CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021225 S-031

Trade Name: **MIRENA**

Generic Name: **Levonorgestrel-Releasing Intrauterine System**

Sponsor: **Bayer Healthcare Pharmaceuticals, Inc.**

Approval Date: December 22, 2015

Indications: Mirena is a progestin-containing intrauterine system indicated for:

- Intrauterine contraception for up to 5 years;
- Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021225/S-031

SUPPLEMENT APPROVAL

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Jo-Ann M. Ruane
Deputy Director, Global Regulatory Affairs
P.O. Box 915
Whippany, NJ 07981-0915

Dear Ms. Ruane:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 13, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mirena (levonorgestrel-releasing intrauterine system).

We acknowledge receipt of your amendment dated August 23, 2013, June 25, 2014, July 6, July 23, October 9, and October 19, 2015.

This "Prior Approval" supplemental new drug application provides for changes to the WARNINGS and PRECAUTIONS SECTION, Subsections on Irregular Bleeding and Amenorrhea and on Ovarian Cysts, and the ADVERSE REACTIONS SECTION, Subsection on Clinical Trial Experience, and USE IN SPECIAL POPULATION, Subsection on Pregnancy.

In addition, this supplement includes FDA-requested changes to the WARNINGS and PRECAUTIONS SECTION, Subsection on Breast Cancer, to clarify that more than two observational studies of the risk of breast cancer and Mirena have been conducted, and in the ADVERSE REACTIONS SECTION, Subsection on Postmarketing Experience, to indicate that arterial thrombotic and venous thromboembolic events have been reported.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Christine Nguyen, M.D.
Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
10/22/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIRENA safely and effectively. See full prescribing information for MIRENA.

MIRENA (levonorgestrel-releasing intrauterine system)
Initial U.S. Approval: 2000

----------INDICATIONS AND USAGE----------

Mirena is a progestin-containing intrauterine system indicated for:

- Intrauterine contraception for up to 5 years (1)
- Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. (1)

It is recommended for women who have had at least one child.

----------DOSAGE AND ADMINISTRATION----------

- Initial release rate of levonorgestrel (LNG) is 20 mcg/day; this rate is reduced by about 50% after 5 years; Mirena must be removed or replaced after 5 years. (2)
- To be inserted by a trained healthcare provider using strict aseptic technique. Follow insertion instructions exactly as described. (2.1)
- Patient should be re-examined and evaluated 4 to 6 weeks after insertion; then, yearly or more often if indicated. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- One sterile intrauterine system consisting of a T-shaped polyethylene frame with a steroid reservoir containing 52 mg levonorgestrel packaged within a sterile inserter (3)

----------CONTRAINDICATIONS----------

- Pregnancy or suspicion of pregnancy. Cannot be used for post-coital contraception (4).
- Congenital or acquired uterine anomaly if it distorts the uterine cavity (4)
- Acute pelvic inflammatory disease (PID) or a history of PID unless there has been a subsequent intrauterine pregnancy (4)
- Postpartum endometritis or infected abortion in the past 3 months (4)
- Known or suspected uterine or cervical neoplasia (4)
- Known or suspected breast cancer or other progestin-sensitive cancer (4)
- Uterine bleeding of unknown etiology (4)
- Untreated acute cervicitis or vaginitis or other lower genital tract infections (4)
- Acute liver disease or liver tumor (benign or malignant) (4)
- Increased susceptibility to pelvic infection (4)
- A previous intrauterine device (IUD) that has not been removed (4)
- Hypersensitivity to any component of Mirena (4)

----------WARNINGS AND PRECAUTIONS----------

- Remove Mirena if pregnancy occurs with Mirena in place. If pregnancy occurs, there is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion (including septicemia, shock and death), and premature labor and delivery. (5.1, 5 2)
- Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion. (5 3)
- Before using Mirena, consider the risks of PID. (5.4)
- Bleeding patterns become altered, may remain irregular and amenorrhea may ensue. (5.5)
- Perforation may occur and may reduce contraceptive effectiveness. Risk is increased if inserted in lactating women and may be increased if inserted in women with fixed retroverted uteri and postpartum. (5.6)
- Partial or complete expulsion may occur. (5.7)
- Evaluate persistent enlarged ovarian follicles or ovarian cysts. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥10% users) are alterations of menstrual bleeding patterns, abdominal/pelvic pain, amenorrhea, headache/migraine, genital discharge, and vulvovaginitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Drugs or herbal products that induce certain enzymes, such as CYP3A4, may decrease the serum concentration of progestins. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Small amounts of progestins pass into breast milk resulting in detectable steroid levels in infant serum. (8.3)

See 17 **for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Mirena is indicated for intrauterine contraception for up to 5 years.
- Mirena is also indicated for the treatment of heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception.

Mirena is recommended for women who have had at least one child.

The system should be replaced after 5 years if continued use is desired.

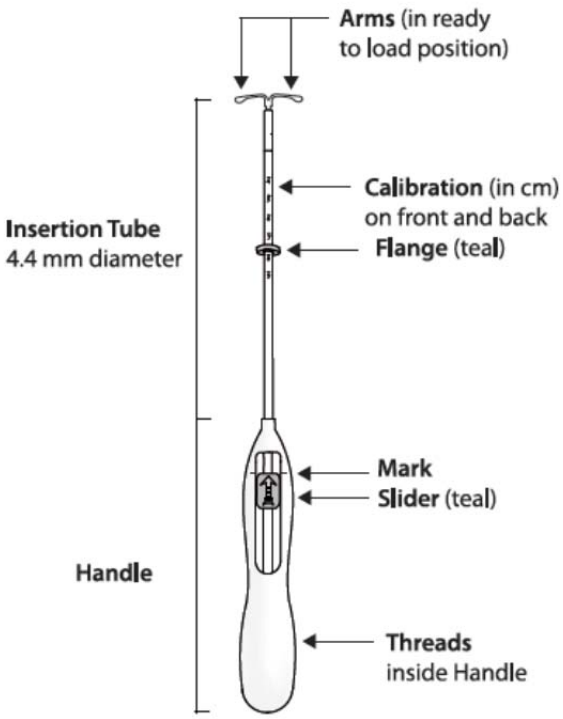
2 DOSAGE AND ADMINISTRATION

Mirena contains 52 mg of levonorgestrel (LNG). Initially, LNG is released at a rate of approximately 20 mcg/day. This rate decreases progressively to half that value after 5 years.

Mirena must be removed by the end of the fifth year and can be replaced at the time of removal with a new Mirena if continued contraceptive protection is desired.

Mirena is supplied within an inserter in a sterile package (see Figure 1) that must not be opened until required for insertion *[see Description (11.2)]*. Do not use if the seal of the sterile package is broken or appears compromised. Use strict aseptic techniques throughout the insertion procedure *[see Warnings and Precautions (5.3)]*.

Mirena and Inserter



2.1. Insertion Instructions

- A complete medical and social history should be obtained to determine conditions that might influence the selection of a levonorgestrel-releasing intrauterine system (LNG IUS) for contraception. If indicated, perform a physical examination, and appropriate tests for any forms of genital or other sexually transmitted infections. *[See Contraindications (4) and Warnings and Precautions (5.10).]*

- Follow the insertion instructions exactly as described in order to ensure proper placement and avoid premature release of Mirena from the inserter. Once released, Mirena cannot be re-loaded.
- Mirena should be inserted by a trained healthcare provider. Healthcare providers should become thoroughly familiar with the insertion instructions before attempting insertion of Mirena.
- Insertion may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, bradycardia), or with seizure in an epileptic patient, especially in patients with a predisposition to these symptoms. Consider administering analgesics prior to insertion.

Timing of Insertion

- Insert Mirena into the uterine cavity during the first seven days of the menstrual cycle or immediately after a first trimester abortion. Back up contraception is not needed when Mirena is inserted as directed.
- Postpone postpartum insertion and insertions following second trimester abortions a minimum of six weeks or until the uterus is fully involuted. If involution is delayed, wait until involution is complete before insertion *[see Warnings and Precautions (5.6, 5.7)]*.

Tools for Insertion

Preparation

- Gloves
- Speculum
- Sterile uterine sound
- Sterile tenaculum
- Antiseptic solution, applicator

Procedure

- Sterile gloves
- Mirena with inserter in sealed package
- Instruments and anesthesia for paracervical block, if anticipated
- Consider having an unopened backup Mirena available
- Sterile, sharp curved scissors

Preparation for insertion

- Exclude pregnancy and confirm that there are no other contraindications to the use of Mirena.
- Ensure that the patient understands the contents of the Patient Information Booklet and obtain the signed patient informed consent located on the last page of the Patient Information Booklet.
- With the patient comfortably in lithotomy position, do a bimanual exam to establish the size, shape and position of the uterus.
- Gently insert a speculum to visualize the cervix.
- Thoroughly cleanse the cervix and vagina with a suitable antiseptic solution.
- Prepare to sound the uterine cavity. Grasp the upper lip of the cervix with a tenaculum forceps and gently apply traction to stabilize and align the cervical canal with the uterine cavity. Perform a paracervical block if needed. If the uterus is retroverted, it may be more appropriate to grasp the lower lip of the cervix. The tenaculum should remain in position and gentle traction on the cervix should be maintained throughout the insertion procedure.
- Gently insert a uterine sound to check the patency of the cervix, measure the depth of the uterine cavity in centimeters, confirm cavity direction, and detect the presence of any uterine anomaly. If you encounter difficulty or cervical stenosis, use dilatation, and not force, to overcome resistance. If cervical dilatation is required, consider using a paracervical block.
- The uterus should sound to a depth of 6 to 10 cm. Insertion of Mirena into a uterine cavity less than 6 cm by sounding may increase the incidence of expulsion, bleeding, pain, perforation, and possibly pregnancy.

Insertion Procedure

Proceed with insertion only after completing the above steps and ascertaining that the patient is appropriate for Mirena. Ensure use of aseptic technique throughout the entire procedure.

Step 1–Opening of the package

- Open the package (Figure 1). The contents of the package are sterile.

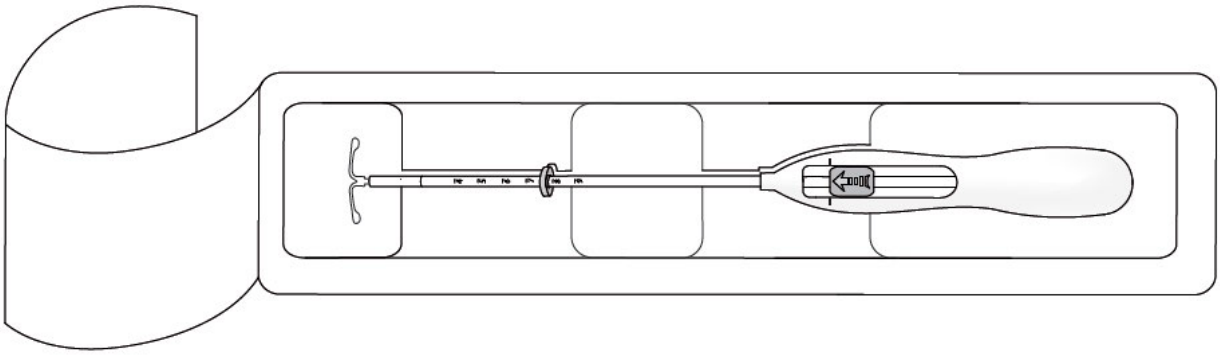


Figure 1. Opening the Mirena Package

- Using sterile gloves lift the handle of the sterile inserter and remove from the sterile package.

Step 2–Load Mirena into the insertion tube

- Push the slider forward as far as possible in the direction of the arrow thereby moving the insertion tube over the Mirena T-body to load Mirena into the insertion tube (Figure 2). The tips of the arms will meet to form a rounded end that extends slightly beyond the insertion tube.

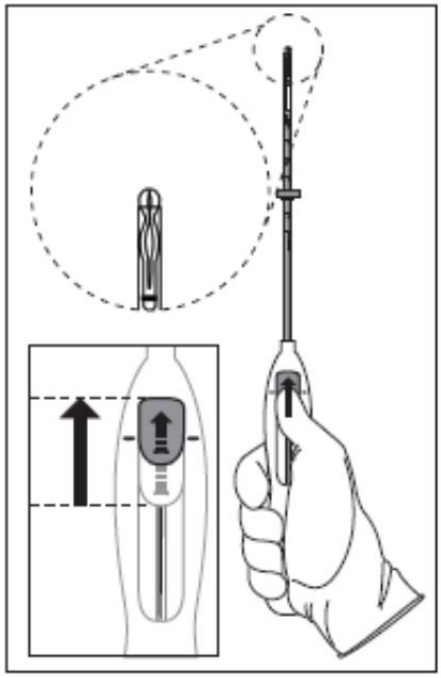


Figure 2. Move slider all the way to the forward position to load Mirena

- Maintain forward pressure with your thumb or forefinger on the slider. DO NOT move the slider downward at this time as this may prematurely release the threads of Mirena. Once the slider is moved below the mark, Mirena cannot be re-loaded.

