Memorandum

Date: 12 September 2010

To: Janet Woodcock, MD

From: Gerald J. Dal Pan, MD, MHS

Re: Recommendations for Regulatory Action for Rosiglitazone and Rosiglitazone-containing Products (NDA 21-071, supplement 035, incoming submission dated August 25, 2009)

This memorandum serves as my recommendation to the CDER Center Director for the regulatory actions to be taken regarding rosiglitazone and rosiglitazone-containing products.[1] I have previously documented my review of the available evidence in both October 2007 [2] and October 2009.[3] Thus, in this memo, I will focus only on a brief review of the new evidence and on my recommendations.

Prior Recommendations

In October 2007, and again in October 2009, I wrote memoranda in which I recommended that rosiglitazone be removed from the market. The rationale for that recommendation is stated in those memoranda. In brief, I concluded that the available clinical trial data generated a substantial signal of a serious risk of myocardial ischemia, and that the observational studies strengthened this signal. Though the data did not provide definitive proof of a risk of myocardial ischemia, I argued that the seriousness of the risk and its public health implications outweighed the uncertainty that the risk is not real. I also expressed concern that the RECORD study,[4] whose final results had been published but were still under internal review at FDA, would not provide sufficient evidence to mitigate concerns over the risk of myocardial ischemia.

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[1] Rosiglitazone is a thiazolidinedione oral antidiabetic agent present in three marketed products: Avandia (rosiglitazone maleate), Avandamet (metformin hydrochloride; rosiglitazone maleate), and Avandaryl (glimepiride; rosiglitazone maleate). The conclusions and recommendations in this document apply to all rosiglitazone-containing products.

[2] Dal Pan, G. Office Director Memorandum for Drug Safety Board Meeting. RCM #2006-331; Review date September 27, 2007.

[3] Dal Pan, G. NDA 21-071/S-022; a) Office Director Memorandum b) Response to Request for Consultation from Office of Regulatory Policy Regarding Citizen Petition (Docket FDA 2008-P-0580). Review date October 23, 2009.

[4] Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009 Jun 20; 373(9681):2125-35.

Recent Activities and Review of New Data

Since I wrote the October 2009 memorandum, FDA has engaged in a number of activities to understand further the cardiovascular risks of rosiglitazone, with particular attention to the risk of myocardial ischemia. These include:

a) reviewing the RECORD clinical trial in detail;
b) completing updated, separate meta-analyses of randomized controlled clinical trials of rosiglitazone and pioglitazone;
c) conducting a systematic review of published observational studies of rosiglitazone and pioglitazone that addressed relevant cardiovascular outcomes;
d) performing an observational study using CMS data comparing cardiovascular outcomes in persons age 65 and older taking rosiglitazone to those in persons age 65 and older taking pioglitazone; and
e) examining some *post hoc* analyses examining cardiovascular outcomes in rosiglitazone-treated patients in two clinical trials (BARI-2D and VADT) that were not designed specifically to address these questions.

The RECORD Study

RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) was a multi-center, randomized, open-label study comparing rosiglitazone in combination with either metformin or a sulfonylurea to the combination of metformin and a sulfonylurea in patients with type 2 diabetes. Patients on background metformin who were inadequately treated were randomized to receive, in addition to metformin, rosiglitazone or a sulfonylurea in a 1:1 ratio. Patients on background sulfonylurea who were inadequately treated were randomized to receive, in addition to the sulfonylurea, rosiglitazone or metformin in a 1:1 ratio. The primary objective of RECORD was to compare the time to experiencing the primary combined endpoint of cardiovascular death and/or cardiovascular hospitalization between the rosiglitazone-containing treatment groups and the non-rosiglitazone-containing treatment group. Secondary efficacy endpoints included: all-cause mortality; definite heart failure; microvascular endpoints and combined cardiovascular hospitalizations or cardiovascular death endpoint plus microvascular endpoints. This trial was designed as a non-inferiority study with the objective of showing that rosiglitazone-containing treatment is non-inferior to the non-rosiglitazone treatment if the upper limit of the 95% CI for the hazard ratio was below 1.20. An interim analysis of RECORD was published in 2007,[5] and the final results were published in 2009.[6]

[5] Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones JP, et al, for the RECORD study group. Rosiglitazone Evaluated for Cardiovascular Outcomes - an interim analysis. N Engl J Med 2007; 357(1):28-38.
[6] Home PD, et al for the RECORD Study Team. Lancet. 2009; op.cit.

While results of the RECORD study met the protocol-specified criterion of non-inferiority (HR 0.99, 95% CI 0.85–1.16) for the primary endpoint, the point estimate for myocardial infarction, although not statistically significant, was greater than one (HR 1.14, 95% CI 0.80–1.63). My previous review of rosiglitazone noted several issues with the design of the RECORD clinical trial, including the open-label design, which could compromise objective end-point ascertainment as well as overall adverse event reporting. The Office of New Drugs[7,8,9] (OND) and the Office of Biostatistics[10] have completed several reviews of the RECORD trial. Medical reviewers across OND appear to differ in their interpretation of the RECORD trial. Nonetheless, it appears that many OND staff share the view that certain design and conduct features of RECORD do not render the study adequate to support a conclusion that rosiglitazone does not increase the risk of myocardial ischemia relative to other non-thiazolidinedione oral anti-diabetic treatments. RECORD also found that heart failure occurs more commonly with rosiglitazone than with the other non-thiazolidinedione oral anti-diabetic agents, a finding that is consistent with the known, labeled toxicity of rosiglitazone. (RECORD did not include pioglitazone, which is also associated with heart failure). Because of the concerns I previously raised about the RECORD trial, and based on the OND reviews of the final RECORD data, I conclude that the RECORD study does not provide meaningful information about the risk of myocardial ischemia with rosiglitazone. Thus, the RECORD study does not change my previous view of rosiglitazone.

