DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

Sharon W. Shapowal, R.Ph.
Director, Avandia
N.A. Regulatory Affairs
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101

OCT 20 2000

RE: Avandia® (rosiglitazone maleate) Tablets
NDA 21-071
MACMIS ID#9308

Dear Ms. Shapowal:

This letter concerns several promotional materials (sales aids AV4062, AV4759, and AV5508; journal advertisement AV3741; customized menus AV3747E-1 and AV3747E-2) for Avandia tablets (rosiglitazone maleate) disseminated by SmithKline Beecham Pharmaceuticals (SB). As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these materials and has concluded that they are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. A description of our objections follows. The violations discussed in this letter do not necessarily constitute an exhaustive list.

Minimizing Hepatic Risk

The hepatic precautions in the approved product labeling (PI) include the following:

1. Although available clinical data show no evidence of Avandia induced hepatotoxicity or alanine aminotransferase (ALT) elevations, rosiglitazone is structurally related to troglitazone, which has been associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death.
2. Pending the availability of the results of additional large, long-term controlled clinical trials and postmarketing safety data following wide clinical use of Avandia to more fully define its hepatic safety profile, it is recommended that patients treated with Avandia undergo periodic monitoring of liver enzymes.
3. Liver enzymes should be checked prior to the initiation of therapy with Avandia in all patients.
4. Therapy with Avandia should not be initiated in patients with increased baseline liver enzyme levels [ALT >2.5X upper limit of normal (ULN)].

5. In patients with normal baseline liver enzymes, following initiation of therapy with Avandia, it is recommended that liver enzymes be monitored every two months for the first twelve months, and periodically thereafter.
6. Patients with mildly elevated liver enzymes (ALT levels one to 2.5X ULN) at baseline or during therapy with Avandia should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with Avandia should proceed with caution and include close clinical follow-up, including more frequent liver enzyme monitoring, to determine if the liver enzyme elevations resolve or worsen.
7. If at any time ALT levels increase to >3X ULN in patients on therapy with Avandia, liver enzyme levels should be checked as soon as possible.
8. If ALT levels remain >3X ULN, therapy with Avandia should be discontinued.

In sales aid AV4759, you misleadingly claim that Avandia is "Appropriate for many patients with type 2 diabetes including: obese, elderly, and renally or hepatically impaired." According to the approved PI, "Therapy with Avandia should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT > 2.5X ULN) at baseline." Therefore, your claim that Avandia is "appropriate" for hepatically impaired patients is misleading. Your presentation of qualifying information in a footnote fails to correct this misleading statement. Moreover, journal advertisement AV3741 includes bullets on the effectiveness of Avandia but fails to mention *any* of the hepatic precautions. DDMAC is seriously concerned that SB has minimized the precautions concerning hepatic effects in its materials.

Misleading Efficacy Claims

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence. Your promotional materials (AV3741, AV4062, and AV4759) prominently present efficacy claims based on an ad hoc analysis in patients with baseline hemoglobin A1c (HbA1c) ≥ 9%. For example, you present claims that Avandia decreased HbA1c by 2.3% (Avandia 4 mg QD) and 1.7% (Avandia 4 mg BID) in drug-naïve patients and previously-treated patients, respectively. The claim involving drug-naïve patients that supposedly demonstrated the 2.3% decrease in HbA1c is based on a study that involved a total of 14 patients. In contrast, the PI (study B) indicates that the same Avandia dose (4 mg QD) in 180 patients with a mean baseline HbA1c of 8.9% decreased HbA1c by 0.8%. Therefore, your presentations that Avandia 4 mg QD decreases HbA1c by 2.3% are misleading because they suggest that Avandia is more effective than has been demonstrated by substantial evidence.

Fair Balance

The promotional materials (AV3741, AV4759, and AV5508) are misleading because they fail to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. For

example, in journal advertisement AV3741, the efficacy data is presented in a large font with bullets while the risk information is presented as a footnote at the bottom.

The "Perfect 10: I can customized menus" (AV3747E-1 and AV3747E-2) lack fair balance because the materials present the product's indication without disclosing risks associated with Avandia. For example, you have exclusively presented the product logo in conjunction with the statement "Help use the natural insulin in you" without any mention of the risk information.

Requested Action

SB should immediately discontinue these and all other promotional materials for Avandia that contain the same or similar claims or presentations. We request that SB respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than November 3, 2000. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

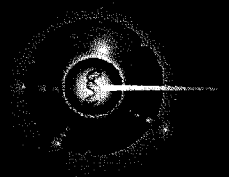
If SB has any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9308 in addition to the NDA number.

