Therapeutic Class Overview
Cholesterol Absorption Inhibitors

INTRODUCTION

- There are several classes of medications used to alter lipids, including the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants, omega-3 fatty acids, and nicotinic acid (niacin). Each medication class differs with respect to the mechanism by which they alter lipids, as well as to what degree; therefore, Food and Drug Administration (FDA)-approved indications for a particular medication class are influenced by the underlying lipid abnormality.

- In addition to the medication classes mentioned above, the cholesterol absorption inhibitors are also effective in the management of hypercholesterolemia and have a unique mechanism of action compared to the other available treatments. Specifically, these agents work to reduce blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol, which results in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately, lower systemic cholesterol levels. ZETIA® (ezetimibe) is the only cholesterol absorption inhibitor available and is FDA-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia.

- The role of ZETIA in the management of hypercholesterolemia is not well established. It is primarily used as monotherapy or in combination with a statin. In patients already receiving a statin, maximizing the dose of the statin can achieve similar reductions in low density lipoprotein cholesterol (LDL-C) as adding ZETIA to treatment. The addition of ZETIA may be helpful in avoiding high doses of statins. Given the results of clinical trials evaluating the safety and efficacy of ZETIA added on to treatment with a statin, use of more established lipid lowering therapies as add on therapy is likely to be a more preferred treatment (Smith et al, 2011).

- Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain essential modalities in the management of patients with hypercholesterolemia (Eckel et al, 2013; Woolley et al, 2013; Grundy et al, 2004; National Cholesterol Education Program [NCEP], 2002). In general, the statins are considered first line therapy for decreasing LDL-C levels (Woolley et al, 2013; Grundy et al, 2004; NCEP, 2002; Perk et al, 2012; Stone 2013). If after 4 to 12 weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a nonstatin therapy should be considered (Smith, 2013).

- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focuses more heavily on a patient’s overall atherosclerotic cardiovascular disease (ASCVD) risk versus achieving target LDL-C and/or non-high density lipoprotein cholesterol (non-HDL-C) levels to guide appropriate treatment. The guidelines also state that adherence to lifestyle modifications and to statin therapy should be re-emphasized before considering the addition of a non-statin drug such as ZETIA (Stone et al, 2013). Updated 2016 ACC guidance recommends ZETIA as the first-line non-statin option for most patient scenarios (Lloyd-Jones et al, 2016).

- The objective of the Synopsis of the Kidney Disease: Improving Global Outcomes (KDIGO) 2013 Clinical Practice Guideline on Lipid Management in Chronic Kidney Disease (CKD) is to offer guidance on the management of dyslipidemia and use of cholesterol lowering medications in all adults and children with known CKD (defined by reduced estimated glomerular filtration rate [eGFR] or markers of kidney damage, such as abnormal albuminuria). A key element was the recommendation for statin or statin with ZETIA treatment of adults aged 50 years or older with eGFR rates < 60 mL/min/1.73m² but not treated with chronic dialysis or kidney transplantation.

<table>
<thead>
<tr>
<th>Table 1. Medications Included Within Class Review</th>
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<tbody>
<tr>
<td>Drug</td>
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<tr>
<td>ZETIA (ezetimibe)</td>
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</table>

(Drugs@FDA, 2016; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2016)
INDICATIONS