Meta-analysis of Controlled Clinical Trials

The most recent meta-analyses of controlled clinical trials of rosiglitazone and pioglitazone are those conducted by CDER's Office of Biostatistics and presented at the July 2010 Advisory Committee meeting.[11] Separate meta-analyses of 52 rosiglitazone controlled clinical trials and of 29 pioglitazone controlled clinical trials were performed to examine the association of these medicines with adverse cardiovascular outcomes. These analyses found that rosiglitazone had a higher risk of myocardial infarction than comparator (OR=1.80, 95% CI: 1.03, 3.25) and a nearly statistically significant increase for MACE[12] versus comparator (OR=1.44, 95% CI: 0.95, 2.20). For pioglitazone, the odds ratio for MACE was less than one and not statistically significant (OR=0.83, 95% CI: 0.56, 1.21). In placebo-controlled trials, rosiglitazone had a higher estimated odds ratio for MACE (OR=1.53, 95% CI: 0.94, 2.54) than pioglitazone (OR=0.56, 95% CI: 0.18, 1.67). This difference was attenuated in active-controlled trials, for which the

[7] Marciniak TA. Cardiovascular events in RECORD, NDA 21-021/S-035, June 14, 2010
[8] Unger EF. Memorandum to the file. June 15, 2010.
[9] Mahoney KM. Preliminary Endocrine Medical Officer Review of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) Trial, and Update on Cardiovascular Safety Information from Large Clinical Trials of Rosiglitazone. June 9, 2010.
[10] Hoberman D. Statistical Review and Evaluation.
[11] Briefing Information for the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm.
[12] MACE refers to "major adverse cardiovascular event", defined as cardiovascular death, stroke, or myocardial infarction.

estimated odds ratios for MACE were 1.05 (95% CI: 0.48, 2.34) for rosiglitazone and 0.88 (95% CI: 0.58, 1.34) for pioglitazone. Both drugs showed an increased risk of heart failure, a known complication of treatment with thiazolidinediones. The biostatisticians who performed these meta-analyses appropriately noted that differences in trial characteristics and study populations between the two meta-analyses limit the ability to make direct cross-drug comparisons. I note, however, that these new meta-analyses, like the multiple meta-analyses that preceded them, continue to provide a strong signal that rosiglitazone, but not pioglitazone, is associated with myocardial ischemia.

In both the rosiglitazone and pioglitazone meta-analyses, the majority of trials were six months or shorter in duration. For rosiglitazone, 70% of rosiglitazone-treated patients in the meta-analysis were in trials of six months duration or less, while in the pioglitazone meta-analysis, 49% of the pioglitazone-treated patents were in trials of six months duration or less. The reason for a clearer signal of the risk of myocardial ischemia for rosiglitazone in studies of six-months duration or less than in long-term studies is not clear. One possibility is that it may relate to individual patient factors, such that individuals who are susceptible to the adverse cardiovascular effects of rosiglitazone experience those effects within six months of treatment initiation, and those who continue in clinical trials for longer than six months are not susceptible and will not experience the adverse cardiovascular effects of the drug. If this is the case, this may explain the stronger signal for myocardial ischemia in short-term (i.e., six-month duration or less) clinical trials.

While some have argued that data from long-term clinical trials are more relevant than data from short-term clinical trials in assessing the cardiovascular risks of anti-diabetic agents, drug utilization patterns suggest that short term data are, in fact, relevant. In my 2009 memorandum, I noted that drug utilization data for rosiglitazone suggest that six months after initiation of treatment, 40% of patients on rosiglitazone monotherapy are no longer taking the drug, 35% of patients on rosiglitazone in combination with either metformin or a sulfonylurea are no longer taking the combination, and 35% of patients on rosiglitazone and insulin are no longer on the combination.[13] Data from the recently conducted observational study[14] using CMS data, which compared the cardiovascular adverse effects of rosiglitazone to pioglitazone, confirm these findings. Six months after initiation of treatment with a thiazolidinedione, 28.5% of rosiglitazone-treated patients are still on the medication and 29.9% of pioglitazone-treated patients are still on the medication. This pattern is similar to that seen with other medications intended for chronic conditions, such as hypertension[15] and hypercholesterolemia,[16] which are often

[13] i3 drug safety. Additional analyses for the study "Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents". July 19, 2007. This analysis was requested by FDA upon its review of the study report "Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents". that GSK submitted to FDA.

[14] Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, Worrall C, Kelman JA. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA. 2010 Jul 28;304(4):411-8. Epub 2010 Jun 28.

