Ezetimibe (Zetia™)

Classification

Antihyperlipidemic agent

Pharmacology

Ezetimibe inhibits the absorption of cholesterol in the small intestine. The drug's target is a specific sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), located at the brush border of the small intestine. Ezetimibe binds to the transporter to prevent the intestine from absorbing cholesterol and phytosterols into the blood and their subsequent transportation to the liver. The overall effect results in a decrease in cholesterol storage within the liver and an increase in cholesterol clearance from the blood.

Indication

Ezetimibe is indicated alone or in combination with a HMG-CoA reductase inhibitor (statin) in primary hyperlipidemia, in combination with fenofibrate in mixed hyperlipidemia, in combination with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia, and in patients with homozygous sitosterolemia (phytosterolemia). For all indications, ezetimibe is indicated as adjunctive therapy to diet.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Upon oral administration, ezetimibe is absorbed and conjugated into an active phenolic glucuronide (ezetimibe-glucuronide). Time to reach ezetimibe peak plasma concentration is 4 to 12 hours and time to reach the glucuronide conjugate peak plasma concentration is 1-2 hours. Consumption of ezetimibe 10mg tablet with food showed no significant alterations in absorption. Consuming high fat meals resulted in a 38% increase in Cmax.
Distribution	Ezetimibe and ezetimibe-glucuronide are highly plasma protein bound (>90%).

Pharmacokinetic Parameter	Details
Metabolism	Ezetimibe undergoes rapid glucuronide conjugation (a phase II reaction) to an active metabolite in the liver and small intestine. Oxidative metabolism (a phase I reaction) of ezetimibe occurs minimally. Both ezetimibe and the conjugate have a half-life of 22 hours. The conjugate is the most common form found in the plasma. Enterohepatic recycling is likely considering the variations in plasma concentration time levels.
Excretion	Ezetimibe undergoes elimination primarily through the biliary tract and kidneys. Upon oral administration of ezetimibe 20 mg, 78% of the administered dose was detected in the stool and 11% in the urine.

Dosage/Administration

- Recommended dose is 10mg daily with or without food.
- Ezetimibe can be taken at the same time as a statin or fenofibrate.
- Ezetimibe should be administered $\geq$2 hours before or $\geq$4 hours after bile acid sequestrants.

Use in Special Populations

Pregnancy**:** There is a lack of quality data in pregnant women. Animal studies have found that ezetimibe crosses the placenta and in rats' doses ~10x the human exposure resulted in increased incidences of common fetal skeletal findings. Ezetimibe should only be used in pregnancy if the benefits outweigh the risks.

Lactation: It is unknown if ezetimibe is excreted into human breast milk. It should only be used in nursing mothers if the benefits outweigh the risks.

Pediatric Use: Ezetimibe has been studied in combination with simvastatin in adolescent boys and girls 10 to 17 years of age with heterozygous familial hypercholesterolemia. The dose for ezetimibe in pediatrics is 10 mg once daily. There were no significant effects on growth or sexual maturation in adolescent boys or girls in the studies. There are no pharmacokinetic differences of ezetimibe between adolescents and adults.

Geriatric Use: No dosage adjustments necessary.

Hepatic Impairment: No dosage adjustment necessary in mild hepatic impairment.

Renal Impairment: No dosage adjustment necessary in renal impairment.

Contraindication

- Pregnancy or woman who may become pregnant
- Breastfeeding
- Known hypersensitivity to any component of the product
- Ezetimibe in combination with a stain is contraindicated in acute liver disease or unexplained persistent elevations in hepatic transaminase levels

Precautions

- Consider discontinuing ezetimibe and/or statin if AST or ALT elevations persist above 3x upper normal limit.
- Ezetimibe with or without a statin may result in myopathy and rhabdomyolysis. If this is suspected or confirmed, ezetimibe and any statin or fibrate should be discontinued immediately.
- Ezetimibe is not recommended in patients with moderate to severe hepatic impairment.

