



† A Division of Health Care Service Corporation, a Mutual Legal Reserve Company, an Independent Licensee of the Blue Cross and Blue Shield Association

Zetia[®] Step Therapy/Quantity Limit Criteria with Medical Diagnoses Option*

* Medical diagnoses are required for implementation of this option.

Program may be implemented with the following options

- 1) Step Therapy (a 1-step edit that requires concurrent therapy with a statin or fenofibrate before Zetia)
- 2) Step Therapy with Quantity Limits
- 3) Quantity Limits

For BlueCross BlueShield of Illinois, BlueCross BlueShield of New Mexico, BlueCross BlueShield of Oklahoma, and BlueCross BlueShield of Texas this program will be implemented as Option 1, Step Therapy only.

Brand	Generic	Dosage Form
Zetia [®]	ezetimibe	oral tablet

FDA APPROVED INDICATIONS¹

Primary Hyperlipidemia

Monotherapy

Zetia (ezetimibe), administered alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B) in patients with primary (heterozygous familial and non-familial) hyperlipidemia.

Combination Therapy with HMG-CoA Reductase Inhibitors (Statins)

Zetia, administered in combination with a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin), is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hyperlipidemia.

Combination Therapy with Fenofibrate

Zetia, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-high-density lipoprotein cholesterol (non-HDL-C) in adult patients with mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

The combination of Zetia and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as and adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia

Zetia is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be only one component of multiple risk-factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to a diet when the response to a diet restricted in saturated fat and cholesterol and other non-pharmacologic measures alone has been inadequate.

RECOMMENDED QUANTITY LIMITS ¹

Table 1: Summary of Recommended Doses and Quantity Limits

Agent	Recommended Dosage	Quantity per Day
Zetia		
10 mg tablets	10 mg once daily	1 tablet

RATIONALE FOR STEP THERAPY AND QUANTITY LIMIT

Step Therapy

The intent of the step therapy edit for Zetia (ezetimibe) is to recommend use of ezetimibe as adjunctive or add on therapy to HMG-CoA reductase inhibitors (statins). Ezetimibe is indicated as monotherapy or combination therapy with a statin for the treatment of hyperlipidemia.¹ Although ezetimibe is approved as monotherapy for the treatment of primary hyperlipidemia, concomitant therapy with a statin has demonstrated effectiveness in improving serum total-C, LDL-C, Apo B, TG, and HDL-C beyond either treatment alone, and in clinical trials, greater effectiveness has been seen from a statin plus ezetimibe than from increased doses of statin monotherapy.¹⁻¹¹ The step therapy edit for ezetimibe requires previous or concomitant use of a statin in patients with primary hyperlipidemia.

Ezetimibe may also be used in combination with fenofibrate to lower total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia. At the present time, ezetimibe lacks long-term morbidity or mortality outcomes data. The longest placebo-controlled blinded trial was 14 weeks. The primary outcome in all trials was the direct measured LDL-C percent lowering from baseline compared with placebo; secondary efficacy measurements included comparisons of percent lowering from baseline (ezetimibe and placebo) on a number of different lipoproteins (total cholesterol, triglycerides [TG], HDL-C, and apolipoprotein B). The step therapy edit for ezetimibe requires previous or concomitant use of a statin or fenofibrate product in patients with mixed hyperlipidemia.

Patients who are currently receiving therapy with Zetia will be allowed continuation of therapy without meeting the above edit requirements if a claim for Zetia is identified within 90 days prior to the new claim. The claims system is designed to identify any claim with a days supply that ends within the 90-day look-back period.

Ezetimibe, the first drug in a new class of agents called cholesterol absorption inhibitors, selectively inhibits the absorption of cholesterol (dietary and biliary) and related phytosterols at the brush border of the small intestine.¹ The result is a decrease in the amount of cholesterol available to the liver and a subsequent decrease in hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.¹ When used concomitantly with statins, which decrease hepatic synthesis of cholesterol, the combination of the two mechanisms of action results in complimentary cholesterol reduction.¹

Primary Hyperlipidemia

The safety and effectiveness of ezetimibe in the treatment of hyperlipidemia disorders has been established from nine short-term (up to 14 weeks) randomized, double-blind, placebo-controlled studies in adolescents and adults, of which five studies are published.^{4-6,9,10} The remaining three placebo controlled

trials are available in abstract or a brief description from the company.³ [see also Formulary Chapter 5.9F: Cholesterol Absorption Inhibitors²]

