Zetia Step Therapy Program

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Policy Origination: 7/2013  Next Review: 8/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for brand name Zetia when the following criteria are met.

When Policy Topic is covered
Step therapy rules have been developed to encourage the use of an HMG-CoA reductase inhibitor medication (single entity, fixed combination HMG products with another medication or packaged in combination with another medication) for hyperlipidemia prior to Zetia without interrupting existing therapy. If the step therapy rule is not met at the point of service, coverage will be determined by prior authorization criteria.

Step 1: generic HMG-CoA reductase inhibitors (i.e., lovastatin, simvastatin, pravastatin, fluvastatin, fluvastatin extended-release, atorvastatin, rosuvastatin, atorvastatin plus amlodipine), brand name HMG-CoA reductase inhibitors (i.e., Lipitor®, Lescol®/Lescol® XL, Altoprev®, Pravachol®, Crestor®, Mevacor®, Zocor®, Livalo®), brand name HMG-CoA reductase inhibitor combination products (i.e., Juvisync™, Caduet®, Vytorin®, Liptruzet™)

Step 2: Zetia

Criteria
Exceptions for Zetia can be made for those who meet one of the following criteria.

1. The patient has tried one HMG-CoA reductase inhibitor (may be brand or generic) or HMG-CoA reductase inhibitor combination product or if Zetia is being initiated in combination with an HMG-CoA reductase inhibitor.

2. Significant drug interactions. The patient is taking or will be taking a medication that has a significant drug interaction with any of the HMG-CoA reductase inhibitors. Examples include: antifungal agents (e.g., itraconazole, ketoconazole), macrolide antibiotics (e.g., erythromycin, clarithromycin), protease inhibitors (e.g., Invirase® [saquinavir capsules and tablets], Norvir® [ritonavir tablets and capsules], Crixivan® [indinavir capsules]).

3. Patient has severe renal impairment (creatinine clearance ≤ 30 mL/minute). No dosage adjustment is needed for Zetia in those with renal impairment. Renal impairment may predispose patients to skeletal muscle adverse effects.

4. Homozygous sitosterolemia (phytosterolemia). Zetia is indicated to reduce elevated sitosterol and campesterol in those with homozygous sitosterolemia (phytosterolemia).

5. The patient is a pregnant woman. HMG-CoA reductase inhibitors are in pregnancy category X and contraindicated in pregnancy. Zetia is in pregnancy category C.

6. The patient has active liver disease or unexplained persistent elevations of serum transaminases. Exceptions are recommended in these circumstances. With Zetia monotherapy, the incidence of increases in serum transaminases appears similar to placebo.¹
However, an HMG-CoA reductase inhibitor alone or the combination of Zetia with an HMG-CoA reductase inhibitor is contraindicated in this patient population. Zetia is not recommended in patients with moderate or severe hepatic impairment.1

7. The patient has been previously diagnosed with myopathy or rhabdomyolysis (either medication related or not medication related) OR the patient has an underlying muscle/muscle-metabolism related disorder (e.g., myositis, McArdle’s disease). HMG-CoA reductase inhibitor therapy has been associated with myopathy and rhabdomyolysis, albeit rare, and the incidence may be higher compared with Zetia monotherapy. However, myopathy and rhabdomyolysis may have other etiologies besides HMG-CoA reductase inhibitor therapy.

When Policy Topic is not covered
The use of Zetia is considered investigational for all other indications.

Considerations
Zetia requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service
Indications and Dosing
Zetia, an inhibitor of intestinal cholesterol (and related phytosterol) absorption, is indicated as an adjunct to diet to: 1) reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apo B) and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia either as monotherapy or in combination with a hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin); 2) reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) in combination with atorvastatin or simvastatin; 3) reduce elevated total-C, LDL-C, apo B, and non-HDL-C in combination with fenofibrate; and 4) reduce elevated sitosterol and campesterol levels in homozygous sitosterolemia (phytosterolemia).1

Zetia reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. A limitation of use is that the effect of Zetia on cardiovascular (CV) morbidity and mortality has not been determined. Also, Zetia has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias. The recommended dose is one 10-mg tablet once daily (QD), with or without food.

