**Zetia® (Ezetimibe) Drug Monograph**

**Clinical clerkship Students (Week 1)**

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**Introduction**

Zetia (Ezetimibe) is a new lipid lowering agent in the management of hyper-cholesterolemia. It's a cholesterol absorption inhibitor. Hopefully, this new class of drug can bring a new management plan
in hypercholesterolemia patients.

**Pharmacological Action**

Ezetimibe belongs to a new class of lipid-lowering agents that selectivity inhibits the intestinal absorption of cholesterol and related plant sterols. The drug is localized at the brush border of the small intestine and it inhibits the absorption of cholesterol. It prevents the transportation of both free cholesterol and plant sterols (phytosterols) from the intestinal lumen into the cell by interfering with the putative sterol transporter system. However, Ezetimibe does not have effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol or fat soluble vitamins A and D.

**Pharmacokinetics**

**Absorption:**
- After oral administration, Ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide.
- Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for Ezetimibe-glucuronide and 4 to 12 hours for Ezetimibe.
- The absolute bioavailability of Ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.
- Ezetimibe 20 mg demonstrated a median maximum concentration (Cmax) of 85ng/mL obtained at a medium time (Tmax) of 1 hour after dosing.

**Distribution:**
- Ezetimibe and Ezetimibe-glucuronide are more than 90% bound to plasma proteins.

**Metabolism:**
- Ezetimibe is metabolized in the small intestine and liver via glucuronide conjugation.
- The active metabolite Ezetimibe-glucuronide accounts for 80-90 % of total drug in plasma. The less active Ezetimibe accounts for 10-20 % of the total drug in plasma.
- About 17 % - 20 % of the total amount of drug absorbed is recycled via the enterohepatic recirculation.

**Excretion:**
- The half life of both Ezetimibe and the metabolite Ezetimibe-glucuronide is about 22 hours.
- There is about 78 % excreted through defecation (mainly Ezetimibe) and about 11% through urination (mainly is Ezetimibe-glucuronide).

**Effect of food on pharmacokinetics:**
- Concomitant food administration (high-fat or non-fat meals) had no effect on the oral bioavailability
of Ezetimibe when administered as Exetimibe 10 mg tablets. Ezetimibe can be administered with or without food.

**Effect of gender on pharmacokinetics:**
Plasma concentrations for total Ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with Ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

**Effect of age on pharmacokinetics:**
In a study comparing pharmacokinetic parameters in 12 healthy young male volunteers (18–45 years old) with 12 healthy elderly volunteers (65 years old), Ezetimibe 10 mg was administered once daily for 10 days. Plasma concentrations for total Ezetimibe are about 2-folds higher in the elderly (65 years old) than in the young (18-45 years old). LDL-C reduction and safety profile are comparable between the elderly and young subjects treated with Ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

**Pharmacokinetics in patients with renal insufficiency:**
After a single 10 mg dose of Ezetimibe in patients with severe renal disease (n=8; mean CrCL ≤ 30 ml/min), the mean AUC for total Ezetimibe was increased approximately 1.5-folds, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

**Pharmacokinetics in patients with hepatic insufficiency:**
Pharmacokinetics in patients with hepatic insufficiency after a single 10 mg dose of Ezetimibe, the mean Area Under Curve (AUC) for total Ezetimibe was increased approximately 1.7-folds in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total Ezetimibe was increased approximately 4-folds on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to unknown effects of the increased exposure to Ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, Ezetimibe is not recommended in these patients.

**Indications**
- Ezetimibe is a cholesterol absorption inhibitor for the management of hypercholesterolemia.
- Ezetimibe is indicated as an adjunct to diet, as monotherapy or in combination with Statins for primary hypercholesterolemia (heterozygous and familial and non-familial) to reduce total cholesterol, LDL-C and apolipoprotein B.
- Ezetimibe is indicated for homozygous familial hypercholesterolemia in combination with
Simvastatins or Atorvastatins either alone or as adjunct to other lipid lowering treatment (e.g. LDL apheresis) for the reduction of total cholesterol and LDL-C.

- Ezetimibe is indicated as an adjunct to diet in those patients with homozygous sitosterolemia for the reduction of elevated sitosterol and campesterol levels.

**Dosage**

- For all indications (either monotherapy or in combination with Statins), the dose is 10mg daily.
- Ezetimibe is taken either with or without food.

