

October 30, 2008

Andrew Von Eschenbach, M.D., Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

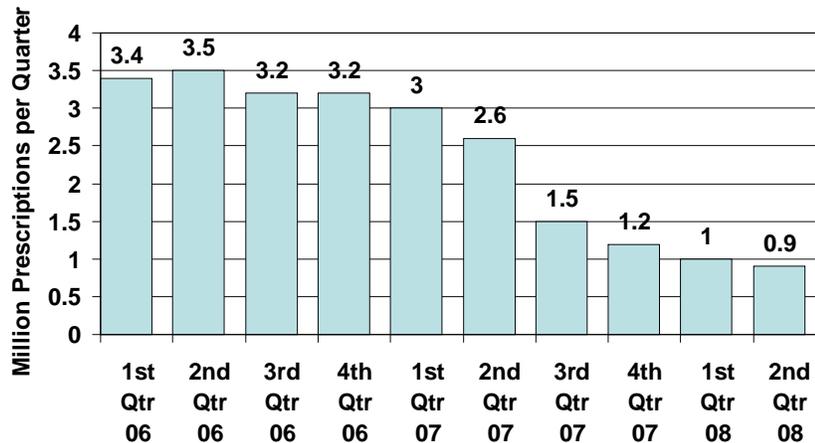
Dear Dr. Von Eschenbach:

Public Citizen, representing more than 80,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately ban the diabetes drug, Avandia (rosiglitazone; GlaxoSmithKline). Our petition is based on rosiglitazone's multiple, serious risks, including one just documented by our new analysis of 14 cases of liver failure, of which 12 resulted in death. In addition there is clear previous evidence of increased risk of heart attacks, heart failure, bone fractures, anemia and macular (retinal) edema with vision loss. The evidence for this unique combination of toxicities is compounded by the accompanying lack of evidence of any clinical benefit, compared to other approved drugs for diabetes, such as metformin, insulin and sulfonylureas. Because of a lack of evidence that benefits are outweighed by risks, both the American Diabetes Association and the European Association for the Study of Diabetes, in a statement submerged in a pre-publication consensus article on treatment of diabetes released last week, concluded that for the treatment of diabetes, "given that other [treatment] options are now recommended, the consensus group members unanimously advised against using rosiglitazone."¹

As evidence of the multiple serious side effects of rosiglitazone has mounted, there has been a sharp decrease in prescriptions for the drug, as shown on page 2 of this document. The peak number of prescriptions was in 2006, with 13.2 million prescriptions filled in the U.S. In the past full year (July 2007-June 2008), there were still 4.6 million prescriptions filled, thus exposing hundreds of thousands of people with diabetes to a drug that is clearly doing more harm than good. This means that each day, approximately 10,000 prescriptions for rosiglitazone are still being filled. Thus, it is urgent for the FDA to immediately ban rosiglitazone.

1 D. M. Nathan & J. B. Buse & M. B. Davidson & E. Ferrannini & R. R. Holman & R. Sherwin & B. Zinman. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* (released electronically 10/22/08) Statement quoted above is on p. 5. Print version: Volume 31, Number 12, December 2008. Online at: <http://care.diabetesjournals.org/cgi/reprint/dc08-9025v1>.

Quarterly Change in Avandia U.S. Prescriptions



Data from IMS; Article about increased risk of heart attacks published 5/07

History of Public Citizen Health Research Group Actions on Avandia

March 2000. Public Citizen petitioned FDA to revise the labeling for rosiglitazone and pioglitazone due to multiple safety issues including cardiac toxicity, liver toxicity, weight gain, edema, anemia, low blood pressure, elevated lipid levels and possible changes in progesterone levels.²

January 2005. In the fourth edition of our book, *Worst Pills, Best Pills*, and on our web site www.worstpills.org we urged readers not to use rosiglitazone.

July 2007. At an FDA hearing on the safety of rosiglitazone, we testified that the risks clearly outweighed the benefits and advocated removing the drug from the market.

Summary of Efficacy and Safety Data (more details and references in the latter part of the petition)

Efficacy

Our review of the published and unpublished (FDA) data revealed the following efficacy concerns:

- When studied head-to-head with metformin and glyburide, rosiglitazone is not as effective in reducing blood sugar and hemoglobin A1c.

² Health Research Petition to the FDA, March 7, 2000.

- Both hemoglobin A1c (HbA1c) and blood sugar levels deteriorate when patients on other types of oral anti-diabetic drugs are switched to rosiglitazone.
- For metformin, sulfonylureas and insulin, long-term data now show a reduction in myocardial infarction and all-cause mortality. No such data exist for rosiglitazone. Rather, it is likely that rosiglitazone increases the risk of myocardial ischemia.

Safety

Our review of the data revealed the following safety concerns:

- *Liver Failure*: Severe hepatotoxicity ultimately led to withdrawal of troglitazone from the market, first in Great Britain, then in the United States. Acute liver failure has also been reported in relation to rosiglitazone use. We have identified 14 cases of rosiglitazone-induced acute liver failure, including 12 deaths, from the FDA Adverse Event Reporting System (AERS) after careful review of MedWatch forms. Most of these cases have not been reported in the literature.
- *Myocardial Ischemia*: Three recent meta-analyses have demonstrated an increased risk of myocardial ischemia or myocardial infarction with rosiglitazone. The approximate increase in the risk of heart attacks is 40%.
- *Congestive Heart Failure*: Rosiglitazone was associated with fluid overload and heart failure in early clinical trials, and several large randomized controlled trials (RCTs) have confirmed this toxicity, which likely occurs through PPAR-mediated sodium retention. Several meta-analyses estimate the increased risk to be approximately two-fold.
- *Macular Edema*: Rosiglitazone causes a generalized edema in many patients as a result of leakage of plasma from blood into tissues. When this leakage occurs in the eye, there is damage to the retina, including the vision-critical macular portion, often causing a decrease in vision. The rate of reports to the FDA of macular edema with rosiglitazone, adjusted for the relative amounts of prescriptions, was 39 times higher than with the older diabetes drug, glipizide.
- *Anemia*: Rosiglitazone has been consistently associated with decreased hematocrit and hemoglobin in a clear, dose-related fashion, as well as with more severe cases of anemia. This is not due simply to increased plasma volume, as was proposed by the manufacturer, but likely reflects direct hematologic toxicity.
- *Fractures*: Peroxisome proliferator-activated receptor (PPAR gamma), the receptor which rosiglitazone acts upon (see below), is also expressed in bone along with many other tissues. Animal studies have shown that rosiglitazone decreases bone formation; human studies have confirmed this finding and also shown that rosiglitazone results in decreased bone mineral density as well as a doubling in the risk of bone fractures.

Description, indications, and mechanism of action

The glitazones are agonists of a member of the peroxisome proliferator-activated receptor (PPAR) family of nuclear transcription factors, particularly the gamma isoform, PPAR gamma. PPAR gamma receptors are expressed in many tissues and thus are responsible for a multitude of responses, the effects varying depending on the target tissue. When rosiglitazone binds to these receptors, they react in turn by binding to DNA, initiating gene expression. The effect exploited for diabetes treatment is to lower plasma glucose which it does, in part, by converting glucose into fat.