Adverse Effects

In studies of ezetimibe monotherapy, the adverse reactions that occurred in 2% or more of patients and had a higher incidence than placebo included: diarrhea (4.1%), fatigue (2.4%), influenza (2%), sinusitis (2.8%), upper respiratory tract infection (4.3%), arthralgia (3%), and extremity pain (2.7%).

Adverse reactions in studies of ezetimibe with a statin compared to statin monotherapy were similar.

Monitoring

Toxicity: LFTs at baseline; if used in combination with a statin, LFTs when clinically indicated; if used in combination with fenofibrate, monitor LFTs when clinically indicated and signs and symptoms of cholelithiasis

Efficacy: Total cholesterol, HDL, LDL, triglycerides at baseline, 4-12 weeks after starting, then every 3-12 months

Interactions

Agent	Interaction	Management
Cyclosporine	Increased exposure to ezetimibe and cyclosporine	Monitor cyclosporine concentrations Consider risks/benefits of increased ezetimibe exposure

Agent	Interaction	Management
Cholestyramine	Decreased ezetimibe absorption	Take ezetimibe 2 hours before or 4 hours after cholestyramine
Fibrates (ezetimibe has only been studied with fenofibrate)	Increased risk of cholelithiasis	Avoid concurrent use or monitor closely for cholelithiasis
Warfarin	Increased bleeding risk	Monitor INR and adjust dosage accordingly

