

“Statin” Criteria for Use
(Pravastatin, Rosuvastatin, Fluvastatin, Fluvastatin XL, Pitavastatin)
VHA Pharmacy Benefits Management (PBM) Services, Medical Advisory Panel (MAP) and VISN Pharmacist Executives (VPEs)

*The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Department of Veterans Affairs National Formulary includes 4 HMG Co-A Reductase Inhibitors (statins): 1) simvastatin and atorvastatin (high potency-able to reduce LDL-C by greater than 40%), 2) lovastatin, and 3) pravastatin as an option for patients receiving potent inhibitors of cytochrome P450 3A4 (CYP 3A4).

All of the available statins (lovastatin, simvastatin, fluvastatin, atorvastatin, pravastatin, rosuvastatin and pitavastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia and myopathy to rhabdomyolysis.^{1,15} Factors that may increase the risk for myotoxicity with statins are higher statin dosages, drug-drug interactions, hypothyroidism, other myotoxic drugs (e.g. fibrates) and renal impairment.²⁻⁵

There is a lack of evidence to support a difference in the rate of myopathy or rhabdomyolysis for a particular statin when combined with fibrates and/or lipid lowering doses of niacin (≥ 1 gram/day). As a result, these criteria will focus on drug-drug interactions involving statins combined with drugs having the same metabolic pathway (e.g. CYP 3A4, 2C9, etc.).

The primary safety concern, in this case, arises from a drug-drug interaction occurring when potent CYP 3A4 inhibitors (e.g. macrolide antibiotics, azole antifungals, cyclosporine, protease inhibitors [HIV and HCV]) are combined with CYP 3A4 metabolized statins (e.g. lovastatin, simvastatin or atorvastatin). These drug combinations can increase blood levels of the affected statin and may further increase the risk of muscle toxicity. However, combination of these potent inhibitors with non-CYP 3A4 metabolized statins (e.g. pravastatin, fluvastatin (nonformulary) or rosuvastatin (nonformulary)) does not increase blood levels of these statins theoretically affording an additional margin of safety.

Fluvastatin is primarily metabolized via CYP 2C9 and may be vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism (e.g. amiodarone, omeprazole, metronidazole, fluvoxamine). However, many of these drug interactions with fluvastatin are only theoretical and their clinical significance is not known. In 2002, authors queried the Food and Drug Administration (FDA) adverse event reporting system database to determine the number of reported cases of statin-associated rhabdomyolysis over a 29 month period (November 1997-March 2000). Of the 601 reported cases, fluvastatin was implicated in only 1.7% of cases and none of those cases involved the combination of fluvastatin with a CYP 2C9 inhibitor.⁶ Rosuvastatin is also metabolized via CYP 2C9 and may be vulnerable to interactions with drugs known to inhibit CYP 2C9 metabolism.¹⁵ As with fluvastatin, these interactions are only theoretical and the clinical significance is not known. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore not affected by drugs inhibiting metabolism via these pathways.^{1,7,8} However, some statin-drug interactions cannot be fully explained by metabolizing enzymes. There are other mechanisms that may be responsible for altering statin pharmacokinetics and pharmacodynamics and are mediated by transporter proteins including P-glycoprotein (P-gp) and various organic anion transport polypeptides (OATPs) (e.g., pravastatin, rosuvastatin and pitavastatin combined with cyclosporine leads to a significant increase in statin levels).²⁰⁻²¹

There have been reports of excessive anticoagulation in patients receiving statins (lovastatin, simvastatin, fluvastatin and rosuvastatin) in combination with warfarin. As a result, the international normalized ratio (INR) should be monitored closely when statins are initiated, statin dose is adjusted, switched to a different statin or discontinued in patients stabilized on warfarin. These patients should also be warned to observe for signs of bleeding.^{14,15}

All patients receiving treatment with statins should be advised to report any unexplained muscle pain, tenderness or weakness regardless of statin used or concomitant drugs. Patients experiencing any of these symptoms should be advised to discontinue their lipid therapy immediately and providers should obtain a CK level, if clinically indicated.