I. EFFICACY CONCERNS

IA. ROSIGLITAZONE IS NOT AS EFFECTIVE AS GLYBURIDE OR METFORMIN IN REDUCING HbA1c

Studies 020 and 093 are two of the five randomized controlled trials that provided the basis for approval of rosiglitazone for the treatment of Type 2 diabetes mellitus, and the only ones that involved head-to-head comparisons of rosiglitazone with active controls. In Study 020, patients were randomized to either rosiglitazone 2mg bid, rosiglitazone 4mg bid or glyburide (also known as glibenclamide) for 52 weeks of treatment. The results of this study are summarized in Figures 1 and 2.

Figure 1.

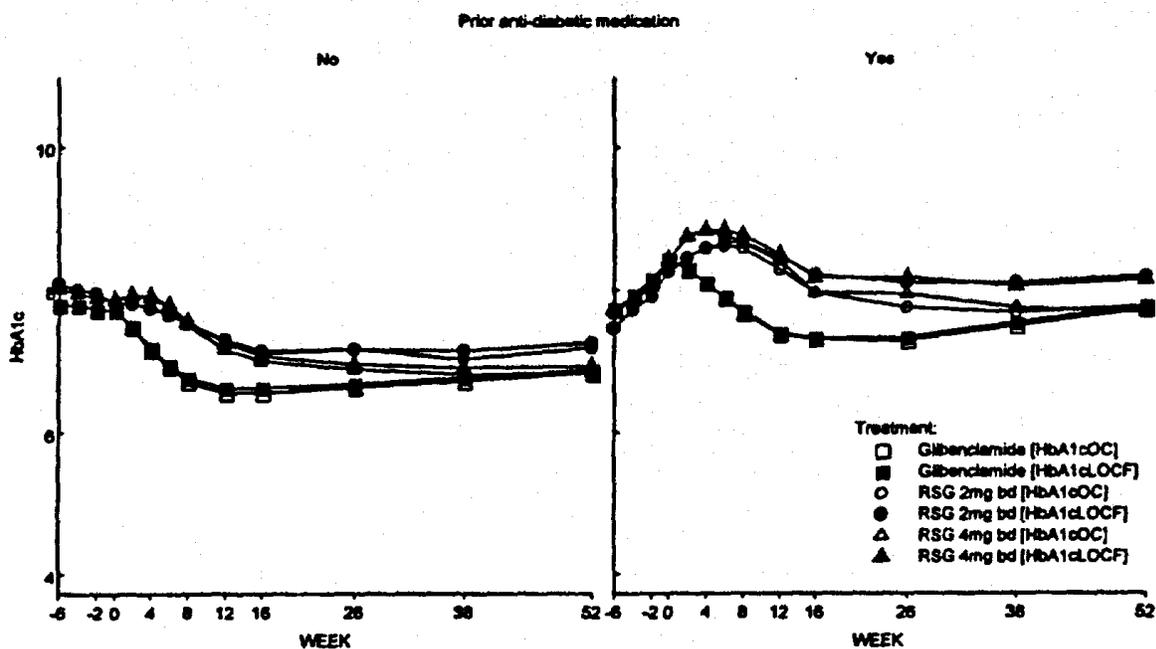


Figure 1: Study 020, HbA1c over 26 weeks of therapy, stratified by prior use of anti-diabetic medications. FDA Statistical Review of Rosiglitazone NDA; May 11, 1999; p.22.

Figure 2.

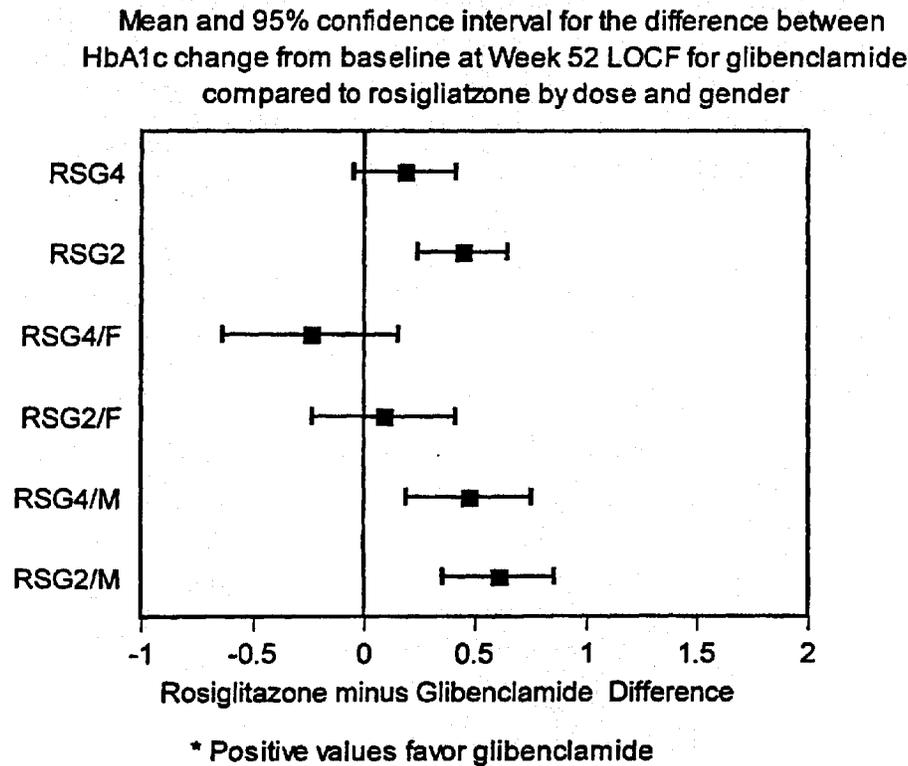


Figure 2: Study 020, rosiglitazone versus glyburide monotherapy. Statistical Review of Rosiglitazone NDA; May 11, 1999; p.24.

The Statistical Review found that “The results for the 2 mg [bid] dose are significantly worse than glibenclamide [glyburide] on the primary efficacy measure” and “The results are borderline for the RSG 4 mg BID dose compared to glibenclamide.”³ Also, the results were biased against seeing a benefit from glyburide as physicians in the study were not allowed to increase doses of glyburide after week 12, even if lack of efficacy warranted a dose increase. Furthermore, withdrawals due to lack of efficacy were much more frequent with rosiglitazone (7.9% for 4mg bid and 11.0% for 2 mg bid) than with glyburide (3.4%).⁴

In Study 093, patients were randomized to rosiglitazone 4mg bid, metformin 2.5g/day, or rosiglitazone and metformin combined. At the end of 26 weeks of therapy, HbA1c increased by 1.3% in the rosiglitazone monotherapy arm, but increased by only 0.1% in the metformin monotherapy arm, a difference that is noted as significant in the Medical Review.^{5,6} This clear difference in efficacy is displayed in Figure 3.