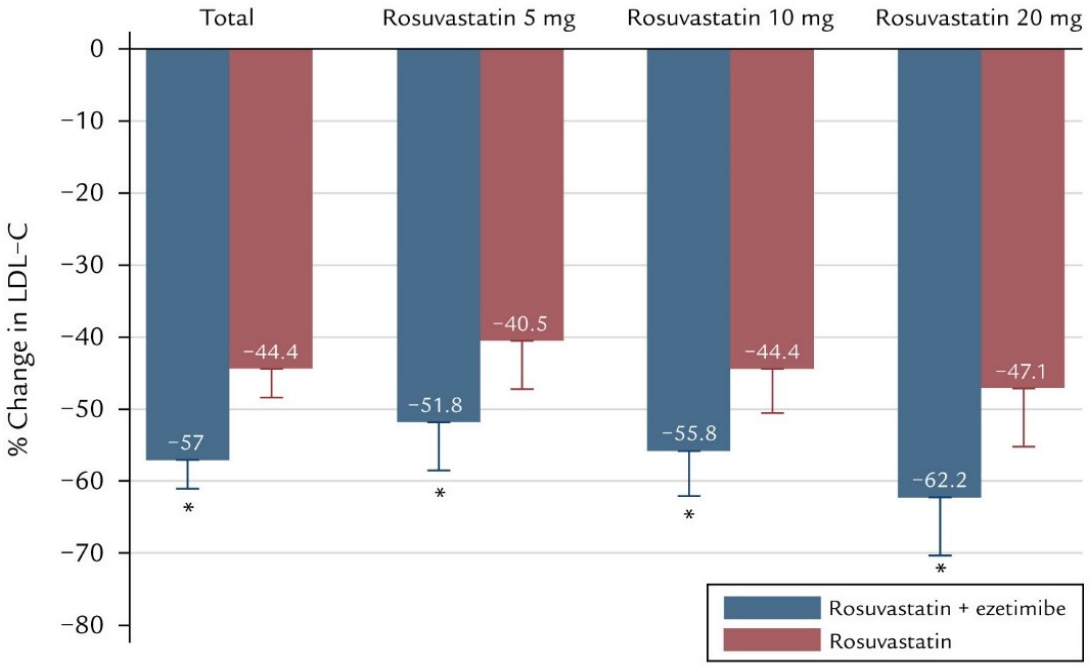
Efficacy

Studies have shown efficacy for ezetimibe in LDL reduction when used alongside statins. The IMPROVE-IT trial, published in 2015, analyzed the effect of simvastatin 40 mg + ezetimibe 10 mg compared to simvastatin 40 mg + placebo in over 18,000 patients. Patients were eligible for inclusion if they were $\geq$50 years of age, had an acute coronary syndrome within the previous 10 days, and had LDL >50 mg/dL. Patients had a follow up visit at 1 month, 4 months, and then every 4 months afterwards. The primary efficacy end point was a composite of death from cardiovascular disease, a major coronary event, or nonfatal stroke. Prespecified goals for LDL-C were < 70 mg/dL and for high sensitivity C-reactive protein (hs-CRP) were < 2 mg/L at 1 month. 50.6% of patients in the ezetimibe/simvastatin group met both of these outcomes compared to 30.5% in the simvastatin group ($p<0.001$). The combination of ezetimibe/simvastatin provided 24% further reduction of LDL cholesterol when compared to simvastatin alone. At 1 year, total cholesterol, triglycerides, non-HDL-C, apolipoprotein B, and hs-CRP were also significantly lower in the combination group compared to the simvastatin monotherapy group. Event rates for the primary efficacy end points were 32.7% in the combination group compared to 34.7% in the monotherapy group ($p=0.016$). There were no significant differences in side effects among the two groups.

In another efficacy study (I-ROSETTE), ezetimibe + rosuvastatin was compared to rosuvastatin alone in those with hypercholesterolemia. In this 8 week phase III, multicenter, double-blind, randomized controlled trial, participants were randomized to receive either ezetimibe 10mg/rosuvastatin 20mg, ezetimibe 10mg/rosuvastatin 10mg, ezetimibe 10mg/rosuvastatin 5mg, rosuvastatin 20mg, 10mg, or 5mg.

The primary end point was the mean percent change in LDL-C levels from baseline to 8 weeks between the combination ezetimibe/rosuvastatin group compared to the monotherapy rosuvastatin group. 396 subjects completed the study and 389 were analyzed. Results showed that the percent changes in LDL-C from baseline to week 8 were -57.0% and -44.4% in the total combination and total rosuvastatin groups, respectively. The number of participants who reached target LDL-C levels according

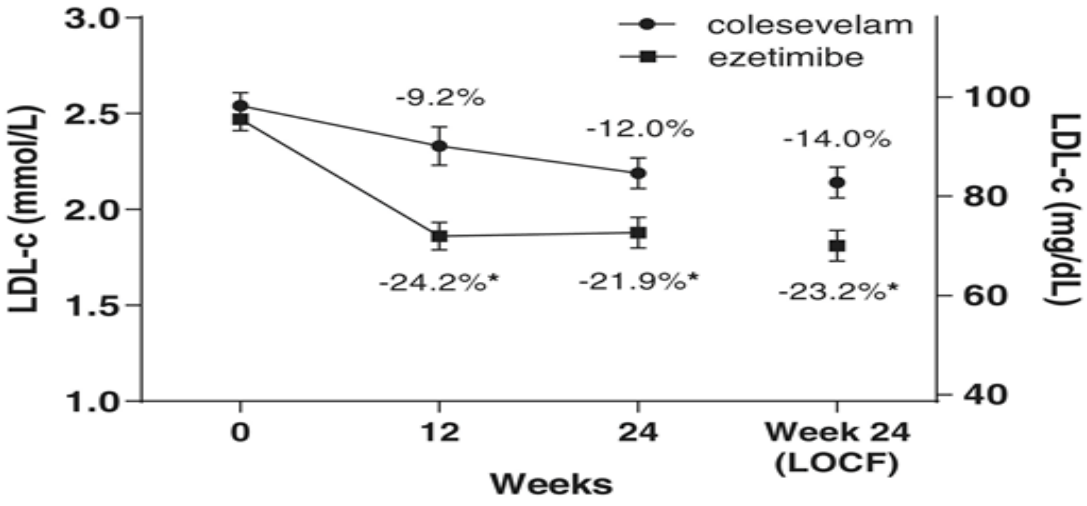
to the NCEP ATP III guidelines were significantly greater in the total ezetimibe/rosuvastatin group (180 [92.3%]) than in the rosuvastatin monotherapy arm (155 [79.9%]) (p<0.001). The two most common adverse effects (AEs) were infections in the rosuvastatin 5mg arm at 6.2% and gastrointestinal disorders in the ezetimibe 10mg/rosuvastatin 20mg group at 6.1%. No significant differences were found in reported AEs and adverse drug reactions between the four treatment groups. All safety parameters collected and analyzed were determined to be similar among the treatment arms.