Step 3–Setting the flange

- Holding the slider in this forward position, set the upper edge of the flange to correspond to the uterine depth (in centimeters) measured during sounding (Figure 3).

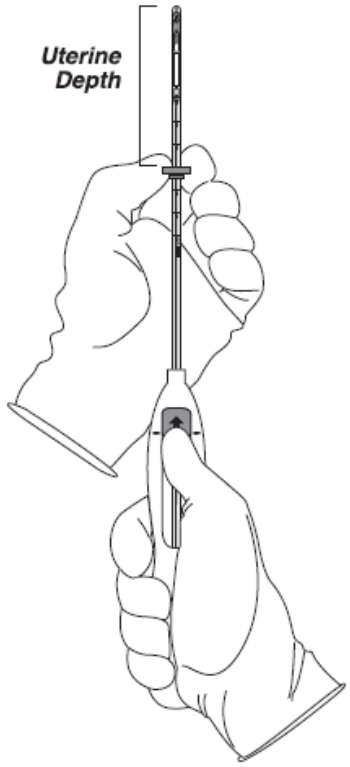


Figure 3. Setting the flange

Step 4–Mirena is now ready to be inserted

- Continue holding the slider in this forward position. Advance the inserter through the cervix until the flange is approximately 1.5–2 cm from the cervix and then pause (Figure 4).

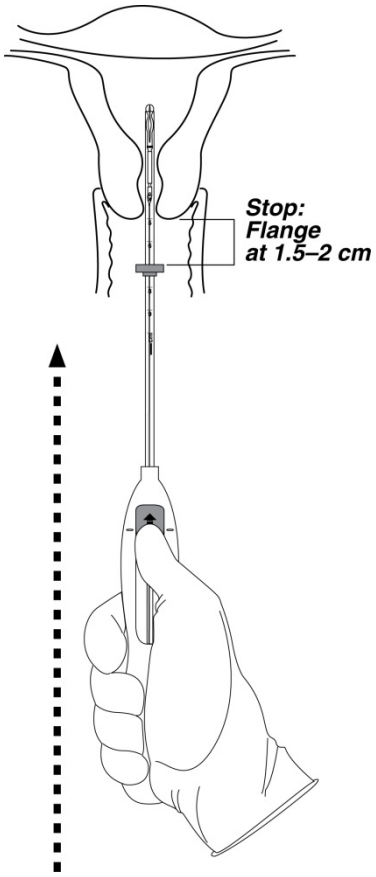


Figure 4. Advancing insertion tube until flange is 1.5 to 2 cm from the cervix

Do not force the inserter. If necessary, dilate the cervical canal.

Step 5–Open the arms

- While holding the inserter steady, move the slider down to the mark to release the arms of Mirena (Figure 5). Wait 10 seconds for the horizontal arms to open completely.

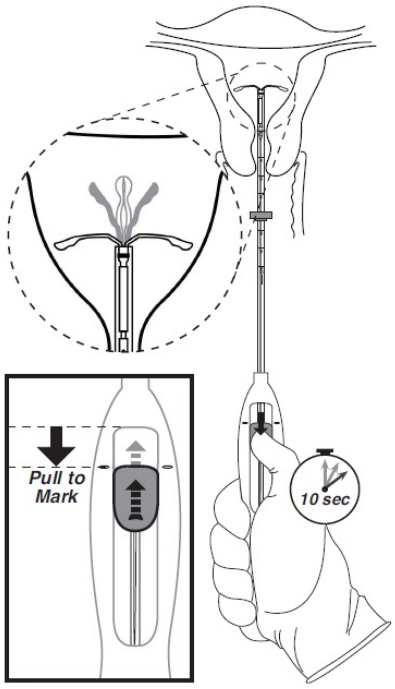


Figure 5. Move the slider back to the mark to release and open the arms

Step 6–Advance to fundal position

- Advance the inserter gently towards the fundus of the uterus until the flange touches the cervix. If you encounter fundal resistance do not continue to advance. Mirena is now in the fundal position (Figure 6). Fundal positioning of Mirena is important to prevent expulsion.

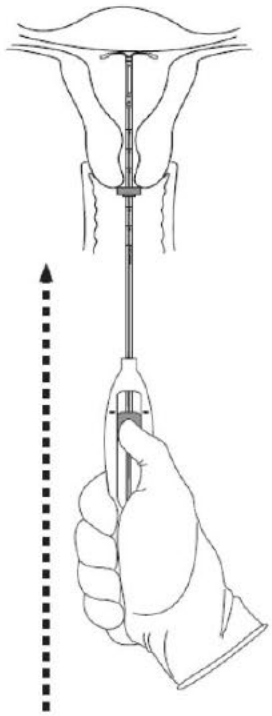


Figure 6. Move Mirena into the fundal position

Step 7–Release Mirena and withdraw the inserter

- Holding the entire inserter firmly in place, release Mirena by moving the slider all the way down (Figure 7).

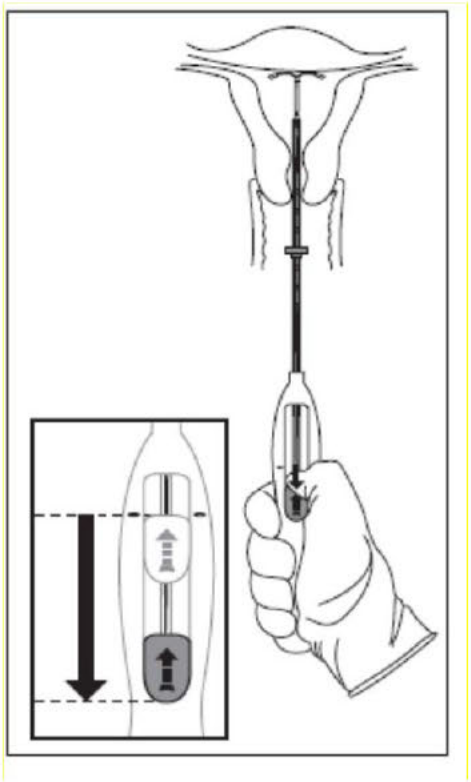


Figure 7. Move the slider all the way down to release Mirena from the insertion tube

- Continue to hold the slider all the way down while you slowly and gently withdraw the inserter from the uterus.
- Using a sharp, curved scissor, cut the threads perpendicular, leaving about 3 cm visible outside of the cervix [cutting threads at an angle may leave sharp ends (Figure 8)]. Do not apply tension or pull on the threads when cutting to prevent displacing Mirena.

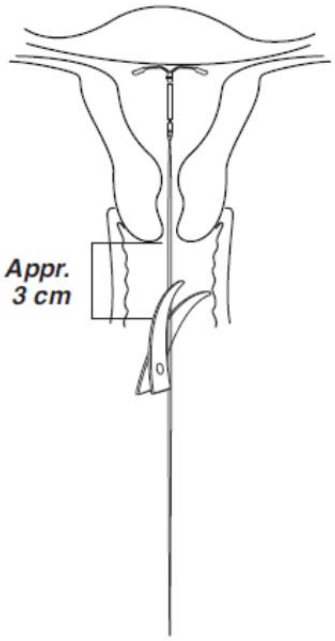


Figure 8. Cutting the threads

Mirena insertion is now complete. Prescribe analgesics, if indicated. Keep a copy of the Consent Form with lot number for your records.

Important information to consider during or after insertion

- If you suspect that Mirena is not in the correct position, check placement (for example, using transvaginal ultrasound). Remove Mirena if it is not positioned completely within the uterus. A removed Mirena must not be re-inserted.
- If there is clinical concern, exceptional pain or bleeding during or after insertion, appropriate steps (such as physical examination and ultrasound) should be taken immediately to exclude perforation.

2.2 Patient Follow-up

- Reexamine and evaluate patients 4 to 6 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

2.3 Removal of Mirena

Timing of Removal

- Mirena should not remain in the uterus after 5 years.
- If pregnancy is not desired, the removal should be carried out during menstruation, provided the woman is still experiencing regular menses. If removal will occur at other times during the cycle, consider starting a new contraceptive method a week prior to removal. If removal occurs at other times during the cycle and the woman has had intercourse in the week prior to removal, she is at risk of pregnancy. *[See Dosage and Administration (2.4).]*

Tools for Removal

Preparation

- Gloves
- Speculum

Procedure

- Sterile forceps

Removal Procedure

- Remove Mirena by applying gentle traction on the threads with forceps. (Figure 9).

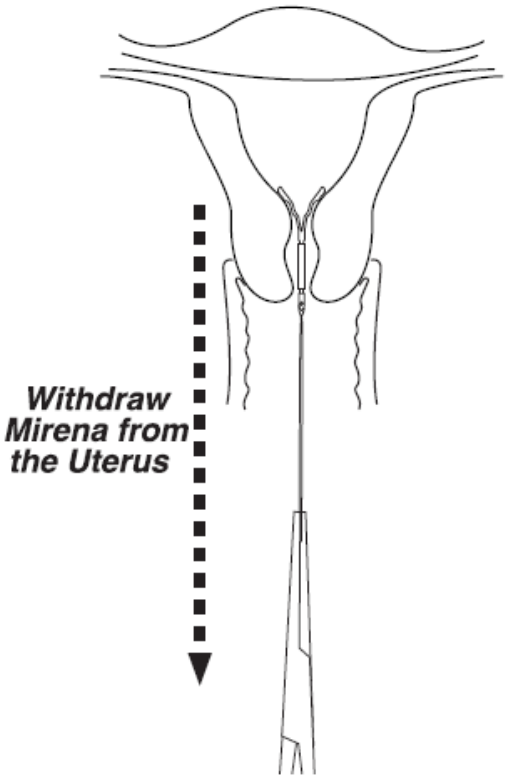


Figure 9. Removal of Mirena

- If the threads are not visible, determine location of Mirena by ultrasound *[see Warnings and Precautions (5.10)]*.
- If Mirena is found to be in the uterine cavity on ultrasound exam, it may be removed using a narrow forceps, such as an alligator forceps. This may require dilation of the cervical canal. After removal of Mirena, examine the system to ensure that it is intact.
- Removal may be associated with some pain and/or bleeding or vasovagal reactions (for example, syncope, or a seizure in an epileptic patient).

2.4 Continuation of Contraception after Removal

- If pregnancy is not desired and if a woman wishes to continue using Mirena, a new system can be inserted immediately after removal any time during the cycle.
- If a patient with regular cycles wants to start a different birth control method, time removal and initiation of new method to ensure continuous contraception. Either remove Mirena during the first 7 days of the menstrual cycle and start the new method immediately thereafter or start the new method at least 7 days prior to removing Mirena if removal is to occur at other times during the cycle.

- If a patient with irregular cycles or amenorrhea wants to start a different birth control method, start the new method at least 7 days before removal.

3 DOSAGE FORMS AND STRENGTHS

Mirena is a LNG-releasing IUS consisting of a T-shaped polyethylene frame with a steroid reservoir containing a total of 52 mg LNG.

4 CONTRAINDICATIONS

The use of Mirena is contraindicated when one or more of the following conditions exist:

- Pregnancy or suspicion of pregnancy; cannot be used for post-coital contraception *[see Warnings and Precautions (5.2)]*
- Congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity
- Acute pelvic inflammatory disease or a history of pelvic inflammatory disease unless there has been a subsequent intrauterine pregnancy *[see Warnings and Precautions (5.4)]*
- Postpartum endometritis or infected abortion in the past 3 months
- Known or suspected uterine or cervical neoplasia
- Known or suspected breast cancer or other progestin-sensitive cancer, now or in the past
- Uterine bleeding of unknown etiology
- Untreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled
- Acute liver disease or liver tumor (benign or malignant)
- Conditions associated with increased susceptibility to pelvic infections *[see Warnings and Precautions (5.4)]*
- A previously inserted intrauterine device (IUD) that has not been removed
- Hypersensitivity to any component of this product *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Evaluate women for ectopic pregnancy if they become pregnant with Mirena in place because the likelihood of a pregnancy being ectopic is increased with Mirena. Up to half of pregnancies that occur with Mirena in place are likely to be ectopic. Also consider the possibility of ectopic pregnancy in the case of lower abdominal pain, especially in association with missed periods or if an amenorrheic woman starts bleeding.

The incidence of ectopic pregnancy in clinical trials with Mirena, which excluded women with a history of ectopic pregnancy, was approximately 0.1% per year. The risk of ectopic pregnancy, in women who have a history of ectopic pregnancy and use Mirena is unknown. Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry a higher risk of ectopic pregnancy. Ectopic pregnancy may result in loss of fertility.

