

Medical Policy



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Title: **Statin Step Therapy Prior Authorization Criteria**

Prior Authorization Form:

<http://www.bcbsks.com/CustomerService/Forms/pdf/6139KSStatinStepTherapy.pdf>

For information concerning Prior Authorization Prescription Drugs:

http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

Professional

Original Effective Date: January 1, 2010

Revision Date(s):

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Institutional

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Brand	Generic	Dosage Form
Advicor [®]	niacin extended-release/lovastatin	extended/immediate release tablet
Altoprev [®]	lovastatin	extended-release oral tablet
Mevacor [®]	lovastatin ^a	immediate-release oral tablet
Crestor [®]	rosuvastatin	immediate-release oral tablet
Lescol [®]	fluvastatin	immediate-release oral capsule
Lescol [®] XL	fluvastatin	extended-release oral tablet
Lipitor [®]	atorvastatin	immediate-release oral tablet
Pravachol [®]	pravastatin ^a	immediate-release oral tablet
Simcor [®]	niacin extended-release/ simvastatin	extended release oral tablet
Vytorin [®]	ezetimibe/simvastatin	immediate-release oral tablet
Zocor [®]	simvastatin ^a	immediate-release oral tablet

a - currently available as a generic

DESCRIPTION
FDA APPROVED INDICATIONS

Table 1: FDA-Approved Indications and Clinical Trials Data¹⁻²²

FDA Approved Indication (indicated by ✓)	Atorva	Fluva	Lova	Prava	Simva	Rosuva	Simva/ ezetimib	Niacin ER/	Niacin ER/ Iova
Primary hypercholesterolemia and mixed dyslipidemia (IIa, IIb) ↓ Total-C, ↓ LDL-C, ↓ Apo B, ↓ TG, ↑ HDL-C	✓ ^a	✓	✓ ^b	✓	✓	✓	✓	✓	✓
Hypertriglyceridemia (IV)	✓	Data	Data	✓	✓	✓		✓	
Primary dysbetalipoproteinemia (III)	✓		Data	✓	✓	✓			
Familial homozygous hyperlipidemia	✓		Data	Data	✓	✓	✓		
Familial heterozygous hyperlipidemia in children	✓ ^c	✓ ^c	✓ ^c	✓ ^d	✓ ^c				
Primary Prevention of Heart Disease	Yes	No	Yes	Yes	Yes	No	No	No	No
↓ risk of myocardial infarction	✓		✓	✓	Data				
↓ risk of undergoing a revascularization procedure	✓		✓	✓	Data				
↓ risk of cardiovascular mortality with no increase in death from non-cardiovascular causes			Data	✓	Data				
↓ risk of stroke	✓								
↓ risk of unstable angina	✓		✓						
Secondary Prevention of Cardiovascular Events	Yes	Yes	Yes	Yes	Yes	No	No	No	No
↓ risk of total mortality by decreasing coronary death	✓			✓	✓				
↓ risk of myocardial infarction	✓	Post PCI	Post CABG	✓	✓				
↓ risk of undergoing a revascularization procedure	✓	✓	Post CABG	✓	✓				
↓ risk of stroke and TIA	✓			✓	✓				
Slow progression of coronary atherosclerosis	Data	✓	✓	✓	Data	✓			
↓ risk of angina	✓								
↓ risk of hospitalization for CHF	✓								

a - indicates has FDA approved indication b - not indicated to ↓ Apo B, ↓ TG, ↑ HDL; produces changes similar to others
 c - adolescents ages 10 to 16/17 years d - children and adolescents 8 years and older
 Data indicates that there are large studies demonstrating efficacy; Post CABG and Post PCI indicate efficacy data exist but for a select population (i.e., post CABG or post PCI); CABG = coronary artery bypass graft;
 PCI = percutaneous coronary intervention; TIA = transient ischemic attack; CHF = congestive heart failure

POLICY
PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Step Therapy

The intent of the *PA Criteria for Approval* for statin step therapy is to ensure that patients who have been unable to tolerate the generic statin agent(s), or have not had adequate response to one of these agents, have the option of treatment with another statin.

Approval will be given to patients who have a history of use and failure outside of the 999 day look-back period or outside of the current benefit plan. A brand statin may be approved if the patient is unable to use a generic because of allergy, intolerance,

contraindication, or treatment failure. Crestor will be approved if the patient is already being treated with Crestor.