Table 2. Food and Drug Administration Approved Indications

<table>
<thead>
<tr>
<th>Indication(s)</th>
<th>ZETIA</th>
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</thead>
<tbody>
<tr>
<td><strong>Homozygous Familial Hypercholesterolemia</strong></td>
<td>✓</td>
</tr>
<tr>
<td>In combination with atorvastatin or simvastatin to reduce elevated total</td>
<td>✓</td>
</tr>
<tr>
<td>cholesterol and low density lipoprotein cholesterol levels in patients with</td>
<td>✓</td>
</tr>
<tr>
<td>homozygous familial hypercholesterolemia, as an adjunct to other lipid</td>
<td>✓</td>
</tr>
<tr>
<td>lowering treatments (e.g., low density lipoprotein apheresis) or if such</td>
<td>✓</td>
</tr>
<tr>
<td>treatments are unavailable.</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Homozygous Sitosterolemia</strong></td>
<td>✓</td>
</tr>
<tr>
<td>Adjunctive therapy to diet for the reduction of elevated sitosterol and</td>
<td>✓</td>
</tr>
<tr>
<td>campesterol levels in patients with homozygous familial sitosterolemia.</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Primary Hyperlipidemia</strong></td>
<td>✓</td>
</tr>
<tr>
<td>Adjunctive therapy to diet for the reduction of elevated total cholesterol,</td>
<td>✓</td>
</tr>
<tr>
<td>low density lipoprotein cholesterol, apolipoprotein B (Apo B), and non-high-</td>
<td>✓</td>
</tr>
<tr>
<td>density lipoprotein cholesterol in patients with primary (heterozygous</td>
<td>✓</td>
</tr>
<tr>
<td>familial and non-familial) hyperlipidemia.</td>
<td>✓</td>
</tr>
<tr>
<td>Adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A</td>
<td>✓</td>
</tr>
<tr>
<td>reductase inhibitor (statin) to diet for the reduction of elevated total</td>
<td>✓</td>
</tr>
<tr>
<td>cholesterol, low density lipoprotein cholesterol with primary (heterozygous</td>
<td>✓</td>
</tr>
<tr>
<td>familial and non-familial) hyperlipidemia.</td>
<td>✓</td>
</tr>
<tr>
<td>Adjunctive therapy in combination with fenofibrate to diet for the reduction</td>
<td>✓</td>
</tr>
<tr>
<td>of elevated total cholesterol, low density lipoprotein cholesterol,</td>
<td>✓</td>
</tr>
<tr>
<td>apolipoprotein B and non-high density lipoprotein cholesterol in adult</td>
<td>✓</td>
</tr>
<tr>
<td>patients with mixed hyperlipidemia.</td>
<td>✓</td>
</tr>
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</table>

*(ZETIA prescribing information, 2013)*

- In December 2015, the FDA’s Endocrinologic and Metabolic Advisory Committee met to discuss Merck’s application for a label update to be applied to all ezetimibe-containing products. Based on results from the IMPROVE-IT trial, the proposed indication was ZETIA in combination with a statin are indicated to reduce the risk of cardiovascular (CV) events in patients with coronary heart disease (CHD). The FDA advisory panel voted 10-5 against expanding the use of ZETIA plus statin therapy for the reduction of CV events in patients with CHD. A few of those reasons cited with the FDA transcript included:
  - Many panel members were not convinced that the IMPROVE-IT trial results were clinically robust. Effect was small even before considering the issues regarding missing observation time.
  - Those high risk subgroups which demonstrated improved benefit, including diabetics and patients aged ≥ 75 years, were promising, but some members felt these results were currently at the point of hypothesis.
  - Some felt “CHD” was too broad for the population studied within the IMPROVE-IT trial.
  - Overall safety was generally favorable and not concerning, but some panelists expressed concerns over the small but troubling risk for hemorrhagic stroke in the ZETIA group.

- The FDA issued a complete response letter rejecting Merck’s application for a secondary-prevention indication for ezetimibe-containing products (FDA transcript, 2015).

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

**CLINICAL EFFICACY SUMMARY**

- ZETIA has consistently demonstrated superiority over placebo in the management of hypercholesterolemic conditions. ZETIA significantly lowered total cholesterol (TC), LDL-C, Apo B, non-HDL-C, and triglycerides (TG), and increased HDL-C compared to placebo in clinical studies ranging in length from 8 to 26 weeks (Salen et al, 2004; Musliner et al, 2008; Dujovne et al, 2002; Gonzalez-Ortiz et al, 2006; Knopp et al, 2003; Wierzbicki et al, 2005; Kalogirou et al, 2007).

