



TRANSMITTED BY FACSIMILE

JP Garnier
Chief Executive Officer
GlaxoSmithKline
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

RE: Avandia® (rosiglitazone maleate) Tablets
NDA 21-071
MACMIS ID#10215

WARNING LETTER

Dear Mr. Garnier:

This Warning Letter concerns GlaxoSmithKline's (GSK) promotional activities for the marketing of Avandia (rosiglitazone maleate) tablets. The materials and activities were reviewed by the Division of Drug Marketing, Advertising and Communications (DDMAC) as part of its routine monitoring and surveillance program. DDMAC has concluded that GSK has promoted Avandia in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. See 21 U.S.C. §§ 331(a),(b), and 352(a),(n).

Specifically, during the 10th Annual American Association of Clinical Endocrinologists (AACE) Meeting in San Antonio, Texas, on May 2-6, 2001, representatives of GSK made oral representations denying the existence of serious new risks associated with Avandia at GSK's promotional exhibit booth. Additionally, GSK displayed exhibit panels (AV013G) at this meeting that minimized these new risks associated with Avandia.

Your promotional activities that minimize serious new risks are particularly troublesome because we have previously objected, in two untitled letters, to your dissemination of promotional materials for Avandia that failed to present any risk information about Avandia or minimized the hepatic risk associated with Avandia. Despite your assurances that such violative promotion of Avandia had ceased, your violative promotion of Avandia has continued.

Background

Avandia was approved on May 25, 1999, for the treatment of Type 2 diabetes mellitus as monotherapy or in combination with metformin. Since Avandia's approval, the product labeling (PI) was changed in direct response to significant new risk information about Avandia. Specifically, the Food and Drug Administration (FDA) approved revisions to Avandia's PI on February 8, 2001. These revisions to the PI included a new warning regarding cardiac failure and other cardiac effects, such as:

- **The use of Avandia in combination therapy with insulin is not indicated**
- In clinical studies, an increased incidence of heart failure and other cardiovascular adverse events were seen in patients on Avandia and insulin combination therapy compared to insulin plus placebo
- Three of 10 patients who developed heart failure on Avandia plus insulin combination therapy had no known prior evidence of congestive heart failure (CHF) or pre-existing cardiac failure
- Avandia alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure
- Patients should be observed for signs and symptoms of heart failure
- Avandia should be discontinued if any deterioration of cardiac status occurs

Furthermore, a new precaution was added to the PI concerning the following postmarketing hepatic risk information:

- Reports of hepatitis and hepatic enzyme elevations to three or more times the upper limit of normal have been received
- Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established

In a letter dated February 22, 2001, DDMAC informed GSK that all promotional materials for Avandia should be revised to prominently include the new risks, no later than March 8, 2001. In your response, dated March 1, 2001, you committed to include the new risk information by March 8, 2001, as we requested. Despite your written commitment to disclose these serious risks, you have denied their existence at a major meeting of endocrinologists and minimized them in certain labeling pieces.

False or Misleading Promotional Activities by GSK Sales Representatives

GSK's sales representatives have engaged in false or misleading promotional activities with respect to the new risk information in Avandia's PI. Specifically, two GSK sales representatives made false or misleading statements about Avandia to a DDMAC reviewer at GSK's AACE promotional exhibit booth.

On May 3, 2001, a GSK sales representative stated that there had been no changes to the PI concerning the risk of congestive heart failure with Avandia. This representative also stated that Avandia could be used in combination with metformin, a sulfonylurea, or insulin, and further stated that he was unaware of any information concerning postmarketing hepatic events with Avandia.

On May 4, 2001, a different GSK sales representative also stated that there had been no changes to the Avandia PI. He further stated that he was unaware of any new risk information concerning congestive heart failure or postmarketing hepatic events associated with Avandia. This sales representative also stated that Avandia may be used in combination with metformin, a sulfonylurea, or insulin.

These statements are clearly inconsistent with Avandia's labeling change and its current PI. Indeed, not only did your representatives fail to disclose the important new risks about Avandia that prompted the February, 2001 labeling change, they actually denied that any changes to the Avandia PI had

occurred and stated that they were not aware of any new risks concerning CHF and postmarketing liver events. They also stated that Avandia may be used in combination with insulin, notwithstanding the new bolded warning that states “[t]he use of Avandia in combination therapy with insulin is not indicated.”

False or Misleading Exhibit Panels

Your exhibit panels (AV013G) that were used at AACE to make representations about Avandia are similarly violative because they fail to present the precaution concerning postmarketing hepatic experience with Avandia. Additionally, they fail to present the warning from the PI that, in clinical trials, there was an increased incidence of CHF and other cardiovascular adverse events in patients on Avandia and insulin combination therapy compared to insulin plus placebo. Furthermore, the bolded warning that “**Avandia is not indicated for use in combination with insulin**” is not presented prominently. Specifically, your exhibit panel minimizes this important information by presenting it under the header “Other considerations” section of the exhibit panel.

