." Obstetrics and gynecology. 91(2): 241-6.

Pregnancy Events

The Adiana device is placed transcervically. Although there is some small risk associated with hysteroscopy, it is minimal compared to the risk associated with laparoscopic or laparotomy transabdominal sterilization approaches (see preceding section). The only real risk associated with the device or procedure is related to the risk of pregnancy.

Of the 570 women who were followed after successful bilateral device placement and tubal occlusion by HSG, there were six pregnancies during the one-year follow-up; this corresponded to a pregnancy rate of 1.08% (95% CI, 0.2-1.9%; Life Table Analysis, Two-sided). Three of these pregnancies were attributable to recognized physician errors of management/HSG interpretation and may be preventable with targeted physician training. The remaining three pregnancies are considered method failures. There were three additional method failure pregnancies in Year 2, and one in Year 4. The one-year and two-year pregnancy prevention rates observed in the EASE study are statistically comparable to the rates reported in the CREST study (see the PMA Clinical Report, pages 214-223).[39] Determinations of accurate pregnancy rates after the third and fourth-year of follow-up are compromised due to incomplete data.

Pregnancy outcome

Over the course of the EASE study, 15 pregnancies have been reported by relying and non-relying patients. One patient was lost to follow-up following ultrasound confirmation of an intrauterine pregnancy ; the outcome of her pregnancy is unknown. Of the remaining 14 pregnancies, six resulted in uncomplicated intrauterine pregnancies with normal deliveries, three ended with decisions to terminate, three had empty sac/missed abortions or spontaneous 1st trimester abortions, and the final two were ectopic (tubal pregnancies). The ectopic pregnancies were diagnosed at 5 and 6 weeks after the patients' last menstrual periods. One patient was treated conservatively with methotrexate and subsequent salpingectomy at the time of her laparoscopic tubal sterilization. The second

[39] Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol 1996;174:1161–8;discussion 1168–70.

patient underwent laparoscopic treatment and bilateral tubal sterilization. Both women had uncomplicated surgical interventions.

Spontaneous/Missed Abortion/Ectopic Pregnancy Rate:

The EASE study had too few pregnancies to determine the statistical rates of spontaneous abortion/missed abortion/ectopic pregnancy as an extraordinary outcome. The DSMB, however, considered the observed rates to be within the expected range for the general population (see the PMA Clinical Report, pages 299-301).

Overall Conclusion

In the US, around 43 million women are of reproductive age, at risk for unintended pregnancy, and in need of an effective contraceptive method. In fact, nearly half of all reported pregnancies are considered unintended and about half of those are electively terminated. Unintended pregnancies often result in health risks to the mother, fetus, and eventually the newborn infant and arise, in large part, due to the inaccessibility, complexity, or undesirability of using various contraceptive methods. Given this, it is critical to provide women with acceptable pregnancy prevention options that also make compliance relatively simple. No contraceptive method, however, is perfect for all women and patients must select a balance between efficacy rates, ease of compliance/use, and safety profiles.

Currently, sterilization is the most commonly used method of contraception in the US and the advent of laparoscopic surgery has made the option more desirable and safer for women. Nevertheless, surgical complications have resulted in a need for even safer, permanent pregnancy prevention methods. With that goal in mind, the Essure™ transcervical device was introduced. While this product is effective, there still are improvements possible that could yield greater safety outcomes for patients.

To that end, the Adiana System was developed to provide patients with an effective, pregnancy prevention option that offers significant advantages over other sterilization

devices. Specifically, the Adiana System uses a safe biomaterial that does not contain metal or hormones, avoids the risks of intra-abdominal entry, does not require the patient to undergo general anesthesia, leaves nothing in the uterus, and can be placed with substantial success in an average time of less than 12 minutes. While all sterilization methods contain a potential risk for ectopic pregnancy, the Adiana System includes no other major concerns beyond a low, procedure-related risk associated with hysteroscopy and the low potential for device failure. The Adiana System has been shown to have efficacy that that is comparable to the methods reported in the CREST study for the first two years of reliance. Given all of the above, the Adiana System represents a safe and effective method that provides a much needed, additional contraception option for women.

VII. DRAFT LABELING

VII. A. IFU ADIANA TRANSCERVICAL STERILIZATION SYSTEM

Instructions for Use

Adiana Transcervical Sterilization System

Caution: Federal law restricts this device to sale by or on the order of a physician.

Only physicians who have received appropriate training in the use of the Adiana Transcervical Sterilization System (the Adiana System) and who are familiar with hysteroscopy and the principles, clinical procedures, complications, side effects and hazards commonly associated with hysteroscopy should use this product.

For physicians who are inexperienced with transcervical sterilization, completion of the Adiana training program (see below) is required.

