DATE: September 22, 2010

TO: NDA 021071

FROM: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

SUBJECT: Decision on continued marketing of rosiglitazone (Avandia, Avandamet, Avandaryl)

I. Summary of Decision

This memorandum documents my decision on the continued marketing of rosiglitazone (Avandia, Avandamet, Avandaryl). After considering the available data on the cardiovascular risks of the drug, I have determined that rosiglitazone may be permitted to remain on the market if the following actions are taken:

1. GSK is directed to undertake a restricted access program under a REMS with elements to assure safe use, including:

    a. Provision of complete risk information to each patient and documentation in their medical record that the information has been received and understood.
    b. Documentation from health care providers that each patient receiving rosiglitazone falls into one of two categories:
        i. patients currently taking rosiglitazone, or
        ii. patients not already taking rosiglitazone who are unable to achieve glycemic control on other medications and, in consultation with their health care professional, decide not to take pioglitazone for medical reasons[1]
    c. Documentation from health care providers that the risk information has been shared with each patient
    d. Physician, patient, and pharmacist enrollment

2. GSK is required to commission an independent re-adjudication of the RECORD study. This could be conducted in a stepwise manner with initial examination of the mortality finding (see Discussion of Available Safety Data below); if the mortality finding is determined to be valid, then the other MACE[2] elements should be re-adjudicated. Considering the time and effort spent by the thousands of volunteers who participated in RECORD, I believe every effort should be made to learn as much as possible from its results.

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[1] This can be a one-time decision made by the patient and provider. Requiring repetitive documentation of these discussions in the absence of new information seems excessively burdensome on patients and providers.

[2] MACE is a combined measure of nonfatal myocardial infarction, nonfatal stroke, and CV death.

3. The TIDE trial is placed on full clinical hold and the regulatory deadlines for its conduct are rescinded. If reliable information on ischemic risk can be obtained from the re-adjudication of RECORD, the benefit-risk information for rosiglitazone should be re-evaluated and the conduct of further safety studies (including studies versus pioglitazone) re-considered.

II. Basis for Decision

In reaching my decision, I have reviewed the extensive documentation available on this issue, including the materials provided to the Endocrinologic and Metabolic and Drug Safety and Risk Management Advisory Committees in preparation for the July 13-14 meeting on this subject, the proceedings of that Advisory Committee, and subsequent memoranda from multiple members of OND (summarized by Dr. Jenkins' memo of September 2, 2010), OSE (summarized by Dr. Dal Pan on September 12, 2010) and from Dr. Temple, who has contributed a critical analysis of the relevant safety data. I have also reviewed information that became available subsequent to the Advisory Committee meeting, including an observational study by Wertz et al.[3] based on Wellpoint data, published in August 2010.

The evidence pointing to a cardiovascular ischemic risk with rosiglitazone is not robust or consistent (see Discussion of Available Safety Data below). Nevertheless, there are multiple signals of concern, from varied sources of data, without reliable evidence that refutes them. Additionally, evidence available to date, including a randomized trial in high-risk individuals[4], does not reveal a signal of cardiovascular ischemic risk with the other thiazolidinedione (TZD)-class drug available on the US market, pioglitazone. Therefore, based on this safety information, it is necessary to restrict access to rosiglitazone until more substantial evidence of its safety becomes available. The reasons for restriction rather than market removal include:

> (1) the cardiovascular safety profile of rosiglitazone is still an open question because there are conflicting data on the existence and magnitude of the risk, and a detailed re-adjudication and analysis of data from the RECORD study needs to be conducted;
> (2) there are individuals with Type 2 diabetes who may benefit from therapy with a TZD because they are unable to achieve glycemic control on other medications but who cannot tolerate pioglitazone or for whom it may not be the best medical choice (e.g., individuals with Type 2 diabetes and prior bladder cancer); and
> (3) there are individuals currently taking rosiglitazone who, with full knowledge of the potential risk and in consultation with their health care providers, may wish to remain on the drug rather than revise their treatment regimens.

[3] 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.
[4] Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive: a randomized controlled trial. Lancet 2005;366:1279-1289.

