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 (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 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/1.73m^2 but not treated with chronic dialysis or kidney transplantation.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ZETIA (ezetimibe)	Merck	10/25/2002	✔

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication(s)	ZETIA
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 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)

- 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

al, 2007; Stein et al, 2004; Okada et al, 2011; Pearson et al, 2007; Feldman et al, 2006; Ose et al, 2007; Bays et al, 2004; Goldberg et al, 2004; Chenot et al, 2007; Kerzner et al, 2003; Ballantyne et al, 2003).

- In addition, when a cholesterol absorption inhibitor was combined with fenofibrate, significant reductions in LDL-C, TG and TC were also observed as compared to either therapy alone (McKenney et al, 2006; Farnier et al, 2005; Ansquer et al, 2009).
- 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, active-controlled, 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 ZETIA 10 mg/day orally plus alirocumab placebo administered subcutaneously (SC) every two weeks (n=51) or alirocumab 75 mg SC every two weeks plus ZETIA 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 in the ZETIA arm. For the primary efficacy analysis (intention-to-treat 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 ZETIA group, with a statistically significant LS mean (SE) difference between groups of 32 (4)% (P<0.0001). Alirocumab demonstrated tolerability and safety comparable with ZETIA. Alirocumab demonstrated superior efficacy in monotherapy compared with ZETIA 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 ZETIA 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 ZETIA in a 24-week, Phase 3, randomized, double-blind, active-controlled, 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 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, 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).

- Current treatment guidelines recognize ZETIA monotherapy or in combination with statin therapy as an LDL-C lowering option. However, they do not suggest cardiovascular benefits from use of ZETIA (Cuchel et al, 2014; Grundy et al, 2004; Jellinger et al, 2012; Lloyd-Jones et al, 2016; Stone et al, 2013; Woolley et al, 2013).
  - 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

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
ZETIA (ezetimibe)	Tablet: 10 mg	Recommended dose is 10 mg once daily.	May be administered with a statin or with fenofibrate for incremental effect. Dosing of ZETIA should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.	May be taken at the same time as the statin or fenofibrate.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ZETIA (ezetimibe)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	FDA approved for use in children ages 10 to 17 for the treatment of heterozygous familial hypercholesterolemia.	No dosage adjustment required.	No dosage adjustment required in mild hepatic dysfunction. Use is not recommended in moderate to severe hepatic dysfunction.	Pregnancy Category C* Unknown; use with caution.

* 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/1.73m^2 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

- Ansquer JC, Bekaert I, Guy M, et al. Efficacy and safety of coadministration of fenofibrate and ezetimibe compared to each as monotherapy in patients with type IIb dyslipidemia and features of the metabolic syndrome. Am J Cardiovasc Drugs. 2009;9(2):91-101.
- Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003 May 20;107(19):2409-15.
- Bays HE, Ose L, Fraser N, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared to ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther. 2004 Nov;26(11):1758-73.
- Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT). N Engl J Med. 2015;372(25):2387-2397.