Rationale
Clinical Data
Guidelines from the American Association of Clinical Endocrinologists’ (AACE) for the management of dyslipidemia and prevention of atherosclerosis2, updated in 2012, note that studies with Zetia monotherapy in patients with hyperlipidemia led to reductions in LDL-C of approximately -10% to -25%, with favorable changes in triglyceride (TG) levels, apo B, and in some trials high-density lipoprotein cholesterol (HDLC). When used in combination with ongoing statin treatment (simvastatin, atorvastatin, lovastatin, pravastatin or fluvastatin), Zetia produced an additional LDL-C reduction of -23% to -30%. Zetia, when given with fenofibrate, reduces LDL-C by an additional -20% to -22%.2 Data are also available regarding use of Zetia in children.1,9

Outcomes Data
IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) was a double-blind randomized trial that involved patients (n = 18,144) who had been hospitalized for an acute coronary syndrome (ACS) within the last 10 days and had LDL-C levels of 50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not receiving lipid-lowering therapy.7 Patients were randomized in a double-blind manner to receive Zetia 10 mg QD plus simvastatin 40 mg
QD or simvastatin 40 mg QD; standard therapy for the treatment of ACS was also given. At baseline, approximately 35% of patients were receiving a lipid-lowering agent. The mean LDL-C at the index event was 93.8 mg/dL. The median follow-up was 6 years. At this time, 42% of patients in each group had discontinued the study medication without having died or without reaching a primary endpoint. The median time-weighted average LDL-C level during the trial was 53.7 mg/dL in the Zetia plus simvastatin 40 mg group compared with 69.5 mg/dL in the simvastatin 40 mg monotherapy group (P < 0.001). The Kaplan-Meier event rate for the primary endpoint at 7 years (composite of CV death, nonfatal myocardial infarction [MI], unstable angina requiring rehospitalization, coronary revascularization [≥ 30 days after randomization] or nonfatal stroke) was 32.7% with Zetia plus simvastatin 40 mg QD vs. 34.7% with simvastatin 40 mg QD (P = 0.016). Several composite endpoints were also superior for simvastatin, such as death from any cause, major coronary event or nonfatal stroke (38.7% with Zetia plus simvastatin 40 mg QD vs. 40.3% with simvastatin 40 mg QD; P = 0.03).

Guidelines
AACE
The 2012 guidelines from the AACE for the management of dyslipidemia and prevention of atherosclerosis recommends a target LDL-C concentration of < 100 mg/dL in adults and < 70 mg/dL for all patients at very high risk.2 The AACE recommends statins as the drug of choice for LDL-C reduction mainly based on data regarding outcomes trials that demonstrated reduced morbidity and mortality. Zetia is effective as monotherapy and use in combination therapy with statins has had noted benefits in the lipid profile. Zetia also as a role in patients who have experienced adverse events (AEs) with statins (e.g., myopathy/rhabdomyolysis, liver dysfunction). Use of Zetia may also allow patients to utilize the lower statin dose to better tolerate the medication. Zetia was noted to have minimal AEs and in several efficacy and safety trials lasting up to 1 year in combination with statins or fenofibrate, there was no significant difference in the AE profile compared with either monotherapy.

American College of Cardiology (ACC)/American Heart Association (AHA)
In November 2013, the ACC/AHA published guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults.5-6 The guidelines emphasize the appropriate intensity of statin therapy to reduce CV risk. Statins with related doses are categorized as “high-intensity” (lowers LDL-C by approximately ≥ 50%), moderate-intensity (lowers LDL-C by approximately 30% to < 50%), and low-intensity (lowers LDL-C by < 30%). Only atorvastatin and rosuvastatin are categorized as acceptable “high-intensity” statin therapy. The guidelines also identify major groups who should be treated with an appropriate statin-intensive therapy (e.g., patients with clinical atherosclerotic cardiovascular disease [ASCVD]). According to the guidelines, clinical trial evidence clearly shows that ASCVD events are reduced by using the maximum-tolerated statin intensity in groups shown to benefit. There is substantially less evidence for non-statin medications in reducing ASCVD risk. Guidelines recommended adherence to lifestyle and statin therapy before the addition of a non-statin medication is considered. Upon examination of randomized controlled trials evaluating ASCVD the panel could find no data supporting the routine use of non-statin medications combined with statin therapy to further reduce ASCVD events. Physicians treating high-risk patients who have an inadequate response to statins, who are unable to tolerate a less-than-recommended statin intensity, or who are completely statin intolerant, may consider the addition of a non-statin cholesterol-lowering therapy.