Of the six published studies, two trials compared placebo to monotherapy ezetimibe, and three trials were placebo controlled with multiple active treatment arms (monotherapy ezetimibe, varying doses of statin in combination with ezetimibe). In addition, the manufacturer conducted three short-term (up to 12 weeks) studies in heterozygous and homozygous familial disorder patients comparing statin to statin plus ezetimibe, of which one study has been published.³ Primary outcome in all trials was the direct measured low density lipoprotein cholesterol (LDL) percent lowering from baseline compared to LDL percent lowering from baseline in the placebo group. Secondary efficacy measurements included comparisons of percent lowering from baseline of ezetimibe to placebo on a number of different lipoproteins (total cholesterol, TG, high density lipoprotein cholesterol [HDL], and apolipoprotein B).

The following results (for the 10 mg once daily dose) were reported:

- Ezetimibe 10 mg once daily compared to placebo was found to be superior in lowering LDL and positively affecting other lipoproteins in two published trials of patients with primary hypercholesterolemia. LDL lowering is 16.9% to 18.2% compared to baseline. There were minimal changes in TG and HDL.^{9,10}
- Ezetimibe in combination with a statin was found to be superior in lowering LDL and positively affecting other lipoproteins in three published trials of patients with primary hypercholesterolemia. When added to a statin, additional LDL lowering is 14% compared to statin monotherapy. There were minimal changes in TG and HDL. Safety suggests comparable adverse events to placebo, although rates of liver function tests greater than three times the upper limit of normal appear higher in the ezetimibe plus statin group than in the statin plus placebo group.⁴⁻⁶
- Ezetimibe in combination with a statin was found to significantly reduce hs-CRP (high-sensitivity C-reactive protein) levels compared to the statin monotherapy (-38.0% versus -18.2%, p<0.01).⁷
- Ezetimibe added to atorvastatin demonstrated a more effective means of reducing LDL in patients at high risk of coronary heart disease (CHD) than continued doubling of the atorvastatin dose (to 80 mg/day) alone.⁸

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)¹² and the 2004 update from clinical trials¹³ state that LDL-C is the primary target of lipid management and recommends a statin as the usual first-line therapy for lowering LDL-C. However, combination therapy may be required to achieve LDL-C lowering goals. Ezetimibe, bile acid sequestrants, and nicotinic acid are all listed as potential second agents.^{12,13}

Table 2: Progression of Drug Therapy, based on NCEP ATP III^{12,13}

Initiation of drug therapy	If LDL goal is not achieved at 6 weeks	If LDL goal is not achieved at 12 weeks	When LDL goal is achieved
Usually preferred: Statin	Increase dose of statin	Intensify drug therapy	Monitor response every 4-6 months.
Alternative: bile acid sequestrant, nicotinic acid, ezetimibe	Or Add bile acid sequestrant, nicotinic acid, or ezetimibe	Or Refer to lipid specialist	Treat other lipid risk factors: high triglycerides, low HDL

LDL = low density lipoprotein; HDL = high density lipoprotein;
NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III

The National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Guidance on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia¹⁴ states that ezetimibe monotherapy is recommended as an option for patients who would otherwise be initiated on statin therapy (as per NICE guidance TA 94) but who are unable to do so because of contraindications to initial statin therapy or who are intolerant to statin therapy. Ezetimibe coadministered with initial statin therapy is recommended in patients whose LDL-C is not appropriately controlled on statin therapy alone.¹⁴

The ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin versus Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial results were released by the manufacturer on January 14, 2008. The study involved 720 patients with heterozygous familial hypercholesterolemia. Patients were randomized to 80 mg of simvastatin daily with either placebo or 10 mg of ezetimibe per day. The results of the trial showed no significant difference in the primary endpoint (change in the mean carotid intima-media thickness or IMT) between patients treated with ezetimibe and simvastatin versus patients treated with simvastatin alone over a two-year period.¹⁵