The Adiana System should not be relied on for contraception until the patient has undergone a hysterosalpingogram (HSG) which demonstrates bilateral tubal occlusion no less than 3 months after Matrix placement.

This product is intended to prevent pregnancy. It does not protect against either HIV infection or other sexually transmitted diseases.

Do not attempt to use the RF Generator without first reading and understanding the RF Generator Specification and Installation Manual.

The Adiana Transcervical Sterilization System is Manufactured and Distributed by:

Cytyc Surgical Products
250 Campus Drive
Marlborough, MA 01752
(508) 263-2900

This document provides information for the implantation and operation of the Adiana Transcervical Sterilization System including the Radio Frequency Generator (RF Generator) and the Delivery Catheter with implantable Matrix.

Additional information describing specifications and installation information for the RF Generator can be found in the RF Generator Specification and Installation Manual.

The Adana HSG Protocol is available separately.

A Cytyc Training Manual with troubleshooting guide is provided to physicians who undergo training for use of the Adiana Transcervical Sterilization System.

1. DEVICE DESCRIPTION

Indications for Use

The Adiana Transcervical Sterilization System is indicated for women who desire permanent birth control (female sterilization) by occlusion of the fallopian tubes.

Mechanism of Action

Using hysteroscopic visualization, the physician places the Delivery Catheter into the ostium of the fallopian tube. Low power (<3 Watts) RF energy heats the immediate tissue layer, creating a superficial lesion within the tube. A small implant, the Matrix, is then released into the tube. The acute inflammatory response to the superficial thermal injury causes normal, healthy tissue in-growth into the Matrix, resulting in occlusion of the fallopian tube.

Device Components

The Adiana Transcervical Sterilization System consists of three components (See Figure 1):

- The Delivery Catheter with split Introducer
- The implantable Matrix
- The Radio Frequency (RF) Generator

Figure 1: The Adiana Transcervical Sterilization System, showing the Delivery Catheter and the RF Generator

The Delivery Catheter is packaged with a split Introducer with removable mandrel that is used to protect it during hysteroscopic insertion. Both of these are single use and disposable.

The RF Generator is shipped with a connector cable for attachment to the Delivery Catheter, and a power cord. An optional footswitch accessory is available.

Delivery Catheter with Implantable Matrix

The Delivery Catheter, shown in Figures 2 and 4 below, has an electrode sheath configuration at its distal end and is attached to a handle at its proximal end. The Delivery Catheter is delivered to the intramural portion of the fallopian tube through a hysteroscope via a transvaginal and transcervical approach.

Confirmation of correct catheter placement within the intramural fallopian tube is achieved in two ways: first, by means of direct visual assessment through hysteroscope optics (visually confirming that the black mark on the catheter has reached the tubal ostium); and secondly, through the RF Generator via electronic feedback from the position detector array (PDA) sensors located at the distal end of the catheter.

The PDA consists of four electrode sensors circumferentially located around the Delivery Catheter (just proximal to the RF electrode array); the sensors detect tissue contact which is communicated to the RF Generator. When the RF Generator signals that the catheter is correctly positioned and contact made, the clinician can activate the RF Generator which then delivers RF energy through the electrode array. This heating action creates a superficial lesion within the fallopian tube.

A release button incorporated into the Delivery Catheter handle is used to activate Matrix release. Following RF treatment, the clinician presses this button which retracts the electrode array and releases the Matrix within the tube. The catheter is then removed and the procedure repeated with a new catheter in the contralateral tube.

Figure 2: The Delivery Catheter

The implantable Matrix is specifically designed to provide a benign and permanent scaffold for tissue in-growth. Within the region surrounding the solid core of the Matrix, a porous architecture encourages in-growth of tissue and provides stable, long-term occlusion.

