DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Fadwa Almanakly, Pharm.D.
Associate Director, Advertising and Promotions
Bayer HealthCare Pharmaceuticals Inc.
6 West Belt
Wayne, NJ 07470-6806

RE: NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
MACMIS # 18166

Dear Dr. Almanakly:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a script for a live consumer-directed program (program) entitled "Mirena Simple Style Statements Program" (150-74-0002-09) for Mirena® (levonorgestrel-releasing intrauterine system) (Mirena), submitted by Bayer HealthCare Pharmaceuticals Inc. (Bayer) under cover of Form FDA-2253. The program overstates the efficacy of Mirena, presents unsubstantiated claims, minimizes the risks of using Mirena, and includes false or misleading presentations regarding Mirena. Thus, the program misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n), and FDA's implementing regulations. *See* 21 CFR 202.1(e)(3)(i), (e)(5) & (e)(6)(i).

Background

According to the DESCRIPTION section of its FDA-approved product labeling (PI),[1] "Mirena® (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem." The steroid reservoir contains the progestogen levonorgestrel, which is secreted slowly into the uterus over time upon the insertion of Mirena by a trained healthcare provider. According to the INDICATIONS AND USAGE section of its PI, Mirena is approved for the following indication:

> Mirena is indicated for intrauterine contraception for up to 5 years. Thereafter, if continued contraception is desired, the system should be replaced.
> Mirena is recommended for women who have had at least one child.

The PI for Mirena also includes numerous contraindications, including "[u]ntreated acute cervicitis or vaginitis, including bacterial vaginosis or other lower genital tract infections until infection is controlled," and "[c]onditions associated with increased susceptibility to pelvic infections."

[1] The most current version of the FDA-approved PI as of the dissemination date indicated on Form FDA-2253 was the July 21, 2008, version, and that is the version referred to in this letter. We note that the PI for Mirena was updated on October 1, 2009.

The use of Mirena is associated with a number of risks, including warnings regarding the increased risk of pelvic inflammatory disease (PID), ovarian cysts, and irregular bleeding and amenorrhea. Additional warnings include the risk of Mirena embedding in, perforating, or being expelled from the uterus, as well as the increased risk of ectopic pregnancy, and the risks to an intrauterine pregnancy that occurs with Mirena in place. Should a woman become pregnant while using Mirena, serious risks include pregnancy loss and a permanent loss of fertility.

In addition to the warnings noted above, the PI details the common adverse reactions that were observed during the clinical trials for Mirena. According to the PI, "Very common adverse reactions" (>10% of clinical trial patients) included "uterine/vaginal bleeding (including spotting, irregular bleeding, heavy bleeding, oligomenorrhea and amenorrhea), and ovarian cysts." Adverse reactions that were reported by 5% or more of clinical trial patients include, among others, abdominal/pelvic pain, nausea, headache, nervousness, back pain, weight increase, breast pain/tenderness, acne, decreased libido, and depressed mood.

The PI also includes precautions that patients should be counseled that Mirena does not protect against HIV infection (AIDS) or other sexually transmitted diseases, and that patients should be instructed to check that the threads attached to Mirena are still in place after each menstrual period, as there is no contraceptive protection if Mirena is displaced or expelled.

Additionally, in regards to patient follow-up following the insertion of Mirena, the DOSAGE AND ADMINISTRATION, Patient Follow-up section of the PI states (in pertinent part):

- Patients should be reexamined and evaluated 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.

Overstatement of Efficacy/Unsubstantiated Claims

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Mirena program is a live presentation designed for a consumer audience of "busy moms." The program is presented in a consumer's home or other private setting (e.g. private restaurant party) by a representative from Mom Central (a social networking internet site) and a nurse practitioner (Ms. Barb Dehn).[2] The script of this program submitted to FDA includes an introduction from the Mom Central representative, a presentation given by Ms. Dehn regarding the use of Mirena, and a "post-party" questionnaire for the audience.