3 Statistical Review of Rosiglitazone NDA; May 11, 1999; p.26.

4 Medical Review of Rosiglitazone NDA; April 16, 1999; p.13.

5 Statistical Review of Rosiglitazone NDA; May 11, 1999; p.33.

6 Medical Review of Rosiglitazone NDA; April 16, 1999; p.21.

Figure 3.

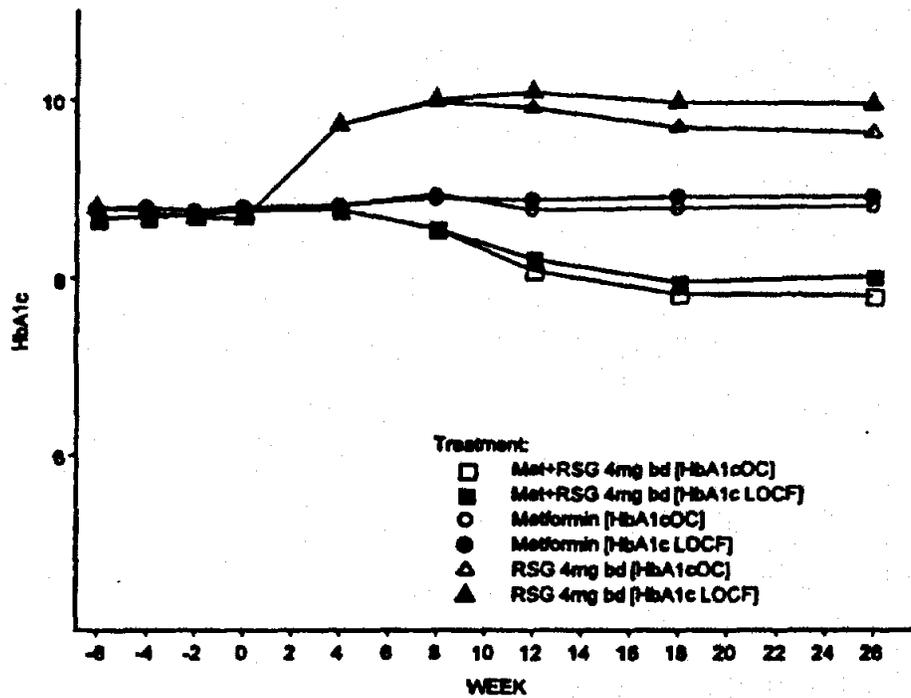


Figure 3: Study 093, HbA1c over 26 weeks of therapy. Statistical Review of Rosiglitazone NDA; May 11, 1999; p.33.

In addition to the lack of efficacy demonstrated in head-to-head comparisons, loss of glycemic control was observed in patients who switched to rosiglitazone from other therapies. In each clinical trial, the subgroup of patients who had been on prior antidiabetic treatment was displayed separately. Patients who had been on prior therapy and were then started on rosiglitazone monotherapy (Studies 011, 020, 024, and 093) either barely or never returned to baseline levels of HbA1c, as displayed in Figure 4. This suggests that changing from another agent to rosiglitazone results in deterioration of glycemic control. When taken with the head-to-head comparisons, rosiglitazone appears to be less effective than other existing therapies.

Figure 4 (A and B).

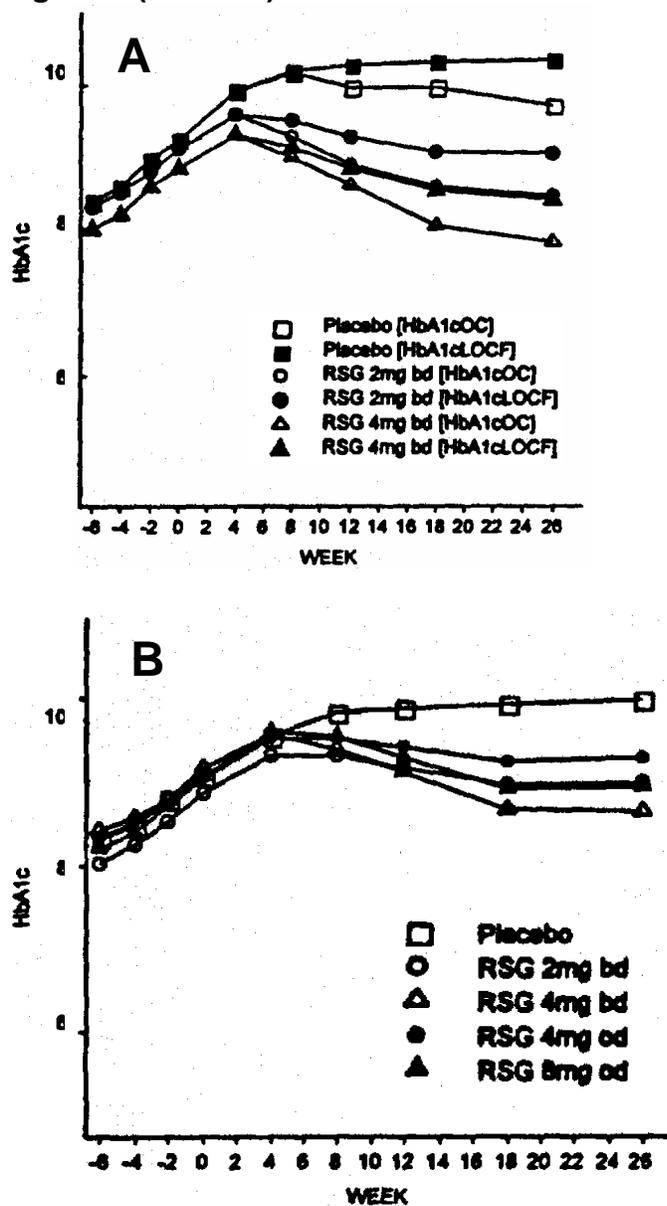


Figure 4: Subgroup of patients taking other anti-diabetic medications prior to randomization from (A) Study 011, (B) Study 024. Taken from Statistical Review of Rosiglitazone NDA; May 11, 1999; p.10, 16.

Figure 4 (C and D).

