National PBM Drug Monograph
Ezetimibe (Zetia®) Addendum
VHA Pharmacy Benefits Management Strategic Healthcare Group and The Medical Advisory Panel

As a result of concern regarding the tolerability profile of the bile acid sequestrants (colestipol and cholestyramine), randomized clinical trials evaluating the safety and effectiveness of a BAS added to a statin were reviewed. A total of 10 trials were identified.

In these 10 trials, patients with secondary causes of hypercholesterolemia (uncontrolled diabetes, thyroid disease, or other endocrine condition), pregnant or lactating women, kidney or liver impairment, excessive alcohol ingestion, baseline creatine kinase (CK) elevation, triglycerides >300-350 mg/dl and those receiving drugs with the potential for drug interactions with statins were excluded. The duration of the clinical trials varied from 8-36 weeks. In all of these trials, statins were administered at least one hour before or 4 hours after the resin.

In most of the included trials, the efficacy analyses were performed on a smaller number of patients than those randomized (that is, the trials did not use intention to treat statistics).

In 5 of the 10 trials, LDL-C reduction was compared with a statin alone versus a statin in combination with a resin. In these trials, the dose of the statin was the same in both groups. The addition of a resin to the statin resulted in an additional LDL-C reduction ranging from 11 to 19%. In 8 of the 10 trials, addition of a resin resulted in an increase in triglycerides of less than 10% which, in most cases, was not statistically significant.

Authors reported compliance with resins to be 80% or > in all but two studies. In those studies, by Sprecher, etal [1] and Leren, etal [3], a reduced compliance rate was attributed to increasing the dose of cholestyramine from 8 to 16 g/d. In all of the studies, reporting of gastrointestinal adverse events was greater in the resin compared to the statin group (notably constipation, abdominal pain and flatulence) and appeared to be dose-related. The reason for withdrawal from the studies was not always clear but in 2 of the studies (Pan, etal. [8] and Simons, etal [10]), withdrawal for adverse GI events was higher in the resin versus the statin monotherapy group.

Conventional thinking is that resins are somewhat poorly tolerated with low compliance rates. This raises the question of applying these data from controlled clinical trial settings to usual care. As a result, the number of compliant patients able to tolerate low dose resins may be lower.

Details of the 10 included trials begin on page 2.

<table>
<tr><th>Study</th><th>Intervention</th><th>LDL-c Reduction</th><th>Compliance with BAS</th><th>Tolerability/Adverse Effects/Withdrawals</th></tr>
<tr>
<td>Sprecher DL, etal. 1994 [1]
R, DB, PC
224 patients (baseline LDL-C 209 mg/dl)
24 weeks
ITT-not reported