[15] Jones JK, Gorkin L, Lian JF, Staffa JA, Fletcher AP. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. BMJ. 1995 July;311:293-295.

not taken chronically (i.e., a several year period), but rather are used for less than a year by a substantial proportion of patients. Thus, amongst diabetic patients in the United States prescribed rosiglitazone, a substantial proportion takes the medication for six months or less. For this reason, risks estimated at the six-month time point are important to persons taking rosiglitazone.

The results of the updated meta-analyses of controlled clinical trials continue to provide a signal of increased risk of myocardial ischemia with rosiglitazone, a signal not seen with pioglitazone.

Systematic Review of Observational Studies

A systematic review[17] of published observational studies was performed to assess further the cardiovascular safety signal for rosiglitazone raised by the meta-analysis of clinical trials. This review used formal criteria to select and assess studies. A review of 1226 abstracts yielded 21 published observational studies that met pre-specified inclusion criteria.[18] Seven studies were nested case-control studies, and 14 were retrospective

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[16] Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, and Platt R. Discontinuation of antihyperlipidemic drugs – Do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med 1995 April;332(17):1125-1131.

[17] Gelperin K, Zhou E, Graham DJ. Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. OSE RCM #2010-277. June 15, 2010. Presented at the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm.

[18] Since the systematic review of observational studies was complete, FDA is aware of two additional observational studies, each of which compared adverse cardiovascular effects between rosiglitazone and pioglitazone. The first study is a study jointly sponsored and conducted by FDA and CMS, which is described later in this memorandum. The second is a published observational epidemiological study conducted by staff of HealthCore, Inc., which was also presented at the July 2010 Advisory Committee meeting. See Wertz DA, Chang C-L, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed-care population. Circ Cardiovasc Qual Outcomes 2010;3:538-545. The authors used propensity-score matching to construct cohorts of rosiglitazone users and pioglitazone users. The primary outcome measure was time to composite event of acute myocardial infarction, acute heart failure, or death. The authors concluded that no significant differences were found in the risk of the acute myocardial infarction, acute heart failure or death. The Office of Surveillance and Epidemiology has reviewed the publication describing this study and its results, and we have found numerous flaws in this study. First, the outcome measure included not only hospitalized events of acute myocardial infarction and acute heart failure, but also emergency department visits for these two diagnoses. The validity of the emergency department claims in this study is not known, but is felt not to be as strong as that of the inpatient claims. Poor validity of the outcomes measures could bias risk estimates. In addition, it is not clear if the investigators, who describe their access to the HealthCore database, had access to all healthcare claims for persons 65 years of age and over, whose health insurance primary payer is Medicare. As supplemental insurers receive claims only for payment that is not covered by Medicare, the HealthCore researchers may not have had access to all outcomes of interest. Additionally, the exposure definition was defined as the days' supply of the drug, along with an additional 50% of days' supply added, to account for nonadherence to prescribed regimens. This additional time is quite extensive, and could mis-classify non-exposed time as exposed time. Finally, the sample size was relatively small compared to other studies, such as the CMS study. Each of these methodological features

cohort studies. Nine of these 21 studies reported results of direct comparisons of rosiglitazone versus pioglitazone for cardiovascular outcomes of interest including myocardial infarction, heart failure, or stroke.[19,20,21,22,23,24,25,26,27] In addition, three studies were identified which compared rosiglitazone or pioglitazone separately to other antidiabetic agents, but for which unadjusted odds ratios comparing rosiglitazone and pioglitazone to each other could be estimated from data available in the published report.[28,29,30] Results were displayed as point estimates and 95% confidence intervals in a series of forest plots, and were presented at the recent Advisory Committee meeting. No formal quantitative meta-analysis was done.

Of particular note, the forest plot describing acute myocardial infarction risk with rosiglitazone versus pioglitazone showed a strikingly asymmetric distribution, with point estimates greater than one for all comparisons, favoring pioglitazone. (See Figure 1)

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could bias the results toward a finding of no difference between groups, which was, in fact, the actual finding. We conclude that this study does not provide additional useful evidence.

[19] Brownstein, J.S.; Murphy, S.N.; Goldfine, A.B.; Grant, R.W.; Sordo, M.; Gainer, V.; Colecchi, J.A.; Dubey, A.; Nathan, D.M.; Glaser, J.P.; Kohane, I.S. Rapid identification of myocardial infarction risk associated with diabetes medications using electronic medical records. Diabetes Care, vol 33, no. 3; 2010.

[20] Dormuth, C.R.; Maclure, M.; Carney, G.; Schneeweiss, S.; Bassett, K.; Wright, J. M. Rosiglitazone and myocardial infarction in patients previously prescribed metformin. PLoS One, vol 4(6), e6080; 2009.

[21] Hsiao, F.Y.; Huang, W.F.; Wen, Y.W.; Chen, P.F.; Kuo, K.N.; Tsai, Y.W. Thiazolidinediones and cardiovascular events in patients with type 2 diabetes mellitus: A retrospective cohort study of over 473,000 patients using the national health insurance database in Taiwan. Drug Safety, 32(8):675-690, 2009.

[22] Juurlink, D.N.; Gomes, T.; Lipscombe, L.L.; Austin, P.C.; Hux, J.E.; Mamdani, M. M. Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: Population based cohort study. BMJ 339:b2942; 2009.