**Adverse Effects**

When ezetimibe is used as the monotherapy:

There would be an increase in the chest pain, dizziness, fatigue, diarrhea and myalgia, while with a reduction of abdominal pain, arthralgia, back pain as compared with that of the Statins. There would be an increased risk in viral infection, pharyngitis, sinusitis and upper respiratory tract infection.

When ezetimibe is used as combination therapy with statins:

There would be an increase in fatigue, abdominal pain, myalgia and back pain, while with a reduction in chest pain, dizziness, diarrhea, arthralgia and infection risks as compared with that of the Statins. Ezetimibe itself does not cause an elevation of serum transaminases elevation, but it does if used with Statins as combination therapy.

**Comparsion of Ezetimibe and other lipid-lowering drugs**

<table>
<thead>
<tr>
<th>Names</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
<th>Therapeutic Benefits / Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol Absorption Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓17%</td>
<td>↑1.3%</td>
<td>↓6%</td>
<td>↓Cholesterol (+/-Statins)</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↓35-60%</td>
<td></td>
<td></td>
<td>↓Cholesterol (ATO, FLU, LOV, PRA, SIM, ROS), Atherosclerosis (FLU, LOV, PRA, SIM), Coronary Heart Disease (FLU, LOV, PRA, SIM), Stroke (PRA, SIM)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>↓20-35%</td>
<td>↑5-15%</td>
<td>↓7-30%</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↓25-40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↓20-35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>↓40-65%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↓35-50%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Fibrates**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effect on Cholesterol</th>
<th>Effect on Triglycerides</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bezafibrate</td>
<td>↓5-20% (LDL may ↑ if TG very high initially)</td>
<td>↑10-20%</td>
<td>↓20-50%</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Fenofibrate may ↓TG &amp; ↓LDL more than</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil; Clofibrate was associated with ↑mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bile Acid Sequestrants**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effect on Cholesterol</th>
<th>Effect on Triglycerides</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine</td>
<td>↓15-30%</td>
<td>↑15-35%</td>
<td>No change or possible increase</td>
</tr>
<tr>
<td>Colestipol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Nicotinic acid**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Effect on Cholesterol</th>
<th>Effect on Triglycerides</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>↓5-25%</td>
<td>↑15-35%</td>
<td>↑20-50%</td>
</tr>
<tr>
<td>2 g Niacin/day helps HDL&amp;TG but only high doses affect LDL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ezetimibe alone shows smaller reduction of LDL (17%) when compared with Statins (about 30-60%) but a greater reduction of LDL than Fibrates, Niacin and Bile Acid Sequestrants as shown in the above table. Moreover, Ezetimibe shows a synergistic reduction in LDL when added to Statins. Ezetimibe alone also causes a less reduction of TG and less elevation of HDL when compared with other drugs. Yet, Ezetimibe is suggested to be used in combinations with other drugs, usually with Statins, to increase the efficacy.

### Comparison of side effect profile

**Comparison of Ezetimibe with Statins in clinical studies:**

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Placebo (%) (n=259)</th>
<th>Ezetimibe (%) (n=262)</th>
<th>All Statins (%) (n=936)</th>
<th>Ezetimibe + All Statins (%) (n=925)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>1.2</td>
<td>3.4</td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2</td>
<td>2.7</td>
<td>1.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Ezetimibe is tolerable but show relatively more chest pain, dizziness, fatigue, diarrhea and myalgia than all Statins according to the clinical studies done by Merck/Schering-Plough Pharmaceuticals. In combination with Statins, Ezetimibe shows less chest pain, dizziness, arthralgia, myalgia when compared to Ezetimibe alone.

Liver enzymes:
Monotherapy: Ezetimibe causes an elevation of LFT compared to placebo
In combination with statins: Clinically significant elevation of LFT occurred in 1.3% of patients receiving combination therapy while only 0.4% in those receiving Statins alone.