According to the American College of Cardiology (ACC), this study deserves serious thought and follow-up. The overall incidence rates of cardiac events were nearly identical between both treatment groups, and both medicines were generally well tolerated. Further research will be needed in this area to provide conclusive evidence about which lipid lowering strategy is preferred (statin alone versus statin plus ezetimibe). The ACC also notes that this trial is an imaging study and not a clinical-outcome study. Conclusions should not be made until the three large clinical-outcome trials are presented within the next two to three years. The ACC recommends that ezetimibe remains a reasonable option for patients who are currently on a high dose statin but have not reached their LDL cholesterol goal. The ACC also notes that ezetimibe is a reasonable option for patients who cannot tolerate statins or can only tolerate a low dose statin.¹⁶

In January, 2008, the FDA issued a statement:¹⁷ "Merck/Schering Plough Pharmaceuticals issued a press release reporting preliminary results of the study and stated that the study demonstrated no significant differences between the combination product and Zocor on the build up of cholesterol plaque in the carotid (neck) arteries. The study was not designed to detect any difference in risk of having a heart attack or stroke between the two treatments. An ongoing trial called -- Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) -- is underway which is designed to evaluate the effect of Vytorin versus Zocor on heart disease and stroke."¹⁷

Full data from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study were presented at the European Society of Cardiology (ESC) Congress 2008 and published in the *New England Journal of Medicine* in Sept 2008. The trial showed that the cholesterol-lowering combination of simvastatin/ezetimibe was no better than placebo in reducing the primary composite end point of aortic-valve and cardiovascular events in patients with mild to moderate asymptomatic aortic stenosis.¹⁸ The combination was significantly more effective than placebo in reducing the risk of ischemic events, a secondary composite end point that was driven primarily by reductions in coronary artery bypass graft (CABG) surgery, but there were concerns raised over the significantly increase risk of cancer. Despite reducing LDL-cholesterol levels by 61%, down to a mean of 53 mg/dL, treatment with ezetimibe/simvastatin failed to reduce the risk of the primary end point, a composite of major cardiovascular and aortic-valve events. There was a significant 22% reduction in the risk of ischemic events, a finding that was driven primarily by a 32% reduction in the need for CABG surgery.¹⁸

In January 2009 the FDA issued a statement reaffirming its position that lower remains better when it comes to LDL-cholesterol levels and that patients should not stop taking their cholesterol-lowering medications, including Vytorin.¹⁹

- The FDA has completed its review of the final clinical study report of ENHANCE. Following two years of treatment, carotid artery thickness increased by 0.011 mm in the Vytorin group and by 0.006 mm in the simvastatin group. The difference in the changes in carotid artery thickness between the two groups was not statistically significant. However, the levels of LDL cholesterol decreased by 56% in the Vytorin group and decreased by 39% in the simvastatin group. The difference in the reductions in LDL cholesterol between the two groups was statistically significant.
- An ongoing trial known as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) is examining whether treatment with Vytorin reduces the risk for *cardiovascular events* (composite endpoint of CV death, major coronary events, and stroke) compared with simvastatin alone. This trial of 18,000 patients is scheduled to be completed in 2012. IMPROVE-IT will provide additional data regarding Vytorin's effect on the risk for cardiovascular disease.¹⁷

- Pending the results from IMPROVE-IT, patients should not stop taking Vytorin or other cholesterol lowering medications and should talk to their doctor if they have any questions about these medications.¹⁹

Mixed Hyperlipidemia

Mixed or combined hyperlipidemia is characterized by both elevated LDL-C and TGs, a preponderance of small, dense LDL particles, and reduced HDL-C. Beyond lowering LDL-C, NCEP ATP III¹² recommends non-HDL-C as a secondary treatment target for patients with elevated TG. These NCEP ATP III guidelines recommend combining drug therapies to achieve the lipid goals for patients with mixed hyperlipidemia. Statins are commonly used to treat the elevated LDL-C and total cholesterol, but other agents may be needed to improve TG and HDL-C levels.¹²

Studies by Farnier et al.²⁰ and McKenney et al.²¹ studied the combination of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. Farnier et al.²⁰ found that LDL-C, non-HDL-C, and Apo B were all significantly reduced with the combination compared with fenofibrate or ezetimibe alone. TG levels were significantly decreased and HDL-C was significantly increased with fenofibrate plus ezetimibe and fenofibrate alone compared with placebo. Coadministration therapy reduced LDL-C by 20.4%, non-HDL-C by 30.4%, TG by 44.0%, and increased HDL-C by 19.0%. At baseline, >70% of all patients exhibited the small, dense LDL pattern B profile. A greater proportion of patients on fenofibrate plus ezetimibe and fenofibrate alone treatment shifted from a more atherogenic LDL size pattern to a larger, more buoyant, and less atherogenic LDL size pattern at study endpoint than those on placebo or ezetimibe alone.²⁰