[23] Stockl, K.M.; Le, L.; Zhang, S.; Harada, A.S. Risk of acute myocardial infarction in patients treated with thiazolidinediones or other antidiabetic medications. Pharmacoepidemiol and Drug Safety, 18:166-174, 2009.

[24] Ziyadeh, N.; McAfee, A.T.; Koro, C.; Landon, J.; Chan, K.A. The thiazolidinediones rosiglitazone and pioglitazone and the risk of coronary heart disease: A retrospective cohort study using a US health insurance database. Clinical Therapeutics, vol 31, 2665-2677; 2009.

[25] Walker, A.M.; Koro, C.E.; Landon, J. Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database 2000-2007. Pharmacoepidemiol and Drug Safety, 17:760-768; 2008.

[26] Winkelmayer, W.C.; Setoguchi, S.; Levin, R.; Solomon, D.H. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. Arch Intern Med, 168(21): 2368-2375; 2008.

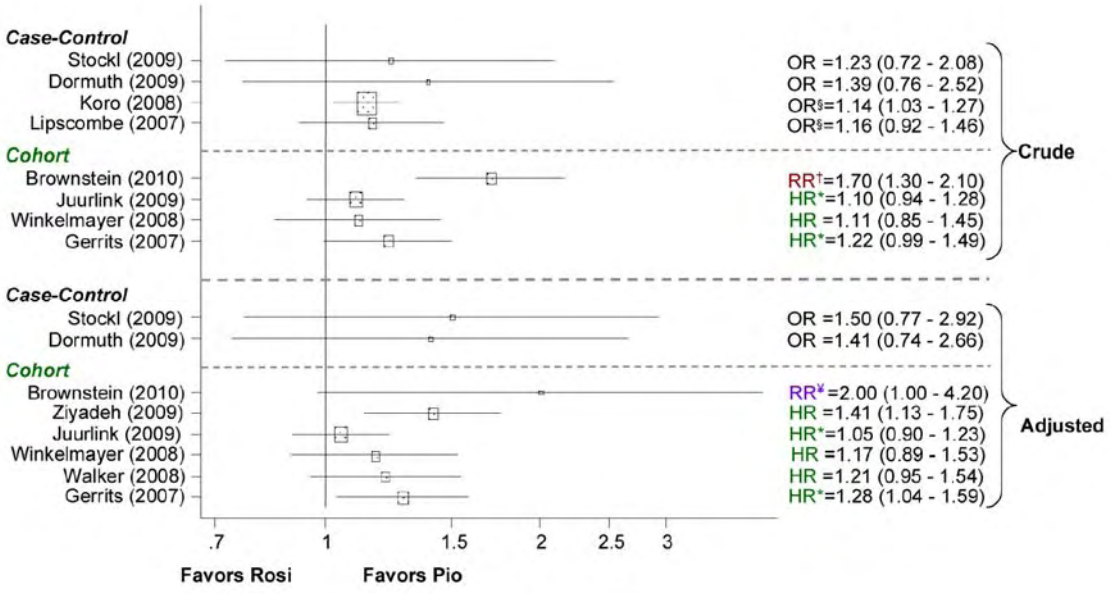
[27] Gerrits, C.M.; Bhattacharya, M.; Manthena, S.; Baran, R.; Perez, A.; Kupfer, S. A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes. Pharmacoepidemiol and Drug Safety, 16:1065-1071; 2007.

[28] Koro, C.E.; Fu, Q.; Stender, M. An assessment of the effect of thiazolidinedione exposure on the risk of myocardial infarction in type 2 diabetic patients. Pharmacoepidemiol and Drug Safety, 17:989-996; 2008.

[29] Lipscombe, L.L.; Gomes, T.; Levesque, L.E.; Hux, J.E.; Juurlink, D.N.; Alter, D.A. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA, vol 298, no 22; 2007.

[30] Azoulay, L.; Schneider-Lindner, V.; Dell'aniello, S.; Filion, K. B.; Suissa, S. Thiazolidinediones and the risk of incident strokes in patients with type 2 diabetes: a nested case-control study. Pharmacoepidemiol and Drug Safety, 2009.

Figure 1: Acute myocardial infarction (comparisons of rosiglitazone vs pioglitazone)[31]



Adjusted point estimates range from 1.05 to 2.00, and are statistically significant in two of the studies, one of which [32] was funded by GSK. The reported crude and adjusted risk estimates from a total of ten different studies are shown on this forest plot. Results are clearly asymmetric, with all point estimates similar in magnitude and direction, and favoring pioglitazone as a safer alternative to rosiglitazone with regard to myocardial infarction risk. In observational studies comparing rosiglitazone to pioglitazone, the risk of heart failure in patients taking rosiglitazone was higher than the risk in patients taking pioglitazone.

When either rosiglitazone or pioglitazone was compared to non-thiazolidinedione anti-diabetic agents, there were no significant differences in the risk of myocardial infarctions. Both agents were numerically associated with higher risk of heart failure than non-thiazolidinedione comparators; statistical significance was reached for rosiglitazone in two of four studies, and in no studies for pioglitazone.

