Lipitor and Diabetes In Women

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Legal Strategies 2013
Case Criteria
- Female, 51-70 years or younger
- BMI of 30 or less at time of Diabetes diagnosis
- Prefer no family history of diabetes
- Took Lipitor consistently for at least two months prior to diagnosis or within six months of last dosage of Lipitor
- No generic except for Greenstone
- No previous cardiac events (heart attacks)
WARNER-LAMBERT AND PFIZER HAD DUTY TO WARN ABOUT DIABETES IN 1997

- Warner Lambert’s Parke Davis division developed Lipitor (generic name Atorvastatin)

- NDA approved by FDA in December 1996.

- Warner-Lambert and Pfizer began marketing in 1997 under a co-marketing agreement.
In 1997, 21 CFR 201.57 provided that the Warning section of pharmaceutical labeling:

- Shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.
Type 2 Diabetes is a “serious hazard” which must be warned about as soon as there is evidence that it is associated with use of a drug.

Type 2 Diabetes Mellitus is characterized by insulin resistance – i.e., cells fail to respond to the normal actions of the hormone insulin resulting in hyperglycemia.
FDA REVIEW OF 1996 NDA

Table 8.8.3. Placebo-Controlled Data Grouping: Clinical Laboratory Abnormalities
[Number (% of Patients)]

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Criteria</th>
<th>Placebo N = 270</th>
<th>Alovastatin 10 mg N = 163</th>
<th>Alovastatin 20 mg N = 36</th>
<th>Alovastatin 40 mg N = 79</th>
<th>Alovastatin 80 mg N = 94</th>
<th>Combined Alovastatin N = 1122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk Phos</td>
<td>$&gt;3.00 \times ULN$</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>3 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>$&gt;ULN$</td>
<td>31 (11)</td>
<td>33 (11)</td>
<td>4 (11)</td>
<td>27 (24)</td>
<td>42 (45)</td>
<td>219 (20)</td>
</tr>
<tr>
<td>AST</td>
<td>$&gt;ULN$</td>
<td>25 (9)</td>
<td>110 (33)</td>
<td>4 (11)</td>
<td>19 (24)</td>
<td>37 (39)</td>
<td>176 (15)</td>
</tr>
<tr>
<td>BUN</td>
<td>$&gt;2.00 \times ULN$</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>CPK</td>
<td>$&gt;5.00 \times ULN$</td>
<td>0 (0)</td>
<td>4 (&lt;1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Glucose</td>
<td>$&gt;1.25 \times ULN$</td>
<td>3 (11)</td>
<td>30 (13)</td>
<td>2 (6)</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>57 (3)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>$&lt;0.75 \times LLN$</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>$&lt;0.75 \times LLN$</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>$&gt;1.50 \times ULN$</td>
<td>1 (&lt;1)</td>
<td>9 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>WBC</td>
<td>$&lt;0.75 \times ULN$</td>
<td>4 (1)</td>
<td>9 (1)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td></td>
<td>$&gt;1.50 \times ULN$</td>
<td>0 (0)</td>
<td>2 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Any Abnormality</td>
<td></td>
<td>44 (16)</td>
<td>214 (25)</td>
<td>8 (22)</td>
<td>33 (42)</td>
<td>50 (53)</td>
<td>314 (28)</td>
</tr>
</tbody>
</table>

A1k Phos = Alkaline Phosphatase; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BUN = Blood Urea Nitrogen; CPK = Creatine Phosphokinase
* Contains data for patients who received 2.5 mg (N = 11), 5 mg (N = 26), and 60 mg (N = 13) alovastatin.
Blood glucose >1.25 x ULN is diagnostic for diabetes
Placebo-controlled NDA Data re Blood Glucose > 1.25 x ULN

- Placebo = 1%
- Atorvastatin = 3%
- RR = 3
- p value = .0329

A statistically significant 3-fold increased risk of blood glucose diagnostic for diabetes is “reasonable evidence of an association of a serious hazard with a drug” requiring a warning at the outset of marketing in 1997 pursuant to 21 CFR 201.57
All-Completed Studies Data re Blood Glucose >1.25 x ULN

- Placebo = 1%
- Atorvastatin = 7%
- RR = 7

Medical Officer’s review on FDA webpage did not provide sufficient information to calculate a Fisher’s Exact Test with the all-completed studies data but with a relative risk of 7 and a larger pool of subjects it almost certainly is.
POST-MARKETING EVIDENCE OF LIPITOR’S DIABETES HAZARD

The beat goes on…
Episodes of pre-specified abnormal elevation of fasting blood glucose were fairly frequently observed during the one year study.

Abnormal elevation was more severe for blood glucose than for other laboratory measurements.

Atorvastatin was not on market in Japan until 2000 so the 1999 study was probably funded by Parke Davis

All subjects were diabetics using atorvastatin over 34 weeks

Blood glucose levels increased 9%, p value = .001

Fructosamine levels increased 22%, p value = .0001

One of the authors was a Parke Davis Mexico employee

Japanese publication graphically presented HbAlc values of 26 diabetic subjects before and after atorvastatin treatment.

HbAlc increased markedly in a few individuals and also decreased substantially in an almost equal number of subjects.

Almost immediately after introduction in 2000, two independent medical research groups in Japan reported patients with diabetes experiencing worsened glycemic control.