In June 2011, the FDA announced restriction of the highest dose of simvastatin (80 mg), new contraindications and more aggressive dose limits for simvastatin when combined with certain drugs.¹⁶ The VA PBM-MAP-VPEs released guidance to address these changes and providers are encouraged to review these guidance documents prior to switching statins ([Simvastatin 80 mg-Summary Guidance for Providers](#) or [Simvastatin 80 mg-Detailed Guidance for Providers](#)).¹⁷⁻¹⁸

Formulary Criteria for Using Pravastatin (non CYP 3A4 metabolized statin)

- Patients requiring a statin and long-term treatment with an agent(s) known to be a potent CYP 3A4 inhibitor (including but not limited to: clarithromycin, erythromycin, HIV or HCV protease inhibitors, delavirdine, itraconazole, fluconazole, verapamil, amiodarone, etc.).
Patients receiving lovastatin, simvastatin or atorvastatin who require short-term treatment with a potent CYP 3A4 inhibitor should have their statin therapy temporarily withheld or closely monitored during their course of therapy. (In general, there is no need to switch to pravastatin in these patients unless the course of CYP 3A4 inhibitor therapy becomes prolonged, e.g. longer than 2-4 weeks).
- Patients experiencing muscle pain or weakness, without elevation in creatine kinase (CK), on formulary statins (simvastatin or lovastatin or atorvastatin) may receive a trial of pravastatin with close follow up.

Nonformulary Criteria for using Fluvastatin or Fluvastatin XL in Place of Simvastatin, Lovastatin or Pravastatin (One must be checked to be eligible)

- In patients who clinically require cyclosporine or gemfibrozil and statin therapy, providers can consider using fluvastatin. *The combination of a statin and gemfibrozil is generally contraindicated; however, if the risks of the combination are felt to be outweighed by the potential benefit, then the safest statin to use appears to be fluvastatin (as fluvastatin concentrations are less affected by combination with gemfibrozil). Use of statin-fibrate combinations is discouraged in VA due to the known safety risk and unproven benefit of the combinations beyond use of statins alone.¹⁷⁻¹⁹ However, in those patients with very high triglyceride levels (TG >500 mg/dl), despite attention to secondary causes and lifestyle interventions, or a history of TG induced pancreatitis, consider use of fish oils. Alternatively, niacin in the setting of elevated TG with a need for greater LDL-C lowering can be considered. If an alternative such as fish oils or niacin can be used rather than gemfibrozil, then use of a high potency statin (simvastatin or atorvastatin) is preferred. If a high potency statin is preferred in a patient with TG >500 mg/dl and niacin or fish oils are inadequate, use of simvastatin or atorvastatin with fenofibrate may be considered; but low to moderate statin doses should be used when combined with fenofibrate.*
- Patients requiring the use of a non CYP 3A4 metabolized statin and are experiencing muscle pain or weakness, without elevation in CK, on pravastatin (may receive a trial of fluvastatin or fluvastatin XL with close follow up)

Nonformulary Criteria for Using Rosuvastatin in Place of Atorvastatin, Lovastatin or Simvastatin

The FDA has restricted use of the 80 mg dose of simvastatin, recommending that no new patients be started on this dose ([Simvastatin 80 mg-Summary Guidance for Providers](#)). Because there is no convincing evidence proving a greater benefit on cardiovascular outcomes with 1) high dose simvastatin vs. moderate doses of atorvastatin in patients with acute coronary syndrome (ACS) or stable coronary artery disease (CAD), or 2) high dose atorvastatin vs. moderate dose simvastatin in patients with stable CAD, the following two options can be considered in those patients not achieving their LDL-C goal on simvastatin 40 mg daily:

- **Fixed, Moderate Dose Statin Option:** Continue simvastatin 40 mg daily and check fasting lipid profile and liver function tests (LFTs) as per usual care. (Goal: to reduce LDL-C by 30-40%)
- OR**
- **Treat to LDL-C Target Option:** Prior to increasing statin doses or switching statin therapy in patients, whose LDL-C goals are not reached, ensure patient has been adherent to statin therapy. Patients who have been adherent to statin therapy and have not met their LDL-C goal on simvastatin 40 mg daily, atorvastatin 80 mg or lovastatin 80 mg daily or maximally tolerated or recommended doses of simvastatin, atorvastatin or lovastatin may receive rosuvastatin 10-20 mg daily (Refer to table 1 for recommended rosuvastatin dose limits when combined with certain drugs).