My recommended actions are generally congruent with the recommendations of the Advisory Committee; although it must be pointed out that various members of the Committee had quite disparate opinions on these matters. These differences of opinion stem from varied conclusions about the existing data. A majority of the Advisory Committee members voted that the TIDE trial should continue should the drug remain on the market; however, they did not provide any guidance on how continuation of TIDE would be ethically or practically feasible if drug access in the United States were restricted (a majority voted for either restricted access or withdrawal).

Similarly, several CDER Offices have different recommendations. The Office of Surveillance and Epidemiology, as represented by Dr. Dal Pan, recommends market withdrawal (possibly with a Treatment IND program), or restricted access through a REMS. My reasons for not proceeding to market withdrawal are laid out above. I agree with Dr. Dal Pan's recommendation for restricted access. The purpose of this restriction is to limit initiation of rosiglitazone therapy to individuals for whom it is the preferable TZD option (e.g., for pioglitazone intolerance), to allow patients currently treated with rosiglitazone to continue on the drug if they so choose, and to provide prescribers and patients in both cases with full risk information. I do not support Dr. Dal Pan's proposal to require prescribers to submit extensive documentation of response to treatment, nor do I agree that monitoring of the patients should be stipulated as part of the REMS. I don't find that either of these steps would add any additional safety to a restricted distribution program for rosiglitazone, and I believe they would be excessively burdensome. Diabetes is a complex disorder; patients taking TZDs are usually taking multiple oral hypoglycemic agents; and current treatment guidelines stipulate monitoring procedures and treatment targets. It seems unlikely that a restricted access program could convey meaningful additional directions for individual patients.

CDER's Office of New Drugs recommends additional warnings on the drug label, without restrictions on marketing, and continuation of the TIDE trial, with appropriate modifications to informed consent. The basis of these recommendations is the uncertainty about the existence of the cardiovascular ischemic safety risk. While Dr. Temple does not make a recommendation, his memo clearly lays out some of the inconsistencies and weaknesses in the data signaling such risk.

Despite the lack of clarity in the data, I believe it is most prudent, given the current uncertainty about the safety risk, to restrict access to the product, and ensure that patients and prescribers are fully informed of the evidence of risk, until and unless more information is obtained. The FDA's current "Guidance on Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" calls for achieving an upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio (test drug versus comparators) for major adverse cardiovascular events (MACE) for marketed drugs of less than 1.3, along with a point estimate that is not close to the upper bound. These data can be derived from a prospectively planned meta-analysis of properly designed trials, or from a single large safety trial. Clearly, this level of assurance of cardiovascular safety is not achieved in the FDA meta-analysis for rosiglitazone. The RECORD study was intended be the large cardiovascular safety study to assess this risk,

but we are not currently able to rely on all the data from RECORD. It is possible that the re-adjudication of RECORD may provide evidence that supports the cardiovascular safety of rosiglitazone; however, at this time, the safety data base for rosiglitazone does not achieve the level of assurance of safety set out in the guidance, which is our current target for marketed anti-diabetic drugs.[5]

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[5] Because cardiovascular disease is the leading cause of death in individuals with type 2 diabetes, some have asserted that demonstrating a positive impact on cardiovascular outcomes (using MACE or a similar endpoint) should be required for approval of new anti-diabetic drugs. In fact, no current anti-diabetic drug has been definitively shown to reduce macrovascular complications in type 2 diabetes patients. While it might be possible for a new therapy to show improved MACE outcomes versus a no-treatment arm, such a trial is not ethical; longer-term trials must evaluate new therapies against the best standard care. Thus, showing that a new therapy reduces MACE would require a long-term superiority trial against current therapy. The recent ACCORD trial (New Engl J Med 2008, 358: 24: 2545-59) evaluated, among other things, the effect of more intensive diabetes control (compared to current guidelines) on cardiovascular outcomes in higher-risk patients with type 2 diabetes. The intensive glycemic control arm—which used standard therapies but targeted tighter glycemic control-- was halted after 3.5 years of follow-up due to higher mortality in the intensive therapy group. The factors leading to this result are not known. The ACCORD trial results demonstrate some of the uncertainties around the relationship between level of glycemic control and macrovascular outcomes.

