Introduction

- This training updates prescribers on what is known about the ischemic cardiovascular risk of rosiglitazone.

- Data are inconsistent regarding the ischemic cardiovascular risk with rosiglitazone. However, overall, a review of data has led to the following actions by FDA:
  - Updating of the labeling including removal of myocardial infarction from the boxed warning in the labeling for rosiglitazone products.
  - Removal of the requirement that prescribers of rosiglitazone be certified in the Risk Evaluation and Mitigation Strategy (REMS) program.
  - Removal of the requirement that patients receiving rosiglitazone be enrolled in the REMS program.
  - Removal of the requirement that pharmacies that dispense rosiglitazone be certified in the REMS program.
Synopsis

- Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone versus metformin or sulfonylureas, particularly a cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components.

- Meta-analysis of mostly short-term trials suggested increased risk for myocardial infarction with rosiglitazone compared to placebo.
The Cardiovascular Outcome Trial: RECORD

- Randomized, open label, prospectively designed cardiovascular outcome trial with a mean follow-up of 5.5 years in 4,447 patients

- Compared addition of rosiglitazone to metformin or to a sulfonylurea vs. a control group receiving metformin plus sulfonylurea in patients with type 2 diabetes for the primary composite endpoint of cardiovascular hospitalization or cardiovascular death
The Cardiovascular Outcome Trial: RECORD

- Data from RECORD, a long-term clinical trial of rosiglitazone versus other antidiabetes agents (metformin or sulfonylureas) observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components (stroke, myocardial infarction, cardiovascular death)

Hazard Ratios:

- Composite of cardiovascular hospitalization or cardiovascular death: HR=0.99 (95% CI: 0.85-1.16)
- Stroke: HR=0.72 (95% CI: 0.49, 1.06)
- Myocardial infarction: HR=1.14 (95% CI: 0.80, 1.63)
- Cardiovascular death: HR=0.84 (95% CI: 0.59, 1.18)
Rosiglitazone REMS Program

Data from ADOPT and DREAM

2 Long Term Randomized Controlled Trials
Data from ADOPT (A Diabetes Outcome Progression Trial)

- Multicentre, double-blind, controlled trial with duration over 3 years
- Rosiglitazone was compared to metformin and to sulfonylurea in 4351 drug naive subjects recently diagnosed with type 2 diabetes
- No statistically significant differences for MACE and its components (stroke, myocardial infarction, cardiovascular death) between rosiglitazone and metformin or a sulfonylurea
Data From the DREAM Study

• Prospective assessment of treatment with either ramipril and/or rosiglitazone in 5,269 subjects with Impaired Glucose Tolerance or Impaired Fasting Glucose

• Incidence of cardiovascular events was higher in subjects who were randomized to rosiglitazone in combination with ramipril than in subjects randomized to ramipril alone

• No statistically significant differences for MACE and its components (stroke, myocardial infarction, cardiovascular death) for rosiglitazone vs. placebo
Forest Plots for 3 Long Term Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>MACE n (%)</th>
<th>Myocardial Infarction n (%)</th>
<th>Total Mortality n (%)</th>
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<tbody>
<tr>
<td>RECORD</td>
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<tr>
<td>RSG+SU or MET vs SU+MET</td>
<td>2220</td>
<td>154 (6.9%)</td>
<td>72 (3.2%)</td>
<td>136 (6.1%)</td>
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<tr>
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<td>2227</td>
<td>165 (7.4%)</td>
<td>68 (3.1%)</td>
<td>157 (7.0%)</td>
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<td>ADOPT</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSG vs. SU</td>
<td>1456</td>
<td>35 (2.4%)</td>
<td>20 (1.4%)</td>
<td>12 (0.8%)</td>
</tr>
<tr>
<td>vs. MET</td>
<td>1441</td>
<td>28 (1.9%)</td>
<td>15 (1.0%)</td>
<td>21 (1.5%)</td>
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<tr>
<td></td>
<td>1454</td>
<td>36 (2.5%)</td>
<td>17 (1.2%)</td>
<td>15 (1.0%)</td>
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<tr>
<td>DREAM</td>
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<td></td>
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<tr>
<td>RSG vs. Placebo</td>
<td>1325</td>
<td>15 (1.1%)</td>
<td>5 (0.4%)</td>
<td>15 (1.1%)</td>
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<tr>
<td></td>
<td>1321</td>
<td>14 (1.1%)</td>
<td>7 (0.5%)</td>
<td>17 (1.3%)</td>
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<td>RSG+RAM vs RAM</td>
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<td>18 (1.4%)</td>
<td>12 (0.9%)</td>
<td>15 (1.1%)</td>
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<td>1313</td>
<td>9 (0.7%)</td>
<td>5 (0.4%)</td>
<td>16 (1.2%)</td>
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<td>OVERALL</td>
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<tr>
<td>RSG vs control</td>
<td>6311</td>
<td>222 (3.5%)</td>
<td>109 (1.7%)</td>
<td>178 (2.8%)</td>
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<td>7756</td>
<td>252 (3.3%)</td>
<td>112 (1.4%)</td>
<td>226 (2.9%)</td>
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</tbody>
</table>

RSG = rosiglitazone; SU = sulfonylurea; MET = metformin; RAM = ramipril
* Myocardial infarction includes fatal and non-fatal MI plus sudden death

** Hazard Ratios for the Risk of MACE, Myocardial Infarction, and Total Mortality With Rosiglitazone Compared With a Control Group in Long-term Trials

Reference ID: 3502444
A meta-analysis was conducted of 52 double blind, randomized, controlled clinical trials (mean duration 6 months) designed to assess glucose lowering efficacy in type 2 diabetes.
Data from 52 Clinical-Trial Meta-Analysis

- **Overall**: statistically significant increased risk of myocardial infarction with rosiglitazone vs. pooled comparators (active and placebo) and a statistically non-significant increased risk of MACE with rosiglitazone versus pooled comparators
  - **Placebo-controlled trials**:
    - Statistically significant increased risk of myocardial infarction
    - Statistically non-significant increased risk of MACE
  - **Active-controlled trials**:
    - No increased risk of myocardial infarction or MACE

**Odds Ratios (OR):**

- **Rosiglitazone vs. pooled comparators**
  - Myocardial infarction: rosiglitazone vs. pooled comparators (active & placebo) 0.4% vs. 0.3%; (OR) 1.8, (95% CI 1.03, 3.25)
  - MACE with rosiglitazone versus pooled comparators (OR 1.44, 95% CI 0.95, 2.20)
- **Rosiglitazone vs. placebo**
  - Myocardial infarction: 0.4% vs. 0.2%, OR 2.23 (95% CI 1.14, 4.64)
  - MACE: 0.7% vs. 0.5%, OR 1.53 (95% CI 0.94, 2.54).
Summary

- Data from long-term, prospective, randomized, controlled clinical trials of rosiglitazone versus metformin or sulfonylureas, particularly a cardiovascular outcome trial (RECORD), observed no difference in overall mortality or in major adverse cardiovascular events (MACE) and its components.

- Meta-analysis of mostly short-term trials suggested increased risk for myocardial infarction with rosiglitazone compared to placebo.
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Approved Rosiglitazone Products

- Avandia® (rosiglitazone maleate)
- Avandamet® (rosiglitazone maleate/metformin hydrochloride)
- Avandaryl® (rosiglitazone maleate/glimepiride)
- Generic rosiglitazone products
END OF TRAINING

Thank you for your time