Therapeutic Class Overview
Antihyperlipidemics, Miscellaneous

INTRODUCTION

- Cardiovascular disease (CVD) accounts for nearly 1 in 3 deaths in the United States (U.S.). The core health behaviors including smoking, physical activity, diet and weight; and health factors including cholesterol, blood pressure (BP), and glucose control contribute to cardiovascular (CV) health. Based on data from 2013 to 2016, among adults ≥ 20 years of age, the mean total cholesterol (TC) in the U.S. was 190.8 mg/dL, and the mean low-density lipoprotein cholesterol (LDL-C) was 112.1 mg/dL (*Virani et al 2020*).
- Evidence that serum cholesterol contributes to atherosclerotic CVD (ASCVD) comes from multiple sources, including animal studies, epidemiological studies, and randomized controlled trials (RCTs). U.S. population studies suggest that optimal TC levels are around 150 mg/dL, which corresponds to an LDL-C level of approximately 100 mg/dL. Adult populations with cholesterol concentrations in this range generally have low rates of ASCVD. RCTs of cholesterol-lowering drugs in high risk patients confirm that lowering LDL-C reduces ASCVD, confirming the general principle that "lower is better" for LDL-C levels *(Grundy et al 2019)*.
  - In addition to healthy lifestyle interventions, statins are the cornerstone of lipid-lowering therapy on the basis of morbidity and mortality outcome trials *(Grundy et al 2019, Jellinger et al 2017)*. Based on National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2014, an estimated 38.9 million people in the U.S. are prescribed statins (*Fan et al 2019*).
- There are several classes of medications used to alter lipids, including the hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants, omega-3 fatty acids, nicotinic acid (niacin), cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, and the newest class, ATP-Citrate Lyase (ACL) inhibitors. Each medication class differs with respect to the mechanism of as well as the degree of lipid-lowering; therefore, Food and Drug Administration (FDA)-approved indications for a particular medication class are influenced by the underlying lipid abnormality.
- This review will focus on the cholesterol absorption inhibitors and ACL inhibitors.
  - 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.
  - The ACL inhibitor, bempedoic acid, inhibits an earlier or upstream step in the cholesterol biosynthesis pathway from the statins, resulting in an increase in LDL receptors in the liver and increased clearance of LDL-C from the blood. The guidelines have not been updated to include bempedoic acid and its place in therapy.
- Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain essential modalities in the management of patients with hypercholesterolemia (*Arnett et al 2019, Jellinger et al 2017, Grundy et al 2019, Mach et al 2020*). In general, the statins are considered first-line therapy for decreasing LDL-C levels (*Grundy et al 2019*). Under certain circumstances, nonstatin medications (ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) may be useful in combination with statin therapy (*Grundy et al 2019*).
- Medispan Class: Intestinal Cholesterol Absorption Inhibitors; Antihyperlipidemics, Adenosine Triphosphate-Citrate Lyase Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Nexletol (bempedoic acid)	-
Nexlizet (bempedoic acid/ezetimibe)	-
Zetia (ezetimibe)	✔

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Nexletol (bempedoic acid)	Nexlizet (bempedoic acid/ ezetimibe)	Ezetimibe
Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional lowering of LDL-C	✓	✓	
Adjunct to diet to reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apoB), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia, alone or in combination with a statin			✓
Adjunct to diet to reduce elevated TC, LDL-C, apoB, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate			✓
Adjunct to diet to reduce elevated TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin			✓
Adjunct to diet to reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)			✓

(*Prescribing information: Nexletol 2020, Nexlizet 2020, Zetia 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 is indicated to reduce the risk of 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 Zetia/Vytorin transcript 2015, Merck Press Release 2016).*

CLINICAL EFFICACY SUMMARY

Ezetimibe

- In clinical trials, ezetimibe consistently demonstrated superiority over placebo in the management of hypercholesterolemic conditions. Ezetimibe significantly lowered TC, LDL-C, apoB, 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).*
- Numerous studies have demonstrated that the addition of ezetimibe 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, Hong et al 2018, Kerzner et al 2003, Okada et al 2011, Ose et al 2007, Pearson et al 2007, Sakamoto et al 2017, Shaya et al 2019, Stein et al 2004, Stojakovic et al 2010).