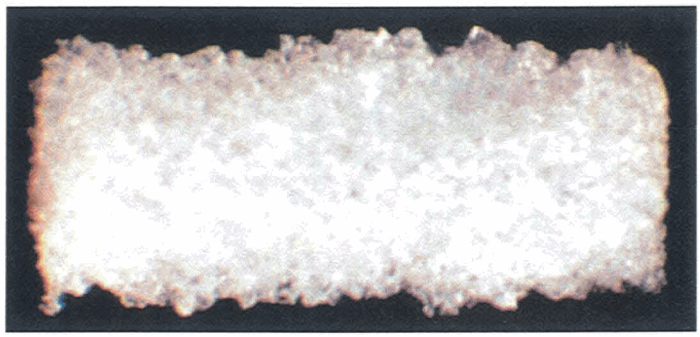

Figure 3: Matrix

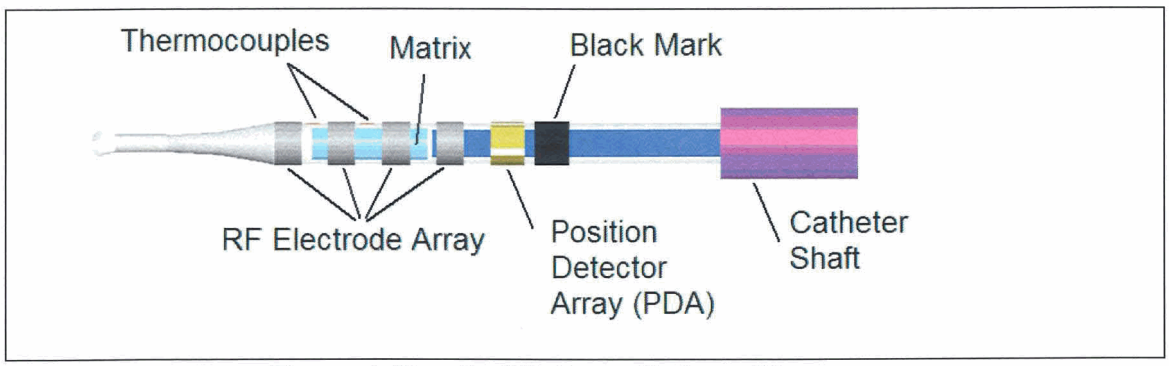

Figure 4: Detail of Delivery Catheter Tip

The RF Generator

The RF Generator is a microprocessor-controlled, bipolar, radiofrequency generator with automatic temperature control and a unique tissue contact sensor. It uses a menu driven display to guide the operator through the procedure. During use, the RF Generator constantly monitors catheter outputs and signals for determining proper device placement, controlling lesion creation, ensuring Matrix delivery, and detecting error conditions.

There are no user-selectable RF controls for RF output, treatment time or treatment temperature. To reach and maintain a pre-set temperature for a pre-determined treatment duration, RF settings are pre-programmed in the controller software. If necessary, the clinician may terminate treatment, however, no other physician control of output power is possible.

Note: The Delivery Catheter can be used only with the RF Generator. The Delivery Catheter will not operate if connected to other generators. Please refer to the RF Generator Specification and Installation Manual for specific instructions regarding operation of the entire system.

An optional accessory footswitch is available for the RF Generator. The footswitch allows for hands-free operation of the RF Generator. The function of the footswitch is equivalent to the RF button on the Generator's front panel.

For additional information on its specifications, installation and operations, see the RF Generator Specification and Installation Manual that is included with the RF Generator.

2. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindications

The Adiana Transcervical Sterilization System should not be used in patients who:

- Are uncertain about their desire to end fertility
- Have presence of gross genital infection, or sepsis
- Have intra-uterine pathology which would prevent access to the tubal ostium and intramural portion of the fallopian tube, such as large submucous fibroids or uterine adhesions
- Are currently taking immunosuppressive medications
- Are pregnant or have suspected pregnancy
- Have had uterine perforation within the last 3 months
- Are currently less than three months since their last delivery or abortion

Warnings

- This product does not protect against HIV infection or other sexually transmitted diseases.
- Should pregnancy occur, as with any device that alters the internal tubal architecture, there is an increased risk of ectopic pregnancy.
- Patients must use alternative contraception for at least three months post treatment and until such time as a hysterosalpingogram (HSG) demonstrates bilateral tubal occlusion.
- Any system delivering high pressure inflow to patient increases the risk for fluid overload. Hysteroscopic fluid intake and outflow should be monitored. To reduce the risk of hypervolemia, the procedure must be terminated if the fluid deficit exceeds 800cc. Additionally, the procedure time should not exceed 30 minutes.
- Sensitive electronic equipment, such as an external pacemaker or internal cardioverter defibrillator, may be affected by use of the RF Generator.
- The safety and effectiveness of this procedure have not been demonstrated in patients under the age of 18 and over the age of 45.
- When introducing the Delivery Catheter into the fallopian tube:
  - Never advance the catheter without visual guidance
  - Do not apply excessive force
  - Do not advance the catheter such that the Black Mark is past the ostium. Excessive advancement of the Delivery Catheter can result in unsatisfactory device placement, or in tubal/uterine perforation which could result in damage to adjacent organs

  - Do not twist or kink the Delivery Catheter during placement and Matrix delivery.
- Women who undergo sterilization at a relatively young age are at greater risk of regretting their decision to undergo sterilization.
- To decrease the possibility of implantation in a patient with an undiagnosed (luteal phase) pregnancy, and to facilitate visualization of the ostia, the procedure should be performed during the early proliferative phase of the menstrual cycle. This treatment should not be performed during menstruation.

Precautions

General Precautions

- Do not attempt to use the RF Generator without first reading the RF Generator Specification and Installation Manual and understanding all of its contents.