Sincerely,

Barbara S. Chong, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

Over 2 Million Prescriptions Dispensed



HARD TO RESIST

FOR TYPE 2 DIABETES

The Most Potent TZD*

- ▶ Effective as monotherapy regardless of baseline HbA_{1c}
- ▶ Proven long-term durability versus glyburide
- ▶ Synergistic effect when combined with metformin
- ▶ Positive effect on HDL
- ▶ Excellent drug interaction profile
- ▶ Convenient and economical as once-daily dosing
- ▶ Appropriate for many patients with type 2 diabetes including: obese, elderly, and renally or hepatically impaired†

* Based on in vitro binding affinity to PPARγ. The clinical significance of these data is unknown.
† Patients on hemodialysis, patients with NYHA Class I and II cardiac status, and patients without active liver disease.

Please see enclosed complete prescribing information.

SB SmithKline Beecham Pharmaceuticals

Bristol-Myers Squibb Company

Avandia is a registered trademark of SmithKline Beecham.

Avandia®
rosiglitazone maleate
Redefining Type 2 Therapy

♻ Printed in U.S.A.

HARD TO RESIST

FOR TYPE 2 DIABETES

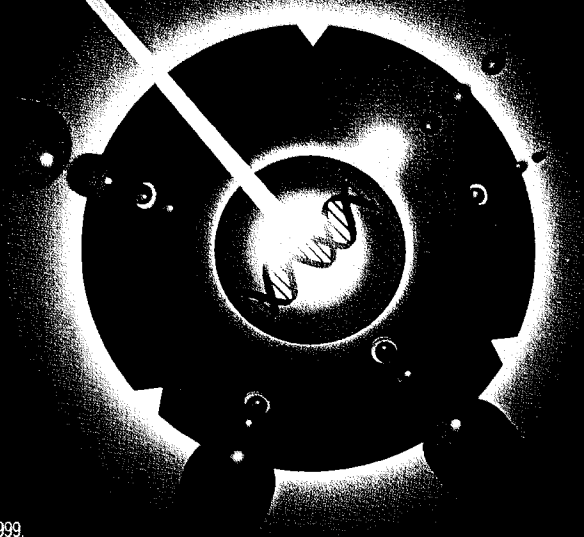
Over 1 Million Prescriptions Dispensed

Impressive Improvement in Glycemic Control

Substantial reductions in HbA_{1c} ↓2.3%*

Proven long-term durability versus glyburide

85% of patients treated with *Avandia* managed on once-daily dosing[1]



Reference 1. Scott-Levin PDDA, September 1999.

* Mean difference from placebo at 26 weeks, adjusted for baseline, in drug-naive patients with baseline ≥9% treated with *Avandia* 4 mg qd (n=14). No dose response was observed between 4 mg qd and 8 mg qd (n=21) in this subset of patients.

Commonly reported adverse events were upper respiratory tract infection and headache, which occurred at frequencies similar to placebo. Mild to moderate edema (4.8%) has also been reported.
***Avandia* may be administered once or twice daily.**

Please see brief summary of prescribing information on the following page.

SB SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

Bristol-Myers Squibb Company

Avandia®

rosiglitazone maleate

Redefining Type 2 Therapy

HARD TO RESIST MONOTHERAPY

Impressive Improvement In Glycemic Control

▶ SUBSTANTIAL REDUCTIONS WITH ONCE-DAILY DOSING*

- 4 mg qd most commonly used dose†

HbA_{1c} **-2.3%**

Drug-naive Patients With Baseline ≥9% 4 mg qd‡

FPG **-63 mg/dL**

▶ IMPRESSIVE IMPROVEMENT IN PATIENTS WHO FAILED ON PRIOR THERAPY*

HbA_{1c} **-1.7%**

Previously Treated Patients With Baseline ≥9% 8 mg Daily in Divided Doses§

FPG **-90 mg/dL**

▶ LOW DROPOUT RATE WITH AVANDIA® DUE TO LACK OF EFFICACY, 5% TO 9% (COMPARED TO PLACEBO, 17% TO 21%) IN ALL PATIENTS

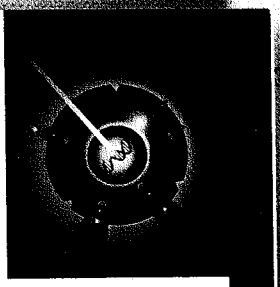
* Mean difference from placebo at 26 weeks, adjusted for baseline.