If a generic statin is not found, a request for the brand is directed through a manual prior authorization (PA) process. This process allows use of the brand agent if there is previous use of a generic that does not appear in the claims history, or if the patient cannot use a generic due to allergy, intolerance, or contraindication. Brand agents may also be approved for use if the patient requires LDL lowering that cannot be achieved with available generic agents.

Step Therapy PA Criteria for Approval ***Brand Statins or Combination Statin Agents (e.g. Advicor, Simcor, Vytorin)***

Initial and Renewal Evaluation

1. Does the patient have a medical diagnosis that puts them at a high risk of major coronary event [defined as myocardial infarction, coronary atherosclerosis disease (CAD), stroke, congestive heart failure, diabetes, or a surgical procedure for a coronary stent placement, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), or intracoronary thrombolysis infusion]?
If yes, approve indefinitely for the brand requested. If no, continue to 2.
2. Is the brand requested Crestor?
If yes, continue to 3. If no, continue to 4.
3. Is the patient currently being treated with Crestor?
If yes, approve indefinitely. If no, continue to 4.
4. Does the patient's medication history include use of a generic statin agent (lovastatin, pravastatin, simvastatin)?
If yes, approve for indefinitely. If no, continue to 5.
5. Does the patient have a contraindication, allergy, or intolerance, to the available generic agents?
If yes, approve indefinitely. If no, continue to 6.
6. Does the patient require LDL lowering that cannot be achieved with the available generic agent(s)? [defined as greater than 40% LDL lowering, which Table 3 lists as achievable with simvastatin 40 mg once daily or lovastatin 40 mg twice daily]
If yes, approve indefinitely. If no, deny.

RATIONALE

Step Therapy

The statin step therapy program encourages the use of cost-effective generic 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG Co-A) reductase inhibitors (statins) prior to the use of brand statins for the management of high blood cholesterol. The program approves for a brand statin (including the combination agents Advicor, Simcor, and Vytorin) when there is history of generic use and approves for brand Crestor for patients already on Crestor therapy. The medical diagnosis option will be implemented to accommodate the use of any statin in those at high risk for a major coronary event.

Background Clinical Information

There are currently three statins available as generics – lovastatin, pravastatin and simvastatin. For each of the diagnoses approved by the Food and Drug Administration (FDA) for statins (primary hyperlipidemia and mixed dyslipidemia, hypertriglyceridemia, dysbetalipoproteinemia, familial homozygous hyperlipidemia, and familial heterozygous hyperlipidemia in children) there is a generic with approved labeling for treatment of the diagnosis.¹⁻¹⁰ There is also a generic with approved labeling for the primary prevention of coronary events in patients without existing coronary heart disease and secondary prevention of cardiovascular events in patients with existing coronary heart disease (see Table 1).¹⁻²² [see also Formulary Chapters 5.9C: Antihyperlipidemic Agents: HMG CoA Reductase Inhibitors and 5.9D: Antihyperlipidemic Agents: HMG CoA Reductase Inhibitor Combinations^{11,12}]

All of the statins, when administered in approximately equivalent doses (see Table 3), can reduce LDL cholesterol up to 40 %.^{11,12,23} Reductions in LDL cholesterol of 40 % to 49 % can be achieved with atorvastatin, rosuvastatin, lovastatin, and simvastatin.²¹ Reductions in LDL cholesterol greater than 49 % may be accomplished with atorvastatin doses of 40 mg daily or greater or rosuvastatin doses of 20 mg daily or greater.^{11,12,23}

Table 2: Doses of Statins Resulting in Similar Percent Reductions in LDL Cholesterol^{a23,24}

atorvastatin	fluvastatin	lovastatin	pravastatin	rosuvastatin	simvastatin
--	40 mg	20 mg	20 mg	--	10 mg
10 mg	80 mg	40 or 80 mg	40 mg	--	20 mg
20 mg	--	80 mg	80 mg	5 or 10 mg	40 mg
40 mg	--	--	--	--	80 mg
80 mg	--	--	--	20 mg	--
--	--	--	--	40 mg	--