National Lipid Association (NLA)
In 2014, the NLA published recommendations for patient-centered management of dyslipidemia.8 The guidelines recommend treatment goals. Regarding LDL-C, patients at low, moderate, or high risk are recommended to obtain an LDL-C level < 100 mg/dL. Patients at very high risk are recommended to achieve an LDL-C level < 70 mg/dL. Patients with ASCVD are included among the patients defined as being very high risk. Patients at high risk include those with an LDL-C ≥ 190 mg/dL, which suggests that patients may have familial hypercholesterolemia (FH). Refer to the full guideline publication for the listing of patients at risk. Unless contraindicated, first-line drug therapy for the treatment of disorders involving dyslipidemia includes a moderate- or high-intensity statin. High-intensity statin therapy includes atorvastatin (40 to 80 mg QD) or rosuvastatin (20 to 40 mg QD), which leads to an LDL-C reduction of ≥ 50%. Moderate-intensity statin therapy (atorvastatin 10 to 20 mg, fluvastatin 40 mg twice
daily [BID], Lescol XL 80 mg, lovastatin 40 mg, Livalo 2 to 4 mg, pravastatin 40 to 80 mg, rosuvastatin 5 to 10 mg, and simvastatin 20 to 40 mg) will generally lower LDL-C by 30% to < 50%. For patients with contraindications for, or intolerance to statin therapy, non-statin medication therapy can be considered. Non-statin medication classes for lipid management include cholesterol absorption inhibitors (Zetia), bile acid sequestrants (e.g., cholestyramine, Welchol® [colesevelam tablets and oral suspension]), nicotinic acid, fibric acids (e.g., fenofibrate, fenofibric acid, and gemfibrozil), and omega-3 fatty acids.

**Adverse Effects**

Zetia is generally well-tolerated. Rates of elevated hepatic transaminases are similar for placebo and Zetia monotherapy. However, when Zetia is added to a HMG-CoA reductase inhibitor the incidence of consecutive elevations (≥ 3 times the upper limit of normal [ULN]) in hepatic transaminases occurred in 1.3% of those given Zetia plus statins vs. 0.4% for those given statin monotherapy.

No excess myopathy or rhabdomyolysis was noted in clinical studies with Zetia. However, cases of myopathy and rhabdomyolysis have been reported in patients treated with Zetia given with an HMG Co-A reductase inhibitor and with Zetia given alone. In clinical trials, the incidence of creatine phosphokinase (CPK) > 10 times the ULN was 0.2% for Zetia vs. 0.1% for placebo and 0.1% for Zetia given with a HMG Co-A reductase inhibitor vs. 0.4% for HMG Co-A reductase inhibitor therapy alone.

Other lipid-lowering drugs, including HMG-CoA reductase inhibitors, fibrates and niacin, may cause muscle toxicity (myalgia and muscle weakness) as well as myopathy and rhabdomyolysis, albeit rare. The risk of skeletal muscle toxicity increases with higher HMG-CoA reductase inhibitor doses, advanced age (> 65 years), hypothyroidism, renal impairment, and sometimes with concomitant use of other medications depending on the statin used. However, it is also important to note that rhabdomyolysis and myopathy may have other etiologies besides HMG-CoA reductase inhibitors including trauma (e.g., burns), metabolic disorders (e.g., hypokalemia), excessive exercise, underlying neuromuscular disease (e.g., McArdle disease, muscular dystrophies), infections, and ischemic events (sickle cell disease).3-4

**Drug Interactions**

Zetia is not an inhibitor or an inducer of the cytochrome P450 (CYP) isozymes (e.g., 1A2, 2D6, 2C8/9, and 3A4) and it is unlikely that Zetia will impact the metabolism of medications metabolized by these enzymes. However, Zetia should be used cautiously when given with cyclosporine due to increased exposure to both medications. The efficacy of co-administration of Zetia and fibrates other than fenofibrate has not been studied. Use of Zetia with cholestyramine decreased the mean area under the curve of Zetia by approximately 50%. If Zetia is added to warfarin, the International Normalized Ratio (INR) should be monitored as clinically indicated. Certain HMG CoA reductase inhibitors are metabolized by CYP isozymes (e.g., lovastatin, simvastatin, and atorvastatin are metabolized by CYP3A4) and have drug interactions with commonly utilized medications. The dosage of certain HMG-CoA reductase inhibitors are limited to a defined maximum if receiving a medication that is associated with a drug-drug interaction (e.g., simvastatin dose is limited to 20 mg QD when given with amlodipine).

**Pregnancy Category**

Zetia is in pregnancy category C. All HMG CoA are known teratogens (Pregnancy Category X).2

**References**


Other References Utilized


**Billing Coding/Physician Documentation Information**

N/A Zetia is considered a pharmacy benefit.

**Additional Policy Key Words**

Policy Number: 5.01.559

**Policy Implementation/Update Information**

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