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 inhibitor Zetia (ezetimibe) is also effective in the management of hypercholesterolemia and has a unique mechanism of action compared to the other available treatments. Specifically, this agent works 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. 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 ezetimibe 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 statin dose can achieve similar reductions in low density lipoprotein cholesterol (LDL-C) as adding ezetimibe to treatment. The addition of ezetimibe may be helpful in avoiding high doses of statins *(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, Canoniero et al 2017).* In general, the statins are considered first line therapy for decreasing LDL-C levels (*Canoniero et al 2017, 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 (*Stone 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 guideline also states that adherence to lifestyle modifications and to statin therapy should be re-emphasized before considering the addition of a non-statin drug such as ezetimibe (*Stone et al 2013).* Updated 2016 ACC guidance recommends ezetimibe as the first-line non-statin option for most patient scenarios (*Lloyd-Jones et al 2016).*

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Zetia (ezetimibe)	✔

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Zetia (ezetimibe)
Homozygous Familial Hypercholesterolemia	
In combination with atorvastatin or simvastatin to reduce elevated total cholesterol and low density lipoprotein cholesterol levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid lowering treatments (e.g., low density lipoprotein apheresis) or if such treatments are unavailable.	✔
Homozygous Sitosterolemia	
Adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.	✔
Primary Hyperlipidemia	
Adjunctive therapy to diet for the reduction of elevated total cholesterol, low density	✔

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Indications	Zetia (ezetimibe)
lipoprotein cholesterol, apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol in patients with primary (heterozygous familial and non-familial) hyperlipidemia.	
Adjunctive therapy in combination with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, apolipoprotein B, and non-high-density lipoprotein cholesterol with primary (heterozygous familial and non-familial) hyperlipidemia.	✔
Adjunctive therapy in combination with fenofibrate to diet for the reduction of elevated total cholesterol, low density lipoprotein cholesterol, apolipoprotein B and non-high density lipoprotein cholesterol in adult patients with mixed hyperlipidemia.	✔

(*Zetia prescribing information 2013)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.
- 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 ezetimibe 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 ezetimibe plus statin therapy for the reduction of CV events in patients with CHD. A few of those reasons cited in 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 ezetimibe group.
- The FDA issued a complete response letter rejecting Merck's application for a secondary-prevention indication for ezetimibe-containing products *(FDA transcript 2015).*

CLINICAL EFFICACY SUMMARY

- In clinical trials, ezetimibe consistently demonstrated superiority over placebo in the management of hypercholesterolemic conditions. Ezetimibe 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 *(Dujovne et al 2002, Gonzalez-Ortiz et al 2006, Kalogirou et al 2007, Knopp et al 2003, Musliner et al 2008, Salen et al 2004, Wierzbicki et al 2005).*
- 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 *(Ballantyne et al 2003, Bays et al 2004, Chenot et al 2007, Constance et al 2007, Feldman et al 2004, Feldman et al 2006, Goldberg et al 2004, Goldberg et al 2006, Hing Ling et al 2012, Kerzner et al 2003, Okada et al 2011, Ose et al 2007, Pearson et al 2007, Stein et al 2004, Stojakovic et al 2010).*
- In addition, when a cholesterol absorption inhibitor was combined with fenofibrate, significant reductions in LDL-C, TG and TC were observed as compared to either therapy alone *(Ansquer et al 2009, Farnier et al 2005, McKenney et al 2006)*.
- The ODYSSEY Mono trial compared the cholesterol absorption inhibitor to the fully human monoclonal antibody against proprotein convertase subtilisin/kexin 9 (PCSK9) alirocumab. It was a 24-week, Phase 3, randomized, double-blind (DB), active-controlled (AC), double-dummy trial of male and female patients aged ≥ 18 years with a 10-year risk of fatal CV events of ≥ 1% and < 5%, based on the European Systematic Coronary Risk Estimation. Patients were not receiving statin or any other lipid-lowering therapy for at least four weeks prior to screening and were randomized (permuted-block design) in a 1:1 ratio to receive either ezetimibe 10 mg/day orally plus SC placebo every 2 weeks (n=51) or alirocumab 75 mg SC every 2 weeks plus oral placebo daily (n=52). The primary endpoint was the percent change from baseline in calculated LDL-C at 24 weeks. Mean baseline LDL-C levels were 141.1 mg/dL in the alirocumab arm and 138.3 mg/dL

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in the ezetimibe arm. For the primary efficacy analysis, least-squares (LS) mean (standard error [SE]) percent reductions in LDL-C from baseline to week 24 were 47 (3)% in the alirocumab group vs. 16 (3)% in the ezetimibe group, with a statistically significant LS mean (SE) difference between groups of 32 (4)% ($p < 0.0001$). Alirocumab demonstrated tolerability and safety comparable with ezetimibe. Alirocumab demonstrated superior efficacy in monotherapy compared with ezetimibe over 24 weeks of treatment *(ClinicalTrials.gov NCT01644474 2014; Roth et al 2014*). A pooled analysis of eight ODYSSEY clinical trials of up to 104 weeks in high-risk patients receiving background statin therapy found that alirocumab reduced LDL-C levels to a significantly greater degree than both ezetimibe and placebo in various pooled analyses, with results sustained up to week 104 *(Farnier et al 2016).*

