Medical Policy

BlueCross BlueShield of Kansas
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Title: Statin Therapy

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/6139KSStatinStepTherapy.pdf
Prime Therapeutics will review Prior Authorization requests

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm

Professional
Original Effective Date: January 1, 2010
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Current Effective Date: January 1, 2014

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Statin Prior Authorization program is to encourage the use of cost-effective generic statins (HMG Co-A reductase inhibitors) prior to the use of brand statins for the management of high blood cholesterol. This program includes all brand statin or statin combination products as targets requiring use of a generic statin or statin combination prior to their use. The program will evaluate use of a brand statin or statin combination product through the prior authorization process when patients are unable to take a generic statin due to documented intolerance, FDA labeled contraindication, or hypersensitivity. Requests for brand statins or statin combinations will be reviewed when patient-specific documentation has been provided.

Target Drugs (brands only)

Advicor® (niacin extended release/lovastatin)[b]
Altoprev® (lovastatin extended release)
Crestor® (rosuvastatin)
Lescol XL® (fluvastatin extended release)
Liptruzet® (ezetimibe/atorvastatin tabs)
Livalo® (pitavastatin)
Simcor® (niacin extended release/simvastatin)
Vytorin® (ezetimibe/simvastatin)

b – generic anticipated in 2013; will be included as a prerequisite in step therapy program when available

FDA Approved Indications and Dosage[1-6,17-23]

Drug	Primary hyper-cholesterolemia	Mixed dyslipidemia	Hypertriglyceridemia	Primary dysbeta-lipoproteinemia	Primary prevention coronary events	Secondary prevention cardiovascular events	Homozygous familial hyperlipidemia	Heterozygous familial hyperlipidemia	Dosage and Administration
Single Ingredient Products									
Altoprev, Mevacor (lovastatin)* tablets	✓[1]				✓	✓		✓[5]	10 mg to 80 mg daily in single or two divided doses
Crestor (rosuvastatin) tablets	✓[1]	✓[2]	✓[3]	✓[4]	✓	✓	✓	✓[5]	5 mg to 40 mg once daily
Lescol (fluvastatin)* Capsules **Lescol XL** (fluvastatin) tablets ER	✓[1]	✓[2]				✓		✓[5]	40 mg to 80 mg once daily or in two divided doses 80 mg once daily

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Single Ingredient Products (con't)									
Livalo (pitavastatin) tablets	✓	✓							1 mg to 4 mg once daily
Lipitor (atorvastatin)* tablets	✓[1]	✓[2]	✓[3]	✓[4]	✓	✓	✓	✓[5]	10 mg to 80 mg once daily
Pravachol (pravastatin)* tablets	✓[1]	✓[2]	✓[3]	✓[4]	✓	✓		✓[5]	10 mg to 80 mg once daily
Zocor (simvastatin)* tablets	✓[1]	✓[2]	✓[3]	✓[4]	✓	✓	✓	✓[5]	5 mg to 80 mg once daily
Combination Products									
Advicor (niacin ER/ lovastatin) tablets	✓[1]	✓[2]							500 mg/20 mg to 1000 mg/20 mg once or twice daily
Liptruzet (ezetimibe/atorvastatin) tablets	✓[1]	✓[2]					✓		10 mg/10 mg to 10 mg/80 mg once daily
Simcor (niacin ER/ simvastatin) tablets	✓[1]	✓[2]	✓[3]						1000 mg/20 mg to 2000 mg/40 mg once daily
Vytorin (ezetimibe/ simvastatin) tablets	✓[1]	✓[2]					✓		10 mg/10 mg to 10 mg/80 mg once daily

1 - Includes heterozygous familial and nonfamilial hypercholesterolemia.
2 - Includes Fredrickson types IIa and IIb.
3 - Includes Fredrickson type IV.
4 - Includes Fredrickson type III.
5 - Also in patients 10-17 years old.
* - generic available

POLICY

Prior Authorization Criteria for Approval

Brand Statins will be approved when ANY ONE of the following is met:

1. The patient's medication history includes use of a generic statin or statin combination
   (evidence of a paid claim within the past 90 days, or patient is new to the claim system within the past 120 days AND a statement by the physician that patient has taken a generic statin agent in the past 90 days)
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the available generic statins or statin combination products