However, since many diabetics have, or will develop, cardiovascular disease, it is important to make sure that new diabetic therapies do not have cardiovascular toxicities. This safety evaluation is distinct from demonstration of efficacy, which can be accomplished by evaluating effects on glycemic control, using HgA1c and other measures. In 2008, FDA issued a Guidance on conducting a cardiovascular safety evaluation of new therapies for Type 2 diabetes. This establishes guidelines for ruling out increases in cardiovascular risk, both at the time of marketing, and to be achieved after marketing. Thus new antidiabetic therapies will have been evaluated for cardiovascular toxicities prior to marketing, and will continue to undergo such evaluation, if very robust assurance of safety has not been achieved at the time of marketing.

Type 2 diabetes mellitus is a progressive metabolic disorder that is very often accompanied by other metabolic disturbances, particularly hypertension and dyslipidemia, frequently in individuals who are overweight or obese, are sedentary, and may smoke. Thus many type 2 diabetic patients have multiple risk factors for cardiovascular disease. In early stages of the disorder, the metabolic abnormalities can be mitigated or even eliminated in many people by (fairly radical) changes in diet, weight loss, salt restriction, and vigorous exercise. Unfortunately many are unable to undertake or maintain these behavioral changes, and have progressive disease. Although drug therapy can treat hyperglycemia, hypertension, and dyslipidemia, it does not follow that medical treatment will have the same benefit as elimination of the inciting factors. However, simultaneous intervention on multiple risk factors is likely required to improve cardiovascular outcomes. The follow-up Steno 2 study (New Engl J Med 2008 358; 6: 580-91) randomized patients with type 2 diabetes to intense lipid, blood pressure and glucose control, along with behavioral modification and other medications. They were then followed for another 13 years without differential recommendations for treatment. For this small but long term study of multifactor intervention, the hazard ratio for death was 0.54 in the treatment group, and the hazard ratio for cardiovascular events was 0.41, with large numerical differences in stroke, MI, PCI, and amputation. It is not possible to sort out which of the interventions were responsible for these effects, but this trial does illustrate that, over the long term, multi-factor intervention in type 2 diabetics can reduce severe cardiovascular outcomes. The issue of how "tight" glycemic control should be, at any given stage of disease, and how this impacts long-term microvascular and macrovascular diabetic complications, still remains an open question. This question is severable from the issue of standards for approval of new anti-diabetic drugs.

While both a majority of the Advisory Committee members and OND recommend continuation of TIDE, I do not believe it should proceed at this time, given the restrictions I have determined are necessary for rosiglitazone and the level of concern about its cardiovascular safety. In many cases, when a drug safety issue arises, conduct of a randomized trial is an appropriate step to resolve the question. However, the results of RECORD, which are currently in question, directly affect the ethics of conducting TIDE. I believe that re-adjudication of RECORD is the appropriate next step, with decisions on whether to conduct further studies or take additional regulatory actions to be based on the results of the re-adjudication and any other data that may become available in the interim. FDA is not rescinding the post-market requirement for the sponsor to study the safety of rosiglitazone compared to pioglitazone, if feasible and appropriate, but is stopping the current trial until all existing information is evaluated, including the data from RECORD, if possible.

This regulatory action places the burden of demonstrating cardiovascular safety on the drug sponsor. The RECORD trial was intended to provide the relevant safety information. The RECORD trial has certain built-in limitations, particularly its open-label design, its relatively small size (for a cardiovascular trial), the choice of primary endpoint, and the provision for investigator option in referring potential events for adjudication. Additionally, during its conduct, fewer events than anticipated were encountered and an unplanned interim analysis was conducted after publication of the meta-analyses regarding cardiovascular safety. Despite these limitations, it is the only large, randomized, long-term trial of the cardiovascular safety of rosiglitazone compared to other drug interventions for Type 2 diabetes—an inquiry that is highly relevant to the findings of the meta-analyses. During the FDA review of RECORD, questions arose about the potential for bias in influencing the results of this open-label study. Whereas the other limitations of the RECORD study can be taken into account when evaluating its results, the unresolved concern about biased referral currently limits the weight that can be placed on evidence from RECORD—for example, its ability to address the standards set forth in the FDA guidance. The questions about bias could not be fully addressed during the limited time period leading up to the Advisory Committee meeting. Therefore, it is reasonable to restrict drug access while further evaluation of RECORD is attempted. It must be noted that, even if all data points are fully verified, RECORD will not answer all questions about rosiglitazone safety, both for the reasons stated above, and because a comparison to pioglitazone was not a part of the study. However, if valid conclusions can be obtained from RECORD (within its known limitations), these findings will contribute more reliable information on the cardiovascular risk of rosiglitazone compared to standard anti-diabetic therapies than is currently available from the meta-analyses that have been done.