Hong SJ et al. Clin Therapeutics 2018; 40:226-241.

More recent studies have continued to evaluate ezetimibe's use particularly in those with type II diabetes already on statin therapy. A study was performed to determine the efficacy and safety of colesevelam and ezetimibe in lowering LDL-C levels in those with type II diabetes. The trial was a 24-week, multicenter, open label, 1:1, randomized, pragmatic clinical study with two treatment arms colesevelam 3.75g once or twice daily with a meal and ezetimibe 10mg once at the same time every day with or without a meal. Subjects enrolled were required to have a diagnosis of T2D for >6 months, HbA1c of 7.1% to 10%, LDL >2.0mmol/L (77.34mg/dL), and stable diabetes medications and a statin medication for at least three months. Laboratory monitoring occurred at baseline, 12 weeks, and 24 weeks and included HbA1c, LDL-C, fasting plasma glucose (FPG), high density lipoprotein-cholesterol (HDL-C), non-HDL-c, triglycerides, ALT, CK, and CRP. 186 subjects were randomized and received a dose of study medication with 89 participants in the

colesevelam group and 97 participants in the ezetimibe group. The primary endpoint was the proportion of patients who achieved the goal levels for both LDL-C (≤2.0mmol/L [77.34mg/dL]) and HbA1c (≤7.0%) at 24 weeks. The proportion of patients in the colesevelam group that achieved both goals was 14.6% compared to 10.5% in the ezetimibe group. These results show that colesevelam was non-inferior to ezetimibe but it was not superior to ezetimibe. Additionally, significant reductions in LDL-C from baseline to 24 weeks were found in both treatment groups (14% for colesevelam and 23.2% for ezetimibe) with the ezetimibe arm showing a significantly greater reduction (p=0.01). Adverse events were significantly higher with colesevelam compared to ezetimibe (20.2% vs. 7.2%, p=0.009). Study drug discontinuation also occurred more frequently in the colesevelam group compared to ezetimibe (31.1% vs. 6.2%, p=<0.001)



Week	0 (baseline)	12	24	24 (LOCF)
colesevelam (n)	82	77	77	82
ezetimibe (n)	94	92	89	94

Bajaj HS et al. Diabetes Obes Metab 2020; 22:1722-1728.

Conclusions from Literature:

For individuals with primary hypercholesterolemia and mixed hyperlipidemia, ezetimibe 10mg in combination with a statin has shown greater lipid lowering benefits in clinical trials than statin monotherapy. In certain instances, such as documented intolerance to the lowest doses of hydrophilic statins (atorvastatin and rosuvastatin) ezetimibe may be used as monotherapy to lower lipid levels. In patients who have atherosclerotic cardiovascular disease and whose LDL-C remains ≥1.8mmol/L (≥70mg/dL) after maximally tolerated statin therapy the AHA/ACC 2018 guidelines recommend initiation of ezetimibe. Compared to statins, the most common adverse effects of ezetimibe have involved gastrointestinal discomfort and

elevated hepatic enzymes but neither have shown to cause significant distress or impairment.

Dosage Forms/Cost

Name	Form	Strength	AWP/tablet	30-day supply (AWP)
Ezetimibe	Tablet	10 mg	~$11	$330

Special Considerations

None

Summary/Conclusion

Ezetimibe is FDA approved as monotherapy or as combination therapy for a variety of lipid abnormalities. In all indications, it is to be given as an adjunctive therapy to diet modifications. Ezetimibe has a favorable side effect profile and is recommended in the 2018 AHA/ACC cholesterol guidelines as 2nd line therapy for LDL-C that remains >70 mg/dL despite being on a maximally tolerated statin.

Recommendation

It is recommended to add ezetimibe to the Texas HHS Psychiatric Drug Formulary.

References

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