



Therapeutic Class ReviewSM

Cholesterol Lowering – HMG CoA Reductase Inhibitors

February 2009

New Products for Review:

HMG-CoA reductase inhibitors (Statins)
ezetimibe (Zetia[®]) [Merck/Schering-Plough]

Dossier Provided by Manufacturer: N/A

Dossier Evaluation: Dossier's not requested

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

Executive Summary

- Generic statins provide the best value for most Regence members. There are multiple preferred/formulary options for the majority of patients who need a lipid lowering agent.
 - Currently available generic statins include simvastatin, lovastatin, and pravastatin.
 - The generic statins can provide up to a 40% (or higher) improvement in LDL-C. [7-9]
 - The generic statins have many studies that demonstrate effectiveness in reducing the risks of cardiovascular and cerebrovascular events. [42, 44-50]
 - Additionally, there is no evidence demonstrating significant differences in safety profiles or discontinuation rates among the available generic statin products, or between generic statins and the brand-name statins. [1-10, 49-54]

- For members who need additional lipid lowering, high-potency statins may be necessary.
 - High potency statins (LDL lowering greater than 40%) include rosuvastatin (Crestor), atorvastatin (Lipitor), Vytorin (ezetimibe/simvastatin) and generic simvastatin.
 - At equipotent dosing, there are no significant differences in efficacy (measured by LDL-C lowering) between the high potency statin products. [1-10, 13-37, 49-50]
 - Additionally, there is no evidence demonstrating significant differences in safety profiles or discontinuation rates among the available high potency statin products. [1-10, 49-54]
 - Among the statin products, rosuvastatin and simvastatin provide the highest LDL-C lowering at the lowest cost when greater than 41% LDL-C lowering is needed. Relative to other high potency statin products, atorvastatin does not provide the best value in LDL-C reduction.

- Several outcomes trials have demonstrated that statins reduce the risks of cardiovascular and cerebrovascular events. ^[38-54]
 - Reductions in cardiovascular and cerebrovascular risk are not unique to any specific statin and have been demonstrated with many of the available statins in a variety of patient populations, such as in patients with coronary heart disease, high cholesterol levels, normal cholesterol levels, hypertension, diabetes and previous stroke. ^[38-54]
 - Several primary or secondary prevention trials with simvastatin, pravastatin, lovastatin, and atorvastatin consistently demonstrate that reductions in cardiovascular events correlate with LDL-C reduction. ^[38-54]
 - There is emerging evidence that elevated C-reactive protein levels may correlate with increased risk, but more research is needed to confirm this association.
- The 2004 update to the NCEP ATP III Guidelines recommends aggressive LDL-C lowering in individuals depending on their risk for heart attack or stroke. ^[48-49]
 - Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. ^[48, 49]
 - In addition, clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. ^[48, 49]
 - Comparative clinical trials have demonstrated that more individuals may achieve NCEP ATP III LDL-C goals with high potency statins (rosuvastatin, atorvastatin, and ezetimibe/simvastatin). ^[48, 49]

Safety

- All marketed statins have safety records that are consistent for the statin class. ^[1-10, 53-54]
 - There appears to be no clinically relevant difference in the incidence of rhabdomyolysis, myopathy, hepatotoxicity, or renal toxicity among the marketed statins.
 - These conclusions are based on over 20 randomized, controlled studies in over 46,000 patients, plus cohort studies and postmarketing surveillance. ^[1-10, 53-54]
- At equipotent doses, there are no differences in rates of clinically relevant elevations in liver function tests (LFTs) among statins. ^[53-54]
- Prescribing information indicates initial and routine LFTs are necessary with all statins.
- Dosage adjustment is not needed for any statin in mild to moderate renal dysfunction. Dosage adjustment may be needed in severe renal dysfunction (Creatinine Clearance [ClCr] < 30 ml/min). ^[1-10]

Evidence

- There is no useful evidence showing that, at equipotent doses, any statin has an advantage in the prevention of cardiovascular morbidity or mortality compared to the rest of the class.
- There is possibly reliable evidence that rosuvastatin reduce the risk of cardiovascular morbidity and mortality in patients with normal LDL-C but elevated CRP.

Decision

Simvastatin-ezetimibe (Vytorin) is non-preferred/non-formulary because:

- It offers no advantages over other brand-name statins in terms of LDL-lowering or improvement in cardiovascular risk at equipotent doses.
- Rosuvastatin (Crestor) and simvastatin remain the best value among high-potency statins.

