Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

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Context  Peroxisome proliferator–activated receptors (PPARs) are nuclear transcription factors that modulate gene expression. Therapeutic agents targeting 2 distinct families of PPARs (α and γ) have been introduced in the United States. The first dual-PPAR agonist, muraglitazar, was reviewed by a US Food and Drug Administration (FDA) advisory committee on September 9, 2005, resulting in a vote of 8:1 recommending approval for its use in controlling blood glucose levels in patients with type 2 diabetes.

Objective  To evaluate the incidence of death, myocardial infarction (MI), stroke, congestive heart failure (CHF), and transient ischemic attack (TIA) in diabetic patients treated with muraglitazar compared with controls.

Design, Setting, and Participants  The source material for this analysis consisted of documents about phase 2 and 3 clinical trials released under public disclosure laws for the FDA advisory committee meeting. All reviewed trials were prospective, randomized, double-blind, multicenter studies enrolling patients with type 2 diabetes and hemoglobin A1c levels between 7% and 10%. Patients (N=3725) were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo as monotherapy or in combination with metformin or gemfibrozil in trials ranging from 24 to 104 weeks.

Main Outcome Measures  The primary outcome was the incidence of death, nonfatal MI, or nonfatal stroke. A more comprehensive composite outcome included these events plus the incidence of CHF and TIA.

Results  In the muraglitazar-treated patients, death, MI, or stroke occurred in 35 of 2374 (1.47%) patients compared with 9 of 1351 (0.67%) patients in the combined placebo and pioglitazone treatment groups (controls) (relative risk [RR], 2.23; 95% confidence interval [CI], 1.07-4.66; P=.03). For the more comprehensive outcome measure that included TIA and CHF, the incidence was 50 of 2374 (2.11%) for muraglitazar compared with 11 of 1351 (0.81%) for controls (RR, 2.62; 95% CI, 1.36-5.05; P=.004). Relative risks for each of the individual components of the composite end point exceeded 2.1 but were not statistically significant. Incidence of adjudicated CHF was 13 of 2374 (0.55%) muraglitazar-treated patients and 1 of 1351 controls (0.07%) (RR, 7.43; 95% CI, 0.97-56.8; P=.053).

Conclusions  Compared with placebo or pioglitazone, muraglitazar was associated with an excess incidence of the composite end point of death, major adverse cardiovascular events (MI, stroke, TIA), and CHF. This agent should not be approved to treat diabetes based on laboratory end points until safety is documented in a dedicated cardiovascular events trial.

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trials performed in diabetic patients, publicly released by the sponsor and FDA for the advisory panel meeting.9,10

**METHODS**

**Analyzed Studies**

We reviewed the FDA briefing documents available via the FDA Web site for the September 9, 2005, public hearing. There were 2 major documents, an analysis of data in the muraglitazar clinical development program provided by FDA staff and a separate document prepared by the developers of the drug (Bristol-Myers Squibb and Merck).10 These documents provide data for 5 clinical trials that assessed safety and efficacy in diabetic patients. Efficacy assessments included primarily the effects of muraglitazar on various measures of glycemic control and lipids. Safety assessment included reporting of major adverse events including cardiovascular outcomes.

Four of the reviewed studies were phase 3 trials and 1 study was identified as phase 2. Two different comparators were studied in these 5 trials: placebo and the approved PPAR-γ agonist pioglitazone. A high rate of edema and CHF with high doses of muraglitazar was observed early in the development program and the sponsor ceased development of daily dosages higher than 5 mg, only requesting regulatory approval for dosages of 5 mg/d or less.10 Accordingly, we restricted our analysis to treatment groups using muraglitazar doses of 5 mg/d or less. This analysis yielded 2374 patients exposed to muraglitazar and 1351 patients exposed to comparators (placebo and pioglitazone) were pooled and compared with event rates for muraglitazar. From the crude event rates, relative risks (RRs), 95% confidence intervals (CIs), and P values were calculated for each individual type of event.

The primary outcome measure was a composite end point commonly used in cardiovascular trials: the combined incidence of death, MI, or stroke. A more specific outcome measure was generated by substituting cardiovascular death for all-cause mortality. A more comprehensive outcome measure was generated by adding CHF and TIA events to the composite. Statistical comparisons between muraglitazar-treated and control patients were calculated using the Wald χ² test and SAS version 8.0 software (SAS Institute Inc, Cary, NC). P ≤ .05 was considered statistically significant.