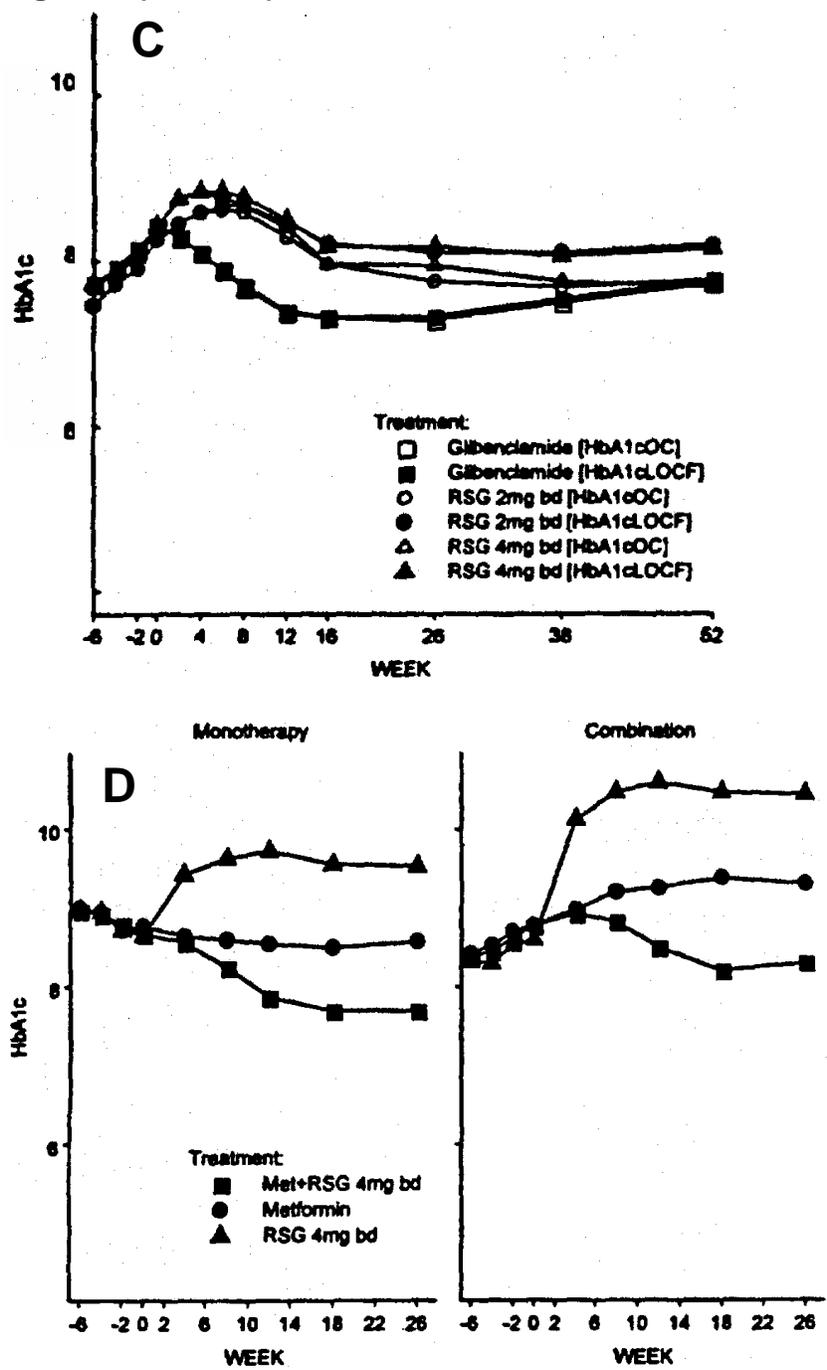


Figure 4: Subgroup of patients taking other anti-diabetic medications prior to randomization from (C) Study 020, (D) Study 093. Taken from Statistical Review of Rosiglitazone NDA; May 11, 1999; p.22, 34.

IB. UNLIKE OTHER EXISTING ORAL THERAPIES, ROSIGLITAZONE HAS NOT BEEN SHOWN TO REDUCE COMPLICATIONS OR MORTALITY FROM TYPE 2 DIABETES MELLITUS

The United Kingdom Prospective Diabetes Study (UKPDS) examined the effect of intensive therapy with a sulfonylurea, insulin or metformin versus conventional therapy with dietary restriction on clinical outcomes in newly diagnosed Type 2 diabetics. The initial findings, after 10 years of follow-up, showed a reduction in microvascular complications with sulfonylurea or insulin therapy, and a reduction of myocardial infarction and all-cause mortality with metformin.^{7,8} Additional nine-year post-trial follow-up, recently published in the *New England Journal of Medicine*, shows a clear reduction in diabetes-related endpoints, myocardial infarction and all-cause mortality in the sulfonylurea-insulin and metformin groups, despite no attempts being made to maintain previously assigned therapies.⁹ This stands in stark contrast to the case of rosiglitazone, which was approved on the basis of reductions of HbA1c and fasting plasma glucose, rather than improvement in any meaningful clinical outcomes. It has been over nine years since the initial approval of rosiglitazone for the treatment of Type 2 diabetes mellitus, and there remains a complete absence of data showing improvement in clinically meaningful diabetes-related outcomes.¹⁰ Furthermore, there is concern that treatment with rosiglitazone actually confers an increased risk of myocardial infarction, as described in Section IIB.

II. SAFETY CONCERNS

IIA. LIVER TOXICITY (Human Data)

Troglitazone, a thiozolidinedione similar in structure to rosiglitazone, was approved for marketing by the FDA in March 1997, but was withdrawn from the market in March 2000 after 94 cases of troglitazone-induced liver failure, the majority of which were fatal, were reported.¹¹ Although the premarketing signal for hepatotoxicity with rosiglitazone was not as strong as the signal with troglitazone, one of the most hepatotoxic drugs ever approved by the FDA, several cases of rosiglitazone-induced hepatotoxicity have been reported in the literature, and many more via the FDA Adverse Event Reporting System (AERS).^{12, 13, 14, 15, 16, 17, , 18, 19}

7 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998 Sep 12;352(9131):837-53.

8 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998 Sep 12;352(9131):854-65.

9 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008 Oct 9;359(15):1577-89.

10 Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Jul 18;(3):CD006063.

11 Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. *Am J Med*. 2003 Mar;114(4):299-306.

12 Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. *Ann Intern*

We performed a query of the FDA AERS using the preferred term “hepatic failure” to find cases of rosiglitazone-induced liver failure reported from 1997 through 2006. We requested and received MedWatch forms from the FDA for all 135 cases, and performed a detailed review of each case to determine which ones represented drug-induced liver failure. After excluding five duplicates, 74 further cases were excluded because they included either (1) too little data on clinical course and laboratory tests to determine if liver failure was present, or (2) too little data on exclusion of other etiologies to assess likelihood of rosiglitazone as the etiology of liver injury. Of the remaining 56 cases, 30 met our definition for liver failure – liver injury accompanied by hepatic encephalopathy, liver transplantation, placement on liver transplant list or death. Of these 30 cases, 14 met our case definition of rosiglitazone-induced liver failure, defined as liver failure that was preceded by the administration of rosiglitazone, with other etiologies (such as viral hepatitis, ischemia, malignancy, obstruction or other likely toxins including drugs) excluded. Cases were described as acute if progression from initial symptoms to liver failure occurred within 26 weeks.

The 14 cases are listed in Table 1, and descriptive statistics in Table 2. Three of these cases have been described in the literature previously. The case-fatality rate was very high (86%), similar to that of troglitazone-induced liver failure (77%). In most cases, fulminant liver failure developed rapidly after the onset of symptoms and did not reverse with discontinuation of rosiglitazone. Of note, many of these patients had received some monitoring of liver-function tests shortly after starting therapy with rosiglitazone, and these were usually found to be either normal or only mildly elevated.

