



Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

HMG-CoA Reductase Inhibitors

Overview:

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) were first introduced in 1987. HMG-CoA reductase inhibitors compete with HMG-CoA for HMG-CoA reductase, thus interfering with the conversion of HMG-CoA to mevalonate, which is a precursor of cholesterol. HMG-CoA reductase inhibitors reduce total cholesterol and low-density lipoprotein cholesterol (LDL-C), increase high-density lipoprotein cholesterol (HDL-C), and modestly reduce triglycerides (TG). The FDA has approved these agents to treat a variety of hypercholesterolemias.

Currently, eight HMG-CoA reductase inhibitors are available in the US. Only lovastatin immediate release, pravastatin, and simvastatin are available generically. Statins are generally well tolerated with few adverse reactions. The adverse reactions of most concern are elevations in liver function tests and myalgia. Rare cases of rhabdomyolysis have been reported. The risk of rhabdomyolysis increases with higher doses and when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, macrolide antibiotics, certain azole antifungals, combination protease inhibitors, or immunosuppressive agents.

All HMG-CoA reductase inhibitors have data supporting their efficacy in lowering total cholesterol, LDL-C, triglycerides, and/or apolipoproteins. Some agents have demonstrated efficacy in outcome studies measuring morbidity and mortality. Lovastatin, pravastatin and simvastatin have been proven to reduce the risk of death or coronary events in patients with a history of myocardial infarction over five years. Pravastatin has demonstrated a benefit in patients with high cholesterol but without a history of coronary events and a reduction in major coronary events in elderly patients (70-82 years of age). Simvastatin demonstrated a reduction in major coronary events, strokes, and revascularization procedures in patients with diabetes, including those without manifest coronary heart disease and those with relatively low LDL-C levels (<116 mg/dL). Atorvastatin reduced the incidence of major cardiovascular events in

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hypertensive patients who were at risk for coronary heart disease but not conventionally deemed dyslipidemic. Atorvastatin received FDA-approval to reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes without clinically evident coronary heart disease (CHD) but with multiple risk factors for CHD. FDA has also recently approved atorvastatin for use in adult patients with clinically evident coronary heart disease to reduce the risk of non-fatal MI, fatal and non-fatal stroke, angina, revascularization procedures, and hospitalizations for congestive heart failure in response to the TNT study. Rosuvastatin has received FDA approval as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels; and for treatment of heterozygous familial hypercholesterolemia in adolescent boys and postmenarchal girls, ages 10 to 17 years of age. In addition, based on the results of the JUPITER trial, the FDA recently approved rosuvastatin for primary prevention of cardiovascular disease, to reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors. Pitavastatin is the most recently approved statin in the U.S. and has LDL-C lowering efficacy similar to atorvastatin and rosuvastatin in equipotent doses. Higher doses of pitavastatin have been associated with severe myopathy.

PROVE IT was designed to determine whether intensive LDL-C lowering would reduce major coronary events more than “standard” LDL-C lowering in high-risk patients. Atorvastatin 80mg was compared to pravastatin 40mg. Patients were treated for 18-36 months with a mean follow-up of 24 months. At the end of two years of therapy, the composite cardiovascular endpoint was reduced by 16% with atorvastatin 80mg compared to pravastatin 40mg. The results of PROVE IT suggest that more intensive LDL-C lowering therapy reduces major cardiovascular events in patients with acute coronary syndrome compared to less intensive therapy over two years. However, 72% of the patients had LDL-C levels <125 mg/dL, and in this large subgroup, the trend toward benefit of atorvastatin over pravastatin was not statistically significant.

Generic Name	Brand Name	Manufacturer	Generic Available
Atorvastatin	Lipitor [®]	Pfizer	No
Fluvastatin	Lescol [®] Lescol [®] XL	Novartis	No
Lovastatin	Mevacor [®]	Merck, various	Yes
Lovastatin ER	Altoprev [™]	Andrx Pharmaceuticals	No
Pitavastatin	Livalo [®]	Kowa	No



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Pravastatin	Pravachol [®]	Bristol-Myers Squibb, various	Yes
Rosuvastatin	Crestor [®]	AstraZeneca	No
Simvastatin	Zocor [®]	Merck, various	Yes

Summary:

Currently, eight HMG-CoA reductase inhibitors are available in the US. Lovastatin immediate release, pravastatin, and simvastatin are available as generic products. The HMG-CoA reductase inhibitors all have data supporting their efficacy and safety in lowering total cholesterol and LDL. However, certain HMG-CoA reductase inhibitors are supported by long-term outcome studies in prevention of cardiovascular events (pravastatin, simvastatin, lovastatin, atorvastatin). Additionally, rosuvastatin is the only HMG-CoA reductase inhibitor indicated as adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients. The potency of the statins may be differentiated by the degree of LDL-C, TG, and total cholesterol reduction and HDL-C improvement, with the newly approved pitavastatin being the most potent agent. However, more clinical data are required to determine whether the potency of a statin translates to a beneficial long-term outcome.