† Based on Scott-Levin PDDA data, September 1999.

‡ 4 mg qd, n=14. In this study, no dose response was observed between 4 mg qd and 8 mg qd (n=21) in this subset of patients.

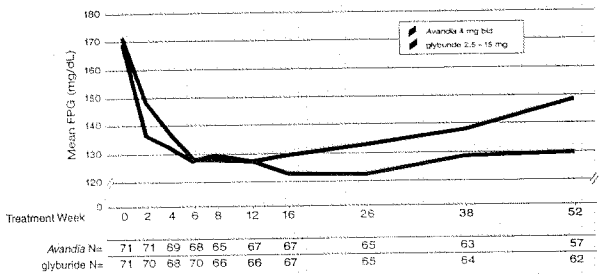
§ 4 mg bid, n=57.

Please see enclosed complete prescribing information.



Proven Long-term Control and Durability

Mean Fasting Plasma Glucose (FPG) Over 1 Year in Drug-naive Patients¶



- Change from baseline HbA_{1c} at 52 weeks: -1.0% (*Avandia* 4 mg bid), -0.9% (glyburide)¶
- Glyburide causes a significant increase in insulin levels over 1 year versus *Avandia* (+14.6 pmol/L with glyburide, -12.5 pmol/L with *Avandia*; $P<.0001$)¶
- *Avandia* has demonstrated a low incidence of hypoglycemia (1.6%) versus glyburide (12.1%)¶

▶ 65% OF PATIENTS ON AVANDIA® ACHIEVED ADA GOAL (HbA_{1c}:<7%)¶,‡

¶ Results from a randomized, double-blind, 52-week study (n=598) comparing *Avandia* 2 mg bid, 4 mg bid, and glyburide titrated to maximum effect (up to 15 mg/day) over first 12 weeks. Reduction in FPG for *Avandia* 2 mg bid was similar to glyburide; reduction in baseline HbA_{1c}, 0.6%; reduction in insulin levels, 6.2 pmol/L at 52 weeks.

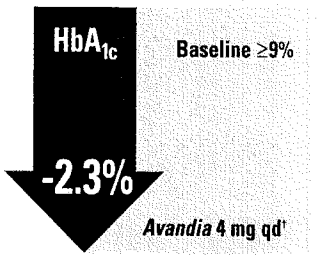
‡ *Avandia* 8 mg daily in divided doses.

Avandia®
rosiglitazone maleate
Redefining Type 2 Therapy

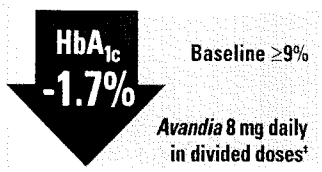
Impressive Improvement in Glycemic Control

- **Significant improvement at all doses versus placebo in overall population (pooled monotherapy data)**
  - Inclusion criteria: no minimum HbA_{1c}, FPG ≥140 mg/dL, C-peptide ≥0.8 ng/mL
  - Demographics: mean baseline HbA_{1c} 8.9%, FPG approximately 228 mg/dL
- **Low dropout rate with AVANDIA® due to lack of efficacy**
  - 5% to 9% (compared to placebo, 17% to 21%) in overall population

▶Drug-naïve patients*



▶Previously-treated patients*



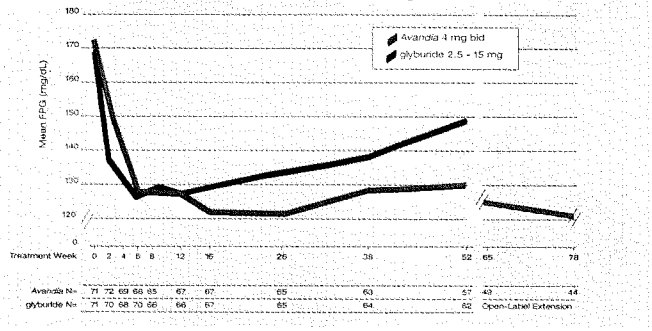
- **71% of drug-naïve patients (n=24) reached HbA_{1c} ≤8% on AVANDIA® 4 mg qd at 26 weeks**

* Mean difference from placebo at 26 weeks, adjusted for baseline.
† 4 mg qd, n=14. In this study, no dose response was observed between 4 mg qd and 8 mg qd (n=21) in this patient subset.
‡ 4 mg bid, n=57.

Please see complete prescribing information.