Med 2000;132:118-21

13 Al-Salman J, Arjomand H, Kemp DG, Mittal M. Hepatocellular injury in a patient receiving rosiglitazone: a case report. *Ann Intern Med* 2000;132:121-4.

14 Dhawan M, Agrawal R, Ravi J, Gulati S, Silverman J, Nathan G, et al. Rosiglitazone-induced granulomatous hepatitis. *J Clin Gastroenterol* 2002;34:582-4.

15 Ravinuthala RS, Nori U. Rosiglitazone toxicity (letter). *Ann Intern Med* 2000;133:658.

16 Gouda HE, Khan A, Schwartz J, Cohen RI. Liver failure in a patient treated with long-term rosiglitazone therapy. *Am J Med* 2001;111:584-5.

17 Bonkovsky HL, Azar R, Bird S, Szabo G, Banner B. Severe cholestatic hepatitis caused by thiazolidinediones: risks associated with substituting rosiglitazone for troglitazone. *Dig Dis Sci* 2002;7:1632-7.

18 Su DH, Lai MY, Wu HP. Liver failure in a patient receiving rosiglitazone therapy. *Diabet Med*. 2006 Jan;23(1):105-6.

19 El-Naggar MH, Helmy A, Moawad M, Al-Omary M, Al-Kadhi Y, Habib B. Late-onset rosiglitazone-associated acute liver failure in a patient with Hodgkin's lymphoma. *Ann Pharmacother*. 2008 May;42(5):713-8.

Table 1.

Age/ Gender	Duration of therapy (weeks)	Acute	Outcome	Pathology
46F	8	Yes	Death	Submassive necrosis, periportal inflammation, cholestasis
48M	15	Yes	Death	Acute hepatitis with necrosis, eosinophils, cholestasis
60M			Death	None
60F	6	Yes	Transplant	Extensive hepatocellular necrosis, inflammatory infiltrate ²⁰
64M	0.5	Yes	Death	Extensive necrosis
71F	225		Death	Complete necrosis, Periportal inflammation with eos
80F	8	Yes	Recovery	None
82M	52	Yes	Death	Acute inflammation with necrosis, granulomas, eos ²¹
57F	7	No	Transplant, death	Mild chronic portal inflammation, fibrosis
70M	4	Yes	Death	Acute necrosis, marked cholestasis
70M	6	Yes	Death	None
72M	58	No	Death	Massive necrosis with collapse of architecture, cirrhosis
73M			Death	None
52M	47	Yes	Death	Cholestasis, no inflammation ²²

Table 1: 14 cases of rosiglitazone-induced liver failure reported to the FDA AERS from 1997 to 2006. Three cases have been described in the literature.

20 Kessler W, Johnson B, Yoo H. Acute fulminant hepatic failure associated with the use of rosiglitazone. Am J Gastro 2003;98:S212.

21 Gouda HE, Khan A, Schwartz J, Cohen RI. Liver failure in a patient treated with long-term rosiglitazone therapy. Am J Med 2001;111:584-5.

22 El-Naggar MH, Helmy A, Moawad M, Al-Omary M, Al-Kadhi Y, Habib B. Late-onset rosiglitazone-associated acute liver failure in a patient with Hodgkin's lymphoma. Ann Pharmacother. 2008 May;42(5):713-8.

Table 2.

Age	67 [57-72]
Male	9/14 (64%)
Duration of treatment, weeks	8 [6-50], n=12
Jaundice	13/13 (100%)
Encephalopathy	12/12 (100%)
Aspartate aminotransferase	906 [131-3741], n=13
Alanine aminotransferase	961 [111-3295]
Alkaline phosphatase	291 [205-522], n=12
Total bilirubin	4.1 [2.1-8.8], n=12
Pathology available	10/14 (71%)
Necrosis	8/10 (80%)
Inflammation	6/10 (60%)
Cholestasis	4/10 (40%)
Fibrosis	2/10 (20%)
History of alcohol use	0/9 (0%)
History of chronic liver disease	0/5 (0%)
Acute	9/11 (82%)
Death	12/14 (86%)
Transplant	2/14 (14%)*
Spontaneous Recovery	1/14 (7%)

Table 2: Descriptive statistics on 14 cases of rosiglitazone-induced liver failure reported to the FDA AERS from 1997 to 2006. Continuous variables are reported as median [interquartile range] due to small sample size. Because data were unavailable for some patients, the denominators are listed. Maximum recorded laboratory values were used for each patient. For several cases, lab values were reported only at time of initial presentation, not at peak of liver injury.

**One of two transplanted patients died*

LIVER TOXICITY (Animal Data)

Liver toxicity was seen in rats, mice and dogs. Liver weights were increased significantly in a both six-month rat and six-month dog studies in both males and females.

Accompanying these liver weight increases in dogs (which are usually a good predictive model for people), the pharmacology reviewer stated that, “There were marked increases in alanine aminotransaminase (ALT) in all high dose animals.” In addition, alkaline phosphatase, aspartate aminotransaminase (AST), lactic dehydrogenase (LDH) and bilirubin were also elevated in high dose males. AST and ALT both increased as a function of the length of time animals were exposed to drug (ALT was increased 220x, 620x, and 1,200x at weeks 5, 12, and 17, respectively).

Demonstrating increased toxicity with more exposure, in a longer (12-month) dog study, there were statistically significant increases in mean ALT for males beginning as low as two times the human exposure (61% at 2x and 83% at 20x).²³ In mice, there was hepatocellular vacuolation in after two years at a dose equivalent to less than four times the human exposure, a very low margin of safety.

IIB. CARDIAC TOXICITY: MYOCARDIAL INFARCTION (Human Data)

Several recent studies have suggested an increased risk of myocardial infarction with rosiglitazone, and were the subject of a July 30, 2007, FDA Advisory Committee meeting. They will be summarized briefly here.

Nissen and Wolski published a meta-analysis of 42 clinical trials in the *New England Journal of Medicine* in June 2007 that showed an increased risk of myocardial infarction (OR 1.43, 95% CI 1.03-1.98) and death from cardiovascular causes (OR 1.43, 95% CI 0.98-2.74) due to rosiglitazone.²⁴ The studies included were of at least 24 weeks duration, and included 15,565 patients on rosiglitazone and 12,282 on placebo or active control, including patients in the DREAM and ADOPT clinical trials. One major weakness of this meta-analysis was that it used study-level data, rather than patient-level data.

A meta-analysis conducted by GlaxoSmithKline (GSK) in 2005, but not released to the public until 2007, also demonstrated an increased risk of myocardial ischemia (HR 1.31, 95% CI 1.01-1.70).²⁵ Although this analysis did not include data from the DREAM and ADOPT studies, it was a patient-level analysis that included time-to-event data on 8,604 patients on rosiglitazone and 5,633 on placebo or active control.