McKenney et al.²¹ conducted a 48-week double-blind extension trial comparing fenofibrate alone with the fenofibrate-ezetimibe combination. Their results showed significantly greater reductions in LDL-C with the combination (22%) than with fenofibrate (9%). There were also significantly greater improvements in TGs, HDL-C, total-C, non-HDL-C, and Apo B with the combination.¹⁷ Both therapies were well-tolerated. The proportion of patients with consecutive elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 3 times ULN [upper limit of normal] were similar between the two groups. No cases of creatine phosphokinase (CPK) elevation ≥ 10 time ULN or myopathy were observed in either group.²¹

Farnier et al.²² also studied the triple combination of simvastatin, ezetimibe, and fenofibrate in patients with mixed hyperlipidemia. Comparisons were made to the simvastatin/ezetimibe combination, fenofibrate alone, and placebo over 12 weeks. Results showed LDL-C significantly reduced with the triple therapy compared with fenofibrate or placebo, not when compared with simvastatin/ezetimibe. HDL-C and Apo A-1 were significantly increased with the triple combination compared with simvastatin/ezetimibe and placebo but not when compared with fenofibrate alone. TG, non-HDL-C, and Apo B were significantly reduced with triple therapy versus all other treatments. The safety profile of the triple therapy was generally similar to simvastatin/ezetimibe or fenofibrate.²²

Homozygous Familial Hypercholesterolemia (HoFH)

The medical management of patients with homozygous familial hypercholesterolemia (HoFH) is difficult because LDL-C levels remain high in most patients despite aggressive therapy with diet, statins, bile acid sequestrants, niacin, fibric acid derivatives, or combination therapy.¹¹ Other treatment options include removal of LDL-C by apheresis, portacaval shunting and liver transplantation. Ezetimibe has been approved for the treatment of homozygous familial hypercholesterolemia in combination with atorvastatin or simvastatin.¹ It is not approved for monotherapy for this indication. A 12-week study enrolling patients with HoFH (N=50) treated with diet and atorvastatin 40 mg or simvastatin 40 mg compared the effects combination ezetimibe/statin therapy to statin monotherapy.¹¹ Patients were randomized to one of three double-blind treatments; 80 mg of atorvastatin or simvastatin, ezetimibe 10 mg plus 40 mg of atorvastatin or simvastatin, or ezetimibe 10 mg plus 80 mg of atorvastatin or simvastatin. At study end, combination therapy demonstrated significantly reduced LDL-C levels from baseline compared with statin alone (-20.7 % versus -6.7 %, p=0.007).¹¹ For this high-risk population, ezetimibe offers an additional treatment option complementary to statin therapy for treatment of HoFH.¹¹

Homozygous Sitosterolemia

Ezetimibe is indicated as monotherapy for treatment of sitosterolemia.¹ Sitosterolemia is a recessively inherited disorder with hyperabsorption of dietary sterols and decreased hepatic excretion of plant sterols and cholesterol. As a consequence of markedly elevated plasma and tissue sitosterol and campesterol levels, premature atherosclerosis develops. Salen, et al.²³ evaluated ezetimibe 10 mg/day in patients with sitosterolemia for 8 weeks. Results showed that sitosterol concentrations decreased by 21% in the ezetimibe group compared with 4 % in the placebo group ($p < 0.001$). Campesterol also progressively declined, with a mean decrease after 8 weeks of 24 % with ezetimibe and a mean increase of 3 % with placebo treatment ($p < 0.001$).²³

Currently, there are no clinical outcome data and only short-term safety data with ezetimibe used alone or in combination with statins.

Safety

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study were presented at the European Society of Cardiology (ESC) Congress 2008 and published in the *New England Journal of Medicine* in Sept 2008. The trial showed that the cholesterol-lowering combination of simvastatin/ezetimibe was no better than placebo in reducing the primary composite end point of aortic-valve and CV events in patients with mild to moderate asymptomatic aortic stenosis.¹⁸ The cancer data, however, were what captured the attention of many in the medical community. The cancer data from the SEAS trial showed a significantly increased risk in the onset of fatal and nonfatal cancer (2.7%/year for active treatment versus 1.7%/year for controls), as well as a significantly increased risk of death from cancer (0.9%/year for active treatment versus 0.5%/year for controls). The site of cancer was nonspecific, but there were numeric increases in the risk of skin, stomach, and prostate cancer.

