

**TRANSMITTED BY FACSIMILE**

Sharon W. Shapowal, R.Ph.
Director, Avandia
U.S. Regulatory Affairs
GlaxoSmithKline
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

RE: Avandia® (rosiglitazone maleate) Tablets
NDA 21-071
MACMIS ID#10171

Dear Ms. Shapowal:

This letter objects to GlaxoSmithKline's (GSK) dissemination of violative promotional materials for Avandia (rosiglitazone maleate) tablets. As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of direct-to-consumer (DTC) broadcast and print advertisements for Avandia that are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. The DTC broadcast ("Real Stories") and print (AV8580B and AV9117) advertisements submitted on Form FDA 2253, are violative for the reasons described below.

Broadcast Advertisement

Avandia's approved product labeling (PI) includes a bolded warning that "**The use of Avandia (rosiglitazone maleate) in combination therapy with insulin is not indicated.**" You present the statement "Avandia is not indicated for use with insulin" in the audio portion of your "Real Stories" broadcast advertisement simultaneously with the super "Avandia-Help use the natural insulin in you." This presentation minimizes the communication of the risk of the Bolded Warning by presenting consumers with conflicting messages about the use of Avandia and insulin. Moreover, your statement "Avandia is not *indicated* for use with insulin" also minimizes the bolded warning because it is not in consumer-friendly language and therefore unlikely to be understood by consumers. In addition, your broadcast advertisement is misleading because you fail to present the precaution from your PI concerning weight gain caused by Avandia.

Print Advertisement

Similarly, the statements in your print advertisements (AV8580B and AV9117) that "In some people, Avandia may cause fluid retention, or swelling. This could lead to or worsen congestive heart failure, particularly in people taking insulin, so tell your doctor if you have a history of these conditions." are misleading because they minimize the Bolded Warning.

Moreover, your print advertisement is misleading because the risk information is presented under the header "Strengthen your body's own ability to help control blood sugar." This presentation of the risk information under such a header relating to Avandia's efficacy minimizes the risks associated with Avandia treatment.

Requested Action

GSK should immediately discontinue these and all other promotional materials and activities for Avandia that contain the same or similar claims or presentations. We request that GSK respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than July 13, 2001. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If you have any questions or comments, please contact me 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 #10171 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Barbara S. Chong, Pharm.D., BCPS
Regulatory Review Officer
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/

Barbara Chong
6/28/01 05:59:19 PM

Avandia
rosiglitazone maleate

TITLE: Real Stories :60
CLIENT: GlaxoSmithKline
DATE: 6/4/01



MUSIC: UP AND UNDER

SUPER: Avandia* ((logo))
rosiglitazone maleate
GSK ((logo))



ROBERT: I have type 2 diabetes.

SUPER: Avandia* ((logo without generic))



JUAN: And I will always take care of myself.

SUPER: Avandia* ((logo without generic))



AC: I stick to my regimen.

SUPER: Avandia* ((logo without generic))



ROBERT: I had to make that commitment to diet and exercise.

SUPER: Avandia* ((logo without generic))



JUAN: It was hard in the beginning.

SUPER: Avandia* ((logo without generic))



JOHN: But diet and exercise weren't enough.

SUPER: Avandia* ((logo without generic))



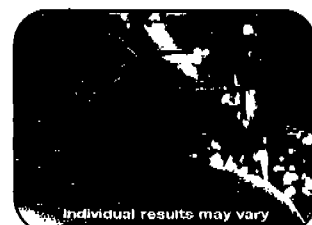
JANE: So my doctor added Avandia to help control my blood sugar.

SUPER: Available by prescription only



FLORETTE: Unlike some diabetes medications, Avandia helps my body use the natural insulin it already makes.

SUPER: Individual results may vary



ROBERT: Avandia has helped keep my blood sugar down for about a year now.