5.2 Intrauterine Pregnancy

If pregnancy occurs while using Mirena, remove Mirena because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Removal of Mirena or probing of the uterus may also result in spontaneous abortion. In the event of an intrauterine pregnancy with Mirena, consider the following:

Septic abortion

In patients becoming pregnant with an IUD in place, septic abortion - with septicemia, septic shock, and death - may occur.

Continuation of pregnancy

If a woman becomes pregnant with Mirena in place and if Mirena cannot be removed or the woman chooses not to have it removed, warn her that failure to remove Mirena increases the risk of miscarriage, sepsis, premature labor and premature delivery. Follow her pregnancy closely and advise her to report immediately any symptom that suggests complications of the pregnancy.

Long-term effects and congenital anomalies

When pregnancy continues with Mirena in place, long-term effects on the offspring are unknown. Congenital anomalies in live births have occurred infrequently. No clear trend towards specific anomalies has been observed. Because of the local exposure of the fetus to LNG, the possibility of teratogenicity following exposure to Mirena cannot be completely excluded. Some observational data support a small increased risk of masculinization of the external genitalia of the female fetus following exposure to progestins at doses greater than those currently used for oral contraception. Whether these data apply to Mirena is unknown.

5.3 Sepsis

Severe infection or sepsis, including Group A streptococcal sepsis (GAS), have been reported following insertion of Mirena. In some cases, severe pain occurred within hours of insertion followed by sepsis within days. Because death from GAS is more likely if treatment is delayed, it is important to be aware of these rare but serious infections. Aseptic technique during insertion of Mirena is essential in order to minimize serious infections such as GAS.

5.4 Pelvic Infection

Pelvic Inflammatory Disease (PID)

Mirena is contraindicated in the presence of known or suspected PID or in women with a history of PID unless there has been a subsequent intrauterine pregnancy *[see Contraindications (4)]***.** IUDs have been associated with an increased risk of PID, most likely due to organisms being introduced into the uterus during insertion. In clinical trials, total combined upper genital infections were reported in 3.5% of Mirena users. More specifically, endometritis was reported in 2.1%, PID in 0.6%, and all other upper genital infections in ≤0.5% of women overall. These infections occurred more frequently within the first year. In a clinical trial with other IUDs[1] and a clinical trial with an IUD similar to Mirena, the highest rate occurred within the first month after insertion.

Promptly examine users with complaints of lower abdominal or pelvic pain, odorous discharge, unexplained bleeding, fever, genital lesions or sores. Remove Mirena in cases of recurrent endometritis or PID, or if an acute pelvic infection is severe or does not respond to treatment.

Women at increased risk for PID

PID is often associated with a sexually transmitted infection, and Mirena does not protect against sexually transmitted infection. The risk of PID is greater for women who have multiple sexual partners, and also for women whose sexual partner(s) have multiple sexual partners. Women who have had PID are at increased risk for a recurrence or re-infection. In particular, ascertain whether the woman is at increased risk of infection (for example, leukemia, acquired immune deficiency syndrome [AIDS], IV drug abuse).

Asymptomatic PID

PID may be asymptomatic but still result in tubal damage and its sequelae.

Treatment of PID

Following a diagnosis of PID, or suspected PID, bacteriologic specimens should be obtained and antibiotic therapy should be initiated promptly. Removal of Mirena after initiation of antibiotic therapy is usually appropriate. Guidelines for PID treatment are available from the Centers for Disease Control (CDC), Atlanta, Georgia.

Actinomycosis

Actinomycosis has been associated with IUDs. Symptomatic women should have Mirena removed and should receive antibiotics. The significance of actinomyces-like organisms on Pap smear in an asymptomatic IUD user is unknown, and so this finding alone does not always require Mirena removal and treatment. When possible, confirm a Pap smear diagnosis with cultures.

5.5 Irregular Bleeding and Amenorrhea

Mirena can alter the bleeding pattern and result in spotting, irregular bleeding, heavy bleeding, oligomenorrhea and amenorrhea. During the first three to six months of Mirena use, the number of bleeding and spotting days may be

increased and bleeding patterns may be irregular. Thereafter the number of bleeding and spotting days usually decreases but bleeding may remain irregular. If bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be taken to rule out endometrial pathology.

Amenorrhea develops in approximately 20% of Mirena users by one year. The possibility of pregnancy should be considered if menstruation does not occur within six weeks of the onset of previous menstruation. Once pregnancy has been excluded, repeated pregnancy tests are generally not necessary in amenorrheic women unless indicated, for example, by other signs of pregnancy or by pelvic pain *[see Clinical Studies (14.1)]*.

In most women with heavy menstrual bleeding, the number of bleeding and spotting days may also increase during the initial months of therapy but usually decrease with continued use; the volume of blood loss per cycle progressively becomes reduced *[see Clinical Studies (14.2)]*.

5.6 Perforation

Perforation (total or partial, including penetration/embedment of Mirena in the uterine wall or cervix) may occur most often during insertion, although the perforation may not be detected until sometime later. Perforation may reduce contraceptive efficacy and result in pregnancy. The incidence of perforation during clinical trials, which excluded breast-feeding women, was < 0.1%.

If perforation occurs, locate and remove Mirena. Surgery may be required. Delayed detection or removal of Mirena in case of perforation may result in migration outside the uterine cavity, adhesions, peritonitis, intestinal perforations, intestinal obstruction, abscesses and erosion of adjacent viscera.

An interim analysis from a large postmarketing safety study shows an increased risk of perforation in lactating women. The risk of perforation may be increased if Mirena is inserted when the uterus is fixed retroverted or not completely involuted during the postpartum period. Delay Mirena insertion a minimum of six weeks or until involution is complete following a delivery or a second trimester abortion.

5.7 Expulsion

Partial or complete expulsion of Mirena may occur resulting in the loss of contraceptive protection. Expulsion may be associated with symptoms of bleeding or pain, or it may be asymptomatic and go unnoticed. Mirena typically decreases menstrual bleeding over time; therefore, an increase of menstrual bleeding may be indicative of an expulsion. The risk of expulsion may be increased when the uterus is not completely involuted. In clinical trials, a 4.5% expulsion rate was reported over the 5-year study duration.

Delay Mirena insertion a minimum of six weeks or until uterine involution is complete following a delivery or a second trimester abortion. Remove a partially expelled Mirena. If expulsion has occurred, Mirena may be replaced within 7 days after the onset of a menstrual period after pregnancy has been ruled out.

5.8 Ovarian Cysts

Because the contraceptive effect of Mirena is mainly due to its local effects within the uterus, ovulatory cycles with follicular rupture usually occur in women of fertile age using Mirena. Sometime atresia of the follicle is delayed and the follicle may continue to grow. Ovarian cysts have been reported in approximately 8% of women using Mirena. Most of these cysts are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.

In most cases the ovarian cysts disappear spontaneously during two to three months observation. Evaluate persistent ovarian cysts. Surgical intervention is not usually required.

5.9 Breast Cancer

Women who currently have or have had breast cancer, or have a suspicion of breast cancer, should not use hormonal contraception because some breast cancers are hormone-sensitive *[see Contraindications (4)]*.

Spontaneous reports of breast cancer have been received during postmarketing experience with Mirena. Observational studies of the risk of breast cancer with use of a LNG-releasing IUS do not provide conclusive evidence of increased risk.

5.10 Clinical Considerations for Use and Removal

Use Mirena with caution after careful assessment if any of the following conditions exist, and consider removal of the system if any of them arise during use:

- Coagulopathy or use of anticoagulants
- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- Exceptionally severe headache
- Marked increase of blood pressure
- Severe arterial disease such as stroke or myocardial infarction

In addition, consider removing Mirena if any of the following conditions arise during use *[see Contraindications (4)]*:

- Uterine or cervical malignancy
- Jaundice

If the threads are not visible or are significantly shortened they may have broken or retracted into the cervical canal or uterus. Consider the possibility that the system may have been displaced (for example, expelled or perforated the uterus) *[see Warnings and Precautions (5.6, 5.7)]*. Exclude pregnancy and verify the location of Mirena, for example, by sonography, X-ray, or by gentle exploration of the cervical canal with a suitable instrument. If Mirena is displaced, remove it. A new Mirena may be inserted at that time or during the next menses if it is certain that conception has not occurred. If Mirena is in place with no evidence of perforation, no intervention is indicated.

6 ADVERSE REACTIONS

The following serious or otherwise important adverse reactions are discussed in elsewhere in the labeling:

- Ectopic Pregnancy *[see Warnings and Precautions (5.1)]*
- Intrauterine Pregnancy *[see Warnings and Precautions (5.2)]*
- Group A Streptococcal Sepsis (GAS) *[see Warnings and Precautions (5.3)]*
- Pelvic Inflammatory Disease *[see Warnings and Precautions (5.4)]*
- Alterations of Bleeding Patterns *[see Warnings and Precautions (5.5)]*
- Perforation *[see Warnings and Precautions (5.6)]*
- Expulsion *[see Warnings and Precautions (5.7)]*
- Ovarian Cysts *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data provided reflect the experience with the use of Mirena in the adequate and well-controlled studies as well as in the supportive and uncontrolled studies for contraception and heavy menstrual bleeding (n=5,091). The data cover more than 12,101 women-years of exposure, mainly in the contraception studies (11,761 women-years). The frequencies of reported adverse drug reactions represent crude incidences.

The most common adverse reactions (≥10% users) are alterations of menstrual bleeding patterns [including unscheduled uterine bleeding (31.9%), decreased uterine bleeding (23.4%), increased scheduled uterine bleeding (11.9%), and female genital tract bleeding (3.5%)], abdominal/pelvic pain (22.6%), amenorrhea (18.4%), headache/migraine (16.3%), genital discharge (14.9%), and vulvovaginitis (10.5%). Adverse reactions reported in ≥ 5% of users are shown in Table 1.

Table 1 Adverse Reactions ≥ 5% Reported in Clinical Trials with Mirena

System Organ Class	Adverse Reactions	% (N= 5,091)
Reproductive system and breast disorders	alteration of menstrual bleeding pattern, including:	
	unscheduled uterine bleeding	31.9
	decreased uterine bleeding	23.4
	increased scheduled uterine bleeding	11.9
	female genital tract bleeding	3.5
	amenorrhea	18.4
	genital discharge	14.9
	vulvovaginitis	10.5
	breast pain	8.5
	benign ovarian cyst and associated complications	7.5
	dysmenorrhea	6.4
Gastrointestinal disorders	abdominal/pelvic pain	22.6
Nervous system disorders	headache/migraine	16.3
Musculoskeletal and connective tissue disorders	back pain	7.9
Skin and subcutaneous tissue disorders	acne	6.8
Psychiatric disorders	depression/depressive mood	6.4

Other adverse reactions occurring in <5% of subjects include alopecia, (partial and complete) device expulsion, hirsutism, nausea, and PID/endometritis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Mirena. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Arterial thrombotic and venous thromboembolic events, including cases of pulmonary emboli, deep vein thrombosis and stroke
- Device breakage
- Hypersensitivity (including rash, urticaria and angioedema)
- Increased blood pressure

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with Mirena.

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the serum concentrations of progestins.

Some drugs or herbal products that may decrease the serum concentration of LNG include:

- Barbiturates
- Bosentan
- Carbamazepine
- Efavirenz
- Felbamate
- Griseofulvin
- Nevirapine
- Oxcarbazepine
- Phenytoin
- Rifabutin
- Rifampin
- St. John's wort
- Topiramate

Significant changes (increase or decrease) in the serum concentrations of the progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Consult the labeling of all concurrently used drugs to obtain further information about interactions with Mirena or the potential for enzyme alterations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The use of Mirena during an existing or suspected pregnancy is contraindicated. Many studies have found no harmful effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted with progestin-only pills have not demonstrated significant adverse effects. *[See Contraindications (4) and Warnings and Precautions (5.1, 5.2).]*

8.3 Nursing Mothers

In general, no adverse effects of progestin-only contraceptives have been found on breastfeeding performance or on the health, growth, or development of the infant. Isolated postmarketing cases of decreased milk production have been reported. Small amounts of progestins were observed to pass into the breast milk of nursing mothers who used Mirena, resulting in detectable steroid levels in infant serum. *[See Warnings and Precautions (*5.6*).]*

8.4 Pediatric Use

Safety and efficacy of Mirena have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Mirena has not been studied in women over age 65 and is not approved for use in this population.

8.6 Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of LNG released from Mirena *[see Contraindications (4)]*.