When the cancer findings became known, it led to an independent analysis of the IMPROVE-IT and SHARP trials by the Oxford investigators to determine whether the cancer risk was real or chance. The analyses failed to confirm the association between ezetimibe and cancer observed in the SEAS trial. In IMPROVE-IT and SHARP, which provided more cancer data than the SEAS trial alone, including more data in patients with at least three years of follow-up, there was no increased risk of incident cancer or cancer mortality. When all three trials were combined, there remained an increased risk of death from cancer in the active-treatment arm.²⁴ The analyses have been submitted to the Food and Drug Administration (FDA) for its review.

Medical Diagnoses Criteria

The intent of the identification of patients with certain medical diagnoses is to allow coverage of ezetimibe in members when combination therapy is not indicated. The medical diagnoses included under homozygous sitosterolemia will be used to identify patients for pre-approval of ezetimibe through the implementation process. The utilization management step therapy program for ezetimibe will not be required for them. Medical claims data will be used to identify plan members with the ICD-9 codes listed below:

EVENT	ICD-9CM Code*
Homozygous sitosterolemia (under Other Disorders of Lipoid Metabolism)	272.8, 272.8X

*The Medical Diagnoses Criteria will approve ICD-9 codes of three or more digits as applicable to ensure that members who have been assigned incomplete codes will be included.

These patients would be exempt from the prior authorization process for prescriptions for ezetimibe.

Quantity Limit

The intent of the recommended quantity limit for ezetimibe is to encourage appropriate prescribing quantities as recommended by FDA-approved product labeling. The quantity limit per day for the ezetimibe has been determined based on product labeling dosing recommendations. For ezetimibe, product labeling recommends dosing once daily.

ELECTRONIC EDITS

Information from below about step therapy or quantity limits will apply only if that program is implemented. If there are both step therapy and quantity limit programs implemented, requirements from both must be met for a claim to process.

Step Therapy

The overall process for step therapy requires that another drug or drugs be tried in a specific previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit.

Table 3: Summary of Zetia Step Therapy

Targeted Agent(s)	Zetia
Is auto-grandfathering implemented? (with look-back time frame)	Yes (90 days ^a)
Prerequisite Agent(s)	Statin, Statin-niacin, or fenofibrate product
Number of prerequisites required	1
Prerequisite look-back time frame	30 days ^b
Age-related edit?	NA
Additional comments	- The 30-day look-back parameter is used to identify recent or concurrent statin or fenofibrate therapy - Patients with homozygous sitosterolemia will not be subject to the step therapy if the diagnosis (ICD-9 code) has been documented in medical claims data.

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 30 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 60 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 120 days.

Table 4: Details of Zetia Step Therapy

Targeted Agents	GPIs (multisource code)	Prerequisites	GPIs (multisource code)	Look-back Time frames
Zetia	39300030*****, M, N, or O	For Prerequisites, ANY ONE of: Statin (lovastatin, pravastatin, simvastatin, Altoprev, Mevacor, Crestor, Lescol/Lescol XL, Lipitor, Pravachol, Zocor,) HMG-niacin combination (Advicor, Simcor) OR Fenofibrate (including choline fenofibrate, fenofibric acid, Antara, Fenoglide, Fibricor, Lofibra, Tricor, Triglide, Trilipix)	3940*****, M, N, O, or Y 39200006*****, 39200024*****, 39200025*****, M, N, O, or Y	Prerequisite look-back time frame: 30 days ^a
		For Auto-grandfathering, ANY ONE of: Zetia	39300030*****, M, N, or O	Auto-grandfathering look-back time frame: 90 days ^b

a - The system searches for a claim with a days supply that begins or ends in the past 30 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 60 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 120 days.

b - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30-day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

Quantity Limit

The overall process for a quantity limit allows only quantities of target drugs that are below the set limit (defined in Recommended Quantity Limits section above) to adjudicate through the claims system. If the patient does not meet the step therapy criteria or is requesting a higher quantity, then the system will reject with the message indicating that prior authorization is necessary. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the Prior Authorization (PA) Criteria for Approval is to provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit.