In summary, there are multiple and conflicting signals of cardiovascular ischemic risk related to rosiglitazone. The current cardiovascular safety database for rosiglitazone does not provide an assurance of safety at the level set out in FDA's guidance for marketed anti-diabetic drugs. There are not similar signals pertaining to the only other drug in the TZD class available in the US, pioglitazone. Marketing of rosiglitazone will be restricted

and the sponsor will be required to commission an independent verification of the RECORD data.

III. Discussion of Available Safety Data

Detailed analyses of extant data on the cardiovascular safety of both rosiglitazone and pioglitazone were presented at the July 2010 Advisory Committee meeting and are summarized in the memoranda from OSE and OND, and in Dr. Temple's analysis of the evidence. Many highly experienced clinical trialists and methodologists, both within and external to the FDA, who have examined these data find it hard to arrive at definitive conclusions about the cardiovascular ischemic risk of rosiglitazone, yet they agree that pioglitazone's data do not suggest such a signal of risk. This uncertainty about the risk of rosiglitazone is overwhelmingly the most important reason for the differing opinions on what regulatory action should be taken.

A. Data Directly Addressing the Meta-analysis Results

The original findings generating concern in 2006 and 2007 were from a group of related meta-analyses of cardiovascular ischemic events and deaths in efficacy trials of varying design evaluating rosiglitazone against placebo or other non-TZD anti-diabetic drugs. Such meta-analyses are often done to look for rare or uncommon problems that would not be detected in individual trials. The FDA 2010 meta-analysis, an update of the 2007 FDA meta-analysis, includes 52 trials. This meta-analysis finds a nominally significant odds ratio (OR) of 1.80 for non-fatal MI, with OR of 1.44, 1.46 and 1.38 for MACE (a combined measure of nonfatal MI, nonfatal stroke, and CV death), cardiovascular death, and all-cause death, respectively, that are not statistically significant but also not reassuring. The OR for non-fatal stroke is 0.86. Thus, the recent meta-analytic findings (which incorporate trials included in the prior analyses and add more) support the original concern that rosiglitazone increases the risk of heart attacks, and thereby might increase the risk of cardiovascular death and all-cause death, when compared to placebo or non-TZD diabetes drugs. Additionally, the vast majority of these events in the meta-analysis come from trials of 12 months duration or less; and the sparse data after 12 months are not revealing (see Table 1 in Dr. Parks' review of August 19, 2010). Therefore, the hypothesis raised by the meta-analysis includes the idea that the risk of MI, and potentially other serious cardiovascular events, occurs promptly after exposure to rosiglitazone, during the first year of therapy.

It has been shown repeatedly that hypotheses generated by meta-analyses may not be verified when studied in randomized controlled trials. (For example, see the recent Perspective article on tiotropium[6] and FDA's 2009 safety communication on cefepime[7].) Other available evidence must also be used to evaluate whether or not rosiglitazone

[6] Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. N Engl J Med 2010; 363:1097-99. [http://www.nejm.org/doi/pdf/10.1056/NEJMp1008502]

[7] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm167254.htm

increases the risk of heart attacks compared to placebo or standard diabetes drugs. After publication of the original meta-analyses, a number of epidemiologic studies evaluated the risk of ischemic CV events in populations where patients with diabetes were taking rosiglitazone or other standard, non-TZD therapies. These studies did not show any consistent increase or decrease in ischemic cardiovascular events (see slide 8 in Dr. Gelperin's AC presentation, or her review) in rosiglitazone treated patients compared to non-TZD treated patients. There were similar results for all-cause death. These findings diminish the likelihood that the meta-analytic results are correct, but do not have enough weight to dismiss them (because of the well-known limitations of epidemiologic studies).