The FDA conducted its own meta-analysis based on concerns raised from the GSK analysis, which confirmed an increased risk of myocardial ischemia (OR 1.4, 95% CO 1.1-1.8) but did not find an increase in cardiovascular death. This analysis also included patient-level data, but in contrast to the GSK analysis, data were not pooled, in order to preserve randomization of groups.²⁶

Most of the studies included in these meta-analyses were of short-duration, and thus not ideal for evaluating cardiovascular events, which typically arise as a long-term complication of diabetes. Also, cardiovascular outcomes were not monitored or adjudicated consistently in most studies. To address these deficiencies, Singh et al performed a meta-analysis to evaluate the risk of cardiovascular events, limited to trials

23 Pharmacology Review. http://www.fda.gov/cder/foi/nda/99/21071_Avandia_pharmr_P1.pdf. p.22.

24 Nissen, SE, Wolski, K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Engl J Med* 2007; 356:2457.

25 GlaxoSmithKline. Study no. ZM2005/00181/01: Avandia Cardiovascular Event Modeling Project. (Conducted 2005, Accessed September 22, 2008, at http://ctr.gsk.co.uk/summary/Rosiglitazone/III_CVmodeling.pdf).

26 FDA meta-analysis, July 3, 2007. <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf>.

of at least 12 months duration that specifically monitored cardiovascular events. This study-level analysis, which included the ADOPT, DREAM and RECORD trials, showed an elevated risk of myocardial infarction due to rosiglitazone (RR 1.42, 95% CI 1.06-1.91), but not an increase in cardiovascular mortality (Figure 5).²⁷

Figure 5.

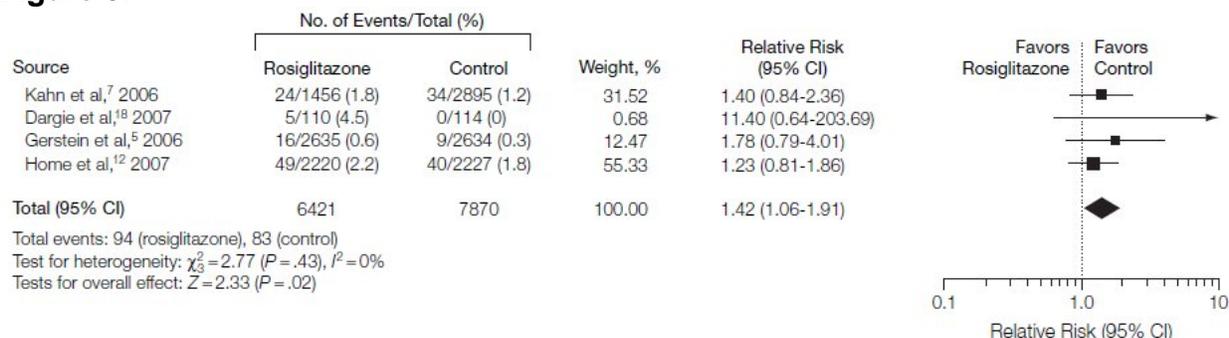


Figure 5: Estimate for myocardial infarction risk due to rosiglitazone based on four long-term RCTs with monitoring of cardiovascular outcomes, taken from meta-analysis by Singh et al (Singh S, Loke YK, Furberg CB. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007; 298:1192).

Taken together, these studies strongly suggest that rosiglitazone poses an increased risk of myocardial ischemia. The absence of a consistent finding of increased cardiovascular mortality most likely reflects the small number of outcomes in controlled studies and large confidence intervals. To date, no large randomized controlled trials have provided evidence that argues against an increased risk of myocardial ischemic or cardiovascular complications, and it is unlikely that ongoing studies will definitely answer this question, as they are underpowered to detect clinical outcomes of interest.

IIC. CARDIAC TOXICITY: HEART FAILURE (Human Data)

At the time of initial FDA approval in 1999, it was known that rosiglitazone caused edema and weight gain. It was later demonstrated in several controlled studies that rosiglitazone precipitates and worsens congestive heart failure. The meta-analysis performed by Singh et al to evaluate the long-term risk of cardiovascular events due to rosiglitazone, which included 14,291 patients, put the relative risk for heart failure at 2.1 (95% CI 1.5-2.9, Figure 6). A similar meta-analysis performed by Lago et al, which included 14,491 patients, produced a relative risk estimate of heart failure of 2.2 (95% CI 1.4-3.3).²⁸

27 Singh S, Loke YK, Furberg CB. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007; 298:1189.

28 Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007;370(9593):1129-36.

Figure 6.

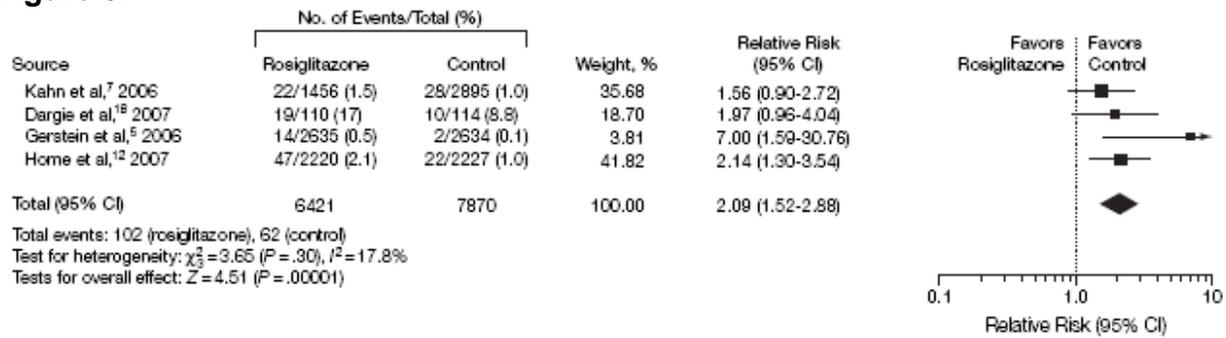


Figure 6: Estimate for heart failure due to rosiglitazone based on four long-term RCTs with monitoring of cardiovascular outcomes, taken from meta-analysis by Singh et al (Singh S, Loke YK, Furberg CB. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007; 298:1192).

The development of heart failure appears to occur through increased plasma volume, as a result of activation of PPAR gamma dependent sodium channels in the collecting ducts.²⁹ Although pre-existing left ventricular dysfunction may have been present in most patients who developed symptomatic heart failure while on rosiglitazone, a higher incidence of heart failure was also noted in the DREAM study, which included patients without diabetes, and in patients without risk factors for heart failure.^{30,31}

IID. MACULAR EDEMA (Human Data)

A meta-analysis of thiazolidinediones and edema found that rosiglitazone and pioglitazone caused a two-fold increase in peripheral edema in type 2 diabetic patients, the risk being greater with rosiglitazone. The authors hypothesized that upregulation of sodium transporters in the nephron caused sodium retention and edema.³²

Peripheral edema has occurred in 5-7% of patients taking glitazones,³³ which can cause or aggravate diabetic macular edema. Three individual cases have been reported in the literature plus a group of 11 from a retrospective analysis.^{34,35,36,37} A warning letter to

29 Zhang H, Zhang A, Kohan DE, Nelson RD, Gonzalez FJ, Yang T. Collecting duct-specific deletion of peroxisome proliferator-activated receptor gamma blocks thiazolidinedione-induced fluid retention. Proc Natl Acad Sci U S A. 2005 Jun 28;102(26):9406-11.