The script includes the following statements to be delivered by the Mom Central representative (emphasis added):

- "This party was brought to you by Mom Central in partnership with Bayer HealthCare Pharmaceuticals' Mirena which may help couples keep life simple!"

[2] The Mirena program submitted to FDA also references a presentation given by a fashion stylist (Ms. Angela Hastings) that immediately follows Ms. Dehn's presentation regarding the use of Mirena. The script of Ms. Hastings' presentation regarding fashion tips was not submitted to FDA.

- "Barb Dehn is a practicing Women's Health Nurse Practitioner, award-winning author and nationally recognized health expert from San Francisco. Barb is going to kick things off with a discussion about romance and how to find simple ways to reconnect with our partners."

The script also includes the following statements to be delivered by Ms. Dehn (emphasis added):

- ". . . And, let's face it, when we feel good about the way we're put together, we feel better about approaching the romance in our lives."

- "What we're here to talk about today - is how to find those simple ways to reconnect with ourselves and our partners."

Following the introduction of the program, the script states that "Barb [Dehn] will begin presentation with an icebreaker - an interactive Q&A - which will touch upon issues such as busy schedules, barriers to intimacy and contraception" (emphasis added). The "icebreaker" questions include the following (in pertinent part; emphasis added):

- "How many of you feel so busy that you often can't find time to take care of yourself? And do you think this impacts your level of intimacy?"

- "Do you ever feel so overwhelmed by your schedule that intimacy is much more of a "to do" on a list than a desire?"

- "If you didn't have to worry about contraception, do you think you would be more likely to be intimate with your partner?"

- "Do you think if you didn't have to worry about taking your birth control everyday, it would help you be more intimate?"

Immediately following the "icebreaker" questions, the script for Ms. Dehn states (emphasis added):

- "So you mentioned that convenience and reliability are among the most important benefits of your birth control method. One strategy that I recommend for busy couples is choosing a birth control method that allows for spontaneous intimacy and which you don't have to think about every day, such as the intrauterine contraceptive Mirena®."

The above statements clearly indicate that the use of Mirena instead of other means of contraception will result in increased levels of intimacy, romance, and by implication, emotional satisfaction. These claims misleadingly overstate the proven efficacy of Mirena. Mirena has been proven to be an effective intrauterine contraceptive device. While we note that Mirena does not involve a daily routine and is not a barrier method of contraception, FDA is not aware of any evidence that suggests that women using Mirena for birth control experience an increase in reconnection, romance, or intimacy with their partners. Claims that state or suggest such quality of life outcomes, such as those described above, must be

supported by substantial evidence, as demonstrated through adequate and well-controlled trials using validated patient assessment instruments to measure the outcomes of interest. If you do, in fact, have data to support these claims, you should submit them to FDA for review.

We note that, according to the Mirena PI, at least 5% of clinical trial patients reported decreased libido as a side effect of Mirena use. Patients also experienced abdominal/pelvic pain, nausea, headache, nervousness, and depressed mood, which could adversely affect a woman's feelings relating to romance or intimacy.

The script also includes the following statements, to be presented by Ms. Dehn (emphasis added):

- "But what this party is really about is looking at the whole picture and figuring out steps to take to simplify your lifestyle while still looking and feeling great. One of those ways is finding a birth control that is compatible with your busy lifestyle."

The above statement goes beyond the suggestion of increased intimacy to suggest that Mirena can help patients "look and feel great." Again, FDA is not aware of any evidence suggesting that women who are using Mirena for birth control look great or feel great. Patients using Mirena may experience various side effects, such as irregular bleeding, ovarian cysts, back pain, weight increase, breast pain/tenderness, and acne, in addition to the side effects indicated above. The experience of these side effects can prevent patients from "looking and feeling great." Such claims of improved patient-reported outcomes must be supported by substantial evidence, as demonstrated through adequate and well-controlled trials using validated instruments to measure these outcomes of interest. If you do, in fact, have data to support these claims, you should submit them to FDA for review.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The script includes the following risk presentation, to be presented by Ms. Dehn (emphasis in original):