Storage and Handling Precautions

- The Delivery Catheter and the split Introducer are provided sterile and intended for single use only. It should not be used beyond the Expiration Date printed on the package label.
- Inspect sealed package before opening. If the seal is broken do not use.
- Carefully inspect the Delivery Catheter prior to use to verify that it has not been damaged during shipment.
- Do not expose any of the system components to extreme hot or cold conditions. Electronics can be damaged by temperature extremes.
- Handle system components with care. Do not drop or submerge electrical components or connections in water.

Placement Precautions

- Both tubal ostia should be identified visually prior to attempting tubal access. Do not implant the Matrix in one tube unless there is a reasonable expectation that the opposite tube is accessible and patent.

Precautions during Implantation

- Do not advance the Delivery Catheter if the patient is experiencing extraordinary pain or discomfort
- Do not use excessive force to advance the Delivery Catheter. Doing so may increase risks of perforation or damage to the Delivery Catheter. If the Delivery Catheter appears damaged or kinked, a new Delivery Catheter should be used.

- To avoid damage to the Delivery Catheter tip, it is necessary to use the split Introducer when passing the Delivery Catheter into the hysterocope.
- Once the Delivery Catheter is introduced into the working channel of the hysteroscope, remove the split Introducer. The working channel stopcock must remain in the open position to avoid damage to the Delivery Catheter.

Precautions Regarding Explanation to Patient

- Patients should be advised that the implantation procedure will not provide pregnancy protection until tubal occlusion is confirmed by HSG. Until HSG confirmation, patients must protect against pregnancy by use of an alternative birth control method. The alternative birth control method should be selected in advance of the implantation procedure.

RF Generator – Specific Precautions

- This equipment generates, uses, and can radiate RF energy and, if not installed and used in accordance with the instructions, may cause harmful interference to other devices in the vicinity.
- When the RF Generator is activated, the conducted and radiated electrical fields may interfere with other electrical medical equipment.

Adverse Events

Between November 13, 2002 and April 28, 2005, a total of 645 women underwent an Adiana Procedure in the pivotal EASE clinical trial to evaluate the safety and effectiveness of the Adiana Transcervical Sterilization System. Some women underwent more than one procedure if successful bilateral placement was not achieved in the initial procedure. Overall, bilateral placement success was achieved in 95% of patients in the trial.

Observed Adverse Events

Table 1 shows adverse events and side effects as a result of the hysteroscopic placement procedure in the clinical trial, reported at an event frequency greater than 0.5%.

Table 1: Side effects reported on day of placement procedure (N=653 procedures)

Event	Percent
Cramping	25%
Vaginal Spotting	24%
Post-procedural Bleeding	10%
Pelvic Pain	9%
Nausea	6%
Back Pain	6%
Headache	4%
Post-procedural Pain	2%
Vaginal Discharge	2%
Dysuria	2%
Vomiting	2%
*Other	2%

*Includes events that occurred at a rate >0.5% and ≤1%: abdominal distension, arthralgia, post-procedural discomfort, and vasovagal reaction.

One event related to the hysteroscopic procedure (hyponatremia), required intervention with medication prior to patient discharge on the day of the procedure. All other events were mild in nature and resolved within a short duration.

The majority of women in the clinical trial reported that the procedure was well-tolerated and that any discomfort or pain experienced during the procedure was the same as or less than they expected. Following the procedure, pain was managed with oral analgesics.

Table 2 summarizes all adverse events in the clinical trial reported to be at least "possibly" related to the Adiana matrices or placement procedure during the first year of reliance on the Adiana System (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 the Adiana System, but were rated by the Investigator as at least "possibly" related to the Adiana System were cramping unrelated to menses (6%), dysmenorrhea (5%) and vaginal bleeding(4%) All other events occurred in less than 3% of women.

Table 2: Adverse Events by Body Systems, First Year of Reliance[1,2]
(N=625 patients implanted with at least one device)

Adverse Events by Body System	Number	Percentage
Abdominal:		
Abdominal pain	2	<1
Nausea	4	1
Vomiting	3	<1
Musculoskeletal:		
Back pain	21	3
Nervous System:		
Headache	4	1
Genitourinary:		
Amenorrhea	2	<1
Cramping – unrelated to menses	35	6
Dysmenorrhea	32	5
Dyspareunia	5	1
Menorrhagia	9	1
Pelvic pain	19	3
Vaginal spotting	6	1
Vaginal bleeding	27	4
Vaginal discharge	3	<1
Pain/discomfort - uncharacterized:		
Discomfort	2	<1
Pain	2	<1

[1]Only severe events occurring at a frequency ≥ 0.5% are reported
[2]Percentages are presented by subject frequency

During the first year of reliance on the Adiana System, one patient experienced an isthmic ectopic pregnancy, which was successfully resolved by treatment with medication.