Sustained Durability Versus Glyburide

Long-Term FPG Results in Drug-Naïve Patients§



- Change in HbA_{1c} at 1 year: *Avandia* 4 mg bid, -1.0%; glyburide, -0.9%§

- **65% of drug-naïve patients (n=37) achieved ADA goal <7% on AVANDIA® 4 mg bid at 1 year**
  - 90% of drug-naïve patients (n=51) reached HbA_{1c} ≤8%
- **Low incidence of hypoglycemia in the overall population**
  - 1.6% with *Avandia* 4 mg bid versus 12.1% with glyburide
- **Insulin levels decreased while glycemic control improved**
  - -12.46 pmol/L with *Avandia* 4 mg bid versus +14.60 pmol/L with glyburide

§ Randomized, double-blind, 52-week study (n=587) comparing *Avandia* 2 mg bid, 4 mg bid, and glyburide titrated to maximum effect (up to 15 mg/day) over first 12 weeks. Reduction in FPG for *Avandia* 2 mg bid at 52 weeks was similar to glyburide; reduction in baseline HbA_{1c} 0.6%. Results from an open-label extension with *Avandia* 4 mg bid. Glyburide was not studied past 12 months.

Avandia®
rosiglitazone maleate

Convenient Once-a-Day Dosing

▶ **75% of patients on AVANDIA® managed on once-daily dosing[17]**

4 mg qd

8 mg qd

- Recommended starting dose 4 mg qd (may also be given as a divided dose)
- May be titrated up to 8 mg daily (in single or divided doses)
- *Avandia* generally lowers FPG within 2 weeks of initiation of therapy and continues to decrease FPG over 2 to 3 months
- May be taken *with or without food*

▶ **May be dosed bid for convenience with concomitant medication schedules**

▶ **No dose adjustments needed in elderly, renally impaired, or hemodialysis patients**

▶ **Most economical TZD***

▶ **Reimbursed on 90% of managed care formularies**

* Based on average wholesale prices comparing *Avandia*, *Actos*, and *Rezulin*; *Red Book Update*, February 2000.

Important Clinical Considerations

Avandia was generally well tolerated in clinical trials. Commonly reported adverse events were upper respiratory tract infection and headache, which occurred at frequencies similar to placebo. Mild to moderate anemia (1.9%) and edema (4.8%) have also been reported. The frequency of anemia was greater with the combination of *Avandia* plus metformin (7.1%) compared to metformin alone (2.2%). Lower pretreatment hemoglobin/hematocrit levels may have contributed to this higher reporting rate.

In patients with clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal) at baseline, therapy with *Avandia* should not be initiated.

Avandia should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis.

Avandia is contraindicated in patients with known hypersensitivity to this product or any of its components.

In premenopausal anovulatory patients with insulin resistance, *Avandia* treatment may result in resumption of ovulation. These patients may be at risk for pregnancy. Thus, adequate contraception should be recommended.

Avandia has not been tested in patients with New York Heart Association (NYHA) Class III and IV cardiac status. Since thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure, patients at risk (particularly those on insulin) should be watched for signs/symptoms of heart failure.†

Improvement in glycemic control was associated with mean increases in weight: 3 kg at 1 year.

The following trademarks, which are not SmithKline Beecham Pharmaceuticals products, appear in this piece: *Actos*, Takeda-Lilly; *Nizoral*, Janssen Pharmaceutica Products L.P.; *Rezulin*, Parke-Davis; *Viagra*, Pfizer Inc.

† *Avandia* is not indicated for use in combination with insulin.

Avandia®
rosiglitazone maleate

Hepatic Safety

- **Over 2 million prescriptions dispensed***
- **No evidence of drug-induced hepatotoxicity or alanine transaminase (ALT) elevations versus placebo in clinical trials of almost 4,600 patients treated with AVANDIA®**

***Avandia* ALT Elevations Similar to Placebo in Controlled, Double-blind Studies**

Percent of Patients With ALT Elevations (>3X ULN[†])

Avandia	N=2,526	0.2%
Placebo	N=601	0.2%
Active Control[‡]	N=851	0.5%

- **Worldwide postmarketing experience in over 700,000 patients (encompassing 175,000 patient-years) consistent with clinical trial findings***

*NDC, April 2000.
† Upper limit of normal.
‡ Metformin, N=225; sulfonylureas, N=626.

Rezulin® (troglitazone) has been associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death have been reported during postmarketing clinical use. In preapproval controlled clinical trials in patients with type 2 diabetes, *Rezulin* was more frequently associated with clinically significant elevations of hepatic enzymes (ALT >3X ULN†) compared to placebo, and very rare cases of reversible jaundice were reported.