Fluvastatin or placebo were double-blind and cholestyramine was open-label</td>
<td>3 phase study: (each 8 weeks)
1st
Pla, F 10, F 20
2nd
Pla, Pla + Ch 8g/d, F10, F10 + Ch 8g/d F20, F20 + Ch 8g/d
3rd
Chol increased to 16 g/d in those groups on 8 g/d.</td>
<td>
<table>
<tr><th rowspan="2">Weeks</th><th colspan="3">Mean Reduction From Baseline (%)</th></tr>
<tr><th>1-8*</th><th>9-15</th><th>16-24</th></tr>
<tr><td>Pla</td><td>1.6</td><td>1.2</td><td>1.1</td></tr>
<tr><td>F10</td><td>20.1</td><td>16</td><td>16.6</td></tr>
<tr><td>F20</td><td>20.2</td><td>19</td><td>19.4</td></tr>
<tr><td>Pla+Ch</td><td>2.3</td><td>13.6</td><td>19.2</td></tr>
<tr><td>F10+Ch</td><td>16.9</td><td>25.2</td><td>28.5</td></tr>
<tr><td>F20+Ch</td><td>22</td><td>30.6</td><td>31.4</td></tr>
</table>
*Ch not added until after first 8 weeks
</td>
<td>F: 92-99%
Ch: 73-87%
Authors commented that compliance with Ch declined over time likely because of the increase to 8 g bid in phase 3.</td>
<td>ADEs were reported as follows:
<table>
<tr><th>Treatment Group</th><th>% Reporting ADEs</th></tr>
<tr><td>Pla</td><td>57</td></tr>
<tr><td>F10</td><td>46</td></tr>
<tr><td>F20</td><td>53</td></tr>
<tr><td>Pla+Ch</td><td>87</td></tr>
<tr><td>F10+Ch</td><td>86</td></tr>
<tr><td>F20+Ch</td><td>81</td></tr>
</table>
The increase in ADEs in the Ch groups was attributed to a 2-3 fold increase in the number of patients reporting GI complaints. Notably, constipation and flatulence were higher in the Ch groups.
<table>
<tr><th>Treatment Group</th><th>Number Reported Constipation (%)</th><th>Number Reported Flatulence (%)</th></tr>
<tr><td>Pla</td><td>3 (8.1)</td><td>1 (2.7)</td></tr>
<tr><td>F10</td><td>1 (2.6)</td><td>2 (5.1)</td></tr>
<tr><td>F20</td><td>2 (5.3)</td><td>0</td></tr>
<tr><td>Pla+Ch</td><td>12 (32.4)</td><td>2 (5.4)</td></tr>
<tr><td>F10+ Ch</td><td>11 (30.6)</td><td>8 (22.2)</td></tr>
<tr><td>F20+Ch</td><td>6 (16.2)</td><td>3 (8.1)</td></tr>
</table>
Six patients dropped out (2 on Ch) because of ADE. Eight others were said to have dropped out due to lack of desire to continue (?). No mention of breakdown of these 8 patients by groups.</td>
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<tr>
<td>Hagen E, etal. 1994 [2]
R (2:1), DB
151 patients (baseline LDL-C 250 mg/dl)
18 weeks
Not ITT

Fluva compared to Ch then Fluva combined with Ch</td>
<td>12 week phase: (2 groups)
Fluva 20 mg/d for 6 weeks then 40 mg/d for the last 6 weeks.
Or
Ch 8 g/d for 1 week then 16g/d the remaining 11 weeks.
Then: (3 groups)
Fluva 20 mg/d combined with Ch 4, 8 or 16g/d for 6weeks.</td>
<td>
<table>
<tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr>
<tr><td>Fluva 40</td><td>28</td></tr>
<tr><td>Ch 16</td><td>35*</td></tr>
<tr><td>F20+Ch 4</td><td>30.4</td></tr>
<tr><td>F20+Ch 8</td><td>35.6</td></tr>
<tr><td>F20+Ch 16</td><td>46.6**</td></tr>
</table>
*p<0.001 vs F40, **p<0.001 vs other Ch groups
</td>
<td>Compliance was reported to be >90% in all groups</td>
<td>3 patients withdrawn from study (2-Fluva, 1-Ch) due to increase in LFTs.
Constipation and flatulence were the most frequent reported ADE and were dependent upon the dose of Ch. Of the 5patients reporting severe constipation or dyspepsia, 3 (6.2%) were on Ch 4 g/d and 2 (4.4%) in Ch 8 g/d (second part of study). There were 45-49 patients in each group.</td>
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<tr>
<td>Leren TP, etal 1988 [3]
OL
30 patients (baseline LDL-C 373 mg/dl)
20 week
Not ITT