Potential Adverse Events Not Observed in Clinical Studies

The following adverse events were not experienced by women who participated in the clinical trial to evaluate the Adiana System but are still possible:

- Perforation of the uterus or fallopian tube;
- perforation of internal bodily structures other than the uterus and fallopian tube;
- adnexal infection/salpingitis;
- adverse events associated with hysterosalpingogram (HSG);
- the effect of future medical procedures that involve the uterus or fallopian tubes on the ability of the Adiana matrices to provide protection against pregnancy; and

- adverse events associated with surgery attempting to reverse the Adiana procedure, as well as adverse events associated with pregnancy following a reversal procedure or an *in vitro* fertilization (IVF) procedure.

Adverse Event Reporting

All Adiana Transcervical Sterilization System-related Adverse Events should be reported immediately. To report an Adverse Event, call (XXX) XXX XXXX. [To Be Determined]

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3. CLINICAL STUDIES

Purpose of the Study

A pivotal clinical trial (called the "EASE" trial) was conducted to demonstrate the safety and effectiveness of the Adiana System in providing permanent contraception. The EASE clinical trial was a prospective, single-armed, multi-center, international trial. The study used findings from the U.S. Collaborative Review of Sterilization (CREST study) as a qualitative benchmark.

Study Endpoints and Design

Primary efficacy endpoint for the clinical trial:

- Pregnancy prevention rate after 12 months of reliance on the Adiana System

Secondary endpoints of the clinical trial included:

- Device placement rate
- Patient satisfaction and comfort with the placement procedure
- Patient satisfaction and comfort with device wearing
- Safety of device placement procedure
- Safety of device wearing

Patients Studied

The study population consisted of 611 women in whom bilateral device was achieved after one or more attempts. All study participants were between 18 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had been pregnant at least once, had regular, cyclical menses and were able and willing to use alternative contraception for the first three months following the Adiana matrices placement.

Methods

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 Adiana Procedure was attempted on each fallopian tube. Participants were instructed to use either barrier contraceptive method or oral contraceptives for the first 3 months following the device placement procedure.

A hysterosalpingogram (HSG) was performed three months post Matrix placement to evaluate fallopian tube occlusion. If both fallopian tubes were occluded, the participant was instructed to discontinue use of alternative contraception and rely on the Adiana matrices for prevention of pregnancy.

Results

Placement Rates

A total of 770 women were enrolled in the EASE trial and 645 of these women had treatment attempted with the Adiana System. Of the 645 women in whom treatment was attempted, bilateral treatment success was achieved in 604/645 (94%) after the first procedure and 611/645 (95%) after a second procedure. Of the 34 women in whom bilateral treatment success was not achieved, 29 were tubal access failures that occurred due to patient anatomy issues (e.g., suspected tubal blockages, extremely lateral tube location; uterine adhesions; poor visualization of ostia; and other varied tubal abnormalities). In one case, the treatment procedure was aborted prior to tubal access or device deployment being attempted because the physician could not maintain adequate uterine distension to perform the procedure due to a patulous cervix.

Reliance Rates

Of the 611 women with bilateral placement, 604 were evaluated for tubal occlusion by HSG. Of these patients, 570 (94%) were ultimately able to rely on the Adiana System for contraception. Inability to rely on the Adiana System for contraception was due to tubal patency identified on HSG.

Pregnancy Prevention Effectiveness

Of the 570 women relying on the Adiana System for pregnancy prevention, all have been followed for 12 months; 321 have been followed for 24 months; and 133 have been followed for 36 months. During the one-year follow-up period, there were six pregnancies: three were attributable to physician error (misinterpretation of HSG results) and the remaining three were due to method failure. During the two-year follow-up period, there were three pregnancies attributable to method failure. Table 3 presents the principle contraceptive effectiveness rates for the EASE clinical trial, as of March 1, 2007.

Table 3: Effectiveness Results as of March 1, 2007

Cumulative Failure Rates	Method Failures	All Pregnancies
One-Year*	0.54% (95% CI 0 to 1.05%)	1.08% (95% CI 0-1.80%)
Two-Year*	1.29% (95% CI 0 to 2.17%)	1.82% (95% CI 0 to 2.84%)
Three-Year*	1.29% (95% CI 0 to 2.17%)	1.82% (95% CI 0 to 2.84%)

*The one-, two-, and three-year effectiveness rates for the Adiana System are comparable to the effectiveness rate for other methods of tubal sterilization at these time points; however, the two and three year data are incomplete and these rates may change as further data are obtained. Follow-up of the women in the EASE trial is ongoing, and will continue to 5 years of follow-up. As updated data regarding longer-term effectiveness rates are available, they will be included in the product labeling.