Products

A. Current Statin products for cholesterol lowering

Drug Products	FDA approval ^a	Patent Expiration(s) ^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^d Any FDA approved statin drug has the potential for off-label use for disease condition(s) that arise as a result of abnormal cholesterol homeostasis, regardless of the specific indications granted to that statin.
atorvastatin (Lipitor [®])	12/96	06/11	<ul style="list-style-type: none"> - Primary hypercholesterolemia,^e - Mixed dyslipidemia,^f - Hypertriglyceridemia,^g - Primary dysbetalipoproteinemia,^h - Homozygous familial hyperlipidemiaⁱ - Prevention of cardiovascular disease^j 	10-80 mg PO	<ul style="list-style-type: none"> - Alzheimer's dementia - Rheumatoid Arthritis - Age related macular degeneration - Atrial fibrillation; Prophylaxis - Deep venous thrombosis; Prophylaxis - Dementia - Diabetic retinopathy; Adjunct - Heart failure, chronic - Impaired cognition - Kidney disease - Non-alcoholic fatty liver - Peripheral vascular disease - Postmenopausal osteoporosis; Prophylaxis - Restenotic lesion of coronary artery; Prophylaxis
fluvastatin (Lescol/XL [®])	12/93	06/12	<ul style="list-style-type: none"> - Primary hypercholesterolemia^e - Mixed dyslipidemia^f - Secondary prevention CV events, - Atherosclerosis - Heterozygous familial hypercholesterolemia in pediatric patients 	20-80 mg PO	<ul style="list-style-type: none"> - Atrial fibrillation; Prophylaxis - Coronary artery bypass graft - Deep venous thrombosis; Prophylaxis - Degenerative disorder of macula; Prophylaxis - Dementia, Early; Adjunct - Heart failure, chronic - Impaired cognition - Nephrotic syndrome - Osteoporosis
lovastatin (Mevacor [®])	08/87	Off patent	<ul style="list-style-type: none"> - Primary hypercholesterolemia,^e - Primary prevention coronary events - Secondary prevention CV events 	10-40 mg PO	<ul style="list-style-type: none"> - Acute myeloid leukemia - Adenocarcinoma of stomach - Adrenoleukodystrophy - Atrial fibrillation; Prophylaxis - Cholesterol ester storage disease - Deep venous thrombosis; Prophylaxis - Degenerative disorder of macula; Prophylaxis - Dementia - Heart failure, chronic - Impaired cognition - Nephrotic syndrome - Osteoporosis - Trash foot

Drug Products	FDA approval^a	Patent Expiration(s)^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses^d Any FDA approved statin drug has the potential for off-label use for disease condition(s) that arise as a result of abnormal cholesterol homeostasis, regardless of the specific indications granted to that statin.
pravastatin (Pravachol [®])	10/91	Off patent	<ul style="list-style-type: none"> - Primary hypercholesterolemia,^e - Mixed dyslipidemia,^f - Hypertriglyceridemia^g - Primary dysbetalipoproteinemia^h - Secondary prevention CV events - Primary prevention of coronary events 	10-40 mg PO	<ul style="list-style-type: none"> - Atrial fibrillation, Primary; Prophylaxis - Deep venous thrombosis; Prophylaxis - Degenerative disorder of macula; Prophylaxis - Dementia - Diabetes mellitus; Prophylaxis - Disorder of prosthetic cardiac valve - Heart failure, chronic - Hypertension - Impaired cognition - Kidney disease, Non-diabetic - Nephrotic syndrome - Osteoporosis
rosuvastatin (Crestor [®])	08/03	01/16 – 08/20	<ul style="list-style-type: none"> - Primary hypercholesterolemia^e - Mixed dyslipidemia^f - Primary dysbetalipoproteinemia^h - Hypertriglyceridemia,^g - Homozygous familial hyperlipidemia - Slowing the progression of atherosclerosis 	5-40 mg PO	<ul style="list-style-type: none"> - Age related macular degeneration; Prophylaxis - Atrial fibrillation; Prophylaxis - Prophylaxis - Heart failure, chronic - Impaired cognition - Metabolic syndrome - Osteoporosis
simvastatin (Zocor [®])	12/91	Off patent	<ul style="list-style-type: none"> - Primary hyperlipidemia - Mixed dyslipidemia, - Hypertriglyceridemia, - Primary dysbetalipoproteinemia - Homozygous familial Hyperlipidemia - Secondary prevention CV events 	5-80 mg PO	<ul style="list-style-type: none"> - Atrial fibrillation; Prophylaxis - Biliary cirrhosis - Cholesterol embolus syndrome - Cholesterol ester storage disease - Degenerative disorder of macula; Prophylaxis - Dementia - Diabetic retinopathy; Adjunct - Heart failure, chronic - High density lipoid deficiency - Hypertension - Impaired cognition - Intermittent claudication - Livedo reticularis - Metabolic syndrome - Nephrotic syndrome - Osteoporosis - Relapsing remitting multiple sclerosis - Rheumatoid arthritis

Drug Products	FDA approval^a	Patent Expiration(s)^c	FDA approved indications	Usual Dose/Route	Potential Off-label Uses^d Any FDA approved statin drug has the potential for off-label use for disease condition(s) that arise as a result of abnormal cholesterol homeostasis, regardless of the specific indications granted to that statin.
ezetimibe (Zetia [®])	10/02	03/14 to 04/17	<ul style="list-style-type: none"> - Primary hyperlipidemia, alone or in combination with a statin - Mixed hyperlipidemia in combination with fenofibrate. - Homozygous familial hypercholesterolemia in 	10 mg PO	None

			combination with atorvastatin or simvastatin - Homozygous sitosterolemia ⁱ		
ezetimibe-simvastatin (Vytorin [®])	07/04	03/14	- Primary hypercholesterolemia (heterozygous familial and non-familial or mixed hyperlipidemia), - Homozygous familial hypercholesterolemia ^j	Ezetimibe 10 mg added to 10-80 mg Simvastatin	- Aortic valve stenosis

^a Date applies to approval date for the original brand name medication where there are now generics available.

^c Based on patents listed in Orange Book as of 12/28/08.

^d As listed in © 1974 - 2008 Thomson MICROMEDEX database or as referenced.

^{a,c} Includes heterozygous familial and nonfamilial hypercholesterolemia;

^{b,f} Includes Fredrickson types IIa and IIb;

^{e,g} Includes Fredrickson type IV;

^{d,h} Includes Fredrickson type III;

^{e,i} Based on CHD outcomes trials (ASCOT, CARDS, PROVE-IT TIMT-4).¹⁻⁴

^{f,j} Homozygous sitosterolemia is a rare inherited deficiency where the small intestine does not prevent absorption of plant sterols into the circulation.

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