- In addition, when ezetimibe 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)*.
- Ezetimibe with PCSK9 inhibitors:
  - The ODYSSEY Mono trial compared ezetimibe to the PCSK9 inhibitor Praluent (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 4 weeks prior to screening and were randomized (permuted-block design) in a 1:1 ratio to receive either ezetimibe 10 mg/day orally plus subcutaneous (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 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]; Roth et al 2014*). A pooled analysis of 8 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).* Another pooled analysis of 10 ODYSSEY trials found that alirocumab reduced non-HDL-C and apoB levels to a significantly greater degree than placebo or ezetimibe at 24 weeks; this effect was maintained for up to 78 weeks (*Bays et al 2017)*.
  - The GAUSS-3 trial compared the PCSK9 inhibitor Repatha (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% confidence interval [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 apoB 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 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 CVD events (3 RCTs) was 1.06% (odds ratio [OR] 0.45; 95% CI, 0.27 to 0.75) with PCSK9 inhibitors compared to ezetimibe plus statins; however, the data were of very low quality so the finding was considered to have considerable uncertainty. Risk of adverse events (AEs) (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).*
  - A network meta-analysis of 15 trials compared different doses of PCSK9 inhibitors to one another and to ezetimibe. Patients in this analysis were on background, maximally tolerated statin therapy. Compared to ezetimibe, the percent LDL-C reductions with evolocumab 140 mg every 2 weeks, alirocumab 75 mg every 2 weeks, and alirocumab 150 mg every 2 weeks were 46.1% (95% CI, 53.28 to 39.06), 26.1% (95% CI, 31.19 to 20.81), and 32.5% (95% CI, 40.77 to 23.87), respectively. The percent LDL-C reductions with evolocumab 420 mg monthly and alirocumab 300 mg monthly compared to ezetimibe were 47.5% (95% CI, 55.22 to 39.89) and 28.3% (95% CI, 38.38 to 17.97), respectively (*Toth et al 2017*).
- CV outcomes
  - 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 myocardial infarction (MI), unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke) compared with those who received simvastatin alone (hazard ratio [HR], 0.94; 95% CI, 0.89 to 0.99; p = 0.016). There were no significant differences in AEs *(Cannon et al 2015).*

- A Bayesian network meta-analysis of 39 RCTs found that PCSK9 inhibitors had the highest probability of having the lowest risk of major adverse CV events (Surface Under Cumulative Ranking Curve [SUCRA] 85%), followed by statins (SUCRA 75%) and ezetimibe plus statins (SUCRA 51%). PCSK9 inhibitors also had the highest probability of having the lowest rate of MI and stroke (SUCRA 84% and 80%, respectively), followed by ezetimibe plus statins (SUCRA 80% and 75%) and statins (SUCRA 42% and 56%). Statins had the highest probability of having the lowest rates of all-cause mortality and CV mortality (SUCRA 82% and 84%, respectively), followed by PCSK9 inhibitors (SUCRA 81% and 78%) and ezetimibe plus statins (SUCRA 44% and 50%) (*Khan et al 2018*).
- A systematic review of 26 RCTs (N = 23,499) evaluated ezetimibe vs placebo or ezetimibe plus other lipid-modifying drugs vs other lipid-modifying drugs alone in adults, with or without CVD, with at least 12 months of follow-up for the prevention of CVD and all-cause mortality. Ezetimibe plus statins probably reduces the risk of MACE compared to statins alone (risk ratio, 0.94; 95% CI, 0.90 to 0.98; a decrease from 284/1000 to 267/1000, 95% CI, 256 to 278; 10 RCTs, N = 21,727; moderate-quality evidence). The IMPROVE-IT study carried 88.8% of the weight. All-cause mortality was not different in analyses of ezetimibe plus statins or fenofibrate (risk ratio, 0.98; 95% CI, 0.91 to 1.05; 8 studies; N = 21,222; high quality evidence). Ezetimibe plus statin reduced the risk of non-fatal MI (risk ratio, 0.88; 95% CI, 0.81 to 0.95; 6 studies; N = 21,145; moderate quality evidence) compared to statin monotherapy. The IMPROVE-IT study carried 97.8% of the weight and also provided the data on any MI and fatal MI. Ezetimibe plus statin reduced the risk of non-fatal stroke (risk ratio, 0.83; 95% CI, 0.71 to 0.97; 6 studies; N = 21,105; moderate quality evidence) compared to statin monotherapy (*Zhan et al 2018*).
- 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).* Similar results were seen in the ZIPANGU trial, which also compared atorvastatin monotherapy with a combination of ezetimibe and atorvastatin (*Ueda et al 2017*). In a study of Chinese patients who had undergone percutaneous coronary intervention, combination therapy with ezetimibe and a moderate-intensity statin produced greater reductions in non-HDL-C, TC, and LDL-C when compared to moderate-intensity statin monotherapy and intensive statin monotherapy (*Dai et al, 2017*). In a study of statin-naive patients who had undergone a percutaneous coronary intervention in Japan, combination therapy with ezetimibe and pitavastatin demonstrated a significant reduction in LDL-C vs the statin alone; however, combination therapy did not result in a significant change in coronary plaque regression or tissue component compared with statin monotherapy (*Hibi et al 2017*).