The most reliable evidence about clinical outcomes comes from well-conducted, randomized trials. Two longer-term randomized, controlled, double-blind trials of rosiglitazone (DREAM and ADOPT) were completed around the time of the original meta-analysis. These trials did not show any signal of increased mortality, but had numerically (not statistically significant) higher rates of MI in the rosiglitazone arms. Neither of these trials had a substantial number of cardiovascular events: this limits how much information they contribute to the question at hand. Dr. Temple finds the post-hoc analyses from the more recently completed BARI-2D trial to weigh against a risk of ischemic CV events due to rosiglitazone, but the results are by no means definitive because of the non-randomized nature of the analysis. This leaves the RECORD trial, a randomized, controlled trial which evaluated the CV safety of rosiglitazone compared to metformin or sulfonylureas (standard diabetes drugs). Although the RECORD study looked at additional endpoints, it included prospective evaluation of heart attacks, CV death, and all-cause death. The problems with RECORD have already been discussed. However, I fully agree with Drs. Temple and Unger that there is every indication that the mortality results of RECORD are reliable, based both on trial retention rates and FDA inspections. These results trend favorably for rosiglitazone and thus pretty strongly (along with the results of ADOPT, DREAM and BARI-2D) weigh against the point estimate for all-cause death or cardiovascular death in the meta-analyses, although the RECORD mortality findings are within the confidence limits of those meta-analytic results. However, without re-adjudication, the results of RECORD cannot be used to help evaluate the risk of excess myocardial infarction.

While not directly addressing the meta-analytic results, a number of published observational studies compared various cardiovascular outcomes of patients taking either rosiglitazone or pioglitazone.(see below) These studies included evaluations of the occurrence of myocardial infarction. Most of these were presented by Dr. Gelperin in her systematic review (see Table 9.3.1.1). Dr. Gelperin points out that many of the studies found a numerical advantage for pioglitazone in rate of MI; however, the majority showed no statistically significant difference between the two drugs. Similarly, the very large FDA/CMS study, and the recent study by Wertz et al. did not detect a difference in the occurrence of myocardial infarction in patients taking rosiglitazone or pioglitazone. Several of the large studies found a statistically significant mortality advantage in favor of pioglitazone, but this was in the absence of a finding of a relative increase in myocardial infarction.

In summary, the main question raised by the various meta-analyses of rosiglitazone—does the drug increase the risk of heart attacks when compared to placebo or non-TZD diabetes drugs?—is still not clearly answered. The updated meta-analysis completed by FDA in 2010 still shows the myocardial infarction risk, but most observational studies completed to date do not find this risk. It also seems less likely, based on current data, that rosiglitazone increases cardiovascular or all-cause death compared to non-TZD diabetes drugs. More information on these questions may be achieved by a re-adjudication of RECORD.[8]

B. Comparisons of rosiglitazone and pioglitazone

As a result of the concerns about rosiglitazone's safety, the question naturally arises: what is the cardiovascular safety profile of pioglitazone, the other drug in the TZD class? Pioglitazone had been studied in a cardiovascular safety trial (PROactive) that enrolled patients at high risk for cardiovascular events. The trial added pioglitazone or placebo to underlying therapy. This trial recorded a large number of cardiovascular events. There was differential dropout due to edema in this trial, mirroring a criticism leveled at the RECORD trial by Dr. Marciniak (see his briefing document for the July 13-14, 2010 advisory committee meeting); such results are likely when a TZD is studied against a non-TZD therapy. FDA review of the study found that it failed to meet its primary endpoint, although a secondary endpoint of MACE had a favorable result, but could not be considered as statistically proven. The MACE result was driven by differences in non-fatal MI and in stroke. There was no difference in CV death or all-cause death between the groups. Thus, pioglitazone, added to background therapy, appeared to have a relatively favorable result on ischemic events, and a neutral effect on death, in a randomized controlled cardiovascular safety trial, when compared to placebo.