Muscle toxicity:
Monotherapy: no difference in myotoxicity between Ezetimibe and placebo
In combination with Statins: no risk for myopathy with Ezetimibe

### Comparison of side effects and contraindications of Ezetimibe and other lipid-lowering drugs:

<table>
<thead>
<tr>
<th>Names</th>
<th>Side effects / Contraindications / Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>↓intestinal cholesterol absorption, contraindicated in hepatic</td>
</tr>
<tr>
<td></td>
<td>dysfunction, monitor LFT and TG levels</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Generally better tolerated than other agents, common side effects</td>
</tr>
<tr>
<td></td>
<td>include upper GI disturbances, muscle pains, headache, rash,</td>
</tr>
<tr>
<td></td>
<td>sleep disturbances, ↑LFT, myopathy, contraindicated in active liver</td>
</tr>
<tr>
<td></td>
<td>disease, high alcohol consumption and pregnancy, monitor LFT</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
</tr>
<tr>
<td>Lovastatin</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>GI upset, rash, abdominal pain, less common (headache, pruritus,</td>
</tr>
<tr>
<td></td>
<td>dizzy, drowsy, arthralgia, ↓glucose, sleep/vision change), rare:</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>anaemia, ↑LFT, myopathy, reversible impotence &amp; increased</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>gallstones, monitor CBC, SCr, LFT</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Constipation, nausea, bloating, dysbetalipoproteinemia,</td>
</tr>
<tr>
<td>Colestipol</td>
<td>contraindicated in biliary obstruction, dysbetalippproteinemia, TG</td>
</tr>
<tr>
<td></td>
<td>greater than 4.6 mmol/l, phenyketonuric, monitor TG and LFT</td>
</tr>
</tbody>
</table>
**Niacin** | Flushing, dry eyes, pruritus, headache, GI upset, ↑glucose, monitor LFT, uric acid and glucose

Ezetimibe is quite tolerable but the use in patients when renal impairment and hepatic dysfunction must be careful because there are limited safety data to support the use of Ezetimibe in these patients.

**Drug interaction 1,2**

**With Fibrates:**  
AUC of Ezetimibe increased by 1.7 folds with administered with Gemfibrozil and with an increase of 1.5 folds when taken with Fenofibrate. Animal studies suggested that concomitant administration of Ezetimibe with Fibrates would lead to an increase in cholesterol in gallbladder and therefore is not recommended used in combination.

**With Cholestyramine:**  
AUC of Ezetimibe is decreased by 55% with concomitant Cholestyramine administration and would be resulted in lower than expected LDL-C reduction.

**With Cyclosporine:**  
Concentration of Ezetimibe would be increased by 12 folds.

**Pregnancy category C:**  
In animal studies, there would be an increase in the incidence of fetal skeletal findings.

**Precaution and Contraindication**

Ezetimibe is contraindicated in patients with known hypersensitivity to any of its components. Ezetimibe in conjunction with a Statins is contraindicated in patients with liver disease or unexplained serum transaminase elevation. Ezetimibe is classified as Pregnancy Category C, and its combined use with Statins is contraindicated in pregnant and nursing women. The use of Ezetimibe in children less than 10 years of age is not recommended, and there is limited data on its use in adolescents aged 11 to 17 years. Ezetimibe has no effect on the CYP450 enzymes, therefore, it is unlikely to interact with drugs metabolized by these enzymes. Concomitant administration of Ezetimibe with Cholestyramine decreases the mean AUC of Ezetimibe by approximately 55%. Ezetimibe dosed at least two hours before or four hours after a Bile-Acid Sequestrant may decrease chances of this interaction. The safety and efficacy of Ezetimibe administered with Fibrates have not been established, and their concomitant usage is therefore not recommended. There was a 12-folds increase in total Ezetimibe.
level in a renal transplant patient receiving Cyclosporine, therefore, close monitoring is recommended for patients receiving concomitant Ezetimibe and Cyclosporine.3,5

**Clinical Evidence**

**Primary hypercholesterolemia:**
In a randomized, double-blinded, placebo-controlled study of 892 patients on dietary control6, the efficacy and safety of Ezetimibe in patients with primary hypercholesterolemia were studied. The study consisted of 3 phases, namely the lipid lowering washout phase, the placebo run-in phase, and the 12-week double-blind treatment phase. The results of the study are summarized in the table below.

<table>
<thead>
<tr>
<th>Percent change from baseline:</th>
<th>% LDL</th>
<th>% HDL</th>
<th>% Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe 10mg</td>
<td>-17.68</td>
<td>+1.31</td>
<td>-5.65</td>
</tr>
<tr>
<td>Placebo</td>
<td>+0.36</td>
<td>-1.6</td>
<td>+5.74</td>
</tr>
</tbody>
</table>

* All differences p < 0.01

The study shows that Ezetimibe was well-tolerated and reduced LDL approximately by 17% within the first 2 weeks and persisted for the duration of the study.