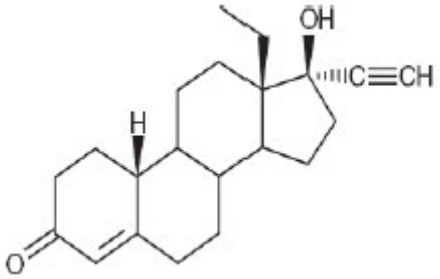
8.7 Renal Impairment

No studies were conducted to evaluate the effect of renal disease on the disposition of LNG released from Mirena.

11 DESCRIPTION

Mirena (levonorgestrel-releasing intrauterine system) contains 52 mg of LNG, a progestin, and is intended to provide an initial release rate of approximately 20 mcg/day of LNG.

Levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, the active ingredient in Mirena, has a molecular weight of 312.4, a molecular formula of $C_{21}H_{28}O_2$, and the following structural formula:



11.1 Mirena

Mirena consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a white or almost white cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a semi-opaque silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body. The polyethylene of the removal thread contains iron oxide as a colorant (see Figure 10).

The components of Mirena, including its packaging, are not manufactured using natural rubber latex.

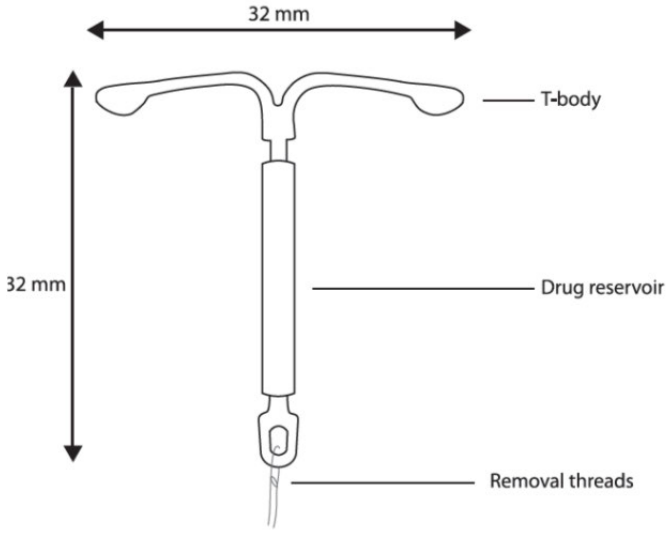


Figure 10. Mirena

11.2 Inserter

Mirena is packaged sterile within an inserter. The inserter (Figure 11), which is used for insertion of Mirena into the uterine cavity, consists of a symmetric two-sided body and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. The outer diameter of the insertion tube is 4.4 mm. The vertical stem of Mirena is loaded in the insertion

tube at the tip of the inserter. The arms are pre-aligned in the horizontal position. The removal threads are contained within the insertion tube and handle. Once Mirena has been placed, the inserter is discarded.

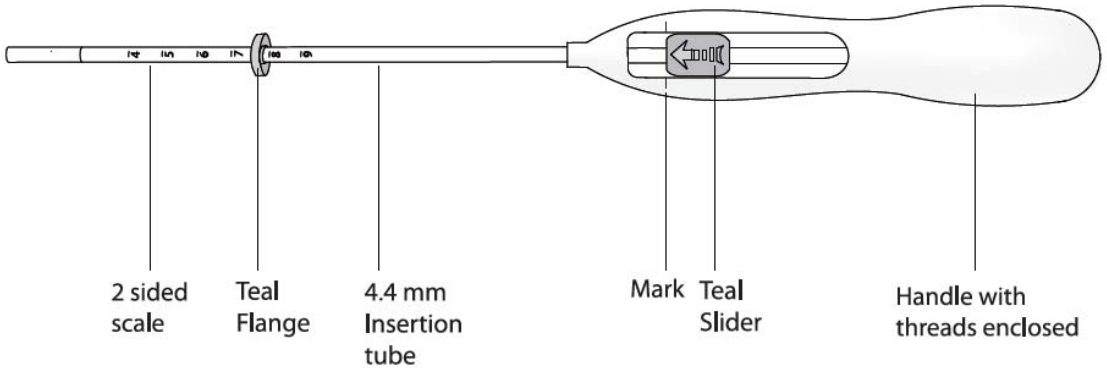


Figure 11: Diagram of Inserter

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The local mechanism by which continuously released LNG enhances contraceptive effectiveness of Mirena has not been conclusively demonstrated. Studies of Mirena and similar LNG IUS prototypes have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into the uterus, inhibition of sperm capacitation or survival, and alteration of the endometrium**.**

12.2 Pharmacodynamics

Mirena has mainly local progestogenic effects in the uterine cavity. The high local levels of LNG[2] lead to morphological changes including stromal pseudodecidualization, glandular atrophy, a leukocytic infiltration and a decrease in glandular and stromal mitoses.

Ovulation is inhibited in some women using Mirena. In a 1-year study, approximately 45% of menstrual cycles were ovulatory, and in another study after 4 years, 75% of cycles were ovulatory.

12.3 Pharmacokinetics

Absorption

Low doses of LNG are administered into the uterine cavity with the Mirena intrauterine delivery system. The initial release rate is approximately 20 mcg/day over the first 3 months tested (day 0 to day 90). It is reduced to approximately 18 mcg/day after 1 year and then decreases progressively to approximately 10 mcg/day after 5 years.

A stable serum concentration, without peaks and troughs, of LNG of 150–200 pg/mL occurs after the first few weeks following insertion of Mirena. LNG concentrations after long-term use of 12, 24, and 60 months were 180±66 pg/mL, 192±140 pg/mL, and 159±59 pg/mL, respectively.

Distribution

The apparent volume of distribution of LNG is reported to be approximately 1.8 L/kg. It is about 97.5 to 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin.

Metabolism

Following absorption, LNG is conjugated at the 17β-OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in serum. Significant amounts of conjugated and unconjugated 3α, 5β- tetrahydrolevonorgestrel are also present in serum, along with much smaller amounts of 3α, 5α-tetrahydrolevonorgestrel and 16β-

hydroxylevonorgestrel. LNG and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for wide individual variations in LNG concentrations seen in individuals using LNG–containing contraceptive products. *In vitro* studies have demonstrated that oxidative metabolism of LNG is catalyzed by CYP enzymes, especially CYP3A4.

Excretion

About 45% of LNG and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The elimination half-life of LNG after daily oral doses is approximately 17 hours.

Specific Populations

Pediatric: Safety and efficacy of Mirena have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatric: Mirena has not been studied in women over age 65 and is not currently approved for use in this population.

Race: No studies have evaluated the effect of race on pharmacokinetics of Mirena.

Hepatic Impairment: No studies were conducted to evaluate the effect of hepatic disease on the disposition of Mirena.

Renal Impairment: No formal studies were conducted to evaluate the effect of renal disease on the disposition of Mirena.

Drug-Drug Interactions

No drug-drug interaction studies were conducted with Mirena *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.9)]

14 CLINICAL STUDIES

14.1 Clinical Trials on Contraception

Mirena has been studied for safety and efficacy in two large clinical trials in Finland and Sweden. In study sites having verifiable data and informed consent, 1,169 women 18 to 35 years of age at enrollment used Mirena for up to 5 years, for a total of 45,000 women-months of exposure. Subjects had previously been pregnant, had no history of ectopic pregnancy, had no history of pelvic inflammatory disease over the preceding 12 months, were predominantly Caucasian, and over 70% of the participants had previously used IUDs (intrauterine devices). The reported 12-month pregnancy rates were less than or equal to 0.2 per 100 women (0.2%) and the cumulative 5-year pregnancy rate was approximately 0.7 per 100 women (0.7%).

About 80% of women wishing to become pregnant conceived within 12 months after removal of Mirena.

14.2 Clinical Trial on Heavy Menstrual Bleeding

The efficacy of Mirena in the treatment of heavy menstrual bleeding was studied in a randomized, open-label, active-control, parallel-group trial comparing Mirena (n=79) to an approved therapy, medroxyprogesterone acetate (MPA) (n=81), over 6 cycles. The subjects included reproductive-aged women in good health, with no contraindications to the drug products and with confirmed heavy menstrual bleeding (≥ 80 mL menstrual blood loss [MBL]) determined using the alkaline hematin method. Excluded were women with organic or systemic conditions that may cause heavy uterine bleeding (except small fibroids, with total volume not > 5 mL). Treatment with Mirena showed a statistically significantly greater reduction in MBL (see Figure 12) and a statistically significantly greater number of subjects with successful treatment (see Figure 13). Successful treatment was defined as proportion of subjects with (1) end-of-study MBL < 80 mL and (2) a ≥ 50% decrease in MBL from baseline to end-of-study.

Figure 12. Median Menstrual Blood Loss (MBL) by Time and Treatment

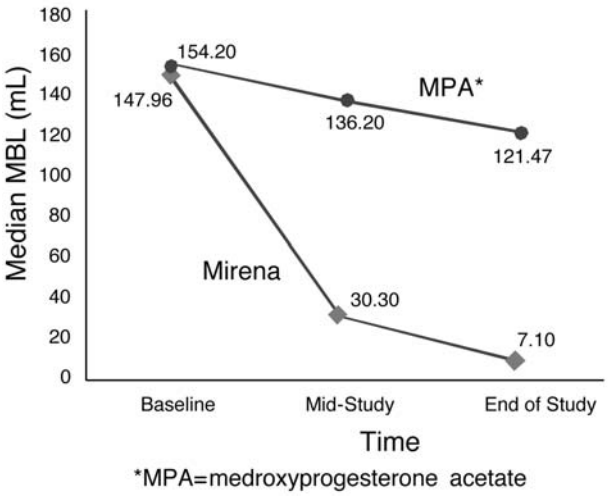
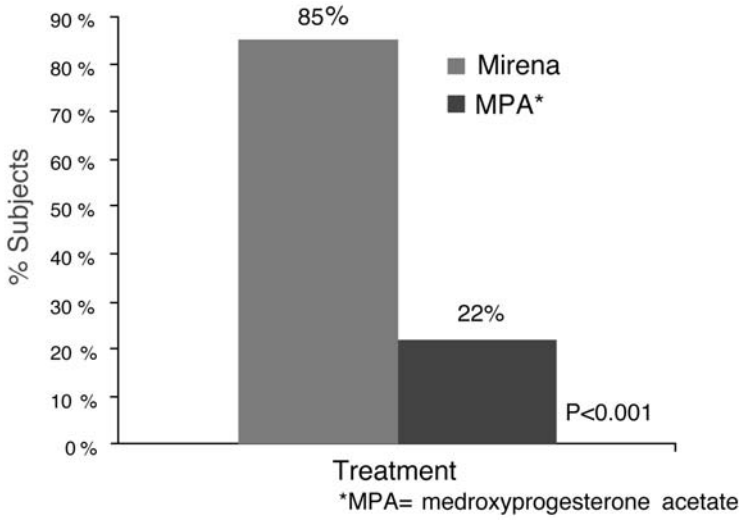


Figure 13. Proportion of Subjects with Successful Treatment



15 REFERENCES

[1]Farley T M M, Rosenberg M J, Rowe P J, Chen J, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet 1992; 339:785-788.

[2]Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentrations of LNG in women using a LNG-releasing IUD. Clinical Endocrinol 1982;17:529-536.

16 HOW SUPPLIED/STORAGE AND HANDLING

Mirena (levonorgestrel-releasing intrauterine system), containing a total of 52 mg LNG, is available in a carton of one sterile unit NDC# 50419-423-01.

Mirena is supplied sterile. Mirena is sterilized with ethylene oxide. Do not resterilize. For single use only. Do not use if the inner package is damaged or open. Insert before the end of the month shown on the label.

Store at 25°C (77°F); with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Counsel the patient that this product does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).
- Counsel the patient on the benefits, risks, and side effects of Mirena prior to insertion. Provide the Patient Information Booklet and give her the opportunity to read the information and discuss fully any questions she may have concerning Mirena as well as other methods of contraception and therapies for heavy menstrual bleeding. Advise the patient that the Full Prescribing Information is available to her upon request.
- Inform the patient about the risks of ectopic pregnancy, including the loss of fertility. Teach her to recognize and report to her healthcare provider promptly any symptoms of ectopic pregnancy.
- Inform the patient about the possibility of pelvic inflammatory disease (PID) and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death. Teach patients to recognize and report to their healthcare provider promptly any symptoms of PID. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever.

- Counsel the patient that irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her healthcare provider.
- Counsel the patient on how she can check that the threads still protrude from the cervix and caution her not to pull on the threads and displace Mirena. Inform her that there is no contraceptive protection if Mirena is displaced or expelled. *[See Warnings and Precautions (5.6, 5.7).]*
- Instruct the patient to contact her healthcare provider if she experiences any of the following:
  - A stroke or heart attack
  - Very severe or migraine headaches
  - Unexplained fever
  - Yellowing of the skin or whites of the eyes, as these may be signs of serious liver problems
  - Pregnancy or suspected pregnancy
  - Pelvic pain or pain during sex
  - HIV positive seroconversion in herself or her partner
  - Possible exposure to sexually transmitted infections (STIs)
  - Unusual vaginal discharge or genital sores
  - Severe vaginal bleeding or bleeding that lasts a long time, or if she misses a menstrual period
  - Inability to feel Mirena's threads
- Complete the Follow-up Reminder Card and give to the patient.

