



## DEPARTMENT OF VETERANS AFFAIRS Veterans Health Administration

October 2003

Dear VA Healthcare Provider:

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 cytochrome P450 (CYP) 3A4.

The Medical Advisory Panel and the VISN Formulary Leaders recommended that a contract for a non-3A4 metabolized statin (e.g. fluvastatin or pravastatin) be sought in order to limit the risk of serious drug-drug interactions with lovastatin and simvastatin.

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) does not increase blood levels of these statins theoretically affording an additional margin of safety.

Fluvastatin has been awarded the non-3A4 metabolized statin contract. Since FDA approval in 1993, fluvastatin has demonstrated an excellent long-term safety profile.<sup>1</sup> Recommendations for when to consider fluvastatin can be found at: <http://www.vapbm.org/criteria/Fluvastatin.pdf>. Nonformulary criteria for using pravastatin and atorvastatin are available in the same document.

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.<sup>1</sup>

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.<sup>2</sup> Fatal rhabdomyolysis has been reported for all statins, except fluvastatin.<sup>3</sup> Factors that may increase the risk for myotoxicity with statins are higher dosages, drug-drug interactions (e.g. 3A4 inhibiting drugs,  $\geq 1$  g/d niacin, etc), other myotoxic drugs (e.g. fibrates) and renal impairment.<sup>4-7</sup>

**When choosing to prescribe a statin, all patients 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.**

As part of the national contract for fluvastatin, providers are requested to switch their patients from pravastatin to fluvastatin. Patients receiving nelfinavir should not have their pravastatin switched to fluvastatin since fluvastatin may reduce blood levels of nelfinavir.

**Table 1.**

| Statin           | Dose (mg/day) | % LDL-C Lowering from Baseline <sup>8-10</sup> | Cost (\$) 30 Day Supply |
|------------------|---------------|--|-------------------------|
| Fluvastatin (IR) | 40 mg         | 22-26  | \$ 9.00                 |
| Fluvastatin (XL) | 80 mg         | 38   | \$ 15.30                |
| Pravastatin      | 20 mg         | 23-29  | \$ 46.80                |
| Pravastatin      | 40 mg         | 25-34  | \$ 50.70                |
| Pravastatin      | 80 mg         | 37   | \$ 45.60                |

IR=immediate release, XL=extended release,

Recommended dose conversion (Table 2), has been derived from head to head clinical trials, comparing percent LDL-C lowering abilities of statins, and from the manufacturers package insert.

**Table 2.**<sup>8-10</sup>

| <b>Pravastatin</b> | <b>Fluvastatin</b> |
|--------------------|--------------------|
| 20 mg              | 40 mg (IR)         |
| 40 mg              | 80 mg (XL)         |
| 80 mg              | 80 mg (XL)         |

If you have any questions regarding the switch from pravastatin to fluvastatin, contact the pharmacy at your facility.

Sincerely,

## References

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7. Biesenback G, Janko O, Stuby U, et al. Myoglobinuric Renal Failure Due to Long-Standing Pravastatin Therapy in a Patient with Pre-existing Chronic Renal Insufficiency. *Nephrol Dial Transplant* 1996;11:2059-2060.
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10. Pravachol Product Information. Bristol-Myers Squibb. July 2001, Princeton, NJ 08543.