Conclusions and Requested Action

The promotional activities described above raise significant public health and safety concerns. In two previous untitled letters, dated June 29, 1999, and October 20, 2000, we objected to your dissemination of promotional materials for Avandia that lacked fair balance concerning the risks associated with Avandia, minimized the hepatic risks, and contained misleading efficacy claims. Based upon your written assurances that these violative promotions of Avandia had been stopped, we considered these matters closed. Despite our prior written notification, and notwithstanding your assurances, GSK has continued to engage in false or misleading promotion of Avandia.

It is our understanding that you have re-instructed your representatives on the new risk information in the Avandia PI, including the fact that Avandia is not indicated in combination with insulin. We also understand that you will provide instruction to GSK representatives regarding their roles and responsibilities at promotional booths prior to the next series of scientific meetings at which GSK representatives will participate in the promotion of Avandia.

However, due to the seriousness of your violations and the fact that violative promotion of Avandia has continued despite your written assurances to the contrary, we request that you provide a detailed response to the issues raised in this Warning Letter. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing the dissemination of all promotional activities and materials for Avandia that contain violations like those outlined in this letter.
2. Issuing a “Dear Healthcare Provider” letter to correct false or misleading impressions and information. This proposed letter should be submitted to us for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who were, or may have been exposed to the violative promotion.

3. A written statement of your intent to comply with "1" and "2" above.

Your written response should be received no later than July 31, 2001. If you have any questions or comments, please contact the undersigned, Barbara S. Chong, Pharm.D., BCPS, or Mark Askine, R.Ph., by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #10215 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Avandia, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

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

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

/s/

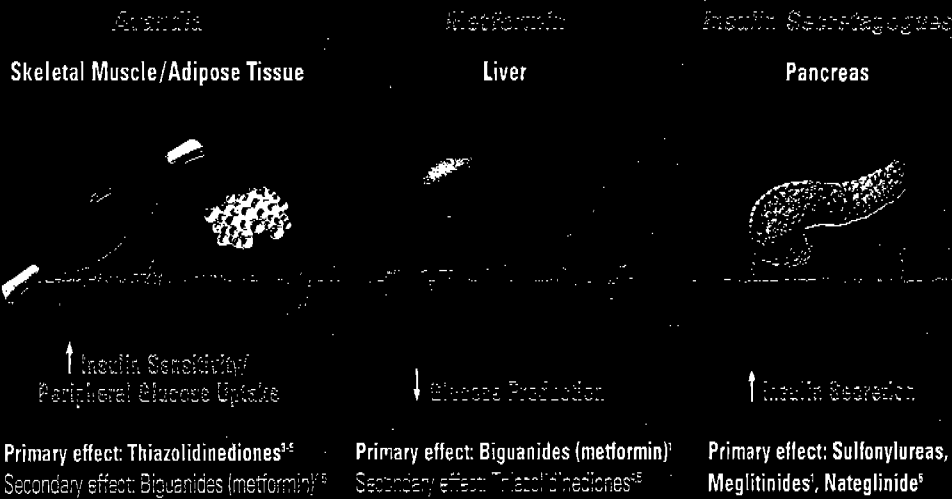
Thomas Abrams
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Avandia®

rosiglitazone maleate

Works Differently From Metformin
And Sulfonylureas

AVANDIA® primarily improves insulin sensitivity in peripheral tissues¹⁻³



Important clinical considerations

Cardiac considerations: Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. Avandia is not recommended in these patients.

Avandia, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention. Avandia may exacerbate or add to heart failure. Patients should be observed for signs and symptoms of heart failure. Avandia should be discontinued if any signs or symptoms of heart failure occur.

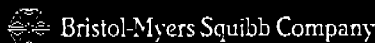
Recommended liver monitoring: Liver monitoring is recommended at baseline, every 2 months for the first 12 months, and periodically thereafter. Avandia should not be initiated in patients with clinical evidence of active liver disease or ALT >2.5X the upper limit of normal.

Other considerations: Avandia is not indicated for use in combination with insulin. **Edema:** Avandia should be used with caution in patients with edema. The weight gain associated with the gain was seen with Avandia.

Please see complete prescribing information available at this display.

References:

1. Johnson BA, Reusch JE. Improving glucose metabolism in type 2 diabetes. *Diabetes Care*. 2000;23(11):1471-1480.
2. Avandia (rosiglitazone maleate) tablets and oral suspension prescribing information.
3. Johnson BA, Reusch JE.
4. Rosiglitazone Maleate Tablets and Oral Suspension Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ.
5. N Engl J Med. 2000;343:2133-2141.
6. See www.drugs.com for more information on Metformin.
7. See www.drugs.com for more information on Sulfonylureas.
8. See www.drugs.com for more information on Nateglinide.



AVANDIA (rosiglitazone maleate) tablets and oral suspension

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