In a randomized, multicentre, double-blinded study of 827 patients on dietary control7, the effect of Ezetimibe on plasma lipids in patients with primary hypercholesterolemia was studied. The study consists of a 4-week placebo lead-in and 12-week study period. The results of the study are summarized in the table below.

<table>
<thead>
<tr>
<th>Percent change from baseline:</th>
<th>% LDL (p&lt;0.01)</th>
<th>% HDL (p&lt;0.01)</th>
<th>% Triglyceride (p=0.09)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe 10mg</td>
<td>-17.7</td>
<td>+1.0</td>
<td>-1.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>+0.8</td>
<td>-1.3</td>
<td>+2.4</td>
</tr>
</tbody>
</table>

In a randomized, double-blinded, placebo-controlled 8-week active treatment phase study of 769 patients8, the followings were assessed. LDL reduction with adding Ezetimibe 10 mg daily versus placebo to stable Statins therapy requiring greater LDL reduction to meet National Cholesterol Education Program (NCEP) goals

Number of individuals achieving NCEP targets with add on Ezetimibe versus placebo

The results of the study were summarized below.
Recent studies have shown that combining Ezetimibe with Statins can further improve cardiovascular risk reduction or enhance safety for the management of dyslipidemia, owing to the serious adverse effects associated with high dose Statins. The mechanism of action of Ezetimibe is complementary to that of Statins, which inhibit cholesterol synthesis in the liver. Using both agents could therefore produce additive effects on LDL-C reduction. Moreover, the addition of 10 mg of Ezetimibe to a low dose of a Statins can avoid the risk of potentially serious adverse effects, e.g. myopathy (which is defined as a Creatinine Phosphokinase elevation of 10 times the upper limit of normal with associated muscle pain or weakness associated with exercise).
The efficacy and safety of adding Ezetimibe to ongoing Statins monotherapy was evaluated in 769 patients with primary hypercholesterolemia, all of whom required further LDL-C lowering than that obtained on Statins monotherapy. In Statins plus Ezetimibe patients, there was an additional mean 21.4% reduction in LDL-C compared with Statins plus placebo patients (25.1% versus 3.7%, \( P < 0.001 \)).\(^\text{10}\)

Also, combination therapy with Statins and Ezetimibe shows a significant advance in treatment of the Homozygous Form of Familial Hypercholesterolemia.

**Homozygous Form of Familial Hypercholesterolemia:**

Homozygous familial hypercholesterolemia (HoFH) is a rare disorder occurring in about 1 per 1,000,000 persons. LDL-C levels are severely elevated, resulting in an extremely high risk for premature CHD. Treatment with 10 mg of Ezetimibe plus a Statins (either 40 or 80 mg) produced a greater reduction in LDL-C (20.7% versus 6.7%, \( P = 0.007 \)).\(^\text{9}\)

**To sum up, the possible candidates for the combination therapy of Statins and Ezetimibe are:**

1. Persistent elevation of LDL-C despite adequate dosage of Statins
2. Patients with elevated LDL-C and homozygous form of familial hypercholesterolemia

**Safety of combination therapy:**

Unlike Gemfibrozil which can cause muscle side effect when used with Statins (with the exception of Fluvastatin), Ezetimibe is safe to use with Statins. Ezetimibe, although undergoing glucuronidation, does not affect Statins concentration. Ezetimibe used a different family of UGT that does not compete with the Statins glucuronidation enzymes (UGTIA1 and UGTIA3). In >3,000 patients evaluated with Ezetimibe in combination with a Statins, there have been no reports of myopathy.\(^\text{11}\)

However, clinical studies on the combination with other lipid lowering agents like Fibrates, Niacin and Bile Acid Resins are not as well established as that with Statins. Ezetimibe and Niacin with or without a Statins may be an option for aggressive treatment of some severe lipid disorders. Additional data are needed to assess efficacy of the co-administration of Ezetimibe and Bile Acid Resins because of the drug-drug interaction.

**Price**

Ezetrol ®Tablets, Ezetimibe 10 mg, net price 28–tab pack = £26.31 (~HKD$290)

**Reference**

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


4) DRUGDEX Editorial Staff-Ezetimibe (Drug Monograph). Hutchison TA, Shahan DR (Eds):DRUGDEX® System. MICROMEDEX,Greenwood Village, Colorado, (Edition expires [03/03]).