**RESULTS**

The 5 clinical trials in patients with diabetes who were exposed to muraglitazar or a comparator are summarized in Table I. These studies varied in duration from 24 to 104 weeks and included patients who received muraglitazar monotherapy or muraglitazar in combination with 2 other diabetes treatments, either metformin or glyburide. Several features were common to all 5 trials. Patients were aged 18 to...
70 years, had a body mass index less than 41, triglycerides lower than 600 mg/dL (6.8 mmol/L), and hemoglobin A1c levels between 7% and 10%.9,10 Patients with class III or IV CHF were excluded. Also excluded were patients with a history of MI, unstable angina, stroke, TIA, angioplasty, or coronary artery bypass graft surgery within 6 months prior to enrollment. The following narratives briefly describe these studies.

CV 168006 was a phase 2 monotherapy dose-ranging trial designed to explore the effects of a 40-fold range of daily doses (from 0.5 to 20 mg) in patients with type 2 diabetes. During the first 24 weeks, mean glucose concentrations were monitored and dosages were titrated subsequently to meet prespecified levels of glycemic control. There was a long-term extension phase of 104 weeks. A single control group was included that received 15 mg/d of pioglitazone, which could be titrated up to 45 mg/d to achieve glycemic control. Because 24.9% of patients receiving the 10-mg muraglitazar dose and 40.1% of those receiving 20 mg experienced edema, these 2 doses were not used in subsequent trials.9,10

CV 168018 was a phase 3 monotherapy study of the 2.5- and 5-mg muraglitazar doses compared with a matching placebo. Only patients never previously treated with an antidiabetic agent were eligible. This trial was recently published.11

CV 168021 was a phase 3 placebo-controlled study comparing 2.5 or 5 mg of muraglitazar with placebo in diabetic patients with hyperglycemia not adequately controlled with glyburide. There was a blinded 102-week long-term phase, but these results were not available at the time of the FDA advisory panel meeting.

CV 168022 was a randomized, double-blind, placebo-controlled study that compared muraglitazar 2.5 or 5 mg with placebo in patients with hyperglycemia not adequately controlled with metformin alone.

CV 168025 was a phase 3 study of the effect of addition of 5 mg of muraglitazar compared with 30 mg of pioglitazone in patients whose hyperglycemia was not adequately controlled with metformin alone.

### Table 2. Baseline Demographic and Laboratory Characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy Studies (CV 168006, CV 168018)</th>
<th>Combination Therapy Studies (CV 168021, CV 168022, CV 168025)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Muraglitazar (n = 729)</td>
<td>Comparators (n = 366)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>53.5 (10)</td>
<td>52.5 (9.6)</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>417 (57.2)</td>
<td>198 (54.1)</td>
</tr>
<tr>
<td>White race, No. (%)</td>
<td>595 (81.6)</td>
<td>290 (79.2)</td>
</tr>
<tr>
<td>Body weight, mean (SD), kg</td>
<td>89.2 (17.9)</td>
<td>89.7 (18.5)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>31.2 (4.9)</td>
<td>31.6 (4.9)</td>
</tr>
<tr>
<td>Hemoglobin A1c, mean (SD), %</td>
<td>8.1 (1.1)</td>
<td>8.2 (1.1)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mean (SD), mg/dL</td>
<td>178 (64)</td>
<td>184 (51)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>129 (14.8)</td>
<td>129.4 (15.3)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79.7 (8.7)</td>
<td>80.1 (8.30)</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mg/dL</td>
<td>123.7 (33.3)</td>
<td>128.4 (37.6)</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mg/dL</td>
<td>43.0 (9.9)</td>
<td>43.7 (10.6)</td>
</tr>
<tr>
<td>Statin use, No. (%)</td>
<td>148 (20.3)</td>
<td>64 (17.5)</td>
</tr>
</tbody>
</table>

Abreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversions: To convert glucose to mmol/L multiply values by 0.0555; to convert cholesterol to mmol/L multiply values by 0.0259.
*Values represent the number of patients for which data were submitted by the study sponsors.9,10
†Calculated as weight in kilograms divided by height in meters squared.

### Table 3. Mortality and Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy Studies (CV 168018)</th>
<th>Combination Therapy Studies (CV 168021, CV 168022, CV 168025)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality event rates</td>
<td>136 (18.7%)</td>
<td>134 (18.0%)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>8 (1.1%)</td>
<td>7 (1.0%)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>128 (17.6%)</td>
<td>127 (17.7%)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>128 (17.6%)</td>
<td>127 (17.7%)</td>
</tr>
</tbody>
</table>

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Table 3. Adverse Cardiovascular Events in the Muraglitazar Program

