Fibrate Safety & Metabolism

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FDA Indications for TriCor

TriCor is indicated as adjunctive therapy to diet to **reduce elevated** LDL-C, Total cholesterol, Triglycerides and Apo B, and to **increase** HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia.
TriCor (fenofibrate) Tablets

- **Contraindicated** in those with a hypersensitivity to fenofibrate, hepatic or severe renal dysfunction and pre-existing GB disease.

- Is associated with rises in aminases: periodic LFT monitoring is required

- May lead to cholelithiasis: if confirmed TriCor should be discontinued

- May increase effects of coumadin
Fibrate Chemical Structures

- **Fenofibrate**
- **Clofibrate**
- **Gemfibrozil**
# FDA Indications for TriCor

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Occurrence</th>
<th>Lipoprotein Present in Excess</th>
<th>Chol</th>
<th>Trig</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Rare</td>
<td>Chylomicrons</td>
<td>250-400</td>
<td>&gt;2500</td>
</tr>
<tr>
<td>II A</td>
<td>Common</td>
<td>LDL</td>
<td>&gt;250</td>
<td>&lt;150</td>
</tr>
<tr>
<td>II B</td>
<td>Most common</td>
<td>LDL, VLDL</td>
<td>&gt;250</td>
<td>150-400</td>
</tr>
<tr>
<td>III</td>
<td>Rare</td>
<td>VLDL remnants</td>
<td>375-500</td>
<td>600-800</td>
</tr>
<tr>
<td>IV</td>
<td>Common</td>
<td>VLDL</td>
<td>225-275</td>
<td>375-500</td>
</tr>
<tr>
<td>V</td>
<td>Rare</td>
<td>Chylomicrons, VLDL</td>
<td>350-400</td>
<td>1700-2500</td>
</tr>
</tbody>
</table>

**TriCor is indicated in IIA, IIB, IV, V**
Drug-Drug Interactions

Statin/Fibrates

- **Combined use of fibrates and statins** has been associated with rhabdomyolysis, markedly elevated creatine kinase levels, and myoglobinuria.

- **The combined use of fenofibrate and statins should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination**.
Fenofibrate Pharmacokinetics

- Well absorbed from GI tract
- Peak plasma levels within 6-8 hours
- Excreted mainly in the urine
- Half-life of 20 hours
- *In vivo* data indicate that neither fenofibrate nor fenofibric acid undergoes oxidative metabolism (eg, cytochrome P450) to a significant extent

Drug-Drug Interactions

- Potentiation of coumarin-type anticoagulants has been observed, with prolongation of the INR
  - Caution should be exercised when coumarin anticoagulants are given in conjunction with TriCor
- Fenofibrate should be taken at least 1 hour before, or 4-6 hours after, taking a bile acid-binding resin, to avoid impeding its absorption

In vivo data indicate that neither fenofibrate nor fenofibric acid undergoes oxidative metabolism (eg, cytochrome P450) to a significant extent.
In a **single-dose drug interaction study** in 23 healthy adults the **concomitant administration** of **TriCor and pravastatin** resulted in **no clinically important difference** in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolites, 3a-hydroxy iso-pravastatin when compared to either drug given alone.
Fenofibrate Does not Increase Pravastatin Plasma Concentrations

Simvastatin Product Information Sheet

- The use of simvastatin should **not exceed 10 mg** daily in patients receiving concomitant gemfibrozil. The combined use of simvastatin and gemfibrozil should be avoided unless benefits are likely to outweigh the risks.

- **Caution should be used** when prescribing simvastatin with other lipid lowering drugs (fibrates or > 1gm niacin).

- The benefits of further alterations in lipids with combined use of fibrates and niacin should be weighed carefully against the potential risk of these combinations.
Effects of High-Dose Statins

Additional LDL-C lowering benefit of high-dose statins may be outweighed by the LFTs and increased risk of myositis.

Davidson MH. Am J Cardiol. 2002;90(suppl):50K-60K.
Glucuronidation: Explanation of Fibrate/Statin Interaction

- "Glucuronidation is a pathway for the elimination of the active hydroxy acid metabolites of simvastatin, atorvastatin, and cerivastatin."

- "The most recent evidence suggests that gemfibrozil inhibits simvastatin, atorvastatin, and, more prominently, cerivastatin glucuronidation."

- "Fenofibrates, however, appear to have a significantly less inhibitory effect on statin glucuronidation, and this may explain the lack of significant drug interaction between fenofibrate and statins."

Davidson MH. Am J Cardiol. 2002;90(suppl):50K-60K.
Glucuronidation: ? Explanation of Fibrate/Statin Interaction

- "Glucuronidation is a pathway for the elimination of the active hydroxy acid metabolites of simvastatin, atorvastatin, and cerivastatin"
- "Initially, the PK interaction between statins and gemfibrozil was thought to be the result of an interaction with cytochrome P450 pathways."
- "The most recent evidence suggests that gemfibrozil inhibits simvastatin, atorvastatin, and, more prominently, cerivastatin glucuronidation."
- "Fenofibrates, however, appear to have a significantly less inhibitory effect on statin glucuronidation, and this may explain the lack of significant drug interaction between fenofibrate and statins."

