FORMULARY Criteria For Using Fluvastatin or Fluvastatin XL And
NONFORMULARY Criteria for Using Pravastatin or Atorvastatin in Veteran Patients.

VHA Pharmacy Benefits Management Strategic Healthcare Group And The Medical Advisory Panel

These criteria are based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

The Department of Veteran's Affairs National Formulary now includes 3 HMG Co-A Reductase Inhibitors (statins): 1) simvastatin (high potency-able to reduce LDL-C by 40% or more), 2) generic lovastatin, and 3) fluvastatin (both immediate and extended-release products) as an option for patients receiving potent inhibitors of CYP 3A4.

All of the available statins (lovastatin, simvastatin, fluvastatin, atorvastatin and pravastatin), when administered alone, have been associated with infrequent myotoxic adverse effects ranging from myalgia and myopathy to rhabdomyolysis.[1] Factors that may increase the risk for myotoxicity with statins are higher dosages, drug-drug interactions, 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, stems from a drug-drug interaction occurring most commonly when potent CYP 3A4 inhibitors (e.g. macrolide antibiotics, azole antifungals, cyclosporine, protease inhibitors) are combined with CYP 3A4 metabolized statins (e.g. lovastatin, simvastatin or atorvastatin (nonformulary)). 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-3A4 metabolized statins (e.g. fluvastatin or pravastatin (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 Administrations (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] 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]

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 as soon as possible, if clinically indicated.

There have been reports of excessive anticoagulation in patients receiving statins (lovastatin, simvastatin, fluvastatin and pravastatin) in combination with warfarin. As a result, the international normalized ratio (INR) should be monitored closely when statins are initiated or discontinued in patients stabilized on warfarin. These patients should also be warned to observe for signs of bleeding.[14]

Formulary Criteria For Using Fluvastatin or Fluvastatin XL

1. Patients requiring statin therapy and long-term therapy with agents known to be potent inhibitors of CYP 3A4 including but not limited to: clarithromycin, erythromycin, cyclosporine, protease

inhibitors (except nelfinavir), delavirdine, itraconazole, fluconazole, ketoconazole, and nefazodone.

2. Patients receiving lovastatin or simvastatin, requiring short-term treatment with a potent CYP 3A4 inhibitor, should have their statin temporarily withheld or closely monitored during their course of therapy. In general, there is no need to switch to fluvastatin in these patients unless the course of CYP 3A4 inhibitor therapy becomes prolonged.
3. Patients experiencing muscle pain or weakness, without elevation in creatine kinase (CK), on formulary statins (simvastatin or lovastatin) may receive a trial of fluvastatin with close follow up.

Nonformulary Criteria for Using Pravastatin in Place of Simvastatin, Lovastatin or Fluvastatin

1. Patients receiving nelfinavir. (The active metabolite of nelfinavir is formed via CYP 2C19.[9] It has been postulated that since fluvastatin is both a substrate and an inhibitor of CYP 2C9, it may lower the concentration of the active metabolite of nelfinavir. However, in a small study of 16 patients receiving fluvastatin or placebo in combination with protease inhibitors, serum concentrations of nelfinavir and ritonavir were measured as markers for drug interactions. The authors concluded that there were no apparent interactions with these protease inhibitors and fluvastatin.[10])
2. Those patients not achieving their LDL-C goals on the maximum dose of fluvastatin and requiring the use of a non-CYP 3A4 metabolized statin based upon the criteria for using fluvastatin or fluvastatin XL.
3. Patients experiencing muscle pain or weakness, without elevation in creatine kinase (CK), on fluvastatin and receiving potent CYP 3A4 inhibitors may receive a trial of pravastatin with close follow up.

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

1. Inadequate LDL-C lowering response to maximum dose simvastatin in patients not receiving potent CYP 3A4 inhibitors.

Dose Conversion of Pravastatin to Fluvastatin, Metabolic Fate of Statins and Summary of Criteria

Approximate Equivalent Daily Doses of Statins: LDL-C Lowering Data From Clinical Trials.[11]					
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**
	20 mg	10 mg	40 mg	20 mg	--
	40 mg	20 mg	80 mg	40 mg	10 mg
	80 mg	40 mg	--	**	20 mg
	--	80 mg	--	--	40 mg
	--	--	--	--	80 mg
Metabolic Fate:					
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**
Primary Metabolic Enzymes	CYP 3A4	CYP 3A4	CYP 2C9	Sulfation	CYP 3A4
Lipophilicity	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Formulary Status of Statins					
	Lovastatin	**Simvastatin**	**Fluvastatin**	**Pravastatin**	**Atorvastatin**
Formulary or Nonformulary	**Formulary**	**Formulary**	**Formulary**	**Nonformulary**	**Nonformulary**
Recommendations For Using a Particular Statin			Those on potent CYP 3A4 inhibitors.*	**Criteria for NF Use:** Those receiving nelfinavir or those on potent CYP 3A4 inhibitors and having an inadequate LDL-C lowering response to fluvastatin.	**Criteria for NF Use:** Inadequate LDL-C lowering response to maximum dose simvastatin and not receiving potent CYP 3A4 inhibitors.

	Lovastatin	Simvastatin	Fluvastatin	Pravastatin	Atorvastatin
Monthly Cost ($) (30 day supply)	20 mg 7.80 40 mg 7.80 80 mg 15.60	10 mg 7.80 20 mg 13.20 40 mg 19.80 80 mg 26.70	20 mg 6.90 40 mg 9.00 80 mg XL 15.30	20 mg 46.80 40 mg 50.70 80 mg 45.60	10 mg 32.70 20 mg 55.20 40 mg 64.80 80 mg 64.80

**If a patient is receiving pravastatin 80 mg daily, conversion to fluvastatin XL 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), protease inhibitors, delavirdine, cyclosporine and nefazodone.

For more detailed information on statins refer to the following website: http://www.vapbm.org/reviews/HMGStatins04-09-03.pdf

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Prepared by: Cathy Kelley, Pharm.D.
Reviewed by: Chester B. Good, M.D., Chairman Medical Advisory Panel