<table>
<thead>
<tr>
<th>Study and Therapy</th>
<th>No. of Patients Exposed</th>
<th>Noncardiovascular</th>
<th>Cardiovascular</th>
<th>MI</th>
<th>Stroke</th>
<th>CHF</th>
<th>TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV 168006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muraglitazar 0.5 mg</td>
<td>236</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Muraglitazar 1.5 mg</td>
<td>259</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Muraglitazar 5 mg</td>
<td>245</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pioglitazone 15 mg</td>
<td>251</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CV 168018</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Muraglitazar 2.5 mg</td>
<td>111</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Muraglitazar 5 mg</td>
<td>114</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Placebo</td>
<td>115</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CV 168021</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Muraglitazar 2.5 mg + glyburide</td>
<td>191</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Muraglitazar 5 mg + glyburide</td>
<td>193</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Placebo + glyburide</td>
<td>199</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CV 168022</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Muraglitazar 2.5 mg + metformin</td>
<td>233</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
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<td>0</td>
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<tr>
<td>Muraglitazar 5 mg + metformin</td>
<td>205</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Placebo + metformin</td>
<td>214</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CV 168025</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muraglitazar 5 mg + metformin</td>
<td>587</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pioglitazone 30 mg + metformin</td>
<td>572</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Totals</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Muraglitazar ≤5 mg</td>
<td>2374</td>
<td>8</td>
<td>8</td>
<td>15</td>
<td>9</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Pioglitazone or placebo</td>
<td>1351</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; TIA, transient ischemic attack.

Table 4. Event Rates and Relative Risks

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Muraglitazar (n = 2374)</th>
<th>Control (n = 1351)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV 168006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>0.7%</td>
<td>0.5%</td>
<td>1.4 (0.6-3.0)</td>
<td>.26</td>
</tr>
<tr>
<td>MI</td>
<td>1.1%</td>
<td>0.7%</td>
<td>1.5 (0.9-2.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.0%</td>
<td>4.2%</td>
<td>1.2 (0.8-1.8)</td>
<td>.23</td>
</tr>
<tr>
<td>CV 168018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>0.3%</td>
<td>0.2%</td>
<td>1.6 (0.9-2.9)</td>
<td>.12</td>
</tr>
<tr>
<td>MI</td>
<td>1.3%</td>
<td>0.8%</td>
<td>1.7 (1.0-2.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.4%</td>
<td>5.8%</td>
<td>1.3 (0.9-1.9)</td>
<td>.15</td>
</tr>
<tr>
<td>CV 168021</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>0.3%</td>
<td>0.2%</td>
<td>1.6 (0.9-2.9)</td>
<td>.12</td>
</tr>
<tr>
<td>MI</td>
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<td>5.8%</td>
<td>1.3 (0.9-1.9)</td>
<td>.15</td>
</tr>
<tr>
<td>CV 168022</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>0.3%</td>
<td>0.2%</td>
<td>1.6 (0.9-2.9)</td>
<td>.12</td>
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<tr>
<td>MI</td>
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<td>0.8%</td>
<td>1.7 (1.0-2.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Stroke</td>
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<td>5.8%</td>
<td>1.3 (0.9-1.9)</td>
<td>.15</td>
</tr>
<tr>
<td>CV 168025</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>0.3%</td>
<td>0.2%</td>
<td>1.6 (0.9-2.9)</td>
<td>.12</td>
</tr>
<tr>
<td>MI</td>
<td>1.3%</td>
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<td>1.7 (1.0-2.9)</td>
<td>.10</td>
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<tr>
<td>Stroke</td>
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<td>5.8%</td>
<td>1.3 (0.9-1.9)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; TIA, transient ischemic attack.
documents submitted to the FDA for consideration of approval may constitute the only publicly available source of objective information for newly approved pharmaceutical agents. This has been the case for muraglitazar for which the public disclosure of phase 2 and 3 data occurred via the FDA Web site shortly before the advisory panel convened to consider the drug for approval on September 9, 2005.

From these public disclosure documents, we observed a numerical excess of adverse cardiovascular events for patients treated with muraglitazar compared with controls (patients treated with either placebo or pioglitazone). Therefore, to determine the incidence of death and major adverse cardiovascular events, we carefully reviewed the clinical trial data available within these documents and included all trials performed in diabetic patients submitted to the FDA. We excluded from analysis patients treated with the higher 10- and 20-mg doses of muraglitazar because further development of these dosages was terminated after a phase 2 trial demonstrated a high incidence of peripheral edema. We also did not include a small, short-term phase 2 trial that administered the drug to persons without diabetes to examine its effects on lipid levels. The remaining patients consisted of 2374 participants exposed to 5 mg/d or less of muraglitazar and 1351 exposed to placebo or pioglitazone.

The results of this analysis are concerning. For the most widely accepted composite end point of death, MI, and stroke, the RR for muraglitazar was 2.23. Other end points using narrower definitions (including only cardiovascular death) or broader composites (including CHF and TIA events) showed similar risks. The most inclusive composite end point that included all-cause mortality, nonfatal MI, stroke, TIA, and CHF showed a highly significant increase in RR for muraglitazar-treated patients (2.62; \(P = .004\)).