- One study evaluated the safety and efficacy of ezetimibe in children aged 6 to 10 years with HeFH (ezetimibe is approved for children aged 10 to 17 years) for 12 weeks. TC, non-HDL-C, and apoB 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 HeFH included evidence as it related to treatment with ezetimibe. In 1 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 reductions of 28% (95% CI, -31% to -25%) from baseline and a negligible change with placebo after 12 weeks (*Lozano et al 2016).*

Bempedoic acid

- The effects of bempedoic acid on the lipid parameters were studied in the Cholesterol Lowering via bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) study series, which included 2 trials in patients with ASCVD or HeFH (CLEAR WISDOM and CLEAR HARMONY) and 2 trials in patients with statin intolerance (CLEAR SERENITY and CLEAR TRANQUILITY).
  - CLEAR WISDOM (N = 779) and CLEAR HARMONY (N = 2230) were both 52-week, Phase 3, DB, MC, PC RCTs that evaluated bempedoic acid 180 mg daily in high-risk patients or patients with ASCVD or HeFH on maximally tolerated statins (*Goldberg et al 2019, Ray et al 2019*).
    - In the ASCVD/HeFH or high-risk population on maximally tolerated statins, bempedoic acid significantly reduced the mean LDL-C level by 17.4% in the CLEAR WISDOM trial to 18.1% in the CLEAR HARMONY trial at week 12 vs placebo. In CLEAR WISDOM, significant reductions were also observed for non-HDL-C, TC, and apolipoprotein

B (apoB). Significant reductions in high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, were also observed at week 12 in the bempedoic acid group compared to placebo.
    - In the CLEAR HARMONY trial, rates of AEs (primary endpoint) were similar overall in the bempedoic acid and placebo group. The rate of discontinuation due to AEs was higher in the bempedoic acid group (10.9% vs 7.1%; p = 0.005). Gout occurred more frequently in the bempedoic acid group (1.2% vs 0.3%; p = 0.03). The incidence of new-onset or worsening of diabetes mellitus (DM) was lower in the bempedoic acid group compared to placebo (3.3% vs 5.4%, respectively; p = 0.02). As a secondary endpoint, the difference from placebo in the mean LDL-C change from baseline for LDL-C was 18.1% (95% CI, -20.0 to -16.1%; p < 0.001).
  - The 24-week CLEAR SERENITY (N = 345) and the 12-week CLEAR TRANQUILITY (N = 269) trials were Phase 3, DB, MC, PC, RCTs that evaluated the mean percent change from baseline in LDL-C at week 12 in patients with statin intolerance on bempedoic acid 180 mg daily or placebo (*Ballantyne et al 2018, Laufs et al 2019*).
    - In the CLEAR SERENITY trial, statin intolerance was defined as the inability to tolerate ≥ 2 statins, with 1 trial of a low-dose statin. Approximately one-third of patients were on ezetimibe or omega-3 fatty acids, and 8.4% of patients were on very low dose statin therapy.
    - In the CLEAR TRANQUILITY trial, all patients were maintained on open-label (OL) ezetimibe 10 mg daily, and despite being statin intolerant (intolerance to ≥ 1 statin), approximately one-third of the study population was on at least some background statin therapy with 11.6% of patients on atorvastatin 10 mg daily.
    - In the statin intolerant population, bempedoic acid significantly reduced LDL-C by a range of 21.4% to 28.5%.
      - In both trials, bempedoic acid significantly reduced all secondary endpoints at week 12 including non-HDL-C, TC, apoB, and hs-CRP (all p < 0.001).
- The fixed-dose combination of simvastatin/ezetimibe 180 mg/10 mg was evaluated in 301 patients on maximally tolerated statins with high risk for CVD (*Ballantyne et al 2019*). Patients were randomized to the fixed dose combination of bempedoic acid/ezetimibe, bempedoic acid 180 mg daily, ezetimibe 10 mg daily, or placebo. The mean LDL-C baseline level was 149.7 mg/dL. At week 12, bempedoic acid/ezetimibe reduced LDL-C by 38.0% compared to placebo (95% CI, -46.5 to -29.6; p < 0.001), by 19.0% compared to bempedoic acid monotherapy (95% CI, -26.1 to -11.9; p < 0.001) and by 13.1% compared to ezetimibe monotherapy (95% CI, -19.7 to -6.5; p < 0.001).
- CLEAR OUTCOMES is an ongoing, event-driven, DB, MC, PC RCT that will evaluate bempedoic acid for the occurrence of major adverse cardiovascular events (MACE), defined as CV death, nonfatal MI, nonfatal stroke, or coronary revascularization, in approximately 12,600 patients who are statin intolerant with LDL-C ≥ 100 mg/dL, at high risk for, or have established CVD (*ClinicalTrials.gov [NCT02993406]*). Statin intolerance is defined as the inability to tolerate ≥ 2 statins, with 1 at low dose. The CLEAR OUTCOMES trial is anticipated to be completed in 2022.