Step Therapy

The intent of the PA criteria for step therapy for ezetimibe is to ensure that patients who are starting therapy with ezetimibe are concomitantly treated with a statin unless a contraindication to statin therapy exists (i.e., in patients with active liver disease, unexplained persistent elevations in serum transaminases, and in women who are pregnant or nursing) or if the patient is intolerant of statin therapy. The criteria also provide for coverage of ezetimibe when used with a fenofibrate product for mixed hyperlipidemia. Patients who are currently receiving therapy with ezetimibe will be allowed continuation of therapy without meeting the above edit requirements.

Ezetimibe therapy in patients with homozygous sitosterolemia or those failing statin monotherapy will be approved indefinitely because therapy is expected to be long-term without changes in the requirements for approval. Indefinite approvals granted through the Clinical Review PA process may be re-evaluated at some future time if new information changes selection criteria or safety issues develop that may place these patients at risk. Approvals in patients receiving concomitant fenofibrate therapy will be approved for 12 months at a time, to allow for annual re-evaluation of concurrent therapy.

Quantity Limit

The intent of the *PA Criteria for Approval* for the ezetimibe quantity limit is to allow for review of requests for quantities exceeding the set limit. Requests for larger quantities will be reviewed when the prescriber provides documentation supporting dosing outside of FDA labeling for the patient.

Step Therapy/Quantity Limit PA Criteria for Approval

Step Therapy with or without Quantity Limit

Zetia (ezetimibe)

Initial and Renewal Evaluation

1. Has the Zetia/ezetimibe criteria been implemented with the step therapy option?
If yes, continue to 2. If no, go to quantity limit only criteria question set.
2. Is the patient currently being treated with Zetia?
If yes, approve for 12 months. If no, continue to 3
3. Has Zetia/ezetimibe been previously approved under step therapy criteria and now is rejecting for a quantity over the set limit?
If yes, continue to 9. If no, continue to 4.
4. Does the patient have a diagnosis of homozygous sitosterolemia?
If yes, continue to 9. If no, continue to 5.

5. Does the patient have a diagnosis of mixed hyperlipidemia?
If yes, continue to 6. If no, continue to 7.
6. Is the patient currently being treated with a fenofibrate product?
If yes, continue to 9. If no, continue to 7.
7. Is the patient currently being treated with a statin or statin-niacin combination?
If yes, continue to 9. If no, continue to 8
8. Does the patient have a contraindication, allergy, intolerance, or history of failure on a statin or statin-niacin combination?
If yes, continue to 9. If no, deny.
9. Has the quantity limit edit option been implemented?
If yes, continue to 10. If no, approve as listed:
 - patients with homozygous sitosterolemia – approve indefinitely
 - patients failing statin monotherapy – approve indefinitely
 - patients on concurrent fenofibrate therapy – approve for 12 months.
10. Is the quantity requested greater than the set limit?
If yes, continue to 11. If no, approve as listed:
 - patients with homozygous sitosterolemia – approve indefinitely
 - patients failing statin monotherapy – approve indefinitely
 - patients on concurrent fenofibrate therapy – approve for 12 months.
11. Has the prescriber submitted documentation in support of therapy with a higher dose for the intended diagnosis?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

Quantity Limit Edit Only

Zetia (ezetimibe)

Initial and Renewal Evaluation

1. Has the Zetia/ezetimibe criteria been implemented with the quantity limit only option?
If yes, continue to 2. If no, go to step therapy criteria question set.
2. Is the quantity requested greater than the set limit?
If yes, continue to 3. If no, review is not applicable. Claim will adjudicate.
3. Has the prescriber submitted documentation in support of therapy with a higher dose for the intended diagnosis?
If yes, pharmacist must review and may approve for 12 months based on review of information provided.
If no, deny.

SUMMARY

Step therapy electronic edits are designed to identify patients electronically by their medication history. The step therapy edit for Zetia (ezetimibe) allows for automatic payment of claims when the patient's medication history indicates concurrent use a statin, statin-niacin combination, or fenofibrate product, bypassing the manual PA process. The step therapy process allows for automatic payment of ezetimibe when a patient is stabilized on ezetimibe therapy or if a medical diagnosis of homozygous sitosterolemia is documented. The quantity limit edit of ezetimibe encourages appropriate dosing according to FDA-approved product labeling. Approval of higher quantities will be reviewed when the prescriber provides

documentation on the use of a higher quantity for the intended diagnosis. The program may be implemented with a step therapy edit, a quantity limit edit or a combination of a step and quantity limit edit. Review through the manual PA process allows for use outside the edit parameters when appropriate.

