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UNC HEALTH CARE
DIABETES CARE CENTER

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Wednesday, March 15, 2000

Jane Henney, M.D., Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: "CITIZEN'S PETITION TO IMMEDIATELY REQUIRE CLASS LABELING FOR THE DIABETES DRUGS TROGLITAZONE (REZULIN), ROSIGLITAZONE (AVANDIA) AND PIOGLITAZONE (ACTOS)"

Dear Dr. Henney:

I am an endocrinologist with an academic practice focusing on the treatment of diabetes. I also have outreach clinics in a family practice center in rural North Carolina and in an endocrinology private practice in a nearby urban area. I participate in the design, execution and analysis of clinical trials for the NIH and industry. I am very active in the development and delivery of CME in the area of diabetes. I am currently a consultant to Parke-Davis, Lilly and Takeda. I have done consulting work for SmithKline Beecham and Bristol-Myers Squibb in the past. I have or am now conducting industry sponsored trials for all five of the above mentioned companies. I have reviewed the safety and efficacy data available as published manuscripts or abstracts as well as from the FDA through FOI for rosiglitazone and pioglitazone. I have also reviewed the published and unpublished data on the clinical trials with troglitazone.

I am writing to you out of frustration over the irrational attention to the potential risks of this class of antidiabetic drugs in the media, particularly over the last several weeks. The above named petition is a prime example of rampant half-truths regarding the issues at hand. I believe I have had as much access as anyone to the liver safety data regarding troglitazone. My take on the issue is that fatal liver toxicity is rare and arguably less common than fatal lactic acidosis with metformin or fatal hypoglycemia with sulfonylureas or insulin. Furthermore, the well-documented cardiovascular mortality associated with diabetes is extraordinary in comparison to the above named risk, as it is not measured in cases per 100,000 patients but cases per 100 patients per year. If the UKPDS study results apply to the thiazolidinediones, the expected improvement in cardiovascular mortality associated with the additive 1-2% reduction in glycosylated hemoglobin that can be easily achieved with these agents should produce a net survival benefit of 1-2 cases per 100 patients treated per year. The published cardiovascular secondary outcomes studies with troglitazone are extraordinary in their promise. With similar lipid changes, it is possible that pioglitazone will produce similar results. I remain concerned about the safety of rosiglitazone in light of its consistent negative impact on lipids documented in the FDA registration data as well as a worrisome trend in cardiovascular deaths and severe adverse events in the subjects exposed to rosiglitazone versus active comparators. Thus, I have developed little clinical experience with rosiglitazone. In clinical practice, the frequency of mild and serious adverse events that I have seen with troglitazone and pioglitazone is comparable to or less than the number I have observed with other antidiabetic agents.

As someone who has read the reports from which Dr. Wolfe has abstracted his quotes and data, I believe that his view of the class's safety is unbalanced. His major argument regarding limiting the use of the thiazolidinediones to use in combination therapy is that the efficacy of this class of drugs in comparison to sulfonylureas and metformin is poor. This is clearly not the case for troglitazone at maximal doses in clinical practice or where appropriate clinical trial data are available (e.g. Horton et al, Diabetes Care 21:1462, 1998; Inzucchi SE et al. N Engl J Med 338:867-872, 1998). I do believe that rosiglitazone is perhaps less effective than sulfonylurea and metformin at the doses

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most aggressively marketed (4 mg or 8 mg once daily). Its efficacy is equivalent to full dose troglitazone or pioglitazone when dosed twice daily. There is no data for pioglitazone.

I agree that the heart failure issue is not completely resolved with this class of drugs. Only rosiglitazone has been shown to increase cardiac weight in non-rodents. In significant experience treating patients with pre-existing heart failure with troglitazone and pioglitazone there is often a need to increase diuretics. I have never had to stop a thiazolidinedione because of clinical edema that could not be adequately controlled. I suspect that the calcium channel theory of edema may play a small part, but it is probably largely due to the twin effects of a loss of the diuretic effect of glycosuria and amplified insulin effects of salt and water retention by the kidney. In two cases I have seen shortness of breath develop in the setting of thiazolidinedione therapy. In retrospect, those patients almost certainly had cardiac dysfunction predating their treatment with thiazolidinediones by history, in addition to some level of renal impairment. They responded well and promptly to increases in their diuretic therapy.

With regards to weight gain, there are good data on troglitazone suggesting that visceral fat is reduced and that the weight gain is perhaps more important from a cosmetic point of view than from a physiologic point of view. The hypothesis that the class works by mobilizing lipid stores from muscle and fat and depositing them in subcutaneous fat is interesting and seems to hold true under multiple techniques of assessment. Thus, weight gain is likely to be a cosmetic issue and not a health issue for the thiazolidinediones. However, it is worthy of mention in the package inserts.

Anemia with thiazolidinediones again has not been a treatment-limiting effect in the clinical trials. For troglitazone there are two-year safety data that do not support the myelophisthic anemia that Dr. Wolfe suggests may operate. Again, the more logical conclusion is that the minimal drop in hemoglobin is a result of volume expansion and vasodilatation producing greater renal blood flow and increased oxygen delivery to the juxtaglomerular apparatus producing a physiologic, but not pathologic response.