Patient Demographics for the EASE trial

The patient population of the EASE trial consisted of 645 women in whom treatment was attempted. 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 been pregnant at least once, had regular, cyclical menses and were able and willing to use alternative contraception for the first three months following Matrix placement. Table 4 presents age distribution and other patient demographics.

Table 4: Age Distribution and Patient Demographics (N=645)

Age (mean years)	31.5
Age group	
18-27 years	24.2%
28-33 years	47.7%
34-45 years	28.1%
Race	
Caucasian	488
Hispanic	98
African-American	47
Other	12
Gravidity (mean, range)	2.9 (1-9)
Parity (mean, range)	2.2 (0-7)
Weight (mean, range [lbs])	161.8 (98.0-355.0)
Height (mean, range [in])	64.7 (51.3-74.0)

Pregnancy Rates for Birth Control Methods

(For One Year of Use)

The following table provides estimates of the percent of women likely to become pregnant while using a particular contraceptive method for one year. These estimates are based on a variety of studies.

"Typical Use" rates mean that the method either was *not always used correctly* or was *not used with every act of sexual intercourse* (e.g., sometimes forgot to take a birth control pill as directed and became pregnant), or was *used correctly* but *failed anyway*.

"Lowest Expected" rates mean that the method was *always used correctly* with *every act of sexual intercourse* but *failed anyway* (e.g., always took a birth control pill as directed but still became pregnant).

Method	*Typical Use Rate of Pregnancy*	*Lowest Expected Rate of Pregnancy*
Sterilization:		
Male Sterilization	0.15%	0.1%
Female Sterilization	0.5%	0.5%
Hormonal Methods:		
Implant *(Norplant™ and Norplant™-2)*	0.05%	0.05%
Hormone Shot *(Depo-Provera™)*	0.3%	0.3%
Combined Pill *(Estrogen/Progestin)*	5%	0.1%
Minipill *(Progestin only)*	5%	0.5%
Intrauterine Devices (IUDs):		
Copper T	0.8%	0.6%
Progesterone T	2%	1.5%
Barrier Methods:		
Male Latex Condom [1]	14%	3%
Diaphragm [2]	20%	6%
Vaginal Sponge *(no previous births)* [3]	20%	9%
Vaginal Sponge *(previous births)* [3]	40%	20%
Cervical Cap *(no previous births)* [2]	20%	9%
Cervical Cap *(previous births)* [2]	40%	26%
Female Condom	21%	5%
Spermicide: *(gel, foam, suppository, film)*	26%	6%
Natural Methods:		
Withdrawal	19%	4%
Natural Family Planning *(calendar, temperature, cervical mucus)*	25%	1-9%
No Method:	85%	85%

[1] Used Without Spermicide
[2] Used With Spermicide
[3] Contains Spermicide

Data adapted from: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, et al. Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Ardent Media, 1998.

Table prepared by FDA: 5/13/97, revised 9/17/98

4. CLINICAL USE INFORMATION

Physician Training

Only physicians who have received appropriate training in the use of the Adiana Transcervical Sterilization System and who are familiar with hysteroscopy and the principles, clinical procedures, complications, side effects and hazards commonly associated with transcervical sterilization should use this device.

Patient Counseling Information

IMPORTANT: Patients should be counseled that this product is intended to prevent pregnancy. It does not protect against HIV infection or other sexually transmitted diseases.

- The following points should be considered when counseling patients about the procedure:
    - As with any tubal sterilization procedure, there is a risk of pregnancy and ectopic pregnancy. Compliance with the pre-HSG alternative contraception regime is essential. Discuss with patients (and/or provide in written form) the risks that are associated with this procedure.
    - If the procedure is successful, the patient will not be able to have any more children. Patients should be instructed that the procedure is permanent and irreversible. Additional information regarding female sterilization can be found in the Patient Counseling Section of the Technical Bulletin from the American College of Obstetricians and Gynecologists (ACOG) (ACOG Technical Bulletin Number 222, April 1996). Alternative temporary methods of birth control are available. FDA's Birth Control Guide contains an expansive listing of alternative methods and can be found on FDA's website.
    - Inform the patient that there is a small possibility that bilateral placement could be unsuccessful during the first attempt. During the EASE clinical trial, initial attempts were sometimes unsuccessful due to pre-existing pathology, anatomic abnormalities, or procedure related difficulties like poor visualization of the tube. In many of these cases, successful bilateral placement was achieved during the second attempt. Before performing the procedure, discuss with the patient a management plan that may be implemented in the event that device placement is not achieved.

- The patient will need to use an alternative form of contraception for a minimum of the first 3 months following the procedure until she has

undergone an HSG. Ensure that the patient is aware of the need for alternative contraceptive.

- Data regarding the effectiveness beyond 3 years of treatment is not available.