Length of approval: 12 months

RATIONALE

According to national and international guidelines, statins are the most effective agents in lowering low-density lipoprotein (LDL) cholesterol and reducing the incidence of morbidity and mortality from coronary heart disease (CHD) and stroke in primary and secondary prevention settings and are considered first line therapy in patients with dyslipidemias.[8-11,23 ~~25~~] Clinical outcomes have demonstrated that every 1 mmol/L (39 mg/dL) reduction in LDL results in a 20% reduction in major cardiovascular events.[7] Along with reducing LDL, statins decrease triglyceride (TG) levels by up to 35%.[7]

When statins are provided in doses that are approximately equipotent (the equivalent daily doses for statins with respect to their LDL-C lowering abilities), a similar percent reduction in LDL-C can be achieved. The chart below shows this comparison (summary estimates from 164 randomized placebo-controlled trials).[21,22]

Dose ranges and efficacy of statins[21,22]

Drug	Dose Range	Effect on LDL-C (% Decrease)	Effect on HDL-C (% Increase)	Effect on Triglycerides (% Decrease)
Statins				
Fluvastatin	20–80 mg	22–35	3–11	17–21
Pravastatin	10–80 mg	22–37	2–12	15–24
Lovastatin	10–80 mg	21–42	2–8	6–21
Simvastatin	5–80 mg	26–47	10–16	12–33
Atorvastatin	10–80 mg	39–60	5–9	19–37
Rosuvastatin	5–40 mg	45–63	8–10	10–30
Pitivastatin	1-4 mg	32-45	3.2-8.0	15-18

Information from cardiovascular outcome studies involving statins are shown in the chart below.[13]

Study	Year of Publication	Journal of Publication	No. of Subjects	Subjects	Age (yrs)	Length of Study (yrs)	Comparison Agents (mg)	Events			Mean LDL-C (mg/dl)			
											Patients		Controls	
								Patients	Control	Relative Risk Reduction	Baseline	End	Baseline	End
MIRACL[1]	2001	*JAMA*	3,086	ACS	Mean 65	0.31	A 80 vs P	14.80%	17.40%	↓16%	124	72	124	135
HPS[2]	2002	*Lancet*	20,526	CAD, PVD, stroke, DM	40–80	5	S 40 vs P	7.60%	9.10%	↓17%	131	90	131	129
ASCOT-LLA[3]	2003	*Lancet*	10,305	SH	40–79	Median 3.3*	A10 vs P	1.90%	3.00%	↓31%	133	90	133	126
PROVE-IT[4]	2004	*NEJM*	4,162	ACS	Mean 58	Mean 2	A 80 vs pravastatin 40	19.7%	22.3%	↓14%	106	62	106	95
CARDS[5]	2004	*Lancet*	3,838	DM	40–75	Median 3.9*	A 10 vs P	9.4%	13.4%	↓37%	117	81	117	120
A to Z[6]	2004	*JAMA*	4,497	ACS	Mean 61	0.5–2	S 40 to S 80 vs P to S 20	14.4%	16.7%	↓11%†	112	66	111	81
TNT[7]	2005	*NEJM*	10,001	CAD, PVD, stroke, DM	Mean 61	Median 4.9	A 80 vs A 10	8.7%	10.9%	↓22%	97	77	98	97
IDEAL[8]	2005	*JAMA*	8,888	MI	<80	Median 4.8	A 80 vs S 20	9.3%*	10.4%*	↓11%†	122	81	121	104
SPARCL[9]	2006	*NEJM*	4,731	Stroke, TIA	Mean 63	Median 4.9	A 80 vs P	11.2%	13.1%	↓16%	133	43	134	129
SEAS[10]	2008	*NEJM*	1,873	AS	Mean 67	Median 4.3	S 40 + E 10 vs P	35.3%	38.2%	↓9%†	140	75	139	134
JUPITER[11]	2008	*NEJM*	17,802	Healthy	Median 66	Median 1.9*	R 20 vs P	0.016%	0.028%	↓47%	108	55	108	109

A=atorvastatin; ACS=acute coronary syndrome; AS=aortic stenosis; CAD=coronary artery disease; DM=diabetes mellitus; MI=myocardial infarction; P=placebo; PVD=peripheral vascular disease; R=rosuvastatin; S=simvastatin; SH=systemic hypertension; TIA=transient ischemia attack. * Stopped early - Study planned for 5 years. † Not significant.