SUPER: Individual results may vary



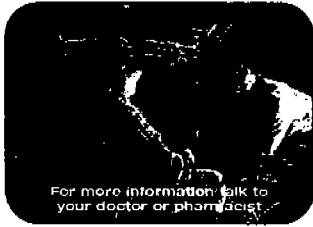
VO: Avandia is not indicated for use with insulin.

SUPER: Avandia* ((logo without generic))
Help use the natural insulin in you
See our ad in U.S. News & World Report



In some people, Avandia may cause fluid retention, or swelling.

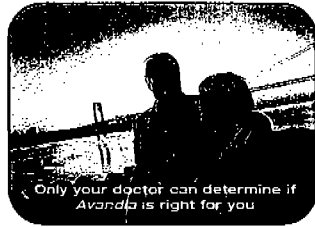
SUPER: For more information talk to your doctor or pharmacist



For more information, talk to your doctor or pharmacist.

which could lead to or worsen heart failure, so talk to your doctor.

SUPER: For more information talk to your doctor or pharmacist



Only your doctor can determine if Avandia is right for you.

Avandia is not for everyone. If you have severe heart failure or active liver disease, Avandia is not recommended.

SUPER: Only your doctor can determine if Avandia is right for you



To check for serious liver problems, blood tests should be conducted before and during Avandia therapy.



1-877-AVANDIA
www.avandia.com

JUAN: Just remember we have three kids.

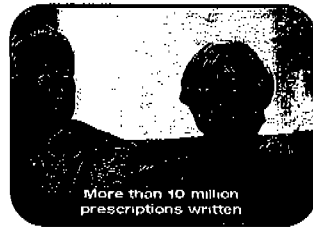
SUPER: 1-877-AVANDIA
www.avandia.com



1-877-282-6342
www.avandia.com

ROBERT: This commitment is for me -- but it's also for my family.

SUPER: 1-877-282-6342
www.avandia.com



More than 10 million prescriptions written

JANE: Eat right. Exercise. And if that's not enough, ask your doctor about Avandia.

SUPER: More than 10 million prescriptions written



AC: So I may always be stronger than diabetes.

SUPER: Avandia® (logo without generic)

For people with type 2 diabetes

**"Taking care of my diabetes takes
real commitment. Always."**

"I've made this commitment for myself...but it's also for my family. I have two beautiful daughters — I live for them. And when I look at them, I know exactly why I'm determined to take care of myself."

"I've been eating right and exercising more. That still wasn't enough, so my doctor added *Avandia*. It helps my body use its own natural insulin more effectively. With *Avandia*, I can really manage my type 2 diabetes."

"*Avandia* has helped me keep my blood sugar down for about a year now. Your results may vary."

**Strengthen your body's own ability
to help control blood sugar.**

Avandia, along with diet and exercise, helps improve blood sugar control. It may be prescribed alone, with Glucophage® (metformin HCl tablets) or with sulfonylureas. When taking *Avandia* with a sulfonylurea, you may be at risk for low blood sugar. Ask your doctor whether you have to lower your sulfonylurea dosage.

In some people, *Avandia* may cause fluid retention, or swelling. This could lead to or worsen congestive heart failure, particularly in people taking insulin, so tell your doctor if you have a history of these conditions. *Avandia* is not for everyone. If you have severe heart failure or active liver disease, *Avandia* is not recommended. If you experience an unusually rapid increase in weight, swelling or shortness of breath while taking *Avandia*, talk to your doctor immediately.

Also, blood tests to check for serious liver problems should be conducted before and during *Avandia* therapy. Tell your doctor if you have liver disease, or if you experience unexplained tiredness, stomach problems, dark urine or yellowing of the skin while taking *Avandia*. See important patient information on the following page.

If you are nursing, pregnant or thinking about becoming pregnant, talk to your doctor before taking *Avandia*.