The data from this systematic review strengthen the signal from the meta-analysis of randomized controlled clinical trials, indicating increased risk of myocardial ischemia with rosiglitazone. The magnitude of this risk is similar to what was found in the meta-analysis of randomized controlled clinical trials. These data are also consistent with the observation from randomized clinical trials that such a risk has not been observed with pioglitazone. The general conclusion from this systematic review is that rosiglitazone carries a higher risk of adverse cardiovascular outcomes, including myocardial infarction, compared to pioglitazone.

[31] Figure 9.3.1.1 reproduced from Gelperin K, Zhou E, Graham DJ. Systematic review of controlled epidemiologic studies of cardiovascular risk in patients treated with rosiglitazone or pioglitazone. OSE RCM #2010-277. June 15, 2010.
[32] Ziyadeh, N.; McAfee, A.T.; Koro, C.; Landon, J.; Chan, K.A. 2009, op.cit.

Observational Study Using CMS Data

The observational study using the CMS data[33] compared the rates of acute myocardial infarction, stroke, hospitalized heart failure, and death in new users of rosiglitazone and pioglitazone. The main findings were that, relative to pioglitazone, rosiglitazone is associated with a higher risk of death, stroke, and hospitalized heart failure, with no statistically significant increase in acute myocardial infarction. Various subgroup and sensitivity analyses confirmed the main study findings. The numerical magnitude of the risk on a relative scale is small (most hazard ratios were in the range of 1.15 to 1.20) and is in the range in which residual confounding might explain the observed results. In these situations, randomized, controlled clinical trials are usually recommended to determine if such findings are not related to residual confounding. However, the results of such a clinical trial are not available at this time, and will likely not be available for several years, if ever. However, certain features of the observational study using CMS data mitigate, at least to some degree, these concerns. First, the rosiglitazone-treated patients and the pioglitazone-related patients were very comparable with respect to multiple baseline cardiac and non-cardiac characteristics, with between-group differences in these measures as small as those seen in large, randomized clinical trials. Second, the adjusted and unadjusted analyses were not substantively different from each other, suggesting that confounding played little role in the overall results. Third, many sensitivity and subgroup analyses yielded the same findings as did the main analysis, suggesting that the findings are robust. Fourth, two other observational studies in the same age group arrived at similar results and conclusions. Given that the rosiglitazone and pioglitazone cohorts are well matched on multiple cardiac and non-cardiac factors, it is difficult to imagine that unmeasured factors are not well matched between the two groups, especially since they correlate with the multiple measured confounders. While this reasoning can not exclude an effect of residual confounding on the observed results, it does underscore the robustness of the findings of the CMS study, which provides an additional signal of risk with rosiglitazone relative to pioglitazone.[34] Even in the absence of a statistically significant difference in acute myocardial infarction rates between the two groups, the data raise significant concerns about stroke, mortality, and heart failure.

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[33] Graham DJ, Ouellet-Hellstrom R, et al. JAMA. 2010 op.cit; full review starts on page 479 of FDA briefing documents for the July 13-14, 2010 Joint Meeting of the EMDAC and DSaRM AC Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm.

[34] To examine the possibility that a very large dataset, such as the CMS dataset used for the TZD analysis, could produce "spurious" results – ie, results that link an outcome to an exposure to which it is clearly known to be not related – the FDA/CMS team analyzed CMS TZD dataset by birth date. Basically, the TZD cohort was divided into those with an even number birth date and those with an odd number birth date. "Even" and "odd" were based on dates in STATA, which uses 01 January 1960 as "Day 0", with dates prior to that assigned a negative number and dates after that assigned a positive number. Each cohort member is assigned a STATA birth data, and the cohort is divided into those with "even" and "odd" number birth dates. When divided into cohorts based on birth date, there were no differences between those with "even" or "odd" number birth dates in terms of baseline characteristics or outcomes, as would be expected. (See Memorandum for David Graham to Gerald Dal Pan. Analysis of Medicare thiazolidinedione study data by date of birth. Review date September 1, 2010.).

Post hoc Analyses of BARI-2D and VADT

The *post hoc* analyses of the BARI-2D[35] and VADT[36] studies, presented at the July 2010 Advisory Committee meeting, do not provide useful information about the cardiovascular safety of rosiglitazone because these trials were not designed to study rosiglitazone. In addition, the *post hoc* analyses designed to study the cardiovascular effects of rosiglitazone did not compare randomized groups.

Advisory Committee Meeting

On 13-14 July 2010, FDA held a joint meeting of the Endocrine and Metabolic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee. [37] GlaxoSmithKline representatives and their consultants presented the company's perspective on rosiglitazone, with a focus on the RECORD trial. FDA staff presented their findings on the RECORD study, the meta-analyses of the rosiglitazone and pioglitazone randomized clinical trials, the systematic review of observational studies, the CMS observational study, and the FDA inspections of the RECORD trial. The committee also heard from several FDA-invited outside speakers, including Dr. Steven Nissen, who presented a critical overview of rosiglitazone; Dr. Maria Mori Brooks, who presented an analysis of rosiglitazone use and cardiovascular outcomes in the BARI-2D trial; Mr. Thomas Moritz, who presented data on the impact of the use of rosiglitazone in the

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[35] According to the study website, BARI 2D, a randomized trial, was designed to determine in patients with Type 2 diabetes and stable heart disease whether: 1) elective coronary revascularization combined with aggressive medical therapy is better for patients compared to aggressive medical therapy with revascularization only if symptoms get worse; and whether 2) providing more insulin (through giving insulin or medication that allows the body to make more insulin), is better for patients than giving medications that increase patients' ability to better use the insulin their bodies already make (reducing insulin resistance) with a target HbA1c level of less than 7.0% for each group. Patient follow-up was completed November 30, 2008. Available at http://www.bari2d.org/public/home.html (accessed September 8, 2010).