REFERENCES

1. Zetia product information. Merck/Schering-Plough Pharmaceuticals. January 2009.
2. Prime Therapeutics Formulary Chapter 5.9F: Cholesterol Absorption Inhibitors. March 2009.
3. Data on file with Merck and Company. Ezetimibe Trials. Provided by Merck & Co. November 2002.
4. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Card* 2002;40:2125-2134.
5. Kerzner B, Corbelli J, Sharp S, et al. Efficacy and Safety of Ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardiol* 2003;91:418-424.
6. Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1084-1091.
7. Sager PT, Melani L, Lipka L, et al. Effect of Coadministration of Ezetimibe and Simvastatin on High –Sensitivity C-Reactive Protein. *Am J Cardiol* 2003;92:1414-1418.
8. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk of severe hypercholesterolemia; efficacy and safety of ezetimibe co-administered with atorvastatin. *Am Heart J*. 2004;148:447-55.
9. Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90:1092-1097.
10. Bays HE, Moore PB, Drehobl MA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin Ther* 2001;23:1209-1230.
11. Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105:2469-2475.
12. National Cholesterol Education Program, National Heart, Lung and Blood Institute, National Institutes of Health. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III Final Report)* Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm. Accessed September 14, 2007.
13. Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-39.
14. National Institute for Health and Clinical Excellence (NICE). Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia, Technology Appraisal Guidance 132, November 2007. Available at: <http://www.nice.org.uk/nicemedia/pdf/TA132guidance.pdf> Accessed May 26, 2009.
15. Kastelein JJP, Akdim F, Stroes ESB, et al, for the ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358:1431-1443.
16. ACC statement on ENHANCE Trial 1/2008. Available at: www.acc.org/enhance.htm Accessed June 11, 2008.
17. FDA. FDA issues early communication about ongoing review of Vytorin. January 25, 2008. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008?NEW01784.html> Accessed May 26, 2009.
18. Rossebo AB, Pedersen TR, Borman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359:13: 1343-1356.
19. FDA. Update of Safety Review of January 25, 2008. Issued January 9,2009. Available at: http://www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin200901.htm. Accessed May 26, 2009.

20. Farnier M, Freeman MW, Macdonell G, et al. for the Ezetimibe Study Group. Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. *Eur Heart J*. 2005;26:897-905.
21. 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;47:1584-7.
22. Farnier M, Roth E, Gil-Extremera B, et al. for the Ezetimibe/Simvastatin + Fenofibrate Study Group. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. *Am Heart J*. 2007;153:335.e1-335.e8.
23. Salen G, von Bergmann K, Lutjohann D, et al. Multicenter Sitosterolemia Study Group. Ezetimibe effectively reduces plasma plant sterols in patients with sitosterolemia. *Circulation*. 2004;109:966-71.
24. Peto R, Emberson J, Landray M, et al. Analyses of data from three ezetimibe trials. *N Engl J Med* 2008;359:1357-1366

Document History – Zetia ST

Client Specific criteria developed 07/2003

Prime Standard 06/2005

Prime Standard criteria approved by External UM Committee 08/2005

Annual Review with changes approved by External UM Committee 05/2006

Annual Review with changes approved by External UM Committee 11/2007

Annual Review with changes approved by P&T UM Committee 08/2008

Initial Client Review, Prime Standard Criteria approved by HCSC Corporate Clinical Committee 08/2008

Document History – Zetia QL (from Lipid Management QL)

Original Prime Standard 05/2005 UM Committee Approval 05/11/2005

Annual Review with changes approved by External UM Committee 05/2006

Annual Review with changes approved by External UM Committee 11/2007

Annual Review with changes approved by P&T UM Committee 08/2008

Document History – Zetia STQL

Annual Review with changes, creation of STQL document, approved by P&T UM Committee 08/2009

Administrative update (clarifying list of fenofibrate products to include all GPIs) 09/2009

Client Specific Annual Review, ST criteria maintained, approved by HCSC Corporate Clinical Committee 11/2009