The lowering of blood pressure with troglitazone and the modest reduction of blood pressure with rosiglitazone can only be viewed positively in light of multiple trials documenting the benefit of every reduction in blood pressure in diabetes.

I have commented briefly on lipids above. In short, the lipid changes with troglitazone and pioglitazone can only be viewed as positive. They are very similar in nature and extent to those recently proven to be associated with a reduction in cardiovascular events associated with fibrates in the VA-HIT study (Rubins et al, N Engl J Med 341:410-8, 1999). As mentioned above, I remain concerned about the lipid changes with rosiglitazone.

To summarize, I believe that we may one day discover that troglitazone is the most effective, safe and beneficial drug in its class. I think that pioglitazone may well turn out to be generally similar. Rosiglitazone is clearly a very different actor. I do not believe rosiglitazone will be proven safer than troglitazone in clinical use under current labeling of the two products. In fact, rosiglitazone may be associated with less beneficial cardiac effects or even adverse cardiac outcomes. I do not object to more stringent labeling of the class. All providers and patients welcome appropriate information. However, the implication that this class of drugs is more dangerous than others is ludicrous. Furthermore it increases the impetus behind the already widely held perception in the primary care community and in the lay public that inadequately treated diabetes may be preferable to treatment with thiazolidinediones. The problem with restricting the drug as monotherapy is that approximately one quarter of subjects with diabetes are intolerant or have a contraindication for the use of metformin. In addition, there are over 5 million patients in the US (all the undiagnosed and most of those with fasting glucose less than 140 mg/dl) who would undoubtedly be bothered by hypoglycemia if treated with sulfonylureas.

I think the FDA has to act forcefully to prevent the rampant abuse of clinical trial data by SmithKline Beecham.

- I believe that they have overstated the safety of the drug with respect to cardiovascular issues. I have been shown glossy materials claiming that rosiglitazone has been uniquely studied in patients with preexisting cardiac disease, including patients with a number of associated conditions (such as unstable angina). I know for a fact that such patients are excluded in clinical trials as I am a PI in one of their trials.

- I have been shown glossy materials for professional education touting the lipid lowering effects of rosiglitazone when the data are from a small subset of patients with triglycerides over 400 mg/dl! The overwhelming

preponderance of data suggests that at high doses the drug is most likely to increase triglycerides than lower them.

- I have seen and been told numerous times that the increase in LDL associated with rosiglitazone is due to a beneficial increase in particle size when there are no appropriate data to support this claim. As an example, there is data that there is a marginal increase in LDL/ApoB ratio, but I have not succeeded in obtaining the ApoB data. I would bet my house that such data exists and demonstrates a greater increase in particle number (ApoB) than particle size (as on reflected but not measured by changes in LDL/ApoB).

- I have heard from numerous primary care doctors that they were detailed by SmithKline Beecham representatives on the safety and efficacy of the other thiazolidinediones to suggest that rosiglitazone's safety and clinical efficacy is greater when there is no comparative data available.

I am sure there have been abuses by representatives of all companies that market drugs, but there is something pervasive and systematic that I detect in my travels regarding the marketing of rosiglitazone. I have to admit that now when I give CME lectures, I spend about half my time discussing these issues. It seems to me that blatant selective manipulation of data has obfuscated relatively straightforward conclusions evident from the FDA data sets.

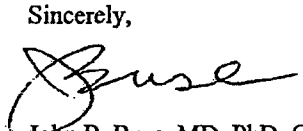
Please do not consider me some fringe lunatic. I am exceptionally careful in my assessments and have spent hours speaking to the principals at each company after reading every published report, abstract and all available information from the FDA. I was an early critic of troglitazone's labeling regarding liver monitoring and its widespread use as monotherapy as well as one of the first people who predicted that it would produce additive effects in combination with metformin. My opinions caused befuddlement and/or bewilderment in some circles. I believe I was eventually proved correct and that I will be in this case, as well.

As action items, I believe the FDA should:

- take the lead in establishing a joint panel of liver experts to review all liver serious adverse events for all three drugs.
- make clear to the manufacturers of all three compounds that marketing outside of labeling will not be tolerated. The FDA should fine and censure to the full extent of the law those that violate FDA policies.
- encourage cardiovascular safety trials in high-risk populations, particularly with rosiglitazone where I believe there is ample cause for concern regarding the potential effects of the detrimental lipid changes.
- demand rapid completion of the 45 mg efficacy and safety trials with pioglitazone.
- encourage all three companies to conduct adequate head to head trials with the other agents in the class or the FDA should ask the NIH to fund such a study.
- encourage through every available means some fair balance in the media regarding the statistically equivalent safety of this class with all other classes of drugs and their potential to save lives by improving diabetes control.

Thank you for your efforts and attention in this very complex and important matter. Please feel to call on me if I can be of help to you or your agency in this regard.

Sincerely,



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