FDA-Approved Patient Labeling

Patient Information

Mirena® (mur-ā-nah)

(levonorgestrel-releasing intrauterine system)

Mirena does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).

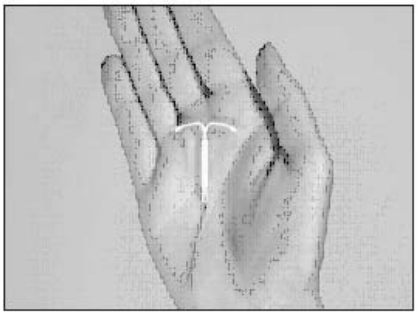
Read this Patient Information carefully before you decide if Mirena is right for you. This information does not take the place of talking with your gynecologist or other healthcare provider who specializes in women's health. If you have any questions about Mirena, ask your healthcare provider. You should also learn about other birth control methods to choose the one that is best for you.

What is Mirena?

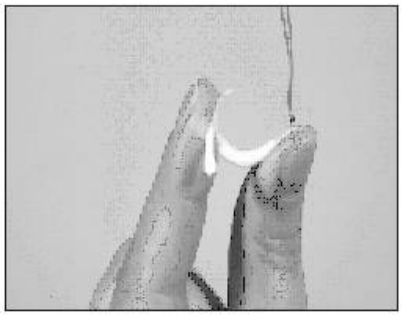
- Mirena is a hormone-releasing system placed in your uterus by your healthcare provider to prevent pregnancy for up to 5 years.
- Mirena can also lessen menstrual blood loss in women who have heavy menstrual flow and who also want to use a birth control method that is placed in the uterus to prevent pregnancy.
- Mirena can be removed by your healthcare provider at any time.
- Mirena is recommended for women who have had at least one child.

Mirena is a small flexible plastic T-shaped system that slowly releases a progestin hormone called levonorgestrel that is often used in birth control pills. Because Mirena releases levonorgestrel into your uterus, only small amounts of the hormone enter your blood. Mirena does not contain estrogen.

Two thin threads are attached to the stem of Mirena. The threads are the only part of Mirena you can feel when Mirena is in your uterus; however, unlike a tampon string, the threads do not extend outside your body.



Mirena is small



and flexible

What if I need birth control for more than 5 years?

Mirena must be removed after 5 years. Your healthcare provider can place a new Mirena during the same office visit if you choose to continue using Mirena.

What if I want to stop using Mirena?

Mirena is intended for long-term use but you can stop using Mirena at any time by asking your healthcare provider to remove it. You could become pregnant as soon as Mirena is removed, so you should use another method of birth control if you do not want to become pregnant.

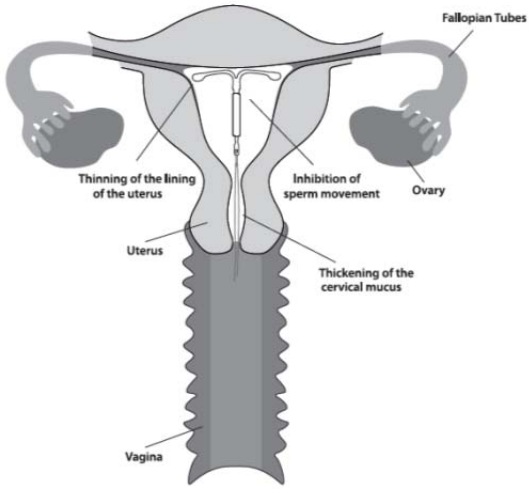
What if I change my mind about birth control and want to become pregnant in less than 5 years?

Your healthcare provider can remove Mirena at any time. You may become pregnant as soon as Mirena is removed. About 8 out of 10 women who want to become pregnant will become pregnant sometime in the first year after Mirena is removed.

How does Mirena work?

Mirena may work in several ways including thickening cervical mucus, inhibiting sperm movement, reducing sperm survival, and thinning the lining of your uterus. It is not known exactly how these actions work together to prevent pregnancy.

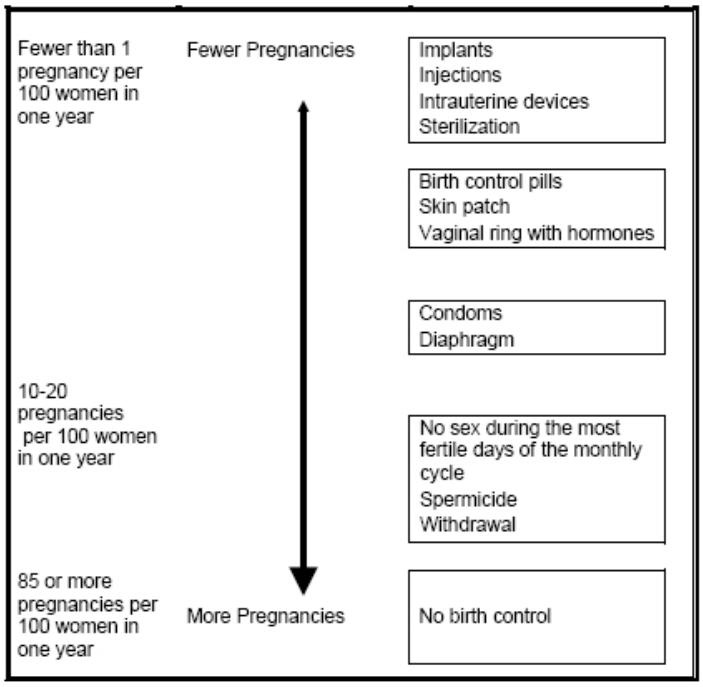
Mirena can cause your menstrual bleeding to be less by thinning the lining of the uterus.



How well does Mirena work for contraception?

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.

Mirena, an intrauterine device (IUD), is in the box at the top of the chart.



How well does Mirena work for heavy menstrual bleeding?

In the clinical trial performed in women with heavy menstrual bleeding and treated with Mirena, almost 9 out of 10 were treated successfully and their blood loss was reduced by more than half.

Who might use Mirena?

You might choose Mirena if you:

- Want long-term birth control that provides a low chance of getting pregnant (less than 1 in 100)
- Want birth control that works continuously for up to 5 years
- Want birth control that is reversible
- Want a birth control method that you do not need to take daily
- Have had at least one child
- Want treatment for heavy periods and are willing to use a birth control method that is placed in the uterus
- Want birth control that does not contain estrogen

Who should not use Mirena?

Do not use Mirena if you:

- Are or might be pregnant; Mirena cannot be used as an emergency contraceptive
- Have had a serious pelvic infection called pelvic inflammatory disease (PID) unless you have had a normal pregnancy after the infection went away
- Have an untreated pelvic infection now
- Have had a serious pelvic infection in the past 3 months after a pregnancy
- Can get infections easily. For example, if you have:
  - Multiple sexual partners or your partner has multiple sexual partners
  - Problems with your immune system

- Intravenous drug abuse.

- Have or suspect you might have cancer of the uterus or cervix
- Have bleeding from the vagina that has not been explained
- Have liver disease or liver tumor
- Have breast cancer or any other cancer that is sensitive to progestin (a female hormone), now or in the past
- Have an intrauterine device in your uterus already
- Have a condition of the uterus that changes the shape of the uterine cavity, such as large fibroid tumors
- Are allergic to levonorgestrel, silicone, polyethylene, silica, barium sulfate or iron oxide

Before having Mirena placed, tell your healthcare provider if you:

- Have had a heart attack
- Have had a stroke
- Were born with heart disease or have problems with your heart valves
- Have problems with blood clotting or take medicine to reduce clotting
- Have high blood pressure
- Recently had a baby or if you are breastfeeding
- Have severe migraine headaches.

How is Mirena placed?

Mirena is placed by your healthcare provider during an in-office visit.

First, your healthcare provider will examine your pelvis to find the exact position of your uterus. Your healthcare provider will then clean your vagina and cervix with an antiseptic solution, and slide a slim plastic tube containing Mirena into your uterus. Your healthcare provider will then remove the plastic tube, and leave Mirena in your uterus. Your healthcare provider will cut the threads to the right length. Placement takes only a few minutes.

You may experience pain, bleeding or dizziness during and after placement. If your symptoms do not pass within 30 minutes after placement, Mirena may not have been placed correctly. Your healthcare provider will examine you to see if Mirena needs to be removed or replaced.

Should I check that Mirena is in place?

Yes, you should check that Mirena is in proper position by feeling the removal threads. It is a good habit to do this once a month. Your healthcare provider should tell you how to check that Mirena is in place. First, wash your hands with soap and water. You can check by reaching up to the top of your vagina with clean fingers to feel the removal threads. Do not pull on the threads. If you feel more than just the threads or if you cannot feel the threads, Mirena may not be in the right position and may not prevent pregnancy. Use non-hormonal back-up birth control (such as condoms and spermicide) and ask your healthcare provider to check that Mirena is still in the right place.

How soon after placement of Mirena should I return to my healthcare provider?

Call your healthcare provider if you have any questions or concerns (see "When should I call my healthcare provider"). Otherwise, you should return to your healthcare provider for a follow-up visit 4 to 6 weeks after Mirena is placed to make sure that Mirena is in the right position.

Can I use tampons with Mirena?

Tampons may be used with Mirena.

What if I become pregnant while using Mirena?

Call your healthcare provider right away if you think you are pregnant. If you get pregnant while using Mirena, you may have an ectopic pregnancy. This means that the pregnancy is not in the uterus. Unusual vaginal bleeding or abdominal pain may be a sign of ectopic pregnancy.

Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.

There are also risks if you get pregnant while using Mirena and the pregnancy is in the uterus. Severe infection, miscarriage, premature delivery, and even death can occur with pregnancies that continue with an intrauterine device (IUD). Because of this, your healthcare provider may try to remove Mirena, even though removing it may cause a miscarriage. If Mirena cannot be removed, talk with your healthcare provider about the benefits and risks of continuing the pregnancy.

If you continue your pregnancy, see your healthcare provider regularly. Call your healthcare provider right away if you get flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge, or fluid leaking from your vagina. These may be signs of infection.

It is not known if Mirena can cause long-term effects on the fetus if it stays in place during a pregnancy.

How will Mirena change my periods?

For the first 3 to 6 months, your period may become irregular and the number of bleeding days may increase. You may also have frequent spotting or light bleeding. Some women have heavy bleeding during this time. After you have used Mirena for a while, the number of bleeding and spotting days is likely to lessen. There is a small chance that your periods will stop altogether.

In some women with heavy bleeding, the total blood loss per cycle progressively decreases with continued use. The number of spotting and bleeding days may initially increase but then typically decreases in the months that follow.

Is it safe to breastfeed while using Mirena?

You may use Mirena when you are breastfeeding if more than six weeks have passed since you had your baby. If you are breastfeeding, Mirena is not likely to affect the quality or amount of your breast milk or the health of your nursing baby. However, isolated cases of decreased milk production have been reported among women using progestin-only birth control pills.

Will Mirena interfere with sexual intercourse?

You and your partner should not feel Mirena during intercourse. Mirena is placed in the uterus, not in the vagina. Sometimes your partner feels the threads. If this occurs, talk with your healthcare provider.

What are the possible side effects of using Mirena?

Mirena can cause serious side effects including:

- **Pelvic inflammatory disease (PID).** Some IUD users get a serious pelvic infection called pelvic inflammatory disease. PID is usually sexually transmitted. You have a higher chance of getting PID if you or your partner have sex with other partners. PID can cause serious problems such as infertility, ectopic pregnancy or pelvic pain that does not go away. PID is usually treated with antibiotics. More serious cases of PID may require surgery. A hysterectomy (removal of the uterus) is sometimes needed. In rare cases, infections that start as PID can even cause death.
- Tell your healthcare provider right away if you have any of these signs of PID: long-lasting or heavy bleeding, unusual vaginal discharge, low abdominal (stomach area) pain, painful sex, chills, or fever.
- **Life-threatening infection**. Life-threatening infection can occur within the first few days after Mirena is placed. Call your healthcare provider immediately if you develop severe pain or fever shortly after Mirena is placed.
- **Perforation.** Mirena may become attached to (embedded) or go through the wall of the uterus. This is called perforation. If this occurs, Mirena may no longer prevent pregnancy. If perforation occurs, Mirena may move outside the uterus and can cause internal scarring, infection, or damage to other organs, and you may need surgery to have Mirena removed. The risk of perforation is increased in breastfeeding women.