The American Association of Clinical Endocrinologists (AACE) Guidelines for the Management of Dyslipidemia and Prevention of Atherosclerosis 2012 includes the following recommendations:[28]

- AACE recommends statins as the drug of choice for LDL-C reduction on the basis of findings from morbidity and mortality outcome trials. Agents currently available are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin.
- Atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin have been approved for the treatment of familial hypercholesterolemia in patients 10 years or older and are recommended by the AACE.

The AHA/American College of Cardiology (ACC)/Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2011 Update state the following:[29]

- Use statin therapy to achieve LDL-C of <100 mg/dL; for very high risk patients an LDL-C <70mg/dL is reasonable; if TG are ≥200 mg/dL, non-HDL-C should be <130 mg/dL, whereas non-HDL-C <100 mg/dL for very high risk patients is reasonable.

The National Lipid Association (NLA) appointed a Statin Safety Task Force to evaluate statin safety, encompassing an assessment of the clinical literature; premarketing pharmaceutical data; spontaneous adverse event reports; meta-analyses of randomized clinical trials and analysis of cohort data; and an analysis of a large healthcare claims database. The NLA results included the following[16]:

- Serious muscle toxicity with currently marketed statins is uncommon but significant (myopathy occurring in 5 patients per 100,000 person-years and rhabdomyolysis in 1.6 patients per 100,000 person-years)
- Elevations of transaminase levels represent a dose-related class effect among statins and are typically asymptomatic and transient (110 cases of significant elevation of liver transaminases per 100,000 person-years). Available data do not establish causality between statin treatment and serious liver dysfunction or failure.

In June 2011 the FDA issued a drug safety communication on the 80-mg dose of simvastatin because of an increased risk for muscle toxicity.[24] Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition toward simvastatin-related myopathy.

- The new changes to the drug labels for simvastatin-containing medicines are based on FDA's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial and other data accumulated by the FDA.
- SEARCH was a seven-year, randomized, double-blind clinical trial comparing the efficacy and safety of simvastatin 80 mg to simvastatin 20 mg, with or without vitamin B12 and folate, in survivors of MI.
- At the end of the trial, the incidence of major vascular events was 25.7% in the 20-mg group versus 24.5% in the 80-mg group [RR=0.094, 95% CI (0.88, 1.01); p=0.10]. Due in part to greater use of off-study LDL-C lowering medication in the simvastatin 20 mg group versus the 80-mg group, the difference in mean levels of LDL-C between the two treatment groups was 13 mg/dL instead of the expected difference of 20 mg/dL. Nonetheless, the 6% reduction in relative risk for major vascular events observed in SEARCH is consistent with the 13 mg/dL lower level of LDL-C in the 80-mg group.
- 52 patients (0.9%) in the 80-mg group versus one patient (0.02%) in the 20-mg group developed myopathy (defined as unexplained muscle weakness or pain with a serum CK >10 times the upper limit of normal [ULN]). This was higher than the labeled risk (based on clinical trial data) of 0.53%. Twenty-two patients (0.4%) in the 80-mg group versus no patient in the 20-mg group developed rhabdomyolysis (defined as unexplained muscle weakness or pain with serum CK >40 times ULN). There were no fatalities related to rhabdomyolysis.
- The risks for myopathy and rhabdomyolysis with simvastatin 80 mg were highest in the first 12 months of treatment, 5 per 1000 person-years and 2 per 1000 person-years, respectively, and decreased to 1 per 1000 person-years and 0.4 per 1000 person-years after that.

In Dec 2011 the FDA issued another update notifying the public that it revised the dose limitation of simvastatin from 10 mg to 20 mg when it is co-administered with amiodarone.[25] "The simvastatin dose limitation when taken with amiodarone (in which the simvastatin dose was lowered from 20 mg to 10 mg) was made in error. Unlike other interacting drugs, there were no pharmacokinetic or clinical trial data to support the simvastatin dose reduction approved with amiodarone. Therefore FDA has determined that the simvastatin dose limitation, when taken with amiodarone, should be restored to 20 mg."

