DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mary Ellen Evanich
Assistant Director, Regulatory Affairs
Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06515

RE: NDA # 21-400
Levitra® (vardenafil HCl) Tablets
MACMIS ID # 13014

Dear Ms. Evanich:

This letter notifies Bayer Pharmaceuticals Corporation (Bayer) and, by copy, Schering Corporation (Schering) and GlaxoSmithKline (GSK), which market Levitra on behalf of Bayer, that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a direct-to-consumer television advertisement (TV ad) for Levitra® (vardenafil HCl) Tablets (Levitra) submitted under cover of Form FDA 2253 (entitled "My Man" ID# LEV680R0/PD3816504). The TV ad fails to disclose the drug's indication, fails to include information relating to the major side effects and contraindications, and fails to make adequate provision for dissemination of the FDA-approved labeling in violation of the Federal Food, Drug and Cosmetic Act (Act), 21 U.S.C. § 352(n), and FDA implementing regulations, 21 CFR §§ 202.1(e)(1) and (e)(3). Moreover, the TV ad is misleading because it contains representations or suggestions that Levitra is superior to other erectile dysfunction treatments when this has not been demonstrated by substantial evidence or substantial clinical experience. See 21 CFR § 202.1(e)(6)(ii).

Background

According to FDA-approved labeling (PI), "LEVITRA is indicated for the treatment of erectile dysfunction" (ED). The Contraindications section of the PI states, in part:

> Administration of LEVITRA with nitrates (either regularly and/or intermittently) and nitric oxide donors is contraindicated (see **CLINICAL PHARMACOLOGY, Pharmacodynamics, Effects on Blood Pressure and Heart Rate when LEVITRA is Combined with Nitrates**). Consistent with the effects of PDE5 inhibition on the nitric oxide/cyclic guanosine monophosphate pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates. A suitable time interval

> following LEVITRA dosing for the safe administration of nitrates or nitric oxide donors has not been determined.
>
> Because the co-administration of alpha-blockers and LEVITRA can produce hypotension, LEVITRA is contraindicated in patients taking alpha-blockers (see **PRECAUTIONS, Drug Interactions**).

The Warnings section of the PI states, in part:

> Physicians should consider the cardiovascular status of the patients, since there is a degree of cardiac risk associated with sexual activity. In men for whom sexual activity is not recommended because of their underlying cardiovascular status, any treatment for erectile dysfunction, including LEVITRA, generally should not be used.
>
> There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) for this class of compounds, including vardenafil. In the event that an erection persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Additionally, the Precautions section of the PI includes the statement, “The use of LEVITRA offers no protection against sexually transmitted diseases.”

According to the Adverse Reactions section of the PI, adverse events associated with Levitra include headache, flushing, rhinitis, dyspepsia, and nausea.

Omission of Indication and Risk Information

"Reminder advertisements are those which call attention to the name of the drug product but do not include indications or dosage recommendations for use of the drug product." In addition, "[t]hese reminder advertisements shall contain . . . no representation or suggestion relating to the advertised drug product." See 21 CFR 202.1(e)(2)(i).

The TV ad makes representations or suggestions that Levitra has a positive effect on the relationship between two intimate individuals, and that Levitra will provide a satisfying sexual experience from the female partner's perspective. For example, the partner of the Levitra patient speaks to the camera while the video flashes-back to moments when she and her “man” appear romantically involved. She states (corresponding visuals in parentheses):

> (Match striking and igniting)
> “In the mood for something different?”
> “How about Levitra?”
> “Ask your doctor if Levitra is right for you.”
> “It’s the best way to experience that difference.”

> "Ask about a free sample. Ask about Levitra. Levitra. When it counts." (Match striking and igniting, with simultaneous SUPERs including: "LEVITRA – When It Counts -- "Individual results may vary")

Another scene shows a smiling man and two other quick scenes depict the couple engaged in flirtatious behavior. In one of these scenes, the man strokes the woman's hair and face as she affectionately puts her hand on his wrist. In the other, she puts her arms around his neck and they embrace.

The totality of the TV ad also represents or suggests that Levitra will provide a satisfying sexual experience from the female partner's perspective. For example, the visual images in the ad show the female partner of the Levitra patient in moments where she appears to be romantically involved with the Levitra patient and the audio portion contains claims from the female partner about how Levitra is the "best way to experience the difference."

The fact that effectiveness claims are being made about Levitra in the TV ad is acknowledged by the sponsor by the inclusion of a qualifier to the claim "Levitra. When it counts" – a concurrent SUPER that states: "Individual results may vary." This disclosure about varying "results" recognizes that the ad makes representations about the drug's efficacy (i.e., it may work to improve sexual activity in some, but not all men with ED).

Because the ad is not a reminder ad, it must present the indication and information relating to the major side effects and contraindications, and must make adequate provision for dissemination of the FDA-approved labeling. See 21 CFR 202.1(e)(1) and (e)(3). The TV ad fails to include the specific indication for the drug (namely, treatment of erectile dysfunction) or the required risk information. The TV ad also fails to make adequate provision for dissemination of the FDA-approved labeling.

Implied Superiority

As described above, the woman in the ad asks "In the mood for something different? How about Levitra?" She then adds, "Ask your doctor if Levitra is right for you. It's the best way to experience that difference." These claims suggest that Levitra is superior to other treatments for ED.

FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Levitra is superior to other ED treatments. If you have data substantiating this claim, please submit them to FDA for review.

Conclusion and Requested Actions

For the reasons discussed above, your TV ad misbrands Levitra under section 502(n) of the Act, 21 U.S.C. § 352(n), and FDA implementing regulations, 21 CFR §§ 202.1(e)(1), (e)(3) & (e)(6)(ii).

DDMAC requests that Bayer immediately cease the dissemination of promotional materials for Levitra the same as or similar to those described above. Please submit a written response to this letter on or before April 27, 2005 describing your intent to comply with this request, listing all promotional materials for Levitra the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug

Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 13014 in addition to the NDA number. 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 comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Joan Hankin, J.D.
Consumer Promotion Analyst
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc: Schering Corporation
Joanne Metzler

GlaxoSmithKline
Randal Batenhorst

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/s/

Joan Hankin

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