DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Stephanie J. Davis, RPh
Director, Regulatory Affairs
Valeant Pharmaceuticals North America, LLC
700 US RT 202/206 N
Bridgewater, NJ 08807

RE: NDA 021478
Zovirax® (acyclovir) Cream 5%
MA# 170

Dear Ms. Davis,

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP), Division of Consumer Drug Promotion (DCDP) of the U.S. Food and Drug Administration (FDA) has reviewed Valeant Pharmaceuticals North America, LLC's (Valeant) webpage[1] for its drug product, Zovirax® (acyclovir) Cream 5% (Zovirax). The webpage is misleading because it overstates the efficacy and makes unsubstantiated superiority claims about Zovirax. Thus, the webpage misbrands Zovirax in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1 (e)(6)(i), (ii), (x); (e)(7)(i).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Zovirax.[2]

According to the Indications and Usage section of the FDA-approved product labeling (PI):

> Zovirax Cream is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

Zovirax is associated with a number of risks. Specifically, Zovirax is contraindicated in patients with known hypersensitivity to acyclovir, valacyclovir, or any component of the formulation. The PI also contains Precautions stating Zovirax is intended for cutaneous use only and should only be used on herpes labialis on the affected external aspects of the lips and face, not in the eye or inside the mouth or nose. Application to human mucous membranes is not recommended because no data are available. Zovirax has a potential for irritation and contact sensitization and the effect of Zovirax has not been established in

[1] Zovirax Cream 5% webpage at http://www.zoviraxhcp.com/sections/cream/default.aspx (last accessed July 18, 2012).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

immunocompromised patients. The most common adverse reactions at the site of topical application with Zovirax were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The webpage claims, "PROVEN EFFECTIVE AT ANY STAGE, Even When Therapy Is Initiated Late[3]." This claim is presented in conjunction with a chart which presents six progressive stages of an untreated herpes lesion (prodrome or early (stage 1), papule or swelling (stage 2), vesicle or blistering (stage 3), ulcer or weeping (stage 4), crust or scabbing (stage 5) and healing (stage 6)). This presentation misleadingly overstates the efficacy of the drug by suggesting that Zovirax is proven effective when initiated during the ulcer or weeping, crust or scabbing, or healing stages (stages 4-6) of a herpes lesion, when this has not been demonstrated by substantial evidence or substantial clinical experience. As described in the Dosage and Administration section of the PI, "[T]herapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear)." Additionally, the Clinical Trials section of the PI describes how the design of the Zovirax's two pivotal trials (ZOVA 3003 and ZOVA 3004) instructed patients to "initiate treatment within 1 hour of noticing signs or symptoms" of an untreated herpes lesion, which included the prodrome, papule and vesicle stages (stages 1-3). Therefore, these clinical trials were not designed to evaluate the effectiveness of Zovirax when treatment is initiated "late," i.e., during the ulcer or weeping, crust or scabbing, or healing stages (stages 4-6), and thus do not support the misleading claims presented in the promotional piece. We note that the promotional piece cites the Spruance, et al.[3] study, in support of efficacy when treatment with Zovirax is initiated late. This reference details the two pivotal trials for Zovirax, and thus do not constitute substantial evidence for the reasons cited above. In addition, the Barbarash [4] article is cited in support of beginning treatment with Zovirax at the ulcer or weeping, crust or scabbing, and healing stages (stages 4-6). However, this reference is a review article that discusses herpes simplex viral infections and various treatment options, and does not constitute substantial evidence to support claims of efficacy at any stage. We note the webpage includes footnotes stating, "Therapy should be initiated as soon as possible following onset of signs and symptoms," and defining "late" stages as papule, vesicle, or ulcer, however this does not mitigate the misleading impression.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The chart cited above presents Zovirax as proven effective when initiated at any of the six stages of an untreated herpes lesion, while Valtrex is only effective when initiated at the prodrome or early stage (stage 1). This presentation, in conjunction with the effectiveness claim cited above,

[3] Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T; for the Acyclovir Cream Study Group. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother*. 2002;46(7):2238-2243.
[4] Barbarash RA. Update on treatments for oral herpes simplex viral infections (cold sores and fever blisters). *Today's Ther Trends*. 2001;19:39-58.

misleadingly implies that Zovirax is clinically superior to Valtrex due to an extended timeframe of treatment initiation. FDA is not aware of substantial evidence or substantial clinical experience to support the implication that Zovirax is superior to Valtrex, regardless of when treatment is begun. Generally, claims of superiority must be supported by two adequate and well-controlled head-to-head clinical trials comparing effectiveness of Zovirax and the comparator drug, however, none of the references cited in the promotional piece support this misleading presentation.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Zovirax in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1 (e)(6)(i), (ii), (x); (e)(7)(i).

OPDP requests that Valeant immediately cease the dissemination of violative promotional materials for Zovirax such as those described above. Please submit a written response to this letter on or before August 1, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Zovirax that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA# 170 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds 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 Zovirax comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Sheetal Patel, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

{See appended electronic signature page}

Michael Sauers, MPP
Team Leader
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

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/s/

SHEETAL PATEL
07/18/2012

MICHAEL A SAUERS
07/18/2012