Avandia has not yet been widely used; however, in clinical trials there was no evidence of drug-induced hepatotoxicity or ALT elevations. Due to experience with *Rezulin*, and because *Avandia* is also a member of the TZD class, periodic monitoring of liver enzymes is recommended.

For patients with normal hepatic enzymes who are switched from *Rezulin* to *Avandia*, a 1-week washout followed by a baseline ALT is recommended.

- **Recommended periodic laboratory tests**
  - Fasting plasma glucose (FPG)
  - Glycosylated hemoglobin (HbA_{1c})
  - Liver enzymes (ALT)
    - — Determine baseline ALT
    - — If ALT normal, initiate therapy and test every 2 months for the first year and periodically thereafter
    - — If ALT >1X to 2.5X ULN at baseline or during therapy, determine cause and consider close follow-up (see complete prescribing information)
    - — If ALT >2.5X ULN at baseline, do not initiate *Avandia* therapy
    - — If ALT >3X ULN during *Avandia* therapy, retest promptly and discontinue if ALT remains >3X ULN

Avandia®
rosiglitazone maleate

Convenient Once-a-Day Dosing

▶ 4 mg qd is most commonly prescribed dose[19]

- Recommended starting dose 4 mg once daily (or divided twice daily)
- May be titrated up to 8 mg daily (in single or divided doses)*
- *Avandia* generally lowers FPG within 2 weeks of initiation of therapy and continues to decrease FPG over 2 to 3 months
- May be taken *with or without food*

▶ May be dosed bid for convenience with concomitant medication schedules

▶ No dose adjustments needed in elderly, renally impaired, or hemodialysis patients

▶ Most economical TZD†

—30% lower cost than Actos™ (pioglitazone HCl)

▶ Reimbursed on 90% of managed care formularies

* Doses of *Avandia* greater than 4 mg daily in combination with a sulfonylurea have not been studied in adequate and well-controlled clinical trials.

† Based on Scott-Levin average retail price data for the most commonly prescribed doses: *Avandia*, 4 mg tablet; pioglitazone HCl, 30 mg tablet.

Please see complete prescribing information.

Important Clinical Considerations

Avandia was generally well tolerated in clinical trials. Patients receiving *Avandia* in combination with a sulfonylurea may be at risk for hypoglycemia and a reduction in the sulfonylurea dose may be necessary. Mild to moderate anemia and edema have also been reported. The frequency of anemia was greater with the combination of *Avandia* plus metformin (7.1%) compared to metformin alone (2.2%). Lower pretreatment hemoglobin/hematocrit levels may have contributed to this higher reporting rate.

Rezulin® (troglitazone) was removed from the market because of rare drug-related cases of death and liver transplant. As a result of this experience, periodic monitoring of liver enzymes is recommended. For patients with normal hepatic enzymes who are switched from troglitazone to *Avandia*, a 1-week washout is recommended prior to starting therapy with *Avandia.*

In patients with normal baseline liver enzymes, following initiation of therapy with *Avandia*, it is recommended that liver enzymes be monitored every 2 months for the first 12 months, and periodically thereafter. In patients with clinical evidence of active liver disease or increased transaminase levels (ALT >2.5X upper limit of normal) at baseline, therapy with *Avandia* should not be initiated (see complete prescribing information).

Avandia should not be used in type 1 diabetes or for the treatment of diabetic ketoacidosis.

Avandia is contraindicated in patients with known hypersensitivity to this product or any of its components.

In premenopausal anovulatory patients with insulin resistance, *Avandia* treatment may result in resumption of ovulation. These patients may be at risk for pregnancy. Thus, adequate contraception should be recommended.

Since thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure, patients at risk (particularly those on insulin) should be watched for signs/symptoms of heart failure.‡

Improvement in glycemic control was associated with mean increases in weight: 3 kg at 1 year.

The following trademarks, which are not SmithKline Beecham Pharmaceuticals products, appear in this piece: *Actos*, Takeda-Lilly; *Baycol*, Bayer Corporation; *Nizoral*, Janssen Pharmaceutica Products L.P.; *Rezulin*, Parke-Davis; *Taxol*, Bristol-Myers Squibb Co.; *Viagra*, Pfizer Inc.

Avandia®
rosiglitazone maleate

‡ *Avandia* is not indicated for use in combination with insulin.

Avandia®

rosiglitazone maleate

Help use the natural insulin in you.

...Revision 2/00 June 2000 AV3747E-1 ♻ Printed in U.S.A.