- Chenot F, Montant PF, Marcovitch O, et al. Co-administration of ezetimibe and simvastatin in acute myocardial infarction. Eur J Clin Invest. 2007 May;37(5):357-63.
- ClinicalTrials.gov NCT01644474. Efficacy and Safety of Alirocumab SAR236553 (REGN727) Versus Ezetimibe in Patients With Hypercholesterolemia (ODYSSEY Mono). Last updated October 7, 2015. Available at: http://clinicaltrials.gov/show/NCT01644474. Accessed December 14, 2016.
- Constance C, Westphal S, Chung N, et al. Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared to atorvastatin 20 mg in patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2007 Jul;9(4):575-84.
- Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146-57.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2016. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed December 14, 2016.
- Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol. 2002 Nov 15;90(10):1092-7.
- Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2960-84.
- Farnier M, Freeman MW, Macdonell G, et al. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. Eur Heart J. 2005; 26:897-905.
- Farnier M, Gaudet D, Valcheva V, et al. Efficacy of alirocumab in high cardiovascular risk populations with or without heterozygous familial hypercholesterolemia: Pooled analysis of eight ODYSSEY Phase 3 clinical program trials. Int J Cardiol. 2016;223:750-757.
- Feldman T, Koren M, Insull W Jr, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004 Jun 15;93(12):1481-6.
- Feldman T, Davidson M, Shah A, et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe coadministered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post hoc analysis of subpopulations from three pooled clinical trials. Clin Ther. 2006 Jun;28(6):849-59.
- Food and Drug Administration (FDA) transcript. Zetia and Vytorin proposed indication: IMPROVE-IT Study. Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting. December 14, 2015. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM484886.pdf. Accessed December 12, 2016.
- Goldberg RB, Guyton JR, Mazzone T, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006 Dec;81(12):1579-88.
- Goldberg AC, Sapre A, Liu J, et al. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2004 May;79(5):620-9.
- Gonzalez-Ortiz M, Martinez-Abundis E, Kam-Ramos AM, et al. Effect of ezetimibe on insulin sensitivity and lipid profile in obese and dyslipidaemic patients. Cardiovasc Drugs Ther. 2006:20(2):143-6.
- Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
- Hing Ling PK, Civeira F, Dan AG, et al. Ezetimibe/simvastatin 10/40 mg versus atorvastatin 40 mg in high cardiovascular risk patients with primary hypercholesterolemia: a randomized, double-blind, active-controlled, multicenter study. Lipids Health Dis. 2012 Jan 31;11:18.
- Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012 Mar-Apr;18 Suppl 1:1-78.
- Kalogirou M, Tsimihodimos V, Gazi I, et al. Effect of ezetimibe monotherapy on the concentration of lipoprotein subfractions in patients with primary dyslipidaemia. Curr Med Res Opin. 2007 May; 23(5):1169-76.
- Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol. 2003 Feb 15;91(4):418-24..
- Knopp RH, Dujovne CA, Le Beaut A, et al. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract. 2003 Jun;57(5):363-8.
- Kusters DM, Caceres M, Coll M, et al. Efficacy and safety of ezetimibe monotherapy in children with heterozygous familial or nonfamilial hypercholesterolemia. J Pediatr. 2015;166(6):1377-1384.e1-3.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. J Am Coll Cardiol. 2016 Jul 5;68(1):92-125.
- Lozano P, Henrikson NB, Dunn J, et al. Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. JAMA. 2016 Aug 9;316(6):645-55.
- McKenney JM, Farnier M, Lo KW, et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol. 2006 Apr 18;47(8):1584-7.
- Musliner T, Cselovszky D, Sirah W, et al. Efficacy and safety of ezetimibe 40 mg vs ezetimibe 10 mg in the treatment of patients with homozygous sitosterolemia. Int J Clin Pract. 2008 Jul;62(7):995-1000.
- National Cholesterol Education Program (NCEP). Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, 2002 [guideline on the internet]. Available at: http://circ.ahajournals.org/content/106/25/3143.short?rss=1&ssource=mfc. Accessed December 12, 2016.
- Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. JAMA. 2016 Apr 19;315(15):1580-90.
- Okada K, Kimura K, Iwahashi N, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism. Circ J. 2011 Sep 22;75(10):2496-504.

- Ose L, Johnson-Levonas A, Reyes R, et al. A multi-centre, randomized, double-blind 14-week extension study examining the long-term safety and efficacy profile of the ezetimibe/simvastatin combination tablet. Int J Clin Pract. 2007 Sep;61(9):1469-80.
- Pearson T, Ballantyne C, Sisk C, et al. Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels. Am J Cardiol. 2007 Jun 15;99(12):1706-13.
- Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2012 Aug;19(4):585-667.
- Roth EM, Taskinen MR, Ginsberg HM, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24-week, double-blind, randomized Phase 3 trial. Int J Cardiol. 2014;176:55-61.
- Salen G, von Bergmann K, Lutjohann D, et al. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. Circulation. 2004;109:966-71.
- Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004 Sep;447-55.
- Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011 Nov 29;58(23):2432-46.
- Stojakovic T, de Campo A, Scharnagl H, et al. Differential effects of fluvastatin alone or in combination with ezetimibe on lipoprotein subfractions in patients at high risk of coronary events. Eur J Clin Invest. 2010;40(3):187-94.
- Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1-45.
- Tonelli M, Wanner C, for the Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid Management in Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 Clinical Practice Guideline. Ann Intern Med. 2014 Feb 4;160(3):182.
- Tsujita K, Sugiyama S, Sumida H, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. J Am Coll Cardiol. 2015;66(5):495-507.
- Wierzbicki AS, Doherty E, Lumb PJ, et al. Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipaemias. Curr Med Res Opin. 2005;21(3):333-8.
- Woolley T, Canoniero M, Conroy W, et al. Institute for Clinical Systems Improvement. Lipid Management in Adults. Updated November 2013. Available at: https://www.icsi.org/_asset/qz5ydq/LipidMgmt-Interactive1111.pdf. Accessed December 12, 2016.
- ZETIA prescribing information. Merck & Co. Inc. Whitehouse Station, NJ. August 2013.

Publication Date: December 20, 2016