Lovastatin titrated bid with subsequent addition of Ch 4 to 8 g bid</td>
<td>All patients were given lova 20 mg bid. It was increased by 20 mg/d every 4 weeks until the maximum dose of 40 mg bid. Then, Ch 4 g bid added for 4 weeks and then increased to 8 g bid.</td>
<td><table><tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr><tr><td>Lova 20 bid</td><td>29</td></tr><tr><td>Lova 40am 20pm</td><td>35.3</td></tr><tr><td>Lova 40 bid</td><td>44.8</td></tr><tr><td>Lova 40 bid+Ch 4 bid*</td><td>55</td></tr><tr><td>Lova 40 bid+Ch 8 bid*</td><td>60.9</td></tr></table>*Data included from 19 patients adhering to Ch therapy.</td>
<td>Lova: “all patients”
Ch: 16.6% (n=5) of patients failed to adhere to therapy at Ch 4 g bid and 30% (n=9) failed to adhere to Ch 8 g bid.</td>
<td>Authors commented that the noncompliance with Ch was due to known ADEs of Ch like pharyngitis, diarrhea, and constipation.

(see compliance section for adherence) No actual patients withdrew from trial due ADEs but analysis was done on only 19 patients in the combination group due to compliance problems.</td>
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<tr>
<td>Tonstad S, etal 1993[4]
R, DB, PC
57 patients (baseline LDL-C 228 mg/dl)
8 weeks
Not ITT

C 5g or 10 g added to Lova 20 mg/d compared to Pla</td>
<td>3 groups:
Lova 20 mg + C 5 g
Lova 20 mg + C 10 g
Pla

Pla group received Lova placebo capsules and C placebo granules.</td>
<td><table><tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr><tr><td>Pla</td><td>1.8%</td></tr><tr><td>Lova 20+C 5g</td><td>33.8%</td></tr><tr><td>Lova 20+C 10g</td><td>34.4%</td></tr></table>No Lova monotherapy group</td>
<td>Compliance with lovastatin and C was 92% with only 1 person consuming <75% of prescribed meds</td>
<td>Incidence of GI symptoms that were attributed possibly or probably to drug treatment were as follows:
Lova+C5 32%
Lova+C10 30%
Pla 50%

6 (15%) of the participants on active treatment reported abdominal ADEs lasting 3 weeks or longer. In the placebo group, the only GI symptom that was reported to last 3 weeks or longer was flatulence.
One patient withdrew due to inconvenience (Lova+C10)</td>
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<tr>
<td>Schrott HG, etal 1995 [5]
R, DB, PC
96 patients (baseline LDL-C 189 mg/dl)
18 weeks
Not ITT

Lova 20 mg with C 5 or 10 g/d vs Lova 40 mg/d or Pla</td>
<td>4 groups:
Pla
Lova 40 mg/d
Lova 20 mg+C 5g/d
Lova 20 mg+C 10 g/d</td>
<td><table><tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr><tr><td>Pla</td><td>1</td></tr><tr><td>Lova 40</td><td>38</td></tr><tr><td>Lova 20+C 5</td><td>38</td></tr><tr><td>Lova 20+C 10</td><td>48*</td></tr></table>*p<0.01</td>
<td>Mean compliance >90% in all groups and no differences were seen between groups.</td>
<td><table><tr><th>Treatment Group</th><th>Percent Reporting Constipation (%)</th><th>Percent Reporting Abdominal Pain (%)</th></tr><tr><td>Pla</td><td>8</td><td>4</td></tr><tr><td>Lova 40</td><td>4</td><td>4</td></tr><tr><td>Lova 20+C 5</td><td>25</td><td>4</td></tr><tr><td>Lova 20+C 10</td><td>21</td><td>13</td></tr></table>3 patients did not complete the study. No information was given regarding their assigned group or reason for withdrawal.</td>
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<table>
<tr>
<td>Denke MA, etal. 1995 [6]
Sequential, OL
26 patients (baseline LDL-C 190 mg/dl
3 treatments 12 weeks each
ITT</td>
<td>All patients received the following separated by a 4-week washout period.
Ch 8g/d
Ch 8g/d + Lova 5
Lova 20 mg/d</td>
<td><table><tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr><tr><td>Ch 8 g/d</td><td>20.5</td></tr><tr><td>Ch 8 g/d + Lova 5</td><td>31*</td></tr><tr><td>Lova 20</td><td>29</td></tr></table>*p<0.005 vs Ch 8g/d</td>
<td>Compliance was reported to be >90% in all groups.</td>
<td>Initially, patients in either Ch group reported indigestion, bloating, and constipation which lessened after the first 6 weeks of therapy.
No patients withdrew from therapy.</td>
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<tr>
<td>Hoogerbrugge N, etal. 1990 [7]
R (2:1), MC, DB
62 patients (baseline LDL-C 336 mg/dl)
28 weeks
Not ITT