CLINICAL GUIDELINES

- In general, statins are recommended first-line for the reduction of LDL-C; if the target goal is not achieved, the addition of ezetimibe, or bile acid sequestrants in select patients, should be considered. If further LDL-C reduction is needed to achieve target LDL-C goals in select patients, PCSK9 inhibitors may be considered (*American Diabetes Association [ADA] 2020, Cosentino et al 2020, Grundy et al 2019, Knuuti et al 2020, Mach et al 2020, Rosenzweig et al 2019*).
  - Statin intolerance: In patients with mild statin-associated AEs, rechallenge with a statin should be considered to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin, or in combination with nonstatin therapy. In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit.
- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guideline recommends LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary therapy to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. In statin intolerant patients, an alternate statin, lower statin dose or frequency, or addition of a nonstatin LDL-C therapy such as ezetimibe should be considered. Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk (*Garber et al 2020, Jellinger et al 2017*).
- 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/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (*Tonelli et al 2014).*

SAFETY SUMMARY

Ezetimibe

- Ezetimibe, administered alone or with statin, is generally well tolerated. For ezetimibe monotherapy, AEs 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. AEs were observed in some animal reproduction studies. Use is contraindicated in pregnant women who require combination therapy with a statin.

Bempedoic acid

- Warnings for the bempedoic acid products include the risk for hyperuricemia and tendon rupture. Bempedoic acid/ezetimibe has additional warnings for liver enzyme elevations, myopathy and/or rhabdomyolysis, and hepatic impairment.
- Concomitant use of bempedoic acid with pravastatin or simvastatin causes an increase in statin concentration and may increase the risk of statin-related myopathy. Bempedoic acid combinations with simvastatin doses of > 20 mg or pravastatin doses > 40 mg should be avoided.
- Bempedoic acid may be used in patients with moderate hepatic impairment (Child-Pugh B) without dosage adjustment; however, bempedoic acid has not been studied in patients with severe hepatic impairment (Child-Pugh C).
- No data are available on bempedoic acid use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Because bempedoic acid decreases cholesterol synthesis and possibly other biologically active substances derived from cholesterol, bempedoic acid may cause fetal harm when administered to pregnant women based on the mechanism of action.
- The most common AEs with bempedoic acid and bempedoic acid/ezetimibe (incidence ≥ 2% and greater than placebo) were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Additional AEs with bempedoic acid/ezetimibe were diarrhea, arthralgia, sinusitis, fatigue, and influenza.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nexletol (bempedoic acid)	Tablets	Oral	Daily	
Nexlizet (bempedoic acid/ ezetimibe)	Tablets	Oral	Daily	• Tablets should be swallowed whole.
Zetia (ezetimibe)	Tablets	Oral	Daily	• Based on available data, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				pediatric population < 10 years of age are not available.

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, HoFH, 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. Efficacy in reducing CV events with simvastatin plus ezetimibe has been demonstrated in the IMPROVE-IT trial; after a median of 6 years, patients randomized to ezetimibe/simvastatin had a 6.4% relative risk reduction (~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 (*Cannon et al 2015*).
- Bempedoic acid is a new lipid lowering agent that reduces LDL-C through ACL inhibition, an upstream step in the cholesterol biosynthesis pathway from the enzyme that statins inhibit, HMG-CoA reductase. The result is decreased cholesterol synthesis in the liver and upregulation of low-density lipoprotein receptors which lower LDL-C in the blood. Bempedoic acid/ezetimibe is a fixed dose combination which lowers LDL-C by ACL inhibition and intestinal cholesterol absorption inhibition.
  - Bempedoic acid has been shown to reduce LDL-C by 17% to 18% over 12 weeks in patients on maximally tolerated statins. In statin intolerant patients, bempedoic acid reduced LDL-C by 21%. Bempedoic acid/ezetimibe in patients on maximally tolerated statins reduced LDL-C by 38% compared to placebo. The effect of bempedoic acid on CV outcomes are pending completion of an ongoing trial.
- The 2018 ACC/AHA cholesterol guidelines emphasize adherence to lifestyle modifications and to statin therapy before considering the addition of a nonstatin drug. The addition of ezetimibe may be considered in very high-risk patients with ASCVD or those with severe primary hypercholesterolemia who have not met their LDL-C target while on statin therapy (*Grundy et al 2019*). 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. The cholesterol management guidelines have not yet addressed the place in therapy for bempedoic acid.

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