Directions for Use

Inspection Prior to Use

- Inspect the package and product prior to use. Do not use if the package is open or damaged.
- The Delivery Catheter should be handled carefully. Prior to use and during the procedure, inspect the Delivery Catheter and components carefully for breaks or other damage. Do not use damaged materials. Using a damaged device may result in inadequate treatment and/or patient injury.
- Upon connection to the RF Generator, ensure that there are no errors and the system recognizes the Delivery Catheter.

Prior to Implantation Procedure

Scheduling the Procedure

- Perform the procedure during the early proliferative phase of the menstrual cycle to reduce the possibility of treatment with an undiagnosed (luteal phase) pregnancy. This timing also enhances visualization of the fallopian tube ostia.
- Matrix placement should NOT be performed during menstruation, or within 3 days of the first day of menstruation.
- A pregnancy test administered by the physician or designee should be conducted within 24 hours prior to the procedure.

NSAIDs

- At the discretion of the treating physician, administration of a non-steroidal anti-inflammatory drug (NSAID) may be considered one to two hours before the procedure. If using only a paracervical block, an anxiolytic agent may also be offered 30 minutes prior to the procedure to reduce anxiety.

Procedure Instructions

Procedure Setting

- The procedure can be performed in an outpatient or office surgery setting. As with all outpatient procedures, ensure that appropriate equipment, medications, staff and training are in place to handle emergency situations.
- Employ sterile technique using universal precautions.

Patient Positioning

- Place patient in a lithotomy position. An UBD (under buttock drape) and fluid collection control pouch should be positioned to collect run-off fluids.

Initiating Treatment / Hysteroscopic Access

- Clean the vagina and vulva with an antiseptic solution.
- Introduce a speculum into the vagina to allow access to the cervix. Prep the cervix with betadine or other suitable antibacterial solution according to standard practice.
- Local anesthesia (e.g. paracervical block), with or without IV or oral sedation, is the recommended method for pain management. Treating physicians should select the appropriate anesthetic approach when utilizing the procedure based on their own experience from other hysteroscopic procedures taking into account the patient's preference.
- Prior to hysteroscope insertion, a cervical dilator may be used (at physician discretion). Do not perform cervical dilatation unless necessary to allow hysteroscope insertion.
- If dilation is necessary, dilate only as much as required to insert the hysteroscope. In order to prevent uterine perforation, the procedure should be terminated if excessive force is required to achieve cervical dilatation.
- Insert a sheathed hysteroscope, with attached fiber optic light source and camera, transcervically, into the uterine cavity.

Achieving Uterine Distension

- In order to successfully visualize and access the fallopian tube ostia, it is essential to maintain adequate uterine distension throughout the procedure.
- Via the inflow channel of the hysteroscope, apply a nonconductive physiologic distention medium (Glycine USP, 1.5%). The Glycine may be pre-warmed to body temperature to minimize fallopian tube spasm.
- Distension media should be flowing.
- Any system delivering high pressure inflow to the patient increases the risk for fluid overload. Duration of hysteroscopy procedure and total volume of fluid applied should be monitored to ensure that fluid overload does not occur. To reduce the risk of hypervolemia the procedure must be immediately terminated if the fluid deficit exceeds 800cc. Additionally, the procedure time should not exceed 30 minutes.

Device Placement and Tubal Access

- Prior to insertion of the Delivery Catheter into the hysteroscope, rotate the hysteroscope to visualize both tubal ostia and ensure the absence of pathology. Note: Both ostia must be identified and assessed before proceeding with the procedure.
- A split Introducer with a removable mandrel is provided with the Delivery Catheter. The Introducer is designed to protect the Delivery Catheter as it is inserted into the hysteroscope past the hysteroscope grommet and pivot valve. Ensure the valve is open, and insert the split Introducer with mandrel into the grommet.
- Remove the mandrel from the split Introducer and insert the Delivery Catheter though the Introducer into the operating channel of the hysteroscope. Once the Delivery Catheter is past the hysteroscope grommet, remove the Introducer sheath.
- Once the tubal ostium is visually localized, use the handle of the Delivery Catheter to guide ts distal end into the tubal ostium.
- Insert the Delivery Catheter into the ostium until the Black Mark on the electrode sheath is located at the tubal ostium and the PDA signals proper placement. When the Delivery Catheter is in adequate contact with the wall of the tube (at four quadrants spaced equally encompassing 360 degrees) all four quadrants will light on the display icon.

Caution: The distal end of the Delivery Catheter should not be inserted into the tubal ostium past the Black Mark.

RF Treatment and Matrix Placement

- For additional information on RF Generator clinical use, see Setting Up the RF Generator (below) and the RF Generator Specifications and Installation Manual.
- Once the Delivery Catheter is placed into the ostium, up to the black mark position, ensure that an adequate hysteroscopic view is achieved that allows observation of the catheter shaft as well as the tubal ostium.
- A tone sounds, the display indicates "Complete RF" and the RF button flashes conveying that the physician should activate RF delivery.
- With the hysteroscope in a fixed position, press the RF Generator button to initiate energy delivery. The RF Generator will automatically deliver RF energy to maintain a constant treatment temperature for 60 seconds.