Furthermore, there was a highly consistent pattern of excess morbidity for all of the components of the major outcome measure with all RRs exceeding 0.8.

2.1. The consistency in magnitude and direction of the adverse effects across multiple cardiovascular end points reduces the likelihood that these findings result from chance alone. These results are particularly concerning because the significant excess of adverse events was observed after only limited drug exposure ranging from 24 to 104 weeks. Moreover, patients who are enrolled in clinical trials often constitute the lowest-risk strata of patients, and the real world exposure would likely substantially amplify the risk. Taken as a whole, these data demonstrate that it is likely that muraglitazar, if approved by the FDA, would constitute an unacceptable patient hazard.

We believe it is always important to weigh efficacy and safety together in deciding the clinical utility of any drug. The efficacy for muraglitazar consisted of a lowering of blood glucose, reduction in triglycerides, and increase in HDL cholesterol. These laboratory end points and must be weighed in the context of the more important clinical outcomes. Drugs that lower blood glucose (sulfonylureas) or low-density lipoprotein cholesterol (ezetimibe) have been approved based on laboratory measures of efficacy. However, these approvals occurred after demonstration of excellent safety in fairly large patient populations. In contrast, muraglitazar does not lower low-density lipoprotein levels and the benefits of lowering blood glucose for other drugs have not always shown a reduction in serious vascular complications. Thus, it is particularly important to weigh the efficacy results against the safety concerns.

It must be emphasized that atherosclerotic cardiovascular disease is particularly common in patients with type 2 diabetes, representing the cause of death in approximately 80% of diabetic patients. Thus, any drug used to treat diabetes requires careful scrutiny for its effects on atherosclerosis-related outcomes, such as MI and stroke. The apparent increase in adverse cardiovascular events in muraglitazar-treated patients is surprising because the drug showed favorable effects on triglycerides and HDL cholesterol in these same clinical trials. A related drug, gemfibrozil, a pure PPAR-\(\alpha\) agent, has demonstrated impressive benefits in 2 major clinical outcome trials. However, other PPAR-\(\alpha\) and \(\gamma\) agonists have shown a variety of potential cardiovascular toxicities in preclinical studies.

The specific choice of composite end point requires additional comment. We emphasized a primary outcome measure that excluded CHF events because peripheral edema and CHF are known hazards of PPAR-\(\gamma\) agents and warnings are included in FDA-approved package inserts for pioglitazone and rosiglitazone. Nonetheless, edema was very prominent in studies of muraglitazar, particularly at higher doses, occurring in 24.9% and 40.1% of patients exposed to the 10- and 20-mg doses, respectively. Whether muraglitazar constitutes a greater or lesser risk for CHF in comparison to existing PPAR-\(\gamma\) drugs such as rosiglitazone and pioglitazone remains to be determined. The currently available data suggest that the incidence of CHF is at least as high with muraglitazar as with approved PPAR-\(\gamma\) agonists. We also excluded TIA from the primary outcome measure because this is a more subjective end point than stroke or MI.

The precise mechanism underlying the increased cardiovascular toxicity observed with muraglitazar is uncertain. In different species, PPAR agonists exhibit a variety of biological effects that, if they occur in humans, might explain the results of this analysis. It must be emphasized that each of the PPARs activate or suppress different genes with only partial overlap in activity. Accordingly, each agent must be considered separately from the efficacy and safety perspective.

The possibility of an interaction between muraglitazar and other antidiabetic therapies must also be considered. Most adverse cardiovascular events occurred in studies in which muraglitazar was combined with gliburide or metformin. However, the
number of events in any single study is too few to draw definitive conclu-
sions about the RRs of muraglitazar with or without concomitant therapy 
with other agents. Other dual-PPARs in development may or may not exhibit 
similar hazards. Major differences in the 
effects of pure PPAR-γ agonists have 
been observed. Pioglitazone and rosi-
glitazone have differing effects on 
lipids11 and neither exhibit the hepato-
toxicity that resulted in market with-
drawal of troglitazone.22 Our findings 
was small, primarily because these 
reported, not centrally adjudicated. 
available. Other than CHF, adverse 
MI, stroke, and other events were not 
databases. The exact definitions for 
not have access to the original trial 
mine incidence rates and RRs were 
our analysis. The data used to deter-
consistency of these RRs suggests that 
this risk is substantial with RRs indicating 
during relatively short-term treat-
size and mortality in diabetic patients 
during repetitive testing for hetero-
genoty. Nonetheless, some important 
came to be substantial with RRs indicat-
ing a doubling for irrevocable, major 
and composite outcomes. The 
consistency of these RRs suggests that 
this result is not due to chance. Ac-
cordingly, muraglitazar should not be 
used or approved to treat patients with 
diabetes until an appropriate dedi-
cated trial to assess cardiovascular out-
comes is performed.

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