30 DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet. 2006 Sep 23;368(9541):1096-105. Erratum in: Lancet. 2006 Nov 18;368(9549):1770.

31 Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. Diabetes Care. 2007;30(8):2148-53.

32 Berlie HD, Kalus JS, Jaber LA. Thiazolidinediones and the risk of edema: a meta-analysis. Diabetes Research and Clinical Practice 2007;76:279-289.

33 Niemeyer NC, Janney LM. Thiazolidinedione-induced edema. Pharmacotherapy 2002;22:924-929.

34 Colucciolo M. Vision loss due to macular edema induced by rosiglitazone treatment of diabetes mellitus. Arch Ophthalmol. 2005;123:1273-5.

35 Kendall C, Woollorton E. Rosiglitazone (Avandia) and macular edema. CMAJ 2006;174:623.

36 Liazos E, Broadbent DM, Beare N, et al. Spontaneous resolution of diabetic macular oedema after

French physicians from GlaxoSmithKline reported 28 cases of new or worsening of pre-existing macular edema in patients taking rosiglitazone, all in North America. Of these, 22 cases were well documented. "Some" improved or recovered with withdrawal or reduction of dose.³⁸

Our own analysis of the FDA's Adverse Event Reporting System (AERS) database from 2000 through the end of 2007 for rosiglitazone revealed 116 cases of macular edema, with 22 of those resulting in an outcome of "disability." During the same time period, there were only two cases of macular edema with the older diabetes drug glipizide. Adjusted for the number of prescriptions filled for both drugs, the rate of reports to the FDA of macular edema per million prescriptions for rosiglitazone was 39 times higher than for glipizide.

IIE. ANEMIA (Human Data)

Rosiglitazone has consistently been shown to cause anemia, both in animal and human studies. This dose-related toxicity was present in monotherapy and combination therapy trials, as displayed in Figure 7, taken from the Statistical Review of the rosiglitazone New Drug Application. Also, the Medical Reviewer noted 13 withdrawals and four hematological SAEs (including one unrelated to the drug) in the premarketing clinical trials.³⁹

discontinuation of thiazolidinediones. *Diabet Med.* 2008;25:860-2.

37 Ryan EH Jr, Han DP, Ramsay RC, et al. Diabetic macular edema associated with glitazone use. *Retina* 2006;26:562-70.

38 Glitazones and macular oedema. *Prescrire International* 2006;15:139.

39 Medical Review of Rosiglitazone NDA; April 6, 1999;

http://www.fda.gov/cder/foi/nda/99/21071_Avandia_medr.pdf. p.35.

Figure 7 (A and B).

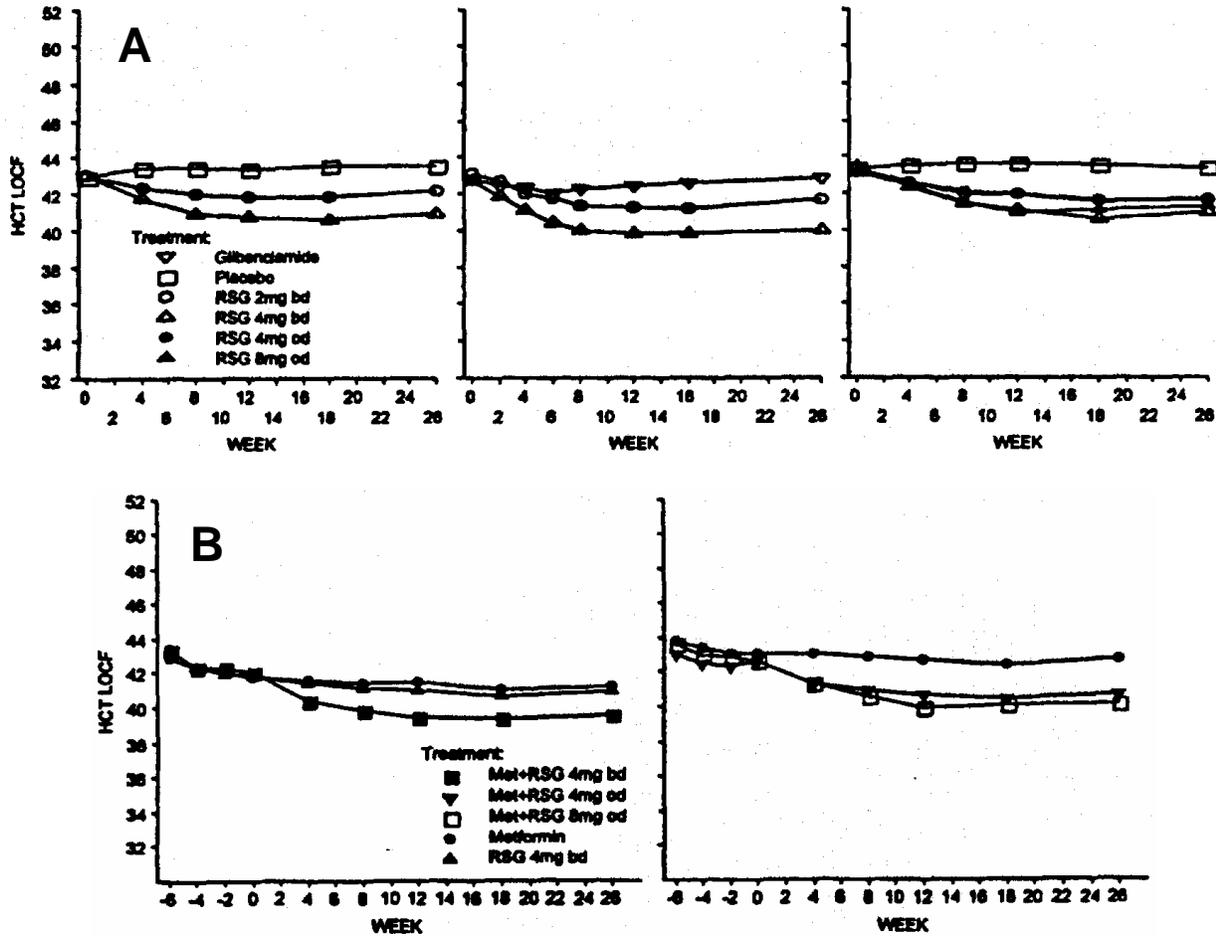


Figure 7: Hematocrit in premarketing clinical trials of rosiglitazone: (A) Monotherapy studies, (B) Combination therapy studies. RSG = rosiglitazone, HCT = hematocrit. Statistical Review of Rosiglitazone NDA; May 11, 1999; p.52.