Note: During RF delivery, maintain a steady position of the Delivery Catheter. It is important to maintain a view of the tubal ostia, and the end of the Delivery Catheter shaft.

- If at any time after the initiation of RF delivery, the following occurs:
  - The Delivery Catheter is inadvertently moved (such that an RF Generator error is triggered), or
  - Energy delivery is interrupted, or
  - The Delivery Catheter is removed before the Matrix is delivered, or
  - There is an RF generator error which can be corrected,

  the operator should correct the source of the error and repeat the procedure PROVIDED that the total RF energy delivery for a single tube does not exceed 120 seconds.

Matrix Release

- At the end of the treatment period, the RF Generator sounds a tone, and the display indicates "Place Matrix". While holding the Delivery Catheter handle, with full attention on the Black Mark that is positioned on the outer shaft, press the Matrix release button on the catheter handle. Within the outer shaft, the electrodes appear to withdraw during this process.
- Visually ensure that the relative distance of the Delivery Catheter shaft to the ostium remains constant during Matrix release. Assure that the

Matrix has been released by visually observing the catheter tip as the sheath is automatically retracted.

- When Matrix release is complete, another tone will sound. Remove the Delivery Catheter from the tubal ostium. Then slowly remove the Delivery Catheter from the operating channel of the hysteroscope.

Contralateral Treatment

- After successful Delivery Catheter placement, RF treatment, and Matrix delivery into the first fallopian tube, a new Delivery Catheter should be connected to the Catheter Cable and inserted into the hysteroscope. The contralateral tube should then be accessed and treated as described above.
- After both treatments are completed, remove the sheathed hysteroscope.

Post-Treatment

- Patients should be monitored and released following the physician's standard post-procedure and release procedures.
- Provide explicit instructions to utilize alternative birth control until successful sterilization confirmation HSG in a minimum of three months.
- Schedule patients for a return confirmation HSG visit no less than 3 months from the date of the procedure.

Follow-up protocol and Hysterosalpingography (HSG)

Patients will need to use alternative contraception during their minimum 3 month waiting period. Once the confirmation HSG is completed and confirms tubal occlusion, post-procedure follow-up is at physician discretion.

- A hysterosalpingogram should be performed to assess tubal occlusion after a minimum of 3 months following the procedure.
- Refer to the HSG Instruction Manual for details on performing the HSG and on interpretation of HSG images.

Setting Up the RF Generator

The steps for operating the RF Generator are described below. Refer to the RF Generator Specification and Installation Manual for additional information about the specifications and operation of this unit.

The RF Generator guides the operator through four steps as described below. These include:

- Connect Catheter
- Access Tube
- Complete RF
- Place Matrix

In addition, the RF Generator performs a 'Self Test' on power up.

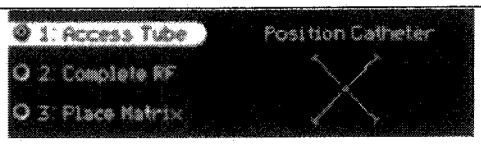
When the Main Power switch is turned off in any mode, all power to the RF Generator is turned off. When the Main Power switch is first switched on, the RF Generator automatically performs a Self Test.

If the system test is successful, the display shows the company logo and software version for 2 seconds, and then the system enters the *Connect Catheter* mode.

Connect Delivery Catheter Step

- This is the first step after a successful internal self-test when the RF Generator is turned on. (It will also be entered from either the *Access Tube* or *Complete RF* modes if the catheter is disconnected.) The display is indicates that the Delivery Catheter should be connected. After the Delivery Catheter is connected, the RF Generator will then transition to the *Access Tube* step.

Access Tube Step

When the Position Detector Array (PDA) senses no tissue contact, the RF Generator displays the following image:	
Each quadrant of the display corresponds to each of the four sides of the Delivery Catheter. When the PDA senses partial tissue contact, (in this case two quadrants) the RF Generator displays this image:	
The tubal contact is complete when the PDA senses sufficient tissue contact on all four sides of the Delivery Catheter and is displayed as seen in this image:	

- The "Progress Tone" sounds when complete contact is made. Also the "Non-progress" tone sounds upon transitioning from complete to incomplete contact.

Complete RF Step

- The next step is entered when there is complete contact around the tip of the Delivery Catheter. Upon pressing the RF button or the footswitch, RF energy delivery will begin. The system measures and monitors relevant parameters such as power, current, voltage, and impedance.

- The display will count down and continuously update the time remaining until the end of the RF application as seen in the above display.