Common side effects of Mirena include:

- Pain, bleeding or dizziness during and after placement. If these symptoms do not stop 30 minutes after placement, Mirena may not have been placed correctly. Your healthcare provider will examine you to see if Mirena needs to be removed or replaced.
- Expulsion. Mirena may come out by itself. This is called expulsion. You may become pregnant if Mirena comes out. If you think that Mirena has come out, use a backup birth control method like condoms and spermicide and call your healthcare provider.
- Missed menstrual periods. About 2 out of 10 women stop having periods after 1 year of Mirena use. If you do not have a period for 6 weeks during Mirena use, call your healthcare provider. When Mirena is removed, your menstrual periods will come back.
- Changes in bleeding. You may have bleeding and spotting between menstrual periods, especially during the first 3 to 6 months. Sometimes the bleeding is heavier than usual at first. However, the bleeding usually becomes lighter than usual and may be irregular. Call your healthcare provider if the bleeding remains heavier than usual or increases after it has been light for a while.
- Cysts on the ovary. About 12 out of 100 women using Mirena develop a cyst on the ovary. These cysts usually disappear on their own in a month or two. However, cysts can cause pain and sometimes cysts will need surgery.

This is not a complete list of possible side effects with Mirena. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to the manufacturer at 1-888-842-2937, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

After Mirena has been placed, when should I call my healthcare provider?

Call your healthcare provider if you have any concerns about Mirena. Be sure to call if you:

- Think you are pregnant
- Have pelvic pain or pain during sex
- Have unusual vaginal discharge or genital sores
- Have unexplained fever, flu-like symptoms or chills

- Might be exposed to sexually transmitted infections (STIs)
- Cannot feel Mirena's threads
- Develop very severe or migraine headaches
- Have yellowing of the skin or whites of the eyes. These may be signs of liver problems.
- Have had a stroke or heart attack
- Or your partner becomes HIV positive
- Have severe vaginal bleeding or bleeding that lasts a long time

General advice about prescription medicines

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet summarizes the most important information about Mirena. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about Mirena that is written for health providers.

For more information, go to www.mirena-us.com or call 1-888-842-2937

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Finland

September 2015

This patient information booklet was updated May 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

MEDICAL REVIEW(S)

ADDENDUM TO Review of Supplemental Labeling Request
Division of Bone, Reproductive and Urologic Products

Application #:	NDA 21-225/Supplement 031
Name of Drug:	Mirena (levonorgestrel-releasing intrauterine system [IUS])
Applicant:	Bayer Healthcare Pharmaceuticals, Inc.
Reviewed by:	Lisa M. Soule, M.D., Clinical Team Leader, DBRUP
Date:	October 21, 2015

1. Background and Summary

Refer to previous review of Supplement 031, dated July 7, 2015. Subsequent to that review, the Division determined that certain labeling changes to other sections of the Mirena Prescribing Information (PI) were warranted; specifically to Section 5.9, Warnings and Precautions, Breast Cancer, and to Section 6.2, Adverse Reactions, Postmarketing Experience. These labeling changes did not rise to the level of "new safety information" and were not required under FDAAA, nor were they considered to represent information that should be signaled as "Recent Major Changes" in the Highlights of the PI.

2. Review of Specific Proposed Changes

New language is underlined and deleted language is shown in strike-through in the following discussion.

The following language was revised in Section 5.9, Breast Cancer:

> ~~Two o~~Observational studies ~~have not provided~~ of the risk of breast cancer with use of a LNG-releasing IUS do not provide conclusive evidence of ~~an~~ increased risk ~~of breast cancer during the use of Mirena~~.

Reviewer's Comment:
The revision was requested following review by and discussion with the Division of Epidemiology II (DEPI) of two new studies addressing the risk of breast cancer in Mirena users. See reviews by Monique Falconer, Ph.D., dated May 21, 2015 (under NDA 203-159) and by Efe Eworuke, Ph.D., dated September 15, 2014.

The Applicant initially declined to add the requested language, stating that the available data do not establish an association between breast cancer and Mirena use in women < 50 years old, and expressing concern that a labeling revision would imply there has been a change in the interpretation of available evidence. The Division agreed that there is no new safety signal regarding breast cancer, but noted that it is no longer accurate to state that there are only two studies. The Applicant agreed to the Division's revised language, shown above. The section is now acceptable.

The following language was added to Section 6.2, Adverse Reactions, Postmarketing Experience:

> The following adverse reactions have been identified during post approval use of Mirena. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Arterial thrombotic and venous thromboembolic events, including cases of pulmonary emboli, deep vein thrombosis and stroke

Reviewer's Comment:
This change was requested based on a review of postmarketing reports in the FAERS database by Miriam Chehab, Pharm.D., of the Division of Pharmacovigilance (DPV), which identified 65 US cases of venous thromboembolic (VTE) and arterial thrombotic events (ATE) in Mirena users < age 35. In 29 of these cases, no other known risk factors for VTE/ATE were noted. See Dr. Chehab's review dated June 30, 2015.

The Applicant initially declined to add the requested language, stating that available data do not indicate an increased risk of VTE or ATE in Mirena users or establish a causal relationship of these events to Mirena use. The Division reiterated that a number of cases in Mirena users without other risk factors have been reported, and that inclusion of an adverse reaction in Section 6 does not require that a causal relationship has definitively been established. In addition, the Division noted that Canadian labeling for Mirena includes extensive mention of VTE/ATE, and that inclusion of these reported events in Section 6.2 is consistent with other US non-oral progesterone-only labeling. The Applicant agreed to retain the proposed language. The section is now acceptable.

3. Recommendation

Agreement on labeling was reached on October 19, 2015. Therefore, I recommend approval of Supplement 031, including the FDA-requested revisions. (b) (4)

[redacted]

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/s/

LISA M SOULE
10/21/2015

Review of Supplemental Labeling Request
Division of Bone, Reproductive and Urologic Products

Application #:	NDA 21-225/Supplement 031
Name of Drug:	Mirena (levonorgestrel-releasing intrauterine system [IUS])
Applicant:	Bayer Healthcare Pharmaceuticals, Inc.
Reviewed by:	Lisa M. Soule, M.D., Clinical Team Leader, DBRUP
Date:	July 7, 2015

1. Background and Summary

The Applicant submitted Supplement 031 on March 13, 2012; this prior approval supplement sought approval of revisions to the Package Insert (PI), specifically to Sections 5.5, 5.9, 6 and 8.1. While the submission was under review, the Applicant submitted additional supplements that incorporated labeling revisions as follows:

- February 14, 2013 – Submission 032, Changes Being Effected, to strengthen the warnings and precaution information related to the risk of perforation if inserted in lactating women; this supplement was approved on August 7, 2013
- February 27, 2013 – Submission 033, Prior Approval, to provide for and describe in labeling a modified inserter and new packaging materials for the container/closure system; this supplement received a Complete Response action on August 30, 2013 and was ultimately approved on May 29, 2014

Supplement 031 was amended on August 23, 2013 to incorporate the revisions approved under Supplement 032. Certain changes approved in Supplement 033 supplanted those proposed in Supplement 031 (see next section). Supplement 031 was amended again on June 25, 2014 to incorporate the revisions approved under Supplement 033.

2. Review of Specific Proposed Changes

New language is underlined and deleted language is shown in strike-through in the following discussion.

The following language was added to Section 5.5, Irregular Bleeding and Amenorrhea:

[redacted] (b) (4)

This change was supported by a justification document that proposed changes due to integrating multiple studies into a single safety database.

Reviewer's Comment:
The Division advised the Applicant that the language regarding [redacted] (b) (4) was not acceptable [redacted] (b) (4) The Applicant agreed to remove this language. The section is now acceptable.

Section 5.9, Ovarian Cysts, was revised as shown:

[redacted] (b) (4)

(b) (4)

Further revisions to this section were approved under Supplement 033, with the following language agreed upon:

> Because the contraceptive effect of Mirena is mainly due to its local effects within the uterus, ovulatory cycles with follicular rupture usually occur in women of fertile age using Mirena. Sometime atresia of the follicle is delayed and the follicle may continue to grow. Ovarian cysts have been reported in approximately 8% of women using Mirena. Most of these cysts are asymptomatic, although some may be accompanied by pelvic pain or dyspareunia.
>
> In most cases the ovarian cysts disappear spontaneously during two to three months observation. Evaluate persistent ovarian cysts. Surgical intervention is not usually required.

In the revised Supplement 031 submitted on June 25, 2014, the second sentence was revised slightly:

(b) (4).

Reviewer's Comment:
The Division advised the Applicant that (b) (4) The Applicant agreed to retain the original language (b) (4) The section is now acceptable.

The following adverse reactions (ARs) were proposed for deletion from Section 6.1:

(b) (4)

The Applicant stated that removal of these ARs had been requested by the Division previously, on the basis that they represented adverse events not likely to be causally related to the drug, rather than ARs.

In the June 25, 2014 amended Supplement 031, harmonizing revisions were made to the corresponding section in Highlights. The Applicant also proposed extensive additional revisions to this section, including presentation of Common ARs in tabular format. The Justification Document submitted to support these changes was reviewed; this document provided the criteria used to distinguish adverse events and adverse reactions.

Reviewer's Comment:
Removal of the original nine terms from the AR listing is acceptable. Other terms were moved from this listing and included in the table of Common ARs (vulvovaginitis, dysmenorrhea, and

back pain). This is acceptable. The listing of Skin Disorders and abdominal distension were removed. This is acceptable, as these are not likely to represent ARs.

Hypertension was proposed for removal from this section and for inclusion as "Increased blood pressure" in the Postmarketing Experience section. Justification Document 30 submitted by the Applicant reported that 4% of subjects reported increased blood pressure or hypertension; the Applicant was advised to restore this term to the listing. The Sponsor responded on July 6, 2015 that

> "In controlled clinical and epidemiological studies no increase in mean blood pressure was observed in Mirena users compared to women not using a hormonal contraceptive. The observed frequency of adverse events reporting hypertension or increased blood pressure [in these trials] in Mirena users reflect the high background incidence of this condition in the population studied, as there were no significant differences when compared to comparator groups, or changes in mean blood pressure over time."

This explanation is acceptable; hypertension will be removed from Section 6.1, and "increased blood pressure" will remain in Section 6.2.

(b) (4)

(b) (4)

Reviewer's Comment:

(b) (4)

The Applicant agreed to remove this section, and to incorporate the information into Section 6.1. This is acceptable. With the pooled reporting, rates of some ARs have changed somewhat:

(b) (4)

The change in frequency for various ARs is supported by pooled data and in some cases, reflects use of different terminology and slightly different "bundling" of similar terms. The revised listing is acceptable.

The section on Postmarketing Experience (b) (4)

(b) (4)

In the revised Supplement 031 submitted on June 25, 2014, the two ARs were bulleted, and "increased blood pressure" was added.

Reviewer's Comment:
The use of bullets is acceptable. Inclusion of the term "increased blood pressure" in the Postmarketing Experience section is acceptable because the Applicant provided supporting case reports, including examples of dechallenge and rechallenge.

The following sentence was added to Section 8.1, Pregnancy:

Use of Mirena is contraindicated during an existing or suspected pregnancy.

Reviewer's Comment:
This change was found acceptable during review of Supplement 033.

In the amended Supplement 031 submitted on June 25, 2014, the Applicant proposed an additional revision, to (b) (4)

(b) (4)

(b) (4)

Reviewer's Comment:
The Division advised the Applicant that the deletion was not acceptable because (b) (4)

The section is now acceptable.

3. Recommendation

Agreement on labeling was reached on July 6, 2015. Therefore, I recommend approval of Supplement 031.

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/s/

LISA M SOULE
07/07/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

Date: July 15, 2014

NDA #/SS#/date: NDA 21225 / SD# 830 / eCTD# 82 / June 25, 2014
SD# 753 / eCTD# 71 / August 23, 2013
SD# 594 / eCTD# 56 / March 13, 2012
Reviewer: Kimberly Hatfield, PhD

Sponsor: Bayer HealthCare Pharmaceuticals, Inc., Global Regulatory Affairs
100 Bayer Blvd., P.O. Box 915, Whippany NJ 07981-0915
Drug: Mirena (levonorgestrel-releasing intrauterine system)
Indication: Intrauterine contraception

RE: Supplement 31 labeling changes

Background:
Changes to the Mirena label were recently approved under CMC Supplement 33 in May 2014. A request was made to the Sponsor to revise the content of any outstanding NDA 21225 supplements that include labeling changes, for which FDA has not yet issued an action letter, with the recently approved labeling of Supplement 33. Supplement 31 was one of these outstanding supplements, and updated labeling has been submitted for review.