<p><u>Nonformulary Criteria for Using Rosuvastatin in Place of Pravastatin</u></p> <ul style="list-style-type: none"> ○ Patients with an inadequate LDL-C lowering response to maximum dose pravastatin in patients receiving potent CYP 3A4 inhibitors. (The initial dose in these patients should be 5 mg daily.)
<p><u>Nonformulary Criteria for Using Pitavastatin in Place of Pravastatin or Rosuvastatin</u></p> <ul style="list-style-type: none"> ○ Patients with an inadequate LDL-C lowering response to maximum dose pravastatin in <u>patients receiving potent CYP 3A4 inhibitors*</u> and an adverse event on rosuvastatin. <i>Since both pravastatin and rosuvastatin have evidence to support a benefit on cardiovascular outcomes, these statins are preferred prior to use of pitavastatin.</i>

Table 1: Recommended Dose Limits/Dose Adjustments/Considerations For Statins When Combined with Certain Drugs or Patient Factors that May the Increase Risk for Skeletal Muscle Injury

Atorvastatin	<ul style="list-style-type: none"> • Avoid combining atorvastatin with telaprevir, tipranavir+ritonavir, gemfibrozil or cyclosporine • Strong CYP 3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors [saquinavir+ritonavir, darunavir+ritonavir, fosamprenavir +/- ritonavir]): Do not exceed atorvastatin 20 mg daily • Lopinavir+ritonavir: use with caution and use the lowest necessary dose of atorvastatin • Boceprevir: Use lowest effective atorvastatin dose, but do not exceed atorvastatin 40 mg daily. • Nelfinavir: Do not exceed atorvastatin 40 mg daily • In patients taking rifampin and atorvastatin, simultaneous co-administration is recommended. • Other fibrates (e.g., fenofibrate) or lipid lowering doses of niacin (>1 g/day): May increase the risk for skeletal muscle effects. Lower starting and maintenance doses of atorvastatin should be considered when combined with fibrates or niacin. In general, statin-fibrate combinations are not recommended. • Cases of myopathy, including rhabdomyolysis, have been reported with co-administration of atorvastatin and colchicine. Caution should be used when prescribing atorvastatin and colchicine.
Fluvastatin	<ul style="list-style-type: none"> • Cyclosporine or fluconazole: Limit fluvastatin to 20 mg daily • Gemfibrozil: concomitant use with fluvastatin should be avoided • Other fibrates (e.g., fenofibrate) or lipid-lowering doses of niacin (>1 g/day): May increase the risk for skeletal muscle effects. Lower starting and maintenance doses of fluvastatin should be considered when combined with niacin. In general, statin-fibrate combinations are not recommended. • Cases of myopathy, including rhabdomyolysis, have been reported with co-administration of fluvastatin and colchicine. Caution should be used when prescribing fluvastatin and colchicine.
Lovastatin+¹	<ul style="list-style-type: none"> • Lovastatin is <u>contraindicated</u> with HCV protease inhibitors (boceprevir or telaprevir), itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors and nefazodone • Avoid combining lovastatin with gemfibrozil or cyclosporine • Danazol, diltiazem or verapamil: lovastatin 20 mg daily • Amiodarone: Do not exceed lovastatin 40 mg daily • Other fibrates(e.g., fenofibrate) or lipid-lowering doses of niacin (>1 g/day): May increase the risk for skeletal muscle effects. In general, statin-fibrate combinations are not recommended. • Avoid large quantities of grapefruit juice (>1 quart daily) • Cases of myopathy, including rhabdomyolysis, have been reported with co-administration of lovastatin and colchicine. Caution should be used when prescribing lovastatin and colchicine. • Risk of myopathy, including rhabdomyolysis, may be increased by concomitant administration of ranolazine. Dose adjustment of lovastatin may be considered when combined with ranolazine. • Severe renal impairment (CrCl <30 ml.min): doses >20 mg daily should be carefully considered and cautiously implemented.
Pravastatin+	<ul style="list-style-type: none"> • Cyclosporine: Limit pravastatin to 20 mg daily • Clarithromycin: Limit pravastatin to 40 mg daily • Boceprevir: Concomitant pravastatin and boceprevir increased exposure to pravastatin. Treatment with pravastatin can be initiated at the recommended dose but close clinical monitoring is warranted. • Other fibrates (e.g., fenofibrate) or lipid-lowering doses of niacin (>1 g/day): May increase the risk for skeletal muscle effects. In general, statin-fibrate combinations are not recommended.
Simvastatin+²	<ul style="list-style-type: none"> • Simvastatin is <u>contraindicated</u> with: itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol, and HCV protease inhibitors [boceprevir and telaprevir]) • Verapamil or diltiazem: Do not exceed simvastatin 10 mg daily • Amiodarone, amlodipine or ranolazine: Do not exceed simvastatin 20 mg daily

