DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Fadwa Almanakly
Associate Director, Global Regulatory Affairs
Bayer Healthcare Pharmaceuticals, Incorporated
6 West Belt-W13
Wayne, NJ 07470

RE: NDA No. 21-400 LEVITRA® (vardenafil HCl) Tablets
NDA No. 21-676, 21-873, 22-045 YAZ® (drospirenone and ethinyl estradiol) Tablets
NDA No. 21-225 Mirena® (levonorgestrel-releasing intrauterine system)
MACMIS ID # 17307

Dear Ms. Almanakly:

This letter notifies Bayer Healthcare Pharmaceuticals, Incorporated (Bayer), and, by copy, Schering Corporation (Schering), which markets Levitra on behalf of Bayer, that, as part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed Bayer's sponsored links on internet search engines (e.g., Google.com) for the following products: LEVITRA® (vardenafil HCl) Tablets (Levitra), YAZ® (drospirenone and ethinyl estradiol) Tablets (YAZ), and Mirena® (levonorgestrel-releasing intrauterine system) (Mirena). The sponsored links cited in this letter are misleading because they make representations and/or suggestions about the efficacy of Levitra, YAZ, and Mirena, but fail to communicate **any** risk information associated with the use of these drugs. In addition, the sponsored links for YAZ and Mirena inadequately communicate the drugs' indications, and the sponsored links for Mirena overstate the efficacy of the drug. Furthermore, all of the sponsored links fail to use the required established name. Thus, the sponsored links misbrand the drugs in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and FDA implementing regulations. *See* 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

Background

Levitra

According to its FDA-approved product labeling (PI), Levitra is indicated for the treatment of erectile dysfunction.

Levitra is associated with a number of risks, as reflected in the Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI.

YAZ

According to its FDA-approved PI, YAZ is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

YAZ is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.

YAZ has not been evaluated for the treatment of premenstrual syndrome (PMS).

YAZ is also indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy, and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

YAZ is associated with a number of risks, as reflected in the Boxed Warning, Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI.

Mirena

According to its FDA-approved PI, 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.

Mirena is associated with a number of risks, as reflected in the Contraindications, Warnings, Precautions, and Adverse Reactions sections of its PI.

Omission of Risk Information

Promotional materials, other than reminder pieces, which include the name of the drug product but do not include indications or other representations or suggestions relative to the drug product (see 21 CFR 200.200, 201.100(f), 202.1(e)(2)(i)), are required to disclose risk and other information about the drug. Such materials are misleading if they fail to reveal facts that are material 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 sponsored links present the following claims:

- Poor Blood Flow & ED
  www.LEVITRA.com Blood Flow May Decrease With High Blood Pressure And May Lead to ED.

- YAZ® Birth Control Pill
  www.Yaz-US.com YAZ® Prevents Pregnancy, May Help Moderate Acne and PMDD.

- Mirena® Birth Control
  www.Mirena-US.com Mirena® - Effective Birth Control That Helps Keep Life Simple.

- Anticonceptivo Mirena
  Descubre La Flexibilidad de Mirena Más Información en Español Aquí
  www.SimplementeMirena.com

These sponsored links make representations and/or suggestions about the efficacy of Levitra, YAZ, and Mirena, respectively, but fail to communicate **any** risk information. This omission of risk information is particularly concerning as one of these products, YAZ, has a Boxed Warning. For promotional materials to be truthful and non-misleading, they must contain risk information in each part as necessary to qualify any claims made about the drug.

By omitting the most serious and frequently occurring risks associated with the drugs promoted in the links above, the sponsored links misleadingly suggest that Levitra, YAZ, and Mirena are safer than has been demonstrated. We note that these sponsored links contain a link to the products' websites. However, this is insufficient to mitigate the misleading omission of risk information from these promotional materials.

Inadequate Communication of Indication/Overstatement of Efficacy

The sponsored link for YAZ provides a very brief statement about what the drug is for; however, this statement is incomplete and misleading, suggesting that YAZ is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the sponsored link for YAZ misleadingly broadens the indication for YAZ by implying that all patients with moderate acne are candidates for YAZ therapy ("YAZ® Prevents Pregnancy, May Help Moderate Acne and PMDD"), when this is not the case. Rather, YAZ's indication is limited to the treatment of moderate acne vulgaris in women **at least 14 years of age who have achieved menarche**, and it should be used for the **treatment of acne only if the patient desires an oral contraceptive for birth control**.

The sponsored links for Mirena overstate the efficacy for Mirena by failing to reveal that Mirena is only indicated for up to 5 years of use before replacement. By omitting this information, the link suggests that the drug can be used indefinitely, when this is not the case. Likewise, the sponsored links for Mirena provide very brief statements about what the drug is for; however, these statements are incomplete and misleading in that they fail to convey the recommended patient population for Mirena (women who have had at least one child), thus suggesting that the drug is appropriate for any woman.

Failure to Use Required Established Name

None of the sponsored links present the full established name of the drugs being promoted, despite the requirement to do so. *See* 21 CFR 201.10(g)(1) & 202.1(b)(1).

Conclusions and Requested Action

For the reasons discussed above, the sponsored links misbrand Levitra, YAZ, and Mirena in violation of the Act and FDA regulations. *See* 21 U.S.C. 352(a) & (n), 321(n); 21 CFR 201.10(g)(1), 202.1(b)(1), (e)(3)(i), (ii) & (e)(6)(i).

DDMAC requests that Bayer immediately cease the dissemination of violative promotional materials for Levitra, YAZ, and Mirena, such as those described above. Please submit a written response to this letter on or before April 9, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for these drugs as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such materials. Finally, we encourage you to review your promotional materials for the other prescription drug products that Bayer promotes in the United States and to discontinue or revise any materials with the same or similar violations, and request that your response address this issue as well.

Please direct your response to the undersigned 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17307 in addition to the NDA numbers. 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 Levitra, YAZ, and Mirena comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Shefali Doshi, M.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc: Casilda Luck-Barnes
Senior Manager, Global Regulatory Affairs
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/s/

Shefali Doshi
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