More recently, the Cochrane Review on rosiglitazone, which included clinical trials published as recently as 2007, reported a reduction in hemoglobin of between 0.5 and 1.0g/dL due to rosiglitazone.⁴⁰ Even the prescribing information for rosiglitazone, under the section “Laboratory Abnormalities,” notes that “Decreases in mean hemoglobin and hematocrit occurred in a dose-related fashion in adult patient treated with AVANDIA (mean decreases in individual studies as much as 1.0 g/dL hemoglobin and as much as 3.3% hematocrit).”⁴¹

The manufacturer has proposed that “Decreases in hematologic parameters may be related to increased plasma volume observed with treatment with AVANDIA

40 Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD006063.

41 Prescribing information, rosiglitazone. Dated July 2008, Accessed September 22, 2008.

[rosiglitazone],” without any evidence to support this assertion.”⁴² A placebo-controlled study of pioglitazone, in which blood counts and total body water were measured serially in 50 patients, demonstrated a reduction in hemoglobin and hematocrit due to pioglitazone without a corresponding change in total body water.⁴³ Pioglitazone is a thiazolidinedione similar in structure and function to rosiglitazone, which exerts a similar effect on blood counts, likely through the same mechanism of action.

ANEMIA (Animal Data)

Data from both six-month rat and six-month dog studies showed “progressive reduction in hemoglobin, packed cell volume and red blood cell counts” in both sexes at the high dose. In the rat study, mean platelet counts were also reduced in both sexes at the high dose and in females at an even lower dose with an exposure equivalent to humans taking the 8 mg/day dose.⁴⁴

IIF. FRACTURES (Human Data)

There is growing evidence that rosiglitazone, and thiazolidinediones as a class, causes fractures. An increase in fracture risk in humans was first reported in the ADOPT study, a randomized controlled trial that lasted almost four years in which rosiglitazone was compared to other oral antidiabetic treatments. In this clinical trial, the hazard ratio for fracture due to rosiglitazone was 1.8 (95% CI 1.2-2.8) compared to metformin, and 2.1 (95% CI 1.3-3.5) compared to glyburide (Figure 8).^{45,46}

42 Ibid.

43 Berria R, Glass L, Mahankali A, Miyazaki Y, Monroy A, De Filippis E, Cusi K, Cersosimo E, Defronzo RA, Gastaldelli A. Reduction in hematocrit and hemoglobin following pioglitazone treatment is not hemodilutional in Type II diabetes mellitus. *Clin Pharmacol Ther.* 2007 Sep;82(3):275-81.

44 Pharmacology NDA review May 11, 1999;

http://www.fda.gov/cder/foi/nda/99/21071_Avandia_pharmr_P1.pdf. pp. 16 & 19.

45 Kahn, SE, Haffner, SM, Heise, MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; 355:2427.

46 Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, Kravitz BG, Yu D, Heise MA, Aftring RP, Viberti G; Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care.* 2008 May;31(5):845-51.

Figure 8.

	Rosiglitazone	Metformin	Glyburide
	<i>number of patients (percent)</i>		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* P<0.01 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).
† P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

Figure 8: Fracture risk in ADOPT study. Kahn, SE, Haffner, SM, Heise, MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006; 355:2427

Supporting this finding of increased fracture risk, two observational studies have shown that rosiglitazone is also associated with accelerated bone loss, as measured by bone densitometry. The HealthABC study was a prospective cohort study of diabetics over the age of 70, and demonstrated that thiazolidinedione use was associated with an additional 0.61% loss of whole body bone mineral density per year in women.⁴⁷ Another, smaller observational study in men showed that rosiglitazone was associated with an additional 1.1% decrease in hip bone mineral density per year.⁴⁸ Finally, a randomized controlled trial of 50 patients conducted specifically to examine the effect of rosiglitazone on bone formation showed that it was associated with decreased osteoblastic activity (decreased bone formation) as well as decreased bone mineral density.⁴⁹

The increase in fracture risk comes in addition to an inherent increased risk for fractures in older white and black adults with diabetes.⁵⁰

FRACTURES (Animal Data)

47 Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, Strotmeyer ES, Resnick HE, Carbone L, Beamer BA, Park SW, Lane NE, Harris TB, Cummings SR. Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab.* 2006 Sep;91(9):3349-54.

48 Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. *Diabetes Care.* 2007 Jun;30(6):1574-6. Epub 2007 Mar 15.

49 Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, Reid IR. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. *J Clin Endocrinol Metab.* 2007 Apr;92(4):1305-10.

50 Strotmeyer ES, Cauley JA, Scharz AV, et al. Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults. *Arch intern med* 2005;165:1612-1617.

In vitro and animal studies have shown that PPAR gamma is expressed in osteoblasts and osteoclast precursors, promoting adipogenesis (the formation of fat cells) at the expense of osteoblastogenesis (cells which are responsible for bone formation). The mechanism appears to involve the diversion of mesenchymal stem cells in the bone marrow from their role as bone forming cells to fat cells. Several studies of thiazolidinediones in animals have demonstrated skeletal adverse effects. Overall, the animal studies suggest that PPAR gamma signaling results in decreased bone mass from impaired bone formation, and this has been confirmed in the clinical studies described above.⁵¹

SUMMARY

The FDA is in possession of clear, unequivocal evidence that rosiglitazone causes a wide variety of toxicities. Many of these are life-threatening, such as heart attacks, heart failure, liver failure and, in addition, there are other toxicities which greatly harm the health of diabetics using this drug. These other toxicities include increased bone fractures, impairment of vision, anemia and edema.

Unlike older treatments for diabetes which actually lessen the risk of heart attacks and all-cause mortality, such as metformin, the sulfonylurea drugs (such as glipizide) and insulin, rosiglitazone increases cardiovascular outcomes such as heart attacks and heart failure.

The recent decrease in prescribing of rosiglitazone still leaves hundreds of thousands of people using this dangerous drug, thereby harming their health and increasing their risk of dying prematurely.

In an unusual move, the American Diabetes Association and the European Association for the Study of Diabetes have concluded that for the treatment of diabetes, "given that other [treatment] options are now recommended, the consensus group members unanimously advised against using rosiglitazone."

The FDA has more than adequate legal authority to immediately start the process of removing this drug from the market in the U.S. Failure to do so will represent a dangerous dereliction of the agency's responsibility as part of the Public Health Service.

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

51 Grey A. Thiazolidinedione-induced skeletal fragility - mechanisms and implications. *Diabetes Obes Metab.* 2008 Jul 29.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Elizabeth Barbehenn, Ph.D., Pharmacologist

James Floyd, M.D., Staff Researcher

Sidney Wolfe M.D.,

Director, Public Citizen's Health Research Group