September 2003; updated January 2004, September 2006, August 2007, September and December 2011 (simvastatin dosing restrictions), February 2012 (added pitavastatin); March 2012 (new drug-interactions-dose limitations); October 2012 (addition of atorvastatin to the VANF

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	<ul style="list-style-type: none"> Other fibrates (e.g., fenofibrate) or lipid-lowering doses of niacin (>1 g/day): May increase the risk for skeletal muscle effects. In general, statin-fibrate combinations are not recommended. Cases of myopathy, including rhabdomyolysis, have been reported with co-administration of simvastatin and colchicine. Caution should be used when prescribing simvastatin and colchicine. Avoid large quantities of grapefruit juice (>1 quart daily) Severe renal impairment (CrCl <30 ml/min): initiate dosing at 5 mg daily and be closely monitored
Rosuvastatin	<ul style="list-style-type: none"> Cyclosporine: Limit rosuvastatin to 5 mg daily Gemfibrozil: Combination should be avoided. If used together, limit rosuvastatin to 10 mg daily Other fibrates (e.g., fenofibrate) and niacin >1 gm/day may increase risk of skeletal muscle effects. In general, statin-fibrate combinations are not recommended. Lopinavir/ritonavir, atazanavir/ritonavir: Limit rosuvastatin to 10 mg daily Patients with severe renal impairment (CrCl <30 ml/min), not receiving dialysis, should be started on rosuvastatin 5 mg daily and limited to 10 mg daily. Initial dose is rosuvastatin 5 mg daily in Asian patients The 40 mg dose of rosuvastatin can be considered only after confirmation of compliance with the lipid-lowering regimen; after a careful assessment of the benefits and risks in an individual patient; and only if the patient has not met their LDL-C goal on 20 mg daily. Factors that can increase the risk for serious adverse events (myopathy and rhabdomyolysis) should be considered in the risk assessment. These factors are noted in the footnote below. If unexplained, persistent proteinuria is noted in a patient receiving rosuvastatin 40 mg daily during routine urinalysis testing, consider reducing the dose of rosuvastatin.
Pitavastatin	<ul style="list-style-type: none"> Pitavastatin is <u>contraindicated</u> with cyclosporine Erythromycin: Limit pitavastatin to 1 mg daily Rifampin: Initiate pitavastatin 1 mg daily (initial dose), maximum dose 2 mg daily Use with fibrate products or lipid-lowering doses of niacin (>1 g/day) may increase the risk for adverse skeletal muscle events; pitavastatin-fibrate combination use is not recommended. Use with niacin may increase the risk for skeletal muscle adverse events Moderate to severe renal impairment (CrCl 30-59 ml/min [moderate], CrCl <30 ml/min [severe]): pitavastatin 1 mg daily (initial dose), maximum dose 2 mg daily

¹Latest label from 6-10-11 is not yet available on FDA website. Changes in lovastatin dose limits may be forthcoming. ²Refer to references 17-18 for evidence and dosing considerations for simvastatin. +VA National Formulary. HCV=Hepatitis C virus, HIV=Human immunodeficiency virus, GFR=glomerular filtration rate