[36] The Veterans Affairs Diabetes Trial (VADT) randomized 1791 military veterans who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. The primary outcome was the time from randomization to the first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene. The median follow-up was 5.6 years. Results showed that intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications, with the exception of progression of albuminuria (P = 0.01). The study was sponsored by the Veterans Affairs Cooperative Studies Program. (Reference: Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009 Jan 8;360(2):129-39. Erratum in: N Engl J Med. 2009 Sep 3;361(10):1028. N Engl J Med. 2009 Sep 3;361(10):1024-5.)

[37] Briefing Information for the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm.

Veterans Affairs Diabetes Trial (VADT); Dr. Hertzel Gerstein, who presented an overview of the TIDE Trial; Dr. Dean Follman, who presented an approach to considering the strengths and limitations of various types of clinical research data; and Drs. Ruth Faden and Steven Goodman, who presented the initial letter from the Institute of Medicine on ethical issues in studying the safety of approved drugs.[38]

The committee members were asked to comment on the strengths and weaknesses of the available data. The committee was then asked to vote on a number of questions related to the cardiovascular risks of, and potential for increased mortality with, rosiglitazone, compared separately to non-thiazolidinedione antidiabetic agents and to pioglitazone. The committee was also asked to vote on a regulatory option for rosiglitazone, as well as on a recommendation whether to continue the TIDE trial.

FDA wrote the four voting questions regarding cardiovascular risk and mortality in a way that sought a definitive response – "…do you find that rosiglitazone increases the risk of…?" The committee members re-worded the question to "…do you find that these data are sufficient to raise significant safety concerns…?" This change in wording likely reflects the challenge the committee had in making conclusions with the available data. Using this revised wording, the committee voted as follows:

- Eighteen of 33 members found that the data were sufficient to raise a significant safety concern about an increased risk of ischemic heart disease with rosiglitazone compared to non-thiazolidinedione comparators.
- Twenty-one of 33 members voted that the data were sufficient to raise a significant safety concern about an increased risk of ischemic heart disease with rosiglitazone compared to pioglitazone.
- One of 33 members found that the data were sufficient to raise a significant safety concern about an increased risk of mortality with rosiglitazone compared to non-thiazolidinedione comparators.
- Seven of 33 members voted that the data were sufficient to raise a significant safety concern about an increased risk of mortality with rosiglitazone compared to pioglitazone.

The committee members voted as follows on a regulatory option for rosiglitazone:

- Three voted for continued marketing with no changes to the current label
- Seven voted for continued marketing and revisions to the current labeling to add additional warnings
- Ten voted for continued marketing, revisions to the current label to add additional warnings, and adding additional restrictions on use
- Twelve voted for market withdrawal
- One member abstained

[38] IOM (Institute of Medicine). 2010. *Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report*. Washington,DC: The National Academies Press.

Nineteen of 33 members voted that, if rosiglitazone remains on the market in the US, the TIDE trial should continue. Eleven voted that the TIDE trial should not continue, two abstained, and one had left the meeting before the final vote.

Discussion

Overall Interpretation of the Data

The body of evidence on rosiglitazone is now larger than it was when I wrote my October 2009 memorandum. As before, no single piece of data provides a definitive answer to the question of myocardial risk with rosiglitazone. Interpretation of the data is challenging, as was reflected in the deliberations and recommendations of the advisory committee members.

The meta-analysis of clinical trials suggests an increased risk of myocardial ischemia, with a point estimate indicating an approximate 46% relative increase in the incidence of serious myocardial ischemic events with rosiglitazone. Larger individual clinical trials appear not to show this signal, though, for the reasons mentioned in my October 2009 memorandum, the lack of this finding does not mitigate the concerns raised by the meta-analyses. Given the multiple problems in its design and execution, the RECORD study does not mitigate this finding. Taken as a whole, the meta-analysis of rosiglitazone controlled clinical trial data do not definitively quantify the risk of myocardial ischemia with rosiglitazone, though they do yield an important finding that can not be ignored. Notably, the meta-analysis of pioglitazone clinical trials does not point to a risk of myocardial ischemia.

The results of the observational studies strengthen the concern over the risks of rosiglitazone, especially when compared to pioglitazone. Observational drug safety studies are often criticized because they lack the experimental design rigor of a controlled clinical trial. Specifically, there is often concern that patients who are prescribed a particular medicine are different from those who are prescribed an alternative treatment, in ways that may be correlated with the outcome of interest. This phenomenon is known as channeling bias, and is often a concern when measures of relative risk are below 2.0, when the effect of unmeasured confounders could account for the observed findings. While this concern is generally valid, it should not be automatically invoked to dismiss the results of observational studies in which the measure of relative risk is below 2.0. Data from the CMS observational study, for example, indicate that rosiglitazone and pioglitazone recipients were similar with regard to multiple cardiac and non-cardiac factors, a finding that suggests minimal channeling bias. Furthermore, the risk estimates from the observational studies are generally similar to those from the meta-analyses of clinical trials. Thus, dismissing the results of the observational studies simply because the observed measures of risk may be due to channeling bias may not be appropriate.