**Talk to your doctor, or for more information
call 1-800-AVANDIA (1-800-282-6342) or
visit www.avandia.com**

 GlaxoSmithKline

 Bristol-Myers Squibb Company

© 2001 The Avandia Division of GlaxoSmithKline
All rights reserved. AV0001

Avandia is a registered trademark of GlaxoSmithKline
GlaxoSmithKline is a registered trademark of GlaxoSmithKline
Bristol-Myers Squibb is a registered trademark of Bristol-Myers Squibb Company

Please see important patient information
on the following page.

 **Avandia**
rosiglitazone maleate

You can be stronger than diabetes

Patient Information about AVANDIA® (rosiglitazone maleate) 2 mg, 4 mg, and 8 mg Tablets

What is Avandia?

Avandia is one product in a class of prescription drugs called thiazolidinediones (thigh-a-zoe-lid-eeen-die-owns). It is used to treat type 2 diabetes by helping the body use the insulin that it is already making. Avandia comes as pills that can be taken either once a day or twice a day to help improve blood sugar levels.

How does Avandia treat type 2 diabetes?

If you have type 2 diabetes, your body probably still produces insulin but it is not able to use the insulin efficiently. Insulin is needed to allow sugar to be carried from the bloodstream into many cells of the body for energy. If insulin is not being used correctly, sugar does not enter the cells very well and builds up in the blood. If not controlled, the high blood sugar level can lead to serious medical problems, including kidney damage, blindness and amputation.

Avandia helps your body use insulin by making the cells more sensitive to insulin so that the sugar can enter the cell.

How quickly will Avandia begin to work?

Avandia begins to reduce blood sugar levels within 2 weeks. However, since Avandia works to address an important underlying cause of type 2 diabetes, insulin resistance, it may take 8 to 12 weeks to see the full effect. If you do not respond adequately to your starting dose of Avandia, your physician may increase your daily dose to improve your blood sugar control.

How should I take Avandia?

Your doctor may tell you to take Avandia once a day or twice a day (in the morning and evening). It can be taken with or without meals. Food does not affect how Avandia works. To help you remember to take Avandia, you may want to take it at the same time every day.

What if I miss a dose?

If your doctor has prescribed Avandia for use once a day:

- As soon as you remember your missed dose, take one tablet anytime during the day.
- If you forget and go a whole day without taking a dose, don't try to make it up by adding another dose on the following day. Forget about the missed dose and simply follow your normal schedule.

If your doctor has prescribed Avandia for use twice a day:

- As soon as you remember the missed dose, take one tablet.
- Take the next dose at the normal time on the same day.
- Don't try to make up a missed dose from the day before.
- You should never take three doses on any single day in order to make up for a missed dose the day before.

Do I need to test my blood for sugar while using Avandia?

Yes, you should follow your doctor's instructions about your at-home testing schedule.

Does Avandia cure type 2 diabetes?

Currently there is no cure for diabetes. The only way to avoid the effects of the disease is to maintain good blood sugar control by following your doctor's advice for diet, exercise, weight control, and medication. Avandia, alone or in combination with other antidiabetic drugs (i.e., sulfonylureas or metformin), may improve these other efforts by

helping your body make better use of the insulin it already produces.

Can I take Avandia with other medications?

Avandia has been taken safely by people using other medications, including other antidiabetic medications, birth control pills, warfarin (a blood thinner), Zantac® (ranitidine, an antiulcer product from GlaxoSmithKline), certain heart medications, and some cholesterol-lowering products. You should discuss with your doctor the most appropriate plan for you. If you are taking prescription or over-the-counter products for your diabetes or for conditions other than diabetes, be sure to tell your doctor. Sometimes a patient who is taking two antidiabetic medications each day can become irritable, lightheaded or excessively tired. Tell your doctor if this occurs; your blood sugar levels may be dropping too low, and the dose of your medication may need to be reduced.

What should I discuss with my doctor before taking Avandia?