Davidson MH. Am J Cardiol. 2002;90(suppl):50K-60K.
“Further studies conducted in human liver microsomes with atorvastatin showed that, as with simvastatin, gemfibrozil was a less potent inhibitor of the CYP3A4-mediated oxidation of this drug than its glucuronidation.”

“However, with cerivastatin, the glucuronidation as well as the CYP2C8- and CYP3A4-mediated oxidation pathways were much more susceptible to inhibition by gemfibrozil than was observed with simvastatin or atorvastatin.”

“Collectively, the results of these studies provide metabolic insight into the nature of drug-drug interaction between gemfibrozil and statins, and a possible explanation for the enhanced susceptibility of cerivastatin to interactions with gemfibrozil.”

Gemfibrozil Increases Simvastatin Plasma Concentrations

Gemfibrozil Increases Cerivastatin Plasma Concentrations

Gemfibrozil, but not Bezafibrate, Increases Lovastatin Plasma Concentrations

Glucuronidation of Fibrates

Gemfibrozil and Fenofibrate

Statins utilize UGT 1A1 and 1A3 for metabolism

UGT = UDP Glucuronyl transferase

Fenofibrate primarily utilizes UGT 1A9 and 2B7 for metabolism

Gemfibrozil competitively competes with statins for UGT 1A1 and 1A3

### Effect on Glucuronidation of Statin Hydroxy Acids - Gemfibrozil Versus Fenofibrate

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Gemfibrozil IC₅₀* (µM)</th>
<th>Fenofibrate IC₅₀* (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin Hydroxy Acid</td>
<td>354</td>
<td>682</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>316</td>
<td>Not Done</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>82</td>
<td>433</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gemfibrozil Cₘₐₓ† (µM)</th>
<th>Fenofibrate Cₘₐₓ† (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-300</td>
<td>15-55§</td>
</tr>
</tbody>
</table>

*Obtained following coincubation of fibrates and simvastatin hydroxy acid in human liver microsomes.
†Reported values following 600 mg BID gemfibrozil or 200 mg QD fenofibrate in humans.
§Measured as fenofibric acid.

Prueksaritanont T, et al. Poster presented at 2002 AHA.
**Effect on Glucuronidation of Statin Hydroxy Acids - Gemfibrozil Versus Fenofibrate**

- Although glucuronidation of all statins is inhibited by gemfibrozil: simvastatin, atorvastatin, and rosuvastatin appear to be less susceptible than cerivastatin.
- Initial studies indicate the **fenofibrate** is much less inhibitory than gemfibrozil on statin glucuronidation.
- For rosuvastatin, the significant effect of gemfibrozil on both glucuronidation and oxidation is similar to cerivastatin, suggesting the potential for a pharmacokinetic interaction between this new statin and gemfibrozil.

*Prueksaritanont T, et al. Poster presented at 2002 AHA.*
Lipophilicity - Hydrophilicity

Most Lipophilic

Simvastatin
Lovastatin
Fluvastatin
Atorvastatin
Rosuvastatin
Pravastatin

Most Hydrophilic

Hydrophilic (low lipophilicity) statins may have greater accumulation in the liver via selective membrane carriers and decreased accumulation in peripheral tissues through passive diffusion and thus inhibit greater selective inhibition of liver HMG-CoA reductase.

J Pharm Sci 1991;80:830-834
Am J Cardiol 2001;97(suppl):28B-32B
Effect of Gemfibrozil and Fenofibrate on Rosuvastatin Plasma Concentrations

Ratio of rosuvastatin AUC in fibrate-treated patients to AUC in placebo-treated patients
Fenofibrate Does Not Increase Rosuvastatin Plasma Concentrations

Geometric mean (SD) plasma concentrations of rosvastatin over time on day 7 after dosing of rosvastatin alone and rosvastatin in combination with fenofibrate

# Combination Therapy: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th></th>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>↑ in $c_{\text{max}}$</td>
<td>No effect</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
<td>Not available</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ $c_{\text{max}}$ by 112%</td>
<td>No effect</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>↑ $c_{\text{max}}$ by 2-3-fold</td>
<td>No effect</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Not available</td>
<td>No effect</td>
</tr>
</tbody>
</table>

Davidson MH. *Am J Cardiol.* 2002;90(suppl):50K-60K.
### Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Simvastatin</strong></td>
<td>↑ in C\textsubscript{max} by 2-fold</td>
</tr>
<tr>
<td><strong>Pravastatin</strong></td>
<td>↑ in C\textsubscript{max} by 2-fold</td>
</tr>
<tr>
<td><strong>Rosuvastatin</strong></td>
<td>↑ in C\textsubscript{max} by 2-fold</td>
</tr>
<tr>
<td><strong>Fluvastatin</strong></td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Lovastatin</strong></td>
<td>↑ in C\textsubscript{max} by 2.8-fold</td>
</tr>
<tr>
<td><strong>Cerivastatin</strong></td>
<td>↑ in C\textsubscript{max} by 2-3–fold</td>
</tr>
</tbody>
</table>