Nonclinical issues and conclusions:
All nonclinical changes made for the Supplement 33 label have been incorporated into the Supplement 31 label. In addition, the Sponsor has not proposed any changes to the nonclinical-related sections of the Mirena label in this supplement. The pharmacology/toxicology team has no further comments regarding this label.

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/s/

KIMBERLY P HATFIELD
07/15/2014

ALEXANDER W JORDAN
07/15/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

OTHER REVIEW(S)

As part of routine post-marketing surveillance assessments, we have identified post-marketing adverse event reports of both arterial and venous thromboembolic events in patients using Mirena (Levonorgestrel-releasing Intrauterine System).

To further assess these adverse events, we request the following information by November 08, 2014:

1. A detailed summary and analysis of all worldwide post-marketing adverse event reports since date of U.S. approval of Mirena with arterial and venous thromboembolic events (see below). Suspect cases should be grouped as follows: a) ≤ 35 years of age and b) > 35 years of age. In addition, cases should be sorted geographically as follows: US, France, and Other Countries.

2. Search your post-marketing safety database for reports of arterial and venous thromboembolic events using the following MedDRA version 17.0 term, at a minimum:
   - SMQ Embolic and Thrombotic Events (broad)

3. An evaluation of potential contributing factors for reports of arterial and venous thromboembolic events defined above, including, but not limited to: patient age, concomitant medications, medical history (including any testing for thrombophilic conditions), smoking history, indication for Mirena use, duration of use, reported weight/BMI, and other relevant factors that you can identify. Please also specify country of report and thromboembolic event type (e.g., PE, DVT, CVA, TIA).

4. Please provide a summary and analysis report for your evaluation as specified in #2. Also, please provide a line listing with corresponding case characteristics.

5. Please address whether you believe adverse event reporting of these events has been impacted by product litigation, and provide any data available to support or refute this possibility.

6. A summary of all safety-related communications worldwide undertaken since product approval that is relevant to Mirena and thromboembolic events.

7. [redacted] (b) (4)

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/s/

ZETA-MAE C WILLIAMSON
10/08/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Epidemiology Review of Published Observational Study

Date:	09/15/2014
Reviewer(s):	Efe Eworuke, PhD Division of Epidemiology II
Team Leader	CDR David Moeny, M.P.H, R.Ph., USPHS, Division of Epidemiology II
Associate Director	Rita Ouellet-Hellstrom, Ph.D., M.P.H Division of Epidemiology II
Subject	Literature review of levonorgestrel-releasing intrauterine systems and their association with cancer
Drug Name(s):	NDA 21225 (Mirena®) (b) (4)
Applicant/sponsor:	Bayer Pharmaceuticals
OSE RCM #:	2014-1339

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review provides an assessment of a recently published observational study examining the standardized incidence ratio (SIR) of all cancers in relation to levonorgestrel-releasing intrauterine systems (LNG IUS) exposure. The Division of Bone, Reproductive and Urologic Products (DBRUP) consulted the Division of Epidemiology II (DEPI II), in the Office of Pharmacovigilance (OPE)/ Office of Surveillance and Epidemiology (OSE) to review the article entitled "*Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland*", comment on the methods and interpretation of the results pertaining to breast cancer, and note if any labeling revisions are warranted based on the findings from this study.

The study identified women aged 30-45 years, from 1994-2009 who filled a prescription for LNG IUS in the Finland National Reimbursement Register of Social Insurance Institution during the study period (1994-2009). Cancer outcome was obtained by linking user records to the Finnish Cancer Registry during follow-up. Other censoring indicators included the end of the study period or emigration, the 55th birthday, bilateral or unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, hysterectomy or death whichever came first. Standardized incidence ratios (SIR) were determined in 5-year age groups. Stratified SIR by age at follow-up and time since first purchase were also presented. A logistic regression model was used to determine the association between selected health indices and LNG IUS exposure.

The study identified 2781 cancer cases, of which 1542 were breast cancer outcomes, corresponding to a SIR of 1.19 (95% confidence interval [CI]: 1.13-1.25). In a subgroup of women who purchased at least 2 LNG IUS, 271 breast cancer cases were observed, yielding a SIR of 1.40 (CI: 1.24-1.57). Stratified analyses revealed increasing SIRs across follow-up in the overall sample. However, this trend was more prominent in the 45-49 and 50-54 age groups.

Strengths of the study included reliable data sources for both outcome and censoring indicators and long follow-up for a large sample of women. Limitations included the absence of important risk factors for breast cancer such as race, parity or nulligravida status, previous and family history of breast cancers necessary for both adjustment of confounding and generalizability of study findings; misclassification of exposure and duration of exposure and absence of a risk-period necessary for incidence estimates are discussed in this review.

The current study suggests a possible increased incidence of breast cancer among LNG IUS users. However, because of the absence of inferential statistics[1] in conducting the analysis and other limitations such as restriction to a population of women with menorrhagia, study design issues especially exposure misclassification and the absence of proper adjustment of possible confounding factors, DEPI recommends that no change be made to the labeling, as the current study does not provide additional information necessitating warnings or labeling changes.

[1] Inferential statistics: use of data analysis to make conclusions about the target population

1 INTRODUCTION

The Division of Bone, Reproductive and Urologic Products (DBRUP) consulted the Division of Epidemiology II (DEPI II) in the Office of Pharmacovigilance (OPE)/ Office of Surveillance and Epidemiology (OSE) to review the recent published article "*Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland*". DEPI was asked to comment on the methods and interpretation of the results pertaining to breast cancer and note whether any labeling revisions are warranted based on the findings from this study.

1.1 BACKGROUND

Levonorgestrel-releasing intrauterine systems (LNG IUS) was developed primarily for contraception, however, the indication has been extended to treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. The contraceptive action of LNG IUS is via the progestogenic effects of sustained release LNG in the amounts 20 µg/day for Mirena (b) (4) It has been shown that high intrauterine concentrations of LNG can cause endometrial decidualization[2] and atrophic changes, making the system a treatment for endometrial hyperplasia.

Although epidemiologic studies indicate that there is a small excess risk of breast cancer with hormonal contraception[1], it remains unknown whether the LNG IUS is associated with breast cancer. Except for a publication by Spira et al 2001[2], the two other observational studies[3,4] suggest a negative association between LNG IUS and breast cancer. The case report by Spira et al. identified 2 cases of breast cancer while using LNG IUS. Both cases had no previous or family history of breast cancer and no gene mutations for breast cancer. Both cases had used LNG IUS for 2-3 years and were diagnosed at stage 1-2. The authors state that the LNG IUD releases LNG into the uterine cavity which is absorbed into the circulatory system. Plasma LNG concentrations reach a plateau of 150-200 pg/ml after the first two weeks. Although there is a gradual decline in plasma LNG over time, the LNG blood levels can be maintained for up to 78 months after insertion. Spira et al suggested that this sustained plasma LNG level may promote or accelerate existing pre-neoplastic lesions.

Based on current evidence available, regulatory activities has been limited to updating the warnings and precautions sections of the current labeling. To determine whether the recent published study warrants labeling revisions, DBRUP asked DEPI to review the recent published article and comment on the methods and interpretation of the results pertaining to breast cancer.

1.2 REGULATORY HISTORY

Mirena® was approved in December, 2000 for intrauterine contraception for up to 5 years; in 2009 a new indication, treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception was added to the labeling. (b) (4) Findings from an interim analysis conducted in postmarketing observational study "European Active Surveillance Study for

[2] Decidualization refers to the response of the uterine cells to progesterone. These changes include eosinophilic proliferation around the arterioles and increased glandular secretion to prepare the uterus for implantation.

Intrauterine Devices" (EURAS-IUD) suggesting an increased risk of uterine perforation for lactating women resulted in updating of the Warning and Precautions section of the labeling (b) (4)

1.3 PRODUCT LABELING

The warnings and precautions section (breast cancer) of the product labeling for Mirena (b) (4)

Women who currently have or have had breast cancer, or have a suspicion of breast cancer, should not use hormonal contraception because breast cancer is a hormone-sensitive tumor. Spontaneous reports of breast cancer have been received during postmarketing experience with Mirena. Because spontaneous reports are voluntary and from a population of uncertain size, it is not possible to use postmarketing data to reliably estimate the frequency or establish causal relationship to drug exposure. Two observational studies have not provided evidence of an increased risk of breast cancer during the use of Mirena.

2 REVIEW METHODS AND MATERIALS

This review provides an assessment of the published study entitled "*Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland"* by Soini et al. 2014. This review was guided by recommendations from the FDA guidance on the best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data[5].

3 REVIEW RESULTS

3.1 STUDY OBJECTIVES

The aim of the study was to test the hypothesis that the incidence of endometrial adenocarcinoma is decreased among premenopausal LNG-IUS users. The second aim was to assess the risk of other common cancers among premenopausal LNG-IUS users.

3.2 STUDY METHODS

3.2.1 Design & Setting

The study population was identified from a database of Finnish women aged 30-49 years in 1994-2007 and who had received a reimbursement for LNG-IUS for the treatment of heavy menstrual bleeding. The source database used in identifying women was the National Reimbursement Register of the Social Insurance Institution.

3.2.1.1 Study Type

The study was described as a retrospective cohort study comprised of women aged 30 to 49 years anytime from 1994 to 2007, who had received at least one reimbursement for LNG IUS for the treatment of heavy menstrual bleeding. Women were followed from the date of the first purchase of the LNG IUS up until

December 1, 2009, emigration, bilateral or unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, hysterectomy or death whichever occurred first. Cancer cases were identified from the Finnish Cancer Registry, while censoring indicators were obtained from the National Discharge Register.

3.2.1.2 Data Sources & Time Period

The source population was identified in the national reimbursement register of the social insurance institution anytime from 1994 to 2007. Using the personal identity code issued by the Finnish population register center since 1967 to all citizens and permanent residents, the investigators were able to link patients to the Finnish cancer registry to identify cancer cases or to the National Discharge Register to identify censoring indicators (bilateral or unilateral salpingectomy, salpingo-oophorectomy or oophorectomy, hysterectomy or death).

3.2.1.3 Selection Criteria

Study entry criteria included attained age of 30 to 49 years with a reimbursement for LNG-IUS for the treatment of heavy menstrual bleeding.

3.2.1.4 Protected Health Information (PHI) Requirements

The study was approved by the institutional review boards of Hyvinkää Hospital and the Helsinki University hospital. The Finnish National Center for Welfare and Health, after consulting the data protection authority, approved the use of the confidential national register data.

3.2.2 Study Exposure

Exposure information was obtained from the National Reimbursement Register of the Social Insurance Institution. The Finnish Drug Reimbursement Register is an administrative database that collects monthly information from all pharmacies. This reimbursement register contains data on purchased prescribed medicines that fall within the reimbursement scheme since 1994. The register includes information on the patient, the medication coded in the anatomical therapeutic chemical classification system, the prescriber, price as well as the dates of prescribing and dispensing. Information on the indication for the prescription is collected but may be incomplete because prescribers code the indications differently.

3.2.3 Study Outcome

The study outcome was comprised of any cancer case reported in the Finnish Cancer Registry. The reporting of new cases to the case registry from diagnosing hospitals and pathology laboratories is mandated by law. In addition, regular quality checks are done between cancer registry data and other administrative registers to ensure the correctness of the data.

3.2.4 Covariates

The association between LNG IUS use and possible cancer risk factors was examined in the sample of women who had completed the national health behavior surveys conducted annually. In this sample, there was information on smoking, alcohol use, physical activity and diet. Socioeconomic information was obtained from the census files of statistics, Finland. Of the sample of women studied, 4056 (4.3%) were LNG IUS users were included.

3.2.5 Sample Size/Power

Being a non-inferential[3] descriptive analysis, sample size and power calculations were not considered.

3.2.6 Statistical Analyses

The at-risk period was defined from the start of the first purchase of the LNG IUS to any of the previously mentioned censoring indicators or the outcome. The at-risk period (in women-years) was classified into 5-year age groups. The expected number of cancers in each of the 5-year age groups was calculated by multiplying the number of woman-years in age group by the respective national age group cancer incidence during the study period to obtain an expected rate. Standardized incidence ratio (SIR) was obtained by dividing the number of observed cancer cases by the number of expected cancer cases. Confidence intervals around incidence ratios were based on the assumption that the number of observed cases followed a Poisson distribution. SIRs at $p<0.1$ were considered statistically significant.

Logistic regression analysis modeling the association between LNG IUS exposure and the health behavior risk factors was used to obtain odds ratio estimates.

3.3 RESULTS

3.3.1 Demographic characteristics of the study population

Over the 15 year study period, a total of 93,843 LNG IUS users were identified and followed for a total of 855,324 women-years. The 35-39 year old category had the highest proportion of LNG IUS users (30.07%). Although more women were classified in the 35-39 year old category, the 40-44 year old group had the longest follow-up (in women-years). Among women who purchased at least two LNG IUS during follow-up, the 40-44 year old women had the highest proportion of LNG IUS users, while the longest follow-up period was in the 45-49 year age group (Table 1 reproduced from article).

