



**TRANSMITTED BY FACSIMILE**

Dr. Jean-Pierre Garnier  
Chief Executive Officer  
GlaxoSmithKline  
P.O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709-3398

**RE: NDA # 18-604**  
**Zovirax<sup>®</sup> (acyclovir) Ointment 5%**  
**MACMIS ID # 14382**

**WARNING LETTER**

Dear Dr. Garnier:

This letter notifies GlaxoSmithKline (GSK), and, by copy, Biovail Pharmaceuticals, Inc. (Biovail), which markets Zovirax<sup>®</sup> (acyclovir) Ointment 5% (Zovirax Ointment) on behalf of GSK, that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the “Clinical Trials” and “What Can I Do To Treat It?” pages of the website for Zovirax Ointment, found at <http://www.zoviraxointment4.com/pro/oint/trials.html> and <http://www.zoviraxointment.com/treat.aspx>, respectively, submitted under cover of Form FDA 2253. We have also reviewed a consumer-directed STD Awareness Deck Card (ZOV490A0306) (deck card) submitted under cover of Form FDA 2253. The web pages and deck card are false or misleading because they contain claims that broaden the indication of Zovirax Ointment, overstate the efficacy of Zovirax Ointment, and omit material facts regarding the drug, including its indication and important risk information associated with its use. Therefore, the web pages and deck card misbrand Zovirax Ointment in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§352(a) & (n); 321(n). These violations are extremely concerning from a public health perspective because they suggest to consumers that Zovirax Ointment may prevent transmission of genital herpes infections - one of the most common sexually transmitted diseases in the United States - when this has not been demonstrated by substantial evidence or substantial clinical experience.

**Background**

According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) for Zovirax Ointment:

ZOVIRAX (acyclovir) Ointment 5% is indicated in the management of initial genital herpes and in limited non-life-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients.

The CLINICAL TRIALS section of the PI states, in pertinent part:

In clinical trials of initial genital herpes infections, ZOVIRAX Ointment 5% has shown a decrease in healing time and, in some cases, a decrease in duration of viral shedding and duration of pain....

In studies of recurrent genital herpes and of herpes labialis in nonimmunocompromised patients, there was no evidence of clinical benefit; there was some decrease in duration of viral shedding.

Furthermore, the following safety information is provided in the PI, in pertinent part:

### **WARNINGS**

ZOVIRAX Ointment 5% is intended for cutaneous use only and should not be used in the eye.

### **PRECAUTIONS, General**

The recommended dosage, frequency of applications, and length of treatment should not be exceeded.... There are no data to support the use of ZOVIRAX Ointment 5% to prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. ZOVIRAX Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of ZOVIRAX Ointment 5% has not been observed, this possibility exists.

### **ADVERSE REACTIONS**

In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by about 30% of patients in both the active and placebo arms; treatment was discontinued in 2 of these patients. Local pruritus occurred in 4% of these patients....

### **Broadening of Indication**

The “What Can I Do To Treat It?” page of the website is false or misleading in that it suggests to consumers that Zovirax Ointment may prevent transmission of genital herpes infections when this has not been demonstrated by substantial evidence or substantial clinical experience. This web page states:

- “Genital herpes is caused by a virus that can be spread to others, so it’s important to treat it with an antiviral medication. ZOVIRAX<sup>®</sup> (acyclovir) Ointment 5% is a prescription topical medication applied at the site of outbreak.”
- “ZOVIRAX<sup>®</sup> Ointment:...Reduces viral shedding, which means it can reduce chances of spreading the virus to others....”

These claims are false or misleading because they suggest that Zovirax Ointment is effective in reducing the transmission of the genital herpes virus to others in direct contradiction to the PI, which states in the Precautions section that “There are no data to support the use of ZOVIRAX Ointment 5% to prevent transmission of infection to other persons....” While it is true that genital herpes is caused by a virus that can be spread to others and that Zovirax Ointment has been shown to decrease the duration of viral shedding, FDA is unaware of substantial evidence or substantial clinical experience that demonstrates that the decrease in duration of viral shedding from treatment with Zovirax Ointment results in a decrease in the spread of the virus to others.

We note that at the bottom of the web page, the full indication for Zovirax Ointment is provided along with the statement “ZOVIRAX Ointment does not prevent transmission of HSV infections.” Nonetheless, the inclusion of this important information does not correct the misleading suggestion conveyed by the web page as a whole that Zovirax Ointment is effective in reducing the transmission of the genital herpes virus to others.