- The GAUSS-3 trial compared PCSK9 inhibitor evolocumab to ezetimibe in a 24-week, Phase 3, randomized, DB, AC, double-dummy trial of 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 ezetimibe 10 mg/day (n=73) or evolocumab 420 mg/month (n=145). Evolocumab significantly outperformed ezetimibe 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 (ezetimibe, -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 (ezetimibe, 28.8% vs. evolocumab, 20.7%; $p = 0.17$). 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).*
- A meta-analysis that compared PCSK9 inhibitors to ezetimibe (2 randomized controlled trials [RCTs]) and ezetimibe and statins (5 RCTs) found an LDL-C reduction of 30.2% (95% CI, 34.18 to 26.23) with PCSK9 inhibitors compared to ezetimibe alone and a reduction of 39.2% (95% CI, 56.15 to 22.26) compared to ezetimibe plus statins. The risk difference (RD) for risk of cardiovascular disease events (3 RCTs) was 1.06% (OR 0.45; 95% CI, 0.27 to 0.75) with PCSK9 inhibitors compared to ezetimibe plus statins; however, the data was of very low quality so the finding was considered to have considerable uncertainty. Risk of adverse events (4 RCTs) were increased with PCSK9 inhibitors compared to ezetimibe plus statins (RD, 3.7%; OR, 1.18; 95% CI, 1.05 to 1.34) *(Schmidt et al 2017).*
- The IMPROVE-IT trial was a multi-center (MC), DB, placebo-controlled (PC), RCT in 18,144 patients designed to assess CV outcomes through the addition of ezetimibe 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 ezetimibe/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 ezetimibe 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 monotherapy *(Tsujita et al 2015).*
- One study evaluated the safety and efficacy of ezetimibe in children aged 6 to 10 years with heterozygous familial hypercholesterolemia (ezetimibe is approved for children aged 10 to 17 years) for 12 weeks. Total cholesterol, non-HDL, and Apo-B were all significantly reduced with ezetimibe compared to placebo, and safety was similar to that seen in other studies with older children and adults *(Kusters et al 2015).* One systematic review in children and adolescents with heterozygous familial hypercholesterolemia included evidence as it related to treatment with ezetimibe. In one trial of 248 patients, ezetimibe with simvastatin resulted in greater LDL-C reductions compared with simvastatin monotherapy after 33 weeks (mean, -54% vs. -38.1% [standard deviation, 1.4% for each group]). One trial of ezetimibe 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).*

CLINICAL GUIDELINES

- Current treatment guidelines recognize ezetimibe monotherapy or in combination with statin therapy as an LDL-C lowering option *(Canoniero et al 2017, Cuchel et al 2014, Jellinger et al 2017, Lloyd-Jones et al 2016, Stone et al 2013).*
  - In 2016, the American College of Cardiology issued expert consensus pathway guidance for non-statin therapy in ASCVD due to gaps in current evidence. Ezetimibe 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 who

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do not tolerate ezetimibe. PCSK9 inhibitors may be considered in higher-risk patients with clinical ASCVD or familial hypercholesterolemia if goals of therapy have not been achieved on maximally tolerated statin and ezetimibe *(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 combination statin/ezetimibe treatment of adults aged 50 years or older with eGFR rates < 60 mL/min/1.73m^2 but not treated with chronic dialysis or kidney transplantation (*Tonelli et al 2013).*

SAFETY SUMMARY

- Ezetimibe, administered alone or with statin, is generally well tolerated. For ezetimibe monotherapy, adverse events that were reported at a frequency ≥ 2% and exceeding placebo included diarrhea, fatigue, upper respiratory tract infection, sinusitis, influenza, arthralgia, and pain in extremity.
- Ezetimibe 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 ezetimibe serum concentrations. In addition, ezetimibe can increase cyclosporine serum concentrations.
- Ezetimibe serum concentrations may be decreased by the concomitant administration of the bile acid sequestrants.
- The use of ezetimibe 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.
- Ezetimibe is Pregnancy Risk Factor C. Adverse events were observed in some animal reproduction studies. Use is contraindicated in pregnant women who require combination therapy with a statin.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Zetia (ezetimibe)	Tablets	oral	Daily	FDA approved for use in children ages 10 to 17 for the treatment of heterozygous familial hypercholesterolemia.

See the current prescribing information for full details

CONCLUSION

- Ezetimibe is the only cholesterol absorption inhibitor available and is FDA-approved for the treatment of primary hyperlipidemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia. Ezetimibe has a unique mechanism of action and reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.
- The results from clinical trials consistently demonstrate that ezetimibe is safe and effective for the management of lipid disorders, whether as monotherapy or in combination with a 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 (*Stone et al 2013).* Recent 2016 ACC expert consensus guidance recommends ezetimibe as the first-line non-statin medication for most patient scenarios *(Lloyd-Jones et al 2016).*
- Ezetimibe is available as a branded or generic 10 mg tablet that is administered once daily. The role of ezetimibe in the management of hypercholesterolemia has not been well established. The primary role of ezetimibe 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.
- Ezetimibe may be helpful for avoiding high doses of statins in patients who are unable to achieve their lipid goals on low- to moderate-dose statin therapy. Additional clinical trials are warranted to further establish the place of ezetimibe in therapy.

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