- In line with treatment guidelines, study results also demonstrated that the addition of a cholesterol absorption inhibitor to a statin has the potential to produce further reductions in LDL-C levels compared to monotherapy with either of the agents alone (Feldman et al, 2004; Stojakovic et al, 2010; Hing Ling et al, 2012; Goldberg et al, 2006; Constance et
One study evaluated the safety and efficacy of ZETIA in children aged 6 to 10 years with heterozygous familial hypercholesterolemia (Kusters et al, 2015). A meta-analysis by Nissen et al (2016) highlighted the importance of LDL-C reduction in high-risk patients. However, it is important to note that ZETIA is approved for children aged 10 to 17 years. At baseline, patients had a mean age of 61 years, 34.6% had CHD, and a mean LDL-C level of 212.3 mg/dL. Patients were administered atorvastatin 20 mg/day and placebo in a 24 week crossover period, in which 42.6% developed muscle symptoms while taking atorvastatin but not while taking placebo. A total of 218 patients were randomized (1:2) to ZETIA 10 mg/day (n=73) or evolocumab 420 mg/month (n=145). A differential discontinuation rate was noted with 25% in ZETIA group who discontinued treatment (19.2% discontinued ZETIA and 5.8% discontinued placebo); and 21% in evolocumab group discontinued treatment (5% discontinued evolocumab and 16% discontinued placebo); however, all patients were included in analysis. Evolocumab significantly outperformed ZETIA for the co-primary end points of mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels (between group mean percent change difference, -37.8%) and from baseline to week 24 levels (ZETIA, -16.7%; 95% CI, -20.5% to -12.9% vs. evolocumab, -54.5%; 95% CI, 57.2% to 51.8%; P<0.001). At 24 weeks, there were no differences between groups in muscle symptoms (ZETIA, 28.8% vs. evolocumab, 20.7%; P=0.17); and 5 (6.8%) ZETIA-treated patients discontinued due to muscle symptoms compared to 1 (0.7%) evolocumab-treated patient. Evolocumab was associated with reduced TC and Apo B levels and increased HDL-C levels (P<0.005 for each), but no significant differences in TG or very low-density lipoprotein cholesterol (VLDL-C) levels (Nissen et al, 2016).

The IMPROVE-IT trial was a MC, DB, PC, RCT in 18,144 patients designed to assess CV outcomes through the addition of ZETIA 10 mg to simvastatin 40 mg compared to simvastatin 40 mg alone in patients hospitalized with acute coronary syndromes. After a median of 6 years, patients randomized to ZETIA/simvastatin had a 6.4% relative risk reduction (or approximately a 2% absolute reduction) of CV events (defined as a composite of CV death, nonfatal MI, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke) compared with those who received simvastatin alone (HR, 0.94; 95% CI, 0.89 to 0.99; p = 0.016). There were no significant differences in adverse events (Cannon et al, 2015).

The PRECISE-IVUS trial evaluated ZETIA with atorvastatin compared with atorvastatin monotherapy in patients who had undergone a percutaneous coronary intervention. Combination therapy resulted in significantly better coronary plaque regression and significantly lower LDL-C levels than the monotherapy group (Tsujita et al, 2015). One study evaluated the safety and efficacy of ZETIA in children aged 6 to 10 years with heterozygous familial hypercholesterolemia (ZETIA is approved for children aged 10 to 17 years) for 12 weeks. Total cholesterol, non-HDL, and Apo-B were all significantly reduced with ZETIA compared to placebo, and safety was similar to that seen in other studies with older children and adults (Kusters et al, 2015). One systemic review in children and adolescents with heterozygous familial hypercholesterolemia included evidence as it relates to treatment with ZETIA. In one trial of 248 patients, the GAUSS-3 trial compared PCSK9 inhibitor, evolocumab, to ZETIA in a 24-week, Phase 3, randomized, double-blind, active-controlled, double-dummy trial of male and female patients who had a history of intolerance to ≥ 2 statins. At baseline, patients had a mean age of 61 years, 34.6% had CHD, and a mean LDL-C level of 212.3 mg/dL. Patients were administered atorvastatin 20 mg/day and placebo in a 24 week crossover period, in which 42.6% developed muscle symptoms while taking atorvastatin but not while taking placebo. A total of 218 patients were randomized (1:2) to ZETIA 10 mg/day (n=73) or evolocumab 420 mg/month (n=145). A differential discontinuation rate was noted with 25% in ZETIA group who discontinued treatment (19.2% discontinued ZETIA and 5.8% discontinued placebo); and 21% in evolocumab group discontinued treatment (5% discontinued evolocumab and 16% discontinued placebo); however, all patients were included in analysis. Evolocumab significantly outperformed ZETIA for the co-primary end points of mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels (between group mean percent change difference, -37.8%) and from baseline to week 24 levels (ZETIA, -16.7%; 95% CI, -20.5% to -12.9% vs. evolocumab, -54.5%; 95% CI, 57.2% to 51.8%; P<0.001). At 24 weeks, there were no differences between groups in muscle symptoms (ZETIA, 28.8% vs. evolocumab, 20.7%; P=0.17); and 5 (6.8%) ZETIA-treated patients discontinued due to muscle symptoms compared to 1 (0.7%) evolocumab-treated patient. Evolocumab was associated with reduced TC and Apo B levels and increased HDL-C levels (P<0.005 for each), but no significant differences in TG or very low-density lipoprotein cholesterol (VLDL-C) levels (Nissen et al, 2016).
patients, ZETIA with simvastatin resulted in greater LDL-C reductions compared with simvastatin monotherapy after 33 weeks (mean, -54% vs. -38.1% [standard deviation (SD), 1.4% for each group]). One trial of ZETIA monotherapy (n = 138) demonstrated mean LDL-C decreases of 28% (95% CI, -31% to -25%) from baseline and a negligible change with placebo after 12 weeks (Lozano et al, 2016).