My assessment of the new data, in conjunction with the previously available data, is that they do not change my overall view concerning the cardiovascular risk of rosiglitazone,

including the risk of myocardial ischemia. There is, at a minimum, a persistent, strong and consistent signal of a clinically important risk of myocardial ischemia with rosiglitazone across all sources of data. This signal is more robust when rosiglitazone is compared to placebo than when it is compared to non-thiazolidinedione oral anti-diabetic agents. Importantly, there is a consistent signal when rosiglitazone is compared to pioglitazone. This latter comparison is the relevant comparison, because practitioners need to decide which thiazolidinedione to prescribe when a thiazolidinedione is needed.

My viewpoint is based on synthesizing all the available data, recognizing that each individual piece of data has its strengths and limitations. Ideally, results of a well-designed, rigorously executed, and carefully analyzed clinical trial designed to answer the question at hand would be available. This is not the case here. Nonetheless, based on the totality of the evidence and the consistency of the signal across data sources, I simply can not conclude, for public health and regulatory purposes, that the observed findings are not real.

The public health significance of the observed risk of myocardial ischemia with rosiglitazone – an approximate 40% relative increase compared to treatment without rosiglitazone – if real, is unacceptably high. Though this may seem like a modest signal from an epidemiological point of view, the public health burden of this level of risk elevation is substantial, given the high background rate (about 2-4%/year) of myocardial infarction in diabetics. With this range of background rate of myocardial infarction and observed relative risk, the absolute risk would be in the range of 0.8-1.6% - i.e., 0.8-1.6% of rosiglitazone-treated patients would experience a myocardial infarction due to rosiglitazone treatment. Given the population significance of this risk, I believe that it is neither necessary nor appropriate to demand definitive proof from a clinical trial before taking action, given the data that are already available. In this case, the impact of the harm, if it is real, outweighs the uncertainty that it may not be real.

Any regulatory decision about a medicine must be made in the context of balancing benefits and risks. Rosiglitazone is an effective anti-diabetic agent, though it appears to be no more effective than pioglitazone. I am not aware of any unique advantage of rosiglitazone over pioglitazone.

Because rosiglitazone does not confer any unique efficacy compared to pioglitazone, I continue to conclude that the benefits of rosiglitazone do not outweigh the risks for the treatment of diabetes.

Regulatory Actions

Because I have concluded that the benefits of rosiglitazone do not outweigh its risks, I continue to support market withdrawal as an appropriate regulatory action. This viewpoint is shared by Drs. David Graham and Kate Gelperin in OSE. However, an acceptable alternative approach would be to allow rosiglitazone to be used in very limited, carefully-defined situations on a restricted basis for persons with Type 2 diabetes

for whom other treatment options do not provide satisfactory diabetic control. My rationale is explained below.

The rationale for permitting limited, restricted use of rosiglitazone is that Type 2 diabetes is a progressive disease, and, in some patients, blood glucose is not adequately controlled by one or several anti-diabetic agents. For these patients, achieving adequate blood glucose control is still important. While rosiglitazone does not have any unique efficacy, it is nonetheless an efficacious treatment for Type 2 diabetes mellitus. It is important to note that the available data, upon which I base my conclusion that the benefits of rosiglitazone do not outweigh its risks, do not allow us to identify prospectively, in an evidence-based manner, any subset of patients for whom the risk of myocardial ischemia due to rosiglitazone is not present. Nonetheless, glycemic control is important and I could envision limited availability of rosiglitazone only to patients for whom rosiglitazone is basically the only available agent that allows treatment goals to be met. Patients and prescribers would have to be fully informed about the risks of rosiglitazone and would have to determine that, on an individual basis, the benefits of rosiglitazone exceed its risks. In this situation, the benefit of rosiglitazone is the achievement of adequate glycemic control when other agents have failed to achieve such control. In this setting, it is reasonable to allow physicians and patients to determine, on an individual basis, if this benefit outweighs the risks of rosiglitazone. While I have not fully developed the criteria to be used in selecting patients for rosiglitazone treatment, which would have to be done in conjunction with diabetes experts, I envision the following broad framework for these criteria:

> A) Patients with Type 2 diabetes mellitus whose diabetes has not been adequately controlled with other non-thiazolidinedione anti-diabetic agents despite documented, adequate trials of those agents;
>
> AND
>
> B) Patients for whom a thiazolidinedione is indicated;
>
> AND
>
> C) Patients whose diabetes has not been adequately controlled on, or who are otherwise not candidates for, pioglitazone.
>
> D) For patients who do meet the criteria and who do receive rosiglitazone, there should be a consent process. Patients will also need to be periodically monitored to insure that treatment goals are being met. I have not specified what the treatment goals should be, as this requires input of diabetes experts, and given the progressive nature of diabetes, may not be a specific numerical target based on blood glucose levels or hemoglobin A_{1c} levels.