Nul

[3] Non-inferential: inability to reach a conclusion about the target population from a statistical or data analysis

3.3.2 Incidence rates for breast cancer

During follow-up, 2,781 cancers were identified yielding an overall cancer incidence rate of 3.25 cases per 1000 women-years. When the study sample was restricted to women who purchased at least 2 LNG IUS, 454 cases were identified, yielding an overall cancer incidence rate of 4.19 cases per 1000 women-years. The standardized incidence ratio (SIR) for all cancers in the overall sample was 1.07 (95% confidence interval [CI]: 1.03-1.11) p<0.001 and 1.20 (CI: 1.09-1.31) p<0.001 among women who purchased at least 2 LNG IUS during the study period.

Of the 2,781 cancers identified, 1,542 were breast cancers resulting in a SIR of 1.19 (CI: 1.13-1.25) p<0.001. The SIR was higher among women who purchased more than 1 LNG IUS during the study period (1.40 [CI: 1.24-1.57] p<0.001).

When the SIR was stratified by time since first purchase and by age at follow-up, the investigators observed an increased incidence ratio as follow-up time increased; from 0.91 (CI: 0.73-1.13) in the 0-0.99 year follow-up period to 1.36 (CI: 1.19-1.53) when women were followed for more than 10 years (table 2). This trend of increasing incidence with follow-up time was more profound among the 45-49 and 50-54 year old categories (see highlighted rows in Table 2) given the non-overlap of confidence intervals.

Table 2: Observed numbers of breast cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals among Finnish women who bought the Levonorgestrel-Releasing Intrauterine System during 1994-2007 in those aged 30-49 years, by age at follow-up and time since first purchase

	0-0.99 years		1-4.99 years		5-9.99 years		More than 10 years		Entire Follow-up	
Age at Follow-up	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI
30-34	0.78	0.16-2.28	1.30	0.56-2.55					1.10	0.55-1.96
35-39	1.03	0.58-1.70	0.55	0.37-0.79	1.23	0.80-1.80			0.80	0.62-1.00
40-44	0.78	0.49-1.17	1.09	0.90-1.28	1.09	0.90-1.30	1.40	0.90-2.06	1.08	0.96-1.20
45-49	**0.96**	**0.68-1.30**	**1.08**	**0.94-1.23**	**1.39**	**1.23-1.55**	**1.33**	**1.07-1.63**	1.23	1.13-1.32
50-54	**1.21**	**0.33-3.09**	**1.31**	**1.10-1.53**	**1.28**	**1.14-1.42**	**1.37**	**1.14-1.61**	1.30	1.20-1.41
Total	0.91	0.73-1.13	1.08	0.99-1.17	1.28	1.19-1.37	1.36	1.19-1.53	1.19	1.13-1.25

In the random sample of women who completed the national health behavior survey, the investigators found that LNG IUS users were less often overweight (body mass index more than 25; OR 0.80 [CI: 0.73-0.87]) and were less often smokers (OR: 0.80 [CI: 0.74-0.87]). They also report that LNG IUS consumed slightly more alcohol and often went to work by car, however the estimates for these associations were not provided.

3.4 CONCLUSIONS

The investigators conclude that the incidence of breast cancer among LNG IUS users was higher than expected in contrast to previous studies. They suggest that the short follow-up period and differences in study methodologies may explain the absence of no association in these other studies.

4 DISCUSSION

The discussion section will provide an assessment of the study's methodology in the light of its limitations. Rationale for labeling revisions will also be presented in the context of the study's findings and the current labeling.

4.1 OVERALL ASSESSMENT OF STUDY METHODOLOGY

Prior to this study, there has been one other observational case-control study[3] and one descriptive analysis[4] comparing the incidence of breast cancer among LNG IUS users to the general population. The case-control study suggested a negative association between LNG IUS and breast cancer while the descriptive analysis did not show any increased incidence of breast cancer among LNG IUS users. A major difference between the current study and previous analyses lies in the population studied. While both previous studies examined the association in all women, this study restricted the analyses to women with menorrhagia. It remains unknown whether menorrhagia modifies breast cancer risk. Strengths of the study include long follow-up of a large sample of women and the use of a cancer registry to identify cases; especially since the reporting of all cases are mandated by law. Therefore, the possibility of outcome misclassification can be considered minimal in this study.

4.1.1 Generalizability of study findings

The current study was conducted among Finnish women prescribed LNG IUS for menorrhagia. The investigators did not provide any information on race, an important risk factor for breast cancer. It is probable that most of the women included in this study were Caucasians, since the study was conducted in the Finnish database. This limits the generalizability of the findings to populations with a different racial distribution. To be included in the national reimbursement register, each beneficiary had to receive reimbursement for LNG IUS. Because reimbursement may be determined by experts at the Bureau of Social Insurance institution[6], it remains unclear whether the women included in this study differ from the target population. In the absence of demographic factors necessary to make inferences to the target population, the generalizability of this study remains unknown.

4.1.2 Study Design

Although the investigators note that the design is a cohort study, they did not define the cohort after an at-risk period, prior to the outcome ascertainment era. The availability of complete cancer information would have allowed the investigators to exclude women with previous history of cancers. Therefore the cases in the numerator for the incidence calculation would include a mix of incident and prevalent cases. Because incidence is a measure of the frequency of onset, setting up an incident cohort as described by the investigators could result in spurious incidence estimates. The inclusion of prevalent cases no longer assesses frequency of onset but rather measures disease status. Therefore caution must be taken in interpreting the results as incidence rates. Secondly, it is not entirely clear if the users of LNG IUS were

new users or repeat users. The modification of breast cancer risk by LNG IUS cannot be disentangled if both new and repeat users comprise the study cohort.

4.1.3 Levonorgestrel-releasing intrauterine system exposure

LNG IUS exposure was based on reimbursement information obtained from the National Reimbursement Register. It was not stated whether information on the insertion of the device or its removal was captured in the database. This raises concerns about exposure misclassification and the reliability of exposure duration reported in this study.

4.1.4 Covariates

The investigators employed a logistic regression model to examine the association between LNG IUS exposure and selected risk factors for breast cancer. It remains unclear why the investigators did not conduct an epidemiological study in the subset of women who had information on health behavior indices. A propensity score for exposure could have sufficed given the small sample size of women. Such study would have provided inferential statistics for the association between LNG IUS and breast cancer. Although, the OR estimates for these potential confounders suggest that LNG IUS users are less likely to have risk factors for breast cancer i.e. less alcohol use and lower BMI, the investigators were not able to use this information for confounding adjustment. Conversely, the study also did not have information on important confounders such as parity, race, family and previous history of breast cancer as well as information on the use of other exogenous hormones.

The statistical approaches employed are non-inferential given the descriptive nature of the study. While the findings lend support to established pharmacological mechanisms of action, plausibility (in terms of an association) or causality cannot be inferred from this study. It seems logical that efforts be directed towards conducting studies that have the ability to carry out inferential analyses, to examine other risk factors or to compare the risk of breast cancer in users with non-users of LNG IUS.

5 CONCLUSIONS

To date, it remains unknown whether there is an association between breast cancer and LNG IUS. Pharmacological mechanisms suggest that since there is a low absorption rate of LNG into the systemic circulation, the risk of breast cancer may be low. On the other hand, prolonged exposure to progestins is thought to be a risk factor for breast cancer. The current study suggests a small but possible increased incidence of breast cancer among LNG IUS users. However, the absence of inferential statistics in conducting the analysis, restriction to a population of women with menorrhagia with unknown risk, study design issues as discussed previously, especially exposure misclassification and the absence of proper adjustment of possible confounding factors limits its utility for regulatory activities.

6 RECOMMENDATIONS

Based on the review of this study, DEPI recommends that no change be made to the labeling regarding the risk of breast cancer in association with the use of LNG IUS. The current study does not provide additional information necessitating warnings or labeling changes.

REFERENCESREFERENCES

1. Kubba AA. Breast cancer and the pill. *Journal of the Royal Society of Medicine.* Jun 2003;96(6):280-283.

2. Spira RM, Peretz T, Hochner-Tzelniker D, Freund HR. Levonorgestrel-releasing IUD and breast cancer. *The Israel Medical Association journal : IMAJ.* Sep 2001;3(9):711.

3. Dinger J, Bardenheuer K, Minh TD. Levonorgestrel-releasing and copper intrauterine devices and the risk of breast cancer. *Contraception.* Mar 2011;83(3):211-217.

4. Backman T, Rauramo I, Jaakkola K, et al. Use of the levonorgestrel-releasing intrauterine system and breast cancer. *Obstetrics and gynecology.* Oct 2005;106(4):813-817.

5. FDA. Center for Drug Evaluation and Research, Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, guidance for industry and FDA staffMay 2013.

6. Klaukka T. The Finnish database on drug utilisation. *Norwegian Journal of Epidemiology.* 2001;11(1):19-22.

APPENDICES

TABLE 1 – DESIGN SUMMARY

	Study
1.1 Objectives/Aims/Scope	To determine the incidence of breast cancer among Levonorgestrel-releasing intrauterine system (LNG IS) users
1.2.1 Design	
1.2.1.1 Type	Retrospective cohort analysis
1.2.1.2 Data Source	Finnish national reimbursement register of social institution Finnish Cancer registry Finnish population register Census files of statistics Hospital Discharge register
1.2.1.3 Time Period	1994-2007
1.2.1.4 Criterion (Selection) Standards	Women aged 30-49 years who were reimbursed for LNG IUS for the treatment of heavy menstrual period.
1.2.1.5 Privacy Health Information	Study was approved by the institutional review boards of Hyvinkää Hospital and the Helsinki University hospital. The Finnish National Center for Welfare and Health, after consulting the data protection authority, approved the use of the confidential national register data.
1.2.3 Exposure/Intervention	Levonorgestrel-releasing intrauterine system
1.2.4 Outcome(s)	Breast cancer
1.2.5 Covariates	No adjustment for confounding, however the association between LNG IUS and BMI, smoking were examined
1.2.6 Sample Size	93,843 LNG IUS users were identified; 1,542 breast cancers were observed.
1.2.7 Statistical Analyses	Standardized incidence ratios (SIR) (95% confidence intervals)
1.2.8 Study results	SIR (all cancers): 1.07 (CI: 1.03-1.11) SIR (breast cancer): 1.19 (CI: 1.13-1.25)

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/s/

EFE EWORUKE
09/15/2014

DAVID G MOENY
09/15/2014

RITA P OUELLET-HELLSTROM
09/15/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021225 S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	REQUEST FOR CONSULTATION

To: DEPI Attn: Efe Eworuke	FROM: Division of Bone, Reproductive and Urologic Products Attn: Charlene Williamson

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 2, 2015		203159 (b) (4)	Finland Study	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Mirena (b) (4)			April 30, 2015

NAME OF FIRM: Bayer Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the attached study and any other recent literature, to update the review done by Efe Eworuke dated 9/15/14 on the epidemiologic data concerning a possible association of LNG IUD use (i.e., Mirena, (b) (4) and breast cancer.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

ZETA-MAE C WILLIAMSON
02/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Attn: Efe Eworuke
Mail: OSE

FROM: Division of Bone, Reproductive and Urologic Products
Attn: Charlene Williamson

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 14, 2014		21225 (b) (4)	Article	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Mirena (b) (4)		Progestin	September 1, 2014

NAME OF FIRM: Bayer Healthcare Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached article and comment on the methods and interpretation of results pertaining to breast cancer (I am less concerned about the other cancers they evaluated) and whether they think that any labeling revisions are warranted on the basis of this study.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ☐ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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ZETA-MAE C WILLIAMSON
07/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21225/S-031

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Bayer Healthcare Pharmaceuticals, Inc.
Attention: Joseph Zuccarini
Deputy Director, Regulatory Affairs
PO Box 1000
Montville, NJ 07045-1000

Dear Mr. Zuccarini:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21225

SUPPLEMENT NUMBER: 031

PRODUCT NAME: Mirena® (levonorgestrel-releasing intrauterine system) 52 mg

DATE OF SUBMISSION: March 13, 2012

DATE OF RECEIPT: March 13, 2012

This supplemental application proposes the following changes to the Physician and Patient Package Inserts regarding the WARNINGS and PRECAUTIONS, ADVERSE REACTIONS, and USE IN SPEICAL POPULATIONS Sections.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 12, 2012, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be September 13, 2012

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-796-1025.

Sincerely,

{See appended electronic signature page}

Z. Charlene Williamson
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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ZETA-MAE C WILLIAMSON
03/30/2012