M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: Comments on the study by Wertz et al. published in Circulation 2010

My observations and remarks regarding this study are presented below.

Introduction:

- Very incomplete assessment of the published literature on studies of cardiovascular risks with rosiglitazone compared with pioglitazone
- No citations describing the HealthCore Integrated Research Database, its use in other pharmacoepidemiologic studies, or validation efforts related to data quality

Methods:

- This was not a new-user (inception) cohort study. It appears that prevalent users were included and may represent a substantial number of subjects among those with an index date during the first year of the study
- Switching from one TZD to the other was allowed if the switch occurred more than 60 days after the end of use of the other
- The primary analysis was ITT and should have been on-treatment only
- A gap allowance of 50% of the preceding prescription's days supply was used. This is longer than most researchers would use
- The outcome definition for AMI and acute heart failure (AHF) did not require hospitalization, but also included diagnoses associated with emergency department visits that were not followed by hospital admission. This definition has not been validated for either AMI or AHF, and one could reasonably argue that such events are qualitatively and clinically less severe and less worrisome than those requiring hospitalization. These results are not readily compared with other studies, all of which excluded emergency department-only events
- The description of the NDI search methods does not provide enough detail to know how the search was conducted (e.g., how was the decision made of whom to perform a search on?) and whether ascertainment of death was complete
- The description of how the propensity score (PS) was estimated is ambiguous and may have been performed incorrectly. The PS is the predicted probability of exposure to a particular drug given a subject's covariate makeup. It is usually calculated to estimate the probability of exposure to the reference medication in a given study. In the present study, the PS should represent the predicted probability of exposure to rosiglitazone if rosiglitazone is the reference group or the predicted probability of exposure to pioglitazone if pioglitazone is the reference. Wertz et al. state that "a logistic regression model was developed to estimate the probability of receiving rosiglitazone *or* pioglitazone" (emphasis added), implying that the PS may have been performed as a probability of exposure to any TZD rather than a specific TZD, which would be analytically incorrect
- There is no mention of which TZD was the reference group within the Methods section (the reference is mentioned only once, as a footnote to table 5)

Results:

- The main results are summarized in table 5.
- It should be noted that the "Age 65+" analysis was not PS-matched, nor was the "All patients" analysis. Also, the "All patients" analysis was not mentioned in Methods
- No difference in risk of the composite end point of AMI, AHF, or death was noted in the primary analysis or sensitivity analyses

Remarks:

There are a number of potential problems with this study. The most important probably relate to the inclusion of emergency department-only events in the outcome, the inclusion of prevalent users in the cohort, and uncertainty about the database itself. In the matched cohort analysis, which is what should be focused on, we can see from table 3 that the greatest number of events is AHF. If many of these are emergency department visits and not hospitalizations, the entire study becomes uninterpretable and cannot be compared with other studies of rosiglitazone vs. pioglitazone, where hospitalized heart failure was required. The inclusion of prevalent users is also a serious liability to study interpretability because of the potential for differential survivor bias, which could be made worse by differential AHF hospitalization rates. Most, if not all, of the studies of rosiglitazone vs. pioglitazone that were included in OSE's systematic review relied on new-user cohorts, thereby avoiding the potential bias introduced by prevalent users. Finally, we know virtually nothing about the data resource, nor do we know how formularies or regional health plans within the database might vary. There is also the concern that the end points in question have not been validated using this data resource.

If we focus on the matched analysis, there were 28 938 patients with about 33 487 person-years and a total of 259 AMIs and 434 deaths, not all of which occurred during TZD-exposed time. Also, an unknown number of the AMIs were not hospitalized and would not be considered to represent a true AMI by other researchers. This is not a very large study compared with others included in OSE's systematic review, all of which reported an increased risk of AMI with rosiglitazone compared with pioglitazone. The effect of the Wertz et al. study on a meta-analysis of the studies from OSE's systematic review would not contribute much weight.

Study	Design	# TZD-exposed	Person-years	TZD- exposed AMIs	#TZD-exposed deaths
Wertz[1]	Cohort	28 938	33 487	259	434
Ziyadeh	Cohort	95 002	72 751	460	NA
Gerrits	Cohort	29 911	37 404	375	NA
Habib	Cohort	4 273	---	---	---
Brownstein	Cohort	2 685	---	---	---
Lipscombe	Case-control	NA	NA	469	599
Koro	Case-control	NA	NA	2 059	NA
Dormuth	Case-control	NA	NA	697	NA
Stockl	Case-control	NA	NA	271	NA

[1] Includes emergency department diagnoses of AMI that were not hospitalized

When we examine studies limited to patients age 65 years or older, the HealthCore study is seen to be relatively speaking, even smaller than for studies that included all ages (table above). The HealthCore was more than 10-fold smaller than the Graham et al. study, and more than 5-fold smaller than either the Juurlink et al. or the Winkelmeyer et al. studies. Each of these latter studies applied more rigorous methods with validated inpatient AMIs and complete ascertainment of death, and all reported clinically meaningful and statistically significant increases in risk for hospitalized heart failure and mortality with rosiglitazone compared with pioglitazone.

Study	Design	# TZD-exposed	Person-years	TZD- exposed AMIs	#TZD-exposed deaths
Wertz[1]	Cohort	5 377	7 600	109	311
Graham	Cohort	227 571	101 323	1 746	2 562
Juurlink	Cohort	39736	38 752	698	1 022
Winkelmeyer	Cohort	28 370	29 060	737	1 869

[1] Includes emergency department diagnoses of AMI that were not hospitalized

In my view, the HealthCore study does not in any way alter the conclusions we reached previously. The observational data overwhelmingly support the conclusion that rosiglitazone increases AMI risk in general populations not restricted to the elderly compared with pioglitazone and that rosiglitazone increases the risk of hospitalized (serious) heart failure and all-cause mortality in the elderly compared with pioglitazone. Important methodologic issues reduce even more the utility or interpretability of the HealthCore study.

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

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/s/

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