The “Clinical Trials” web page is false or misleading because it suggests that Zovirax Ointment is appropriate for the treatment of recurrent episodes of genital herpes when this has not been demonstrated by substantial evidence or substantial clinical experience. Specifically, it presents the following claims:

- **“Help your patients remember: Treat early. Speed healing....”** (emphasis original)  
Remind them that HSV is a recurrent infection....  
Instruct patients that, once a condition triggers the first signs and symptoms of an infection, immediately begin treatment with ZOVIRAX<sup>®</sup> Ointment.”

The totality of these claims misleadingly suggests use of Zovirax Ointment for recurrences. These claims appear to be instructions to physicians about how they should counsel their patients at the time that the patients seek help for their initial infection regarding the treatment of future episodes. However, as stated previously, Zovirax Ointment is only indicated for use in the management of the “initial” or first episode of genital herpes. In fact, the Clinical Trials section of the PI specifically states “In studies of recurrent genital herpes....there was no evidence of clinical benefit....”

### **Overstatement of Efficacy**

The previously cited web pages are also false or misleading because they suggest that Zovirax Ointment is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The “Clinical Trials” web page claims that in a study of the treatment of initial primary genital herpes, the “Time to complete healing was also shortened....7.1 days vs. 10.5 days with placebo....” However, the publication cited as support for the claim reports that this data represents the mean time from the beginning of therapy to **crusting** of Group 1 lesions.<sup>1</sup> The time to complete healing of Group 1 or all external lesions was longer and not significantly different from placebo. Thus, the claim overstates the efficacy of Zovirax Ointment.

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<sup>1</sup> Corey L, Nahmias AJ, Guinan ME, et al. A trial of topical acyclovir in genital herpes simplex infections. N Engl J Med. 1982;306:1313-19.

The “What Can I Do To Treat It?” web page claims that the product provides “Soothing Topical Relief” and “Soothes at the site with its targeted treatment...”<sup>2</sup> However, as discussed above, the PI reports that about 30% of patients treated with the product in controlled clinical trials experienced “mild pain (including transient burning and stinging).” This is inconsistent with claims that the product provides soothing relief. While we note that the web page presents data regarding the duration of itching and pain from the clinical trial used to support the second claim, and states that mild pain has been reported (incidence not specified), this information is not adequate to mitigate the misleading claims.

### **Omission of Indication and Risk Information**

The deck card specifically refers to Zovirax Ointment by the prominent inclusion of the name in the website address, [www.zoviraxointment4.com](http://www.zoviraxointment4.com), on the back and front of the piece. The piece also provides information about genital herpes. The presentation of the website name along with the information about genital herpes makes the deck card a full product piece, as opposed to a help-seeking piece. However, the deck card omits the specific indication for the drug and fails to include any risk information for Zovirax Ointment. Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made in the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. Although the PI for Zovirax Ointment is printed on the inside of the deck card, this does not replace the need for presentation of the indication and risk information in conjunction with the representations on the promotional body of the piece. Furthermore, the PI is only accessible if you dismantle the deck card.

### **Omission of Material Facts**

As indicated above, promotional materials are misleading if they fail to reveal facts that are material in light of the representations made in the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. In this regard, the website pages are misleading because they fail to present important information from the Precautions section of the PI. For example, the Precautions section states “There are no data to support the use of ZOVIRAX Ointment 5% to...prevent recurrent infections when applied in the absence of signs and symptoms. ZOVIRAX Ointment 5% should not be used for the prevention of recurrent HSV infections.”

### **Conclusion and Requested Action**

The web pages and deck card misleadingly broaden the indication for Zovirax Ointment, overstate its efficacy, and omit material facts regarding the drug, including its indication and important risk information associated with its use. Therefore, these pieces misbrand Zovirax Ointment in violation of the Act. See 21 U.S.C. §§352(a) & (n); 321(n).

DDMAC requests that GlaxoSmithKline immediately cease the dissemination of violative promotional materials for Zovirax Ointment such as those described above. Please submit a written response to this letter on or before July 17, 2006, stating whether you intend to comply with this request, listing all

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<sup>2</sup> Corey L, Benedetti JK, Critchlow CW, et al. Double-blind controlled trial of topical acyclovir in genital herpes simplex virus infections. *Am J Med.* 1982;73:326-34.

violative promotional materials for Zovirax Ointment such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional 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, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 14382 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 Zovirax Ointment comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

*{See appended electronic signature page}*

Thomas W. Abrams, RPh, MBA  
Director  
Division of Drug Marketing,  
Advertising, and Communications

cc: Biovail Pharmaceuticals, Inc.  
Dr. Douglas J.P. Squires

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Thomas Abrams

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