Prava vs. Pla. Ch or C added if LDL-C was >193 mg/dl after 10 weeks</td>
<td>2 groups:
Pla (n=22)
Prava 40 mg/d (n=40)
After 10 weeks, if LDL-c was still 193 or >, Ch or C was added up to a maximum of Ch 24 or C 30 g/d</td>
<td>All Pla patients received resins after 10 weeks.
Only 30 of the prava patients received resins. 7 patients LDL-C were <193 mg/dl and 3 required prava reduction to 20 mg/d.<table><tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr><tr><td>Pla</td><td>2</td></tr><tr><td>Ch or C</td><td>22</td></tr><tr><td>Prava</td><td>33</td></tr><tr><td>Prava + Ch or C</td><td>45*</td></tr></table>*Adding resin to prava resulted in an added reduction of 12% vs. prava alone (p<0.01)</td>
<td>Compliance was reported at >90% in all patients completing the study.</td>
<td>No patient had to withdraw due to ADEs. No mention of GI ADEs.
No mention of dose of Ch or C.
Analysis at 28 weeks did not include information for 10 patients in the prava group.</td>
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<tr>
<td>Pan HY, etal., 1990 [8]
R, OL
33 patients (baseline LDL-C 202 mg/dl)
8 weeks
Not ITT

Prava varying doses compared then Ch added to determine effects on lipids.</td>
<td>3 groups: (4 weeks)
Prava 5 bid
Prava 10 bid
Prava 20 bid
Then:
Ch 24 g/d added to each group above for an additional 4 weeks.</td>
<td><table><tr><th>Treatment Group</th><th>Mean Reduction From Baseline (%)</th></tr><tr><td>Prava 5 bid</td><td>23.1</td></tr><tr><td>Prava 10 bid *</td><td>27.6</td></tr><tr><td>Prava 20 bid</td><td>34.5</td></tr><tr><td>Prava 5 bid+ Ch 24</td><td>56.2</td></tr><tr><td>Prava 10 bid+ Ch 24 **</td><td>47</td></tr><tr><td>Prava 20 bid+ Ch 24 ***</td><td>53.1</td></tr></table>*2 patients not included in analysis
**5 patients not included in analysis
***2 patients not included in analysis</td>
<td>No direct mention of compliance. Although in the section pertaining to pharmaco-dynamics, authors included on those patients with 80% or > compliance with study meds. Only 2 patients were not listed both on Ch.</td>
<td>No patients on prava monotherapy withdrew from the study. 2 (6%) patients on Ch withdrew due to “intolerance” to Ch.</td>
</tr>
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<tr>
<td>Ito MK, etal. 1997 [9]
R, OL
59 patients with CAD
18 weeks
ITT

Pravastatin vs. Pravastatin + Ch</td>
<td>2 groups:
Prava 10 mg/d+C 8g/d
Prava 20 mg/d

After 6 weeks, prava increased to 20 mg in the combination group and 40 mg in the monotherapy group if LDL-C>100</td>
<td>
<table>
<tr><th>Treatment Group</th><th>Median Reduction From Baseline (%)</th></tr>
<tr><td>Prava 10 + Ch 8</td><td>36.7</td></tr>
<tr><td>Prava 20 + Ch 8*</td><td>40.5</td></tr>
<tr><td>Prava 20</td><td>29.4</td></tr>
<tr><td>Prava 40</td><td>31.8</td></tr>
</table>
*Statistically greater reduction vs. either prava monotherapy group.
</td>
<td>Prava: >90%
Ch: 86%</td>
<td>Authors reported ADEs, with the exception of constipation to be similar between groups. Only 1 patient required stool softeners while others managed by increasing fluids.