In some people, Avandia may cause fluid retention or swelling. This could lead to or worsen congestive heart failure, particularly in people taking insulin. So talk to your doctor if you have a history of heart failure or swelling. You should also talk to your doctor if you have liver problems, or if you are nursing, pregnant or thinking of becoming pregnant. If you are a premenopausal woman who is not ovulating, you should know that Avandia therapy may result in the resumption of ovulation, which may increase your chances of becoming pregnant. Therefore, you may need to consider birth control options.

What are the possible side effects of Avandia?

Avandia was generally well tolerated in clinical trials. The most common side effects reported by people taking Avandia were upper respiratory infection and headache. As with most other diabetes medications, you may experience an increase in weight. You may also experience edema (swelling) and/or anemia. If you experience any swelling of your extremities (e.g., legs, ankles) or tiredness, notify your doctor. Talk to your doctor immediately if you experience edema, shortness of breath, an unusually rapid increase in weight, or other symptoms of heart failure.

Who should not use Avandia?

You should not take Avandia if you are in the later stages of heart failure. The following people should also not take Avandia: People with type 1 diabetes, people who experienced yellowing of the skin with Rezulin® (troglitazone, Parke-Davis), people who are allergic to Avandia or any of its components and people with diabetic ketoacidosis.

Why are laboratory tests recommended?

Your doctor may conduct blood tests to measure your blood sugar control. Blood tests to check for serious liver problems should be conducted before starting Avandia, every 2 months during the first year, and periodically thereafter.

It is important that you call your doctor immediately if you experience unexplained symptoms of nausea, vomiting, stomach pain, tiredness, anorexia, dark urine, or yellowing of the skin.

How should I store Avandia?

Avandia should be stored at room temperature in a child-proof container out of the reach of children. Store Avandia in its original container.



©2001 The GlaxoSmithKline Group of Companies
All rights reserved. Printed in USA. AV9116 April 2001

For people with type 2 diabetes

**"I will always
take care of my diabetes."**



"I have a lot of great reasons to take care of myself. But the most important one is named Maria.

"She's one of the reasons I'm eating right and exercising more. When that wasn't enough, my doctor added Avandia to help me manage my type 2 diabetes. Avandia works differently than some diabetes medications. It helps my body use its own natural insulin more effectively.

"Since I started taking Avandia about a year ago, my blood sugar level has come down and stayed down. Your results may vary."

**Strengthen your body's
own ability to help control
blood sugar.**

Avandia, along with diet and exercise, helps improve blood sugar control. It may be prescribed alone, with Glucophage® (metformin HCl) tablets or with sulfonylureas. When taking Avandia with a sulfonylurea, you may be at risk for low blood sugar. Ask your doctor whether you need to adjust your sulfonylurea dosage.

In some people, Avandia may cause fluid retention, or swelling. This could lead to or worsen congestive heart failure, particularly in people taking insulin, so tell your doctor if you have a history of these conditions. You should not take Avandia if you are in the later stages of heart failure. If you experience an unusually rapid increase in weight, swelling or shortness of breath while taking Avandia, talk to your doctor immediately.

Also, blood tests to check for serious liver problems should be conducted before and during Avandia therapy. Tell your doctor if you have liver disease, or if you experience unexplained tiredness, stomach problems, dark urine or yellowing of the skin while taking Avandia. See important patient information on the following page.

If you are nursing, pregnant or thinking about becoming pregnant, or if you are a premenopausal woman who is not ovulating, tell your doctor about taking Avandia.

**Talk to your doctor, or for more information
call 1-800-AVANDIA (1-800-282-6342).**

Avandia®
rosiglitazone maleate

You can be stronger than diabetes

 GlaxoSmithKline

 GlaxoSmithKline Company

© 2005 GlaxoSmithKline

Avandia is a registered trademark of GlaxoSmithKline

www.avandia.com

Avandia is not a diet pill. It is a prescription medicine.