A number of observational studies comparing cardiovascular outcomes or mortality in patients prescribed either pioglitazone or rosiglitazone were conducted prior to 2010 and published in the literature. These were presented by Dr. Gelperin at the 2010 Advisory Committee meeting and are discussed in detail in Dr. Gelperin and Graham's June 15,

[8] The data relating to rosiglitazone's cardiovascular safety profile can be confusing even to experts. For example, some people have concluded that the FDA meta-analysis results mean that rosiglitazone causes an 80% increase in heart attacks when compared to standard therapy. This could be the case, but is not established by the meta-analysis, because the results are based on very few MI events (65 total) that were collected from trials that were not designed or executed in a manner to assess cardiovascular risk, and the confidence limits on the 1.8 OR are wide. To illustrate these points, it is generally agreed that there is no signal suggesting that pioglitazone has an ischemic cardiovascular risk. The OR for cardiovascular death in FDA's meta-analysis of pioglitazone trials is 1.18; nevertheless, it is not asserted that pioglitazone increases such deaths by 18%. This is because of the limitations of these particular meta-analyses, and because the 95% confidence limits (roughly speaking, the upper and lower numbers that have a 95% chance of containing the true OR within them) range from 0.6 to 2.34. Obviously, these confidence limits include very good outcomes (life saving) and very poor ones (increased mortality), so they signify a large amount of uncertainty about the actual effect. The 95% confidence limits on the OR for non-fatal heart attacks in the FDA meta-analysis of rosiglitazone are 1.03-3.25.

2010 briefing document to the Advisory Committee. In addition, a very large study[9] conducted by FDA and CMS in the Medicare database was published in June 2010 and was also presented. An additional study by Wertz et al.[10] appeared in the literature soon after the AC meeting. Dr. Gelperin presented forest plots summarizing the results of the published studies looking at MI, congestive heart failure, stroke and death. The point of this presentation was that, in many studies done by many authors, pioglitazone use was fairly uniformly associated with a lower rate of these events than rosiglitazone use--a "weight of the evidence" argument (see slides 13-15 in Dr. Gelperin's AC presentation). However, I find that not all these studies contribute the same weight of evidence. For example, the Hsiao study, while very large overall, included only 495 patients taking pioglitazone. Some of the published observational studies include large numbers of patients on rosiglitazone and pioglitazone (Walker, Winkelmayer, Gerrits, Juurlink, Ziyadeh, Graham and Wertz). The studies by Juurlink, Winkelmayer and Graham found statistically significant increases in all-cause mortality and congestive heart failure in rosiglitazone patients compared to those taking pioglitizone, but no increase in MI. The results of these studies were consistent. Wertz found no difference between the drugs on a composite endpoint of AMI, acute heart failure or all cause mortality. The most striking finding in the very large FDA/CMS (Graham et al) study was an increased rate of stroke in people treated with rosiglitazone compared to pioglitazone. As Dr. Temple explains in his analysis of the data, drawing conclusions from non-randomized comparisons of drugs is difficult, because small differences in the reasons people were treated with each drug can create undetected biases that influence the results. There is more concern with the influence of bias when the differences that are detected are proportionately small.

There are also challenges in interpreting studies that compare two drugs where the performance of the comparator drug is not completely known. For example, if two therapies show equivalent results for some outcome (for example, mortality), it may not be clear if both are better, both worse, or both no different than, for example, a placebo or standard therapy. If one therapy is superior on some outcome (for example, MI), it may not be clear whether that treatment prevents MIs or the other therapy causes them (i.e., compared to placebo if it had been used in a third arm.) This is why it is common to use well-understood drugs as active comparators in clinical trials. Of course, from the point of view of the treating clinician, the question of which drug in a class to use is of utmost importance: this is the point of "comparative effectiveness research" on drugs. However, for the purposes of advancing knowledge (to build the evidence base for disease therapy), and for regulatory purposes, the question of whether (in this case) one drug is superior, or the other has a specific toxicity, or there is really no difference, needs to be determined.