Constipation reported in: 10 (36%) of those receiving Ch and 1 (3%) of those on monotherapy with prava.

Although no actual numbers (of patients or values for ALT) given, ALT was significantly changed from baseline in the combination vs. the prava monotherapy group.</td>
</tr>
<tr>
<td>Simons LA, etal. 1992 [10]
R, DB
64 patients (baseline LDL-C 288 mg/dl)
18 weeks
Not ITT

Pla vs. colestipol 5 or 10 mg. Simva added and titrated</td>
<td>3 groups:
Pla C
C 5
C 10

Each of the 3 groups received simva pla for 6 weeks, simva 20 mg/d for 6 weeks, 40 mg/d for 6 weeks.

Pla group received pla S and pla C</td>
<td>
<table>
<tr><th rowspan="2">Weeks</th><th colspan="3">Mean Reduction From Baseline (%)</th></tr>
<tr><th>6 (Pla-S)</th><th>12 (S-20)</th><th>18 (S-40)</th></tr>
<tr><td>Pla</td><td>2</td><td>36</td><td>38</td></tr>
<tr><td>C 5</td><td>11</td><td>45</td><td>48</td></tr>
<tr><td>C10</td><td>12</td><td>49</td><td>50</td></tr>
</table>
</td>
<td>Mean compliance:
Simva: 97%
C: 95%</td>
<td>3 patients withdrew from study. Two due to severe constipation (1-C5 and 1-C10) and the 3rd due to severe dyspepsia (C10).

19/61 patients reported GI ADEs attributable to study meds that were not severe enough to warrant withdrawal. Of those reporting nausea, dyspepsia, esophageal reflux or bloating, 6/7 (9.8%) were on combination therapy. 9/11 (14%) of those reporting constipation or diarrhea were on combination therapy. One patient on simva monotherapy had a bleeding hemorrhoid.</td>
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</table>

ADEs=adverse events, BAS=bile acid sequestrants, C=colestipol, CAD=coronary artery disease, Ch=cholestyramine, DB=double-blind, F=fluvastatin, ITT=intent to treat, OL=open-label, Pla=placebo, R=randomized, S=simvastatin

References

1. Sprecher DL, Abrams J, Allen JW, etal. Low-Dose Combined Therapy with Fluvastatin and Cholestyramine in Hyperlipidemic Patients. Ann Intern Med 1994;120:537-543.
2. Hagen E, Istad H, Ose L, etal. Fluvastatin Efficacy and Tolerability in Comparison and in Combination with Cholestyramine. Eur J Clin Pharmacol 1994;46:445-449.
3. Leren TP, Hjermann I, Berg K, etal. Effects of Lovastatin Alone and in Combination with Cholestyramine on Serum Lipids and Apolipoproteins in Heterozygotes for Familial Hypercholesterolemia. Atherosclerosis 1988;73:135-141.
4. Tonstad S, Ose L, Gorbitz C, etal. Effectiveness of Low-Dose Lovastatin Combined with Low-Dose Colestipol in Moderate to Severe Primary Hypercholesterolemia. Scand J Clin Lab Invest 1993;53:457-463.
5. Schrott HG, Stein EA, Dujovne CA, etal. Enhanced Low-Density Lipoprotein Cholesterol Reduction and Cost-Effectiveness by Low-Dose Colestipol Plus Lovastatin Combination Therapy. Am J Cardiol 1995;75:34-39.
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9. Ito MK, Shabetai R. Pravastatin Alone and in Combination with Low-Dose Cholestyramine in Patients with Primary Hypercholesterolemia and Coronary Artery Disease. Am J Cardiol 1997;80:799-802
10. Simons LA, Simons J, Parfitt A. Successful Management of Primary Hypercholesterolemia with Simvastatin and Low-Dose Colestipol. Med J Aust 1992;157:455-459.