a - estimates for equipotent doses based on results from head-to-head trials

Table 3: Percent Reduction in LDL Cholesterol with Statins²⁴

Daily Dose	Number of clinical trials ^a	LDL mean % lowering from head-to-head clinical trials only	LDL mean % lowering from manufacturer prescribing information (and ATP-III ²⁵ if available)
Atorvastatin			
10 mg	22	28.9% to 40.2%	39% (37%)
20 mg	8	38.4% to 46.1%	43%
40 mg	5	45.1% to 51.3%	50%
80 mg	6	46.3% to 54%	60% ^b (57%)
Fluvastatin			
20 mg	5	17% to 21.8%	22% (18%) ^f
40 mg	6	22% to 26%	25% ^f
80 mg	2	29.6% to 30.6% ^d	36% (31%) ^{ef}
80 mg XL	0	-- ^c	35% ^f
Lovastatin			
10 mg	2	21.6% to 24%	21%
20 mg	8	21% to 29%	27% (24%)
40 mg	5	27.9% to 33%	31%
80 mg	2	39% to 48%	42% (40%) ^g
Pravastatin			
10 mg	9	18% to 24.5%	22%
20 mg	11	23% to 29%	32% (24%)
40 mg	8	25.2% to 34%	34%
80 mg	0	-- ^c	37% (34%)
Rosuvastatin			
5 mg	6	39.1% to 46%	45%
10 mg	9	37.1% to 50.6%	52%
20 mg	3	45.7% to 52.4%	55%
40 mg	3	53.6% to 58.8%	63%
Simvastatin			
10 mg	17	26% to 33.1%	30%
20 mg	17	18.5% to 40%	38% (35%)
40 mg	7	34.3% to 43%	41%
80 mg	5	43% to 48.8%	47% (46%)

a - Randomized controlled trials that included at least two statins. % LDL-C reduction in clinical trials included in table only if data provided for a specific dosage and not a mean dosage

b - This is based on results of 23 patients. Clinical trial data at atorvastatin 80 mg included more than 1,750 patients.

c - Newly-approved dose or dosage form with no head-to-head clinical trial data against another statin.

d - Given as fluvastatin 80 mg qd or 40 mg bid (does not include XL product)

e - Given as fluvastatin 40 mg bid f - Median percent change g - Given as lovastatin 40 mg bid

Statin combination products with two lipid-lowering agents will be included in this step therapy program – Advicor, Simcor, and Vytorin. Caduet, a combination of amlodipine and atorvastatin, is not included in the criteria because it is not indicated exclusively for the treatment of hypercholesterolemia. Caduet is used in patients who require both lipid management and treatment of hypertension or angina.

There are insufficient head-to-head trials to compare equivalent doses of the combination agents, Advicor, Simcor, or Vytorin. Product labeling for Advicor, Simcor, and Vytorin indicates improved lipid-altering effects with the combination agent compared to each component.^{1,8,9} There are no outcomes studies for Advicor, Simcor, or Vytorin. Outcomes (reduction in morbidity and mortality) from the Scandinavian Simvastatin Survival Study and the Heart Protection Study are applicable to simvastatin only, not the combinations of ezetimibe and simvastatin or niacin and

simvastatin. Current prescribing information for Advicor states that the effect of combined therapy with niacin and lovastatin on cardiovascular morbidity and mortality has not been determined.¹ The HATS trial²⁶ (2001) did find that sustained release niacin (Slo-Niacin) in combination with simvastatin decreased rates of atherosclerotic progression and coronary heart disease (CHD) events.²⁶ Current prescribing information for Simcor states that no incremental benefit of Simcor on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin monotherapy and niacin monotherapy has been established.⁸

Safety and Efficacy – Simvastatin-Ezetimibe

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.²⁷

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.²⁸

In January, 2008, the FDA issued a statement:²⁹ "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."²⁹

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 (CV) events in patients with mild to moderate asymptomatic aortic stenosis.³⁰ 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. 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.³⁰

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.³⁰

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.³¹ The analyses have been submitted to the FDA for its review.

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.³²

- 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 *events* (composite endpoint of cardiovascular 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.³²
- 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.³²

SUMMARY

Step therapy electronic edits are designed to identify patients electronically by their medication history and automatically approve claims that would meet prior authorization criteria. The Statin Step Therapy edit allows for automatic payment of claims for brands when the patient's medication history indicates prior use of generic lovastatin, pravastatin, or simvastatin, or if the patient is being treated with Crestor, bypassing the manual prior authorization (PA) process. The manual PA process provides a member-specific review process where practitioner provided patient-specific parameters are taken into consideration when reviewed. The step therapy protocol for statins optimizes the utilization of cost-effective agents for the individual benefit plan.

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