A 2012 observational study analyzed the data for the Women's Health Initiative (WHI).[26] The study investigated whether the incidence of new-onset DM was associated with statin use among postmenopausal women who participated in the WHI study.

- The WHI recruited 161,808 postmenopausal women aged 50 to 79 years at 40 clinical centers across the US from 1993 to 1998 with ongoing follow-up. The current analysis includes data through 2005. Statin use was captured at enrollment and year three. . Incident DM status was determined annually from enrollment. Cox proportional hazards models were used to estimate the risk of DM by statin use, with adjustments for propensity score and other potential confounding factors. Subgroup analyses by race/ethnicity, obesity status, and age group were conducted to uncover effect modification.

- This investigation included 153,840 women without DM and no missing data at baseline. At baseline, 7.04% reported taking statin medication. There were 10 242 incident cases of self-reported DM over 1 004 466 person-years of follow-up. Statin use at baseline was associated with an increased risk of DM (hazard ratio [HR], 1.71; 95% CI, 1.61-1.83). This association remained after adjusting for other potential confounders (multivariate-adjusted HR, 1.48; 95% CI, 1.38-1.59) and was observed for all types of statin medications. Subset analyses evaluating the association of self-reported DM with longitudinal measures of statin use in 125 575 women confirmed these findings.
- Despite their findings, the researchers said statins address the CV consequences of DM and current American Diabetes Association guidelines for primary and secondary prevention, as well as guidelines for statin use in patients without DM should not change.[26]

Standards of Medical Care in Diabetes 2012 recommend the following:[27] In patients with dyslipidemia and DM 2 statin treatment is recommended if there is an inadequate LDL-C response to lifestyle modifications and improved glucose control, or if the patient has increased cardiovascular risk (e.g., multiple cardiovascular risk factors or long duration of DM).

Since differences in the kinetics and metabolism of individual statins exist, there is a pharmacological basis for switching a patient who is intolerant of a particular statin to an alternative drug within the same class.[15] A retrospective study involving 1100 patients treated with statins identified 40 patients with "statin intolerance." Forty patients (19 male, 21 female, median age 62 years) were identified with intolerance to at least one statin drug but with an absolute indication to be on treatment. Out of the 40 patients, 26 (65%, 11 male, 15 female) were eventually able to tolerate a statin for at least six months without their initial side effect. Overall, this required a median of two switches (range one to four) in statin treatment. Fourteen (35%) were unable to continue treatment after a median of 1.5 switches (range one to three), either because of continued intolerance or a decision not to proceed with more alternatives.[14]

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

There are no specific HCPCS codes for the drugs listed in this policy.

REVISIONS

01-01-2010	Policy added to the bcbsks.com web site.
05-20-2011	Added the following target drugs: Livalo® (pitavastatin)
	Description section updated
	In Policy section: Wording clarified from question format to statement format.
	Rationale section removed

	References section updated
08-30-2012	Removed "Target Drugs" list and added "FDA Approved Indications and Dosage" chart with Target Drugs listed.
	In Policy section: ▪ Removed the following criteria: 1. The patient has a medical diagnosis that puts patient 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) OR 3. The patient requires LDL lowering that cannot be achieved with available generic statins* *defined as greater than 40% LDL lowering, achievable with simvastatin 40 mg once daily or lovastatin 40 mg twice daily ▪ Revised Length of approval from "Indefinite" to "12 months".
	Added Rationale section
	References updated
01-01-2013	Policy Title updated from "Statin Step Therapy Prior Authorization Criteria" to "Statin Prior Authorization"
	In Description section: ▪ Updated description ▪ Added Target Drug Brand Statins list
	In Policy section: ▪ Added the word statin to item #1 to read "The patient's medication history includes use of a generic statin" - This update causes no change to the policy statement meaning.
07-01-2013	Policy posted July 12, 2013.
	Added under Prior Authorization Form link "Prime Therapeutics will review Prior Authorization requests."
	Administrative Update In Description section: ▪ Added Liptruzet (ezetimibe/atorvastatin tabs)
01-01-2014	In Header: ▪ Revised Title from "Statin Prior Authorization" to "Statin Therapy"
	Description section updated
	In Policy section: ▪ In Items 1 and 2 added "or statin combination" ▪ In item 1 added look-back information
	Rationale section updated
	Coding section added
	References updated

REFERENCES

1. Lipitor Prescribing Information. Pfizer. October 2012 June 2009.
2. Lescol/Lescol XL Prescribing Information. Novartis. October 2012 2006.
3. Pravachol Prescribing Information. BMS. October 2012.