Dr. Gelperin makes the point that several of the epidemiologic studies in younger patients found a statistically significant increase in MI in rosiglitazone-treated patients compared to pioglitazone treated patients. This finding reinforces the concern about rosiglitazone

[9] 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;304(4):411-8. Epub 2010Jun28.
[10] Wertz DA, et al; op.cit.

but of course these studies are not able to distinguish between a toxicity of rosiglitazone or a benefit of pioglitazone on myocardial ischemia as suggested in PROactive. Studies in older patients, who are at much greater risk of MI, did not find a difference. The FDA/CMS study, by Graham et al, was very large (over 227,000 patients exposed), was well conducted, and had a very large number of MI events (1746). No statistically significant increase in MI risk was found, and the study primarily looked at early treatment, e.g., the first 18 months, which includes the period of concern raised by the meta-analyses. Moreover, the large Winklemayer and Juurlink studies had similar results. Therefore, although these studies were not positive for rosiglitazone overall, they do not support the idea that there is a specific, early acting toxicity of rosiglitazone that increases myocardial infarction.

The large epidemiologic studies do raise additional concerns about the cardiovascular outcomes of rosiglitazone compared to pioglitazone use, outside of the MI finding. The FDA/CMS study (Graham et al) found a statistically increased rate of stroke (adjusted HR 1.27), heart failure (adjusted HR 1.25) and death (adjusted HR 1.14) in users of rosiglitazone versus pioglitazone. The heart failure finding, if verified, would represent a clear differential toxicity: since no one thinks that pioglitazone prevents CHF, it would suggest that pioglitazone use results in less heart failure than rosiglitazone. The stroke finding is a new one: the meta-analyses and trial results have not suggested that rosiglitazone increases stroke. Winkelmayer found a non-significant difference in stroke in his comparative study. The mortality findings seen in the Juurlink, Winkelmeyer and Graham studies (with hazard ratios between 1.14 and 1.16) are obviously of concern. Of note, the hazard ratios for these outcomes are often referred to as "small." This means there is a proportionally small difference (for example, a 10% increase rather than a three fold increase) that may be more vulnerable to hidden biases in non-randomized data (i.e., in epidemiologic studies). As Dr. Graham has pointed out, it does not mean that the impact would be "small" on a population basis—it could be very significant. Rather, it means that the "small" size of the observed difference makes it more difficult to rely on nonrandomized studies to reach conclusions. In addition, the differences found in these comparative studies (outside of the CHF finding) could have occurred because pioglitazone has a beneficial effect on, for example, mortality, greater than the effect of rosiglitazone (which could also theoretically have had a beneficial effect, albeit smaller). Such comparative superiority claims for survival benefits are usually established by the results of very large, randomized outcome studies; FDA usually requires rigorous evidence to support such comparative claims. If, on the other hand, these findings represent a toxicity of rosiglitazone, perhaps resulting from the fact that it causes more heart failure or from its effects on lipids, then there would be great concern for the use of the drug even in patients who are not candidates for pioglitazone. It is certainly reasonable, as Dr. Gelperin points out, to prefer the use of pioglitazone based on these epidemiologic findings, in the absence of controlled trial data. Interestingly, the Advisory Committee did not seem to place much weight on these data, perhaps because of continuing concerns about the reliability of non-randomized studies. They did not seem to weigh the MI findings from these studies very heavily, and, when explicitly asked about mortality, only 7 voted that they felt the data were sufficient to "raise significant safety concerns for mortality…relative to pioglitazone." (12 voted that the

data were not sufficient, and 14 voted that they were not able to make a make a finding). These votes may reflect ongoing concern about the reliability of results of "small" differences from observational studies. It is for all these reasons that the Office of New Drugs, and Dr. Temple, support continuation of the TIDE trial, which would have the capacity to address all these questions definitively, given that it has a standard therapy arm.

In summary, the existing data from observational studies comparing rosiglitazone to pioglitazone suggest that pioglitazone use may be associated with better cardiovascular outcomes. However, it is difficult to draw definite conclusions from these studies, both because of the small size of the observed effects, and because it is not clear whether the findings, if valid, represent beneficial effects of pioglitazone or toxicities of rosiglitazone.

D. Conclusions Regarding Available Safety Data

The sponsor has not submitted information on rosiglitazone that achieves the standards for assurance of cardiovascular safety set out in FDA's guidance. In addition, existing data raise concerns about a cardiovascular risk. Re-adjudication of RECORD may provide information directly relevant to questions raised by results of the meta-analyses.

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