Reports were published in 2003


- Murakami, et al. Deteriorated FBS with Atorvastatin 5 mg for 3 months and 10 mg for 2 months (2 cases). J Cardiol, 42 (Suppl): S455, 2003
2004 PROVE-IT TIMI 22 STUDY

- The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT TIMI 22) study was a comparative study between Pravachol and Lipitor.

- Atorvastatin was associated with a statistically significant increased risk of developing an HbA1c greater than 6 -- both in non-diabetics and in diabetics.

Multiple case reports at Japanese Medical Society meetings of diabetic patients with deteriorated glucose control after using Lipitor for only several months.

- Katoh, et al. Deteriorated HbA1c with ATR 5 mg for 1 month and with ATR 10 mg for 4 months (2 cases). J Jpn Diab Soc, 48: 71, 2005
- Seguchi, et al. Deteriorated FBS/HbA1c with ATR for 3-6 months (3 cases) J Jpn Diab Soc, 48: 392, 2005
- Fukuniwa, et al. Deteriorated HbA1c with ATR 5 mg for 2 months and then with PRY 10 mg for 2 months (1 case) J Jpn Diab Soc, 48: 451, 2005
Observational study found that HbA1C deteriorated in 28% of Lipitor users after only 2-3 months of use as compared to only 7% of Pravachol users.

Pfizer’s SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) published in NEJM*

- Reduced ischemic strokes by 21 percent
- But increased hemorrhagic strokes by 66 percent
- Overall mortality rate was about the same (five more deaths in Lipitor group)
- Used by Pfizer for promotion of Lipitor for stroke prevention

However, it was not reported in the NEJM article that:

- Incidence of diabetes was 6.1% in the Lipitor group as compared to only 3.8% in the placebo group

- I.e., a statistically significant increased RR of 1.6, p value = .0002

Description of SPARCL was added to labeling in 2012 – i.e., six years later -- but neither the RR or statistical significance was shown.
Examined the effect of atorvastatin 10 mg/day, pravastatin 10 mg/day, and pitavastatin (Livalo) 2 mg/day on glycemic control in diabetic patients after 3 months in a retrospective analysis.

Random blood glucose and hemoglobin A1c levels were increased in the atorvastatin group but not in the other two statin groups. P value = .001

• Atorvastatin 10, 20, 40, and 80 mg given to 4 different treatment groups over 2 month period

• Dose response increase in fasting plasma insulin

• Dose response increase in HbA1c levels

• Dose response decrease in insulin sensitivity

*Koh KK et al. Atorvastatin Causes Insulin Resistance and Increases Ambient Glycemia in Hypercholesterolemic Patients. JACC. 2010; 55(12): 1209-1216
FDA begins investigation to evaluate the effect of statins on increases in HbA1c and fasting plasma glucose.

Prompted by results from JUPITER trial, which reported a 27% increase DM in rosuvastatin subjects.

Increase in men was only 16% but increase in women was 50%

FDA appears not to have recognized the gender effect

FDA aware that atorvastatin had previously been associated with worsening glycemic control in the 2004 PROVE-IT TIMI 22 sub study.
FDA’S Division of Metabolism and Endocrinology Products (DMEP) issued letters to all statin drug manufacturers requesting changes to the labeling so as to furnish adequate information for the safe and effective use of their statin.

Labeling changes were based on FDA’s review of clinical trial data, Adverse Event Reporting System (AERS) reports, the published literature, and the labels of other approved drugs containing information on statin co-administration.
Statin manufacturers (except Pravachol) change the Warning section of label:

5.X Endocrine Function:

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including <<STATIN>>
Epidemiology and Pfizer’s clinical trial data shows that Lipitor/Atorvastatin can cause diabetes.

The association was evident before the drug went on the market in 1997.

Present label still does not warn about the risk of diabetes – indeed, does not even use the word “diabetes”. 
Pfizer claims epidemiological data does not support Plaintiffs’ claims that Lipitor causes diabetes.

Pfizer denies it failed to adequately warn of potential risk of diabetes.
WHY ARE WE FOCUSING ON WOMEN PLAINITIFFS?

Risk of diabetes with statins is higher for women than men

If women do develop diabetes they have a higher incidence of the adverse effects caused by diabetes

No evidence proving that Lipitor benefits women using the drug for primary prevention of CHD

- In fact, Pfizer’s data shows that Lipitor increases the risk of CHD in women
Risk of diabetes with statins is higher for women than men.
If women do develop diabetes they have a higher incidence of the adverse effects caused by diabetes
Diabetes Has A Greater Impact On CVD In Women Than In Men

Age-Adjusted Relative CVD Risk*

- CHD: Men 1.5, Women 3.7
- Peripheral Artery Disease: Men 3.4, Women 6.4
- Cardiac Failure: Men 4.4, Women 8.0

*Relative CVD risk for persons with diabetes versus those without

No evidence proving that Lipitor benefits women using the drug for primary prevention of CHD
For men, the incidence of the primary endpoint appears lower in the atorvastatin group (compared to placebo) almost throughout the study period, with very significant separation near the end of the study. For women, however, the incidence of the primary endpoint actually appears lower in the placebo group throughout most of the study until study cessation (at 3.3 yrs), when the incidence lines appear to suddenly converge.

When normalized to incidence rates, these results were found even for the composite endpoint of cardiovascular events plus procedures. Overall the results for females are not strong and suggest that a comment in the labeling is warranted.
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