4. Zocor Prescribing Information. Merck & Co. October 2012.
5. Crestor Prescribing Information. AstraZeneca. December 2012.
6. Mevacor Prescribing Information. Merck & Co. October 2012.
7. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins Lancet. 2005;366:1267–1278.
8. Third Report of the National Cholesterol Education Program (NCEP III) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults – Final Report. National Heart, Lung, Blood Institute. National Institutes of Health. NIH Publication No. 02-5215. September 2002. http://www.nhlbi.nih.gov/guidelines/cholesterol/. Accessed April 2010.
9. National Institute for Health and Clinical Excellence. Lipid modification for primary and secondary prevention of cardiovascular disease. NICE Clinical Guideline, May 2008. Available at www.nice.org.uk. Accessed April 2010.
10. American Diabetes Association. Standards of medical care in diabetes 2010. Diabetes Care. 2010;33:S4-S10.
11. Pasternak RC, Smith SC, Bairey-Merz N, et al. American College of Cardiology/ American Heart Association/National Heart, Lung, and Blood Institute clinical advisory on the use and safety of statins. J Am Coll Cardiol. 2002;40(3):567-572.
12. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326:1423.
13. Roberts WC. Evaluating Lipid-lowering trials in the twenty-first century. Am J Cardiol. 2009;103:1325-1328.
14. Nair RK, Karadi RL, Kirpatrick ES. Managing patients with statin intolerance: a retrospective study. Br J Cardiol. 2008;16:168-160.
15. De Angelis G. The influence of statin characteristics on their safety and tolerability. Int J Clin Pract. 2004;58:945–55.
16. McKenney JM, Davidson MH, Jacobson, TA, et al. Final Recommendations of the National Lipid Association statin safety assessment Task Force. Am J Cardiol. 2006;97[suppl]:89C-94C.
17. Advicor prescribing information. Kos Pharmaceuticals, Inc. March 2010.
18. Altoprev prescribing information. Andrx Labs, Inc. December 2006.
19. Simcor prescribing information. Abbott Laboratories. July 2010.
20. Vytorin prescribing information. Merck/Schering-Plough Pharmaceuticals. March 2010.
21. Livalo prescribing information. Kowa Pharmaceuticals America, Inc./Lilly USA LLC. January 2010.
22. Eckel R,. Statin therapy review. J Clin Endocrinology Metab. 2010:2009-2689
23. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:517-584.
24. FDA Safety Communication. New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce muscle injury. 6/8/2011. Accessed 2/21/2012 at http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm#Simvastatin_Dose_Limitations
25. FDA Safety Communication. Revised dose limitation of Zocor (simvastatin) when taking amiodarone. 12/15/2011. Accessed 2/21/2012 at http://www.fda.gov/Drugs/DrugSafety/ucm283137.htm.

26. Culver AL, Odkene IS, Balasubramanian R., et al. Statin use and risk of diabetes mellitus in postmenopausal women in the women's health initiative. *Arch Intern Med.* 2012;172(2):144-152.
27. American Diabetes Association. Standards for Medical Care 2012. *Diabetes Care.* 2012;35(supplement 1):S11-S63.
28. Jellinger PS, Smith DA, Mehta,AE,, et al.. American Association of Clinical Endocrinologists (AACE) guidelines for the management of dyslipidemia and prevention of atherosclerosis 2012. *Endocrin Practice.* 2012;18 (Suppl1)3-77.
29. Smith SC, Benjamin EF, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with atherosclerotic vascular disease: 2011 update. *J Am Coll Cardiol.* 2011;58(23):2342-2346.