- Only you and your healthcare professional can decide if Mirena is right for you. **Mirena does not protect against HIV or STDs**. Candidates for Mirena have had a child, and do not have certain cancers or acute pelvic inflammatory disease. In rare cases, perforation or embedment may occur. Mirena may become completely or partially dislodged. In the uncommon event you think you're pregnant, contact your healthcare professional without delay. Ovarian cysts may occur and typically disappear. Changes in bleeding are common in the first few months followed by shorter, lighter periods. Periods, however, may remain irregular.

The risk presentation omits the contraindications regarding untreated lower genital tract infections and conditions associated with increased susceptibility to pelvic infections, and does not adequately convey that should a woman become pregnant while using Mirena, she may lose her baby or her fertility.

We refer you to the December 17, 2008, advisory letter from DDMAC to Bayer, regarding the promotion of Mirena. This advisory letter includes a change of opinion regarding the risk presentation for Mirena. The letter states (in pertinent part, emphasis added):

> Because this constitutes a change in our position, you will be provided a reasonable period of time to revise any Mirena promotional materials currently in use that omit this important risk information. Accordingly, the revisions should be completed within 90 days of receipt of this letter or at the next production of new promotional materials, whichever comes first.

The promotional program at issue here was newly developed, and as stated on the Form FDA-2253 accompanying the materials, it was disseminated on February 28, 2009, after the change of opinion letter was issued. We also refer you to your January 5, 2009, response to the change of opinion letter, stating that you intend to comply with our request.

Additionally, the script minimizes the risks associated with Mirena. Specifically, the "looking and feeling great" statement referenced above, in the context of the program as a whole, minimizes the risks associated with the use of Mirena. As stated in the Background section above, the PI for Mirena includes “very common” (experienced by >10% of clinical trial patients) adverse reactions, in addition to other serious warnings, precautions, and safety issues associated with the use of Mirena. The suggestion that Mirena will help patients “feel great” minimizes the side effects that patients may experience as a result of using the drug.

False/Misleading Statements

The script includes the following statements to be presented by Ms. Dehn (emphasis added):

- “. . . Mirena has no daily, weekly, or monthly routines to comply with as compared to the negatives associated with other birth control methods.”

The above claim that Mirena has “no . . . monthly routines” directly contradicts information contained in Mirena’s PI. According to PRECAUTIONS, Continuation and Removal section (repeated in the DOSAGE AND ADMINISTRATION, Patient Follow-up section) of the PI for Mirena, “[Patients should be] reexamine[d] and evaluate[d] . . . 4 to 12 weeks after insertion and once a year thereafter, or more frequently if clinically indicated.” The PRECAUTIONS, Patient Counseling Information section of the PI also states that patients should check that the threads attached to Mirena are in place after each menstrual cycle (thus on a monthly basis), to ensure that Mirena has not become displaced or expelled, which would result in a loss of contraceptive efficacy. Therefore, the claim that there is no “monthly routine to comply with” is a false statement.

We note that the script includes instructions to check the Mirena threads monthly in a separate part of the presentation; however, this does not correct the false statement highlighted above.

Conclusion and Requested Action

For the reasons discussed above, the program is misleading in violation of the Act, 21 U.S.C. 352(n), and FDA implementing regulations. *See* 21 CFR 202.1(e)(3)(i), (e)(5) & (e)(6)(i).

DDMAC requests that Bayer immediately cease the dissemination of violative promotional materials for Mirena such as those described above. Please submit a written response to this letter on or before January 14, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Mirena that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266; facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 18166 in addition to the NDA number for Mirena. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Mirena comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Carrie Newcomer for
Cynthia Collins, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21225	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	MIRENA(LEVONORGESTREL RELEASING INTRA-UT

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

/s/

CARRIE A NEWCOMER
12/30/2009