I do not believe that increasing the warnings on the rosiglitazone label is an adequate option given the available data, since there is no way to identify prospectively, in an evidence-based manner, any subset of patients for whom the risk of myocardial ischemia due to rosiglitazone is not present. I offer the "restricted" plan above as an alternative to market withdrawal, not as an alternative to increasing the warnings on the label.

If the above restricted distribution plan is adopted, the Agency will need to consider the proper regulatory mechanism to implement it. One option is a Treatment Protocol within an IND. This mechanism assures that no product is available outside of the IND. The main disadvantage is that it is a clumsy mechanism to use if many patients are to receive the medication.

An alternative regulatory approach would be to require a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). The REMS would be used to insure that the limited conditions of use under which the benefits of the drug may outweigh the risks, as described above, are met. I believe that only narrow criteria, such as the ones that I have outlined in the restricted proposal above, are appropriate, since there is no other prospective, evidence-based way of determining which patients are not at risk for myocardial ischemia due to rosiglitazone. In this case, a REMS would be developed mainly to insure a) that patients are treated with rosiglitazone if they meet the criteria (which would also be in a revised labeled indication) and b) that patients are monitored appropriately while on rosiglitazone (which would also be in the revised label). Nothing in the REMS would actually mitigate the risks of rosiglitazone. The REMS would thus be used largely to enforce the labeled indication and monitoring.

The above scenario is for patients who are not currently taking rosiglitazone. Currently, there are about 600,000 patients in the US taking rosiglitazone. The path forward for these patients is less clear. I recognize that many of these patients may be doing well on rosiglitazone, and withdrawal of a successful treatment can be disruptive. Nonetheless, I think that these patients need to be informed of the recent findings regarding rosiglitazone, and, like the proposal above for new users, should sign a consent form and be monitored to insure that treatment goals are being met. Enrollment in a REMS, if that path is chosen, would also be a possibility. Whatever the approach, there will have to be a phased implementation to handling the patients currently on rosiglitazone, given the large numbers involved and the need for continuous treatment of diabetes.

My proposals are consistent with the general recommendations of the advisory committee - of the 32 voting members, 22 voted either to restrict the use of rosiglitazone (n=10) or to withdraw it from the market (n=12).

It is unlikely that withdrawal or extensive restriction of rosiglitazone, based on the available data, would lead to a rash of similar regulatory actions on other drug products each time a meta-analysis or epidemiological study is performed. In the case of rosiglitazone, we have looked at data from a wide range of sources, and have tried to synthesize these various pieces of data. The resulting synthesis has been used to re-examine the risk-benefit balance of rosiglitazone. This has been a careful process. Across

the products whose safety we monitor, we deal with data from a multitude of observational epidemiological studies and from an increasing number of meta-analyses, and we do not automatically recommend drug withdrawal when we identify a risk. Rather, we synthesize the available evidence, and re-assess the risk-benefit profile, prior to making regulatory recommendations.

Further Study

I believe that there is limited value to re-adjudicating the cardiovascular events in the RECORD trial, especially if the process of referring events for adjudication in the first place was flawed, as one OND reviewer has noted.[39] While we might learn something about the original adjudication process, a re-adjudication should be undertaken only if we will learn a sufficient amount of useful information about rosiglitazone to change substantively the overall conclusions about the cardiovascular risks of rosiglitazone. I have previously noted several problematic design issues with the RECORD study. The OND reviews that I have read have noted many of the same problematic design issues. Thus, re-adjudication of the cardiovascular events, by itself, is not likely to be helpful. Rather, re-adjudication of cardiovascular events should be undertaken only if other problematic aspects of the study can also be addressed.

I have not previously commented on the TIDE study. Here I will simply note that if the TIDE trial is to continue it will almost certainly require some modifications. One such modification is strengthening the informed consent process. Current and prospective trial participants will need a full, comprehensible, accurate and unbiased disclosure of the potential benefits and potential risks of the study treatments. Given that enrollment into the TIDE trial has been sluggish, I can only imagine that a revised informed consent process will further slow enrollment, to the extent that completion of the trial will not be attainable. Thus, if rosiglitazone remains on the market for unrestricted use (which I do not recommend) and the TIDE trial continues, there is at least a reasonable possibility that the TIDE trial will not be completed in a reasonable amount of time (if ever), and that the answers we need about rosiglitazone will not become available, a situation that is incompatible with the continued availability of rosiglitazone.

Conclusions and Recommendations

1. The benefits of rosiglitazone do not outweigh the risks for the treatment of diabetes.
2. Market withdrawal remains an appropriate regulatory action.
3. An acceptable alternative to market withdrawal would be to allow rosiglitazone to be available on a limited basis, through a restricted distribution program, to patients for whom rosiglitazone is basically the only option that results in achieving adequate glycemic control.
4. If the product remains marketed for general use, even with increased warning, and the TIDE trial continues, changes to the informed consent process will be needed.

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[39] Marciniak TA. Cardiovascular events in RECORD, NDA 21-021/S-035, June 14, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	SUPPL-35	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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

/s/

GERALD J DALPAN
09/12/2010