  - In 2016, the American College of Cardiology issued expert consensus pathway guidance for non-statin therapy in ASCVD due to the gaps in current evidence. ZETIA is acknowledged as the first non-statin medication that should be considered in most patient scenarios. Bile acid sequestrants may be considered second-line for certain patients whom ZETIA is not tolerated. PCSK9 inhibitors may be considered if the goals of therapy have not been achieved on maximally tolerated statin and ZETIA in higher-risk patients with clinical ASCVD or familial hypercholesterolemia (Lloyd-Jones et al, 2016).

SAFETY SUMMARY
- ZETIA, administered alone or with an HMG-CoA reductase inhibitor, is generally well tolerated. For ZETIA monotherapy, adverse events that were reported at a frequency ≥ 2% and exceeding placebo included fatigue, abdominal pain, diarrhea, influenza, upper respiratory tract infection, pharyngitis, sinusitis, arthralgia, back pain, pain in extremity, and cough.
- ZETIA is contraindicated for use in combination with a statin in patients with active liver disease or unexplained persistent elevations in liver enzymes.
- Cyclosporine may significantly increase ZETIA serum concentrations. In addition, ZETIA can increase cyclosporine serum concentrations.
- ZETIA serum concentrations may be decreased by the concomitant administration of the bile acid sequestrants.
- The use of ZETIA with a specific statin or fenofibrate should be in accordance with the prescribing information of that product. When administered with a statin, assessment of liver function should be performed at baseline and according to the statin prescribing information.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form: Strength</th>
<th>Usual Recommended Dose</th>
<th>Other Dosing Considerations</th>
<th>Administration Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZETIA (ezetimibe)</td>
<td>Tablet: 10 mg</td>
<td>Recommended dose is 10 mg once daily.</td>
<td>May be administered with a statin or with fenofibrate for incremental effect.</td>
<td>May be taken at the same time as the statin or fenofibrate.</td>
</tr>
</tbody>
</table>

|                   |                       |                                        | Dosing of ZETIA should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. |                                                 |
SPECIAL POPULATIONS

Table 4. Special Populations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population and Precaution</th>
</tr>
</thead>
</table>

* Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- ZETIA is the only cholesterol absorption inhibitor available and is Food and Drug Administration-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia. ZETIA has a unique mechanism of action compared to the other well-established lipid lowering medication classes. ZETIA works to reduce blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.
- The results from clinical trials consistently demonstrate that ZETIA is safe and effective for the management of lipid disorders, whether as monotherapy or in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) or fenofibrate.
- The 2013 ACC/AHA guidelines emphasize adherence to lifestyle modifications and to statin therapy before considering the addition of a non-statin drug. When a cholesterol absorption inhibitor is used, it is reasonable to obtain baseline hepatic transaminases before initiating ZETIA (Stone et al, 2013). Recent 2016 ACC expert consensus guidance recommends ZETIA as the first-line non-statin medication for most patient scenarios (Lloyd-Jones et al, 2016).
- A key element of the 2013 KDIGO Clinical Practice Guideline on Lipid Management in CKD includes the recommendation for statin or statin with ZETIA treatment of adults aged 50 years or older with estimated glomerular filtration rates less than 60 mL/min/1.73m² but not treated with chronic dialysis or kidney transplantation (Tonelli et al, 2013).
- ZETIA is available as a branded 10 mg tablet that is administered once daily. The role of ZETIA in the management of hypercholesterolemia has not been well established. The primary role of ZETIA has been as add on therapy with a statin. The statins are considered first-line therapy in the management of hypercholesterolemia as a result of their ability to reduce LDL-C.
- ZETIA may be helpful for avoiding high doses of statins in patients who are unable to achieve their lipid goals on low dose statin therapy.
- Additional clinical trials are warranted to further establish the place of ZETIA in therapy.

REFERENCES


• ZETIA prescribing information. Merck & Co. Inc. Whitehouse Station, NJ. August 2013.

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