Caution: 1) Certain drugs (e.g., daptomycin, fenofibrate, colchicine, etc.) may contribute to muscle injury, regardless of the effect on statin metabolism, potentially causing an additive effect on skeletal muscle. 2) In addition, despite the absence of clear manufacturer recommended dose limits for statins when combined with drugs known to inhibit their metabolism, use of lower statin doses should be considered in these patients. 3) Certain patient factors (e.g., drug-drug interactions, higher statin doses, hypothyroidism, renal or hepatic impairment, small frame, frailty, female gender, advanced age, alcohol abuse and consumption of large quantities of grapefruit juice) may increase the risk for skeletal muscle toxicity with statins. As a result, lower statin doses should be considered in these patients.

Table 2 Approximate Equivalent Statin Doses, Metabolic Fate of Statins and Summary of Use Criteria

Approximate Equivalent Daily Doses of Statins: LDL-C Lowering Data from Clinical Trials. ¹¹							
	Lovastatin	Simvastatin	Fluvastatin	Pravastatin	Atorvastatin	Rosuvastatin	Pitavastatin
	20 mg	10 mg	40 mg	20 mg	--	--	1 mg
	40 mg	20 mg	80 mg	40 mg	10 mg	--	2 mg
	80 mg	40 mg	--	**	20 mg	--	4 mg
	--	80 mg	--	--	40 mg	10 mg	--
	--	--	--	--	80 mg	20 mg	--
Metabolic Fate:							
	Lovastatin	Simvastatin	Fluvastatin	Pravastatin	Atorvastatin	Rosuvastatin	Pitavastatin
Primary Metabolic Enzymes	CYP 3A4	CYP 3A4	CYP 2C9	Sulfation	CYP 3A4	CYP 2C9, 2C19	CYP2C9, 2C8
Lipophilicity	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic
Formulary Status of Statins							
	Lovastatin	Simvastatin	Fluvastatin	Pravastatin	Atorvastatin	Rosuvastatin	Pitavastatin
Formulary or Nonformulary	Formulary	Formulary	Nonformulary	Formulary	Formulary	Nonformulary	Nonformulary

September 2003; updated January 2004, September 2006, August 2007, September and December 2011 (simvastatin dosing restrictions), February 2012 (added pitavastatin); March 2012 (new drug-interactions-dose limitations); October 2012 (addition of atorvastatin to the VANF

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<p>Recommendations For Using a Particular Statin</p>			<p>Criteria for NF Use: Can consider fluva in those patients receiving cyclosporine or gemfibrozil , as fluvastatin conc. are less affected when combined with these agents.</p>	<p>Criteria for Use: Those on potent CYP 3A4 inhibitors*</p>		<p>Criteria for NF Use: For patients not meeting their LDL-C goals on maximum daily or maximally tolerated doses of simva and atorva. Or, inadequate LDL-C lowering response to max dose pravastatin and receiving potent CYP 3A4 inhibitors. Initial dose in these patients should be 5 mg qd.</p>	<p>Criteria for NF Use: Patients with an inadequate LDL-C lowering response to maximum dose pravastatin in <u>patients receiving potent CYP 3A4 inhibitors*</u> and an adverse event on rosuvastatin.</p>
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**If a patient is receiving Fluvastatin XL 80 mg daily, conversion to pravastatin 80 mg daily can produce similar reductions in LDL-C (At 4 weeks, mean change in LDL-C was 37% for pravastatin 80 mg vs. median LDL-C change of 38% for fluvastatin XL 80 mg).¹²⁻¹³ Immediate release fluvastatin should be used only in doses of 20 or 40 mg daily. In those patients requiring 80 mg daily, conversion to fluvastatin XL is recommended.

*Potent CYP 3A4 inhibitors include but are not limited to: azole antifungals (fluconazole, ketoconazole, itraconazole), macrolides (erythromycin and clarithromycin), HIV and HCV protease inhibitors, delavirdine, amiodarone, verapamil, cyclosporine and nefazodone.

For more detailed information on statins refer to the following website:

<http://www.pbm.va.gov/reviews/HMGStatins04-09-03.pdf> .

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