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Davidson MH. *Am J Cardiol*. 2002;90(suppl):50K-60K.
Lipids in Diabetes Study (LDS)

- 4,191 diabetic patients without known CHD and LDL-C < 160 mg/dL from 30 centers in UK
  - Fenofibrate 200 mg + placebo
  - Cerivastatin 0.4mg + placebo
  - Cerivastatin 0.4mg + fenofibrate 200mg
  - Placebo + placebo

- Began May 1999 and closed August 2001
- Data on 1949 followed for a year have been analyzed
- No myositis or rhabomyolysis cases

ADA abstract 317  Neil A et al. The Endocrinologist 2003;13(suppl3):S17
## Fibrate/Statin Risk of Rhabdomyolysis

<table>
<thead>
<tr>
<th>Medication</th>
<th># Cases Reported</th>
<th># Rx Dispensed</th>
<th># Cases Reported per Million</th>
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</thead>
<tbody>
<tr>
<td>Fenofibrate + Any Statin</td>
<td>16</td>
<td>3,519,000</td>
<td>4.55</td>
</tr>
<tr>
<td>Fenofibrate + Cerivastatin</td>
<td>14</td>
<td>100,000</td>
<td>140.00</td>
</tr>
<tr>
<td>Fenofibrate + Other Statins</td>
<td>2</td>
<td>3,419,000</td>
<td>0.58</td>
</tr>
<tr>
<td>Gemfibrozil + Any Statin</td>
<td>590</td>
<td>6,757,000</td>
<td>87.32</td>
</tr>
<tr>
<td>Gemfibrozil + Cerivastatin</td>
<td>533</td>
<td>116,000</td>
<td>4,594.83</td>
</tr>
<tr>
<td>Gemfibrozil + Other Statins</td>
<td>57</td>
<td>6,641,000</td>
<td>8.58</td>
</tr>
</tbody>
</table>

1Adverse Event Reporting System, U.S. Food and Drug Administration.
3Concomitancy Report, VERISPAN, LLC.
Risk of Rhabdomyolysis with Fibrates and Statins

Number of cases of rhabdomyolysis reported per million prescriptions dispensed of statins other than cerivastatin in combination with fibrates.

Number of cases of rhabdomyolysis reported per million prescriptions dispensed of cerivastatin in combination with fibrates.

Jones PH & Davidson MH. A J Card 2005;95:120-122
Number of Cases of Rhabdomyolysis in Combination Therapy With Cerivastatin

Number of Cases of Rhabdomyolysis in Combination Therapy With Statins*


*Excludes cases involving cerivastatin*
Risk of Adverse Events with Fibrates

Reviewed adverse events reported to the United States Food and Drug Administration (FDA)

<table>
<thead>
<tr>
<th>AERs/One Million Rx</th>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AERs</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td>Major AERs</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Myositis</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>Rhabdomyositis</td>
<td>120</td>
<td>80</td>
</tr>
</tbody>
</table>

OR 1.24*  OR 2.41*  OR 0.95  OR 1.78*  OR 10.84*

Risk of Adverse Events with Fibrates

AERs/One Million Rx

Year

Gemfibrozil

Fenofibrate

Cerivastatin Available

Ezetimibe had no clinically significant effect on the pharmacokinetics (e.g. absorption, metabolism and excretion) or pharmacodynamics (e.g. binding action of the drug to certain receptors and consequent effects on CNS, GI tract and other CV parameters) of fenofibrate or vice versa.

Ezetimibe - Fenofibrate Pharmacokinetic Study

32 patients with hypercholesterolemia for 14 days: on strict diet

- LDL-C: -36%*
- TG (median): -32%
- HDL-C: -36%

*P ≤ 0.03 vs placebo or either drug.
Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study


Patients have no physical activity and are on a high carbohydrate low fat diet which lowers HDL-C

Mean (SE) percentage change from baseline in serum lipids on day 14 following oral administration of fenofibrate monotherapy, ezetimibe monotherapy, fenofibrate-ezetimibe co-administration therapy or placebo once daily to 14 healthy subjects with hypercholesterolemia
Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study

Combination therapy produced significantly greater reductions in LDL-C and in small LDL-III. Levels of apoCIII were also reduced greater than monotherapy with either drug.

**Fenofibrate – Ezetimibe Pharmacodynamic and Pharmacokinetic Interaction Study**

Mean (+SD) plasma concentration-time profiles of total ezetimibe (ezetimibe + ezetimibe glucuronide) and ezetimibe on day 14 following multiple dose, once-daily oral administration of either ezetimibe alone or co-administered with fenofibrate.

Concomitant fenofibrate administered as a 200 mg micronized capsule formulation resulted in a significant (~50%) increase in the steady state total ezetimibe exposure. However, this exposure is probably not clinically important. The increased plasma total ezetimibe appear to be due to an increase in ezetimibe bioavailability rather than inhibition of clearance.