INTRODUCTION

- The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/atorvastatin, and ezetimibe/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.

- The statins are the most effective class of oral drugs to lower LDL-C. Depending on the agent selected, moderate-intensity statins can decrease LDL-C by 30 to 49% and high-intensity statins can decrease LDL-C levels ≥ 50%. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) by varying levels (Stone et al, 2013).

- Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

- Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension (HTN), chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).

- Statins that are included in this review are listed in Table 1. All products are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).

- The combinations niacin/lovastatin (ADVICOR®) and niacin/simvastatin (SIMCOR®) were removed from the market because the Food and Drug Administration (FDA) determined that a reduction in TG and increase in HDL-C do not contribute to decreased cardiovascular events according to the newest evidence (AbbVie, 2016).

- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA Approval Date</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTOPREV (lovastatin)</td>
<td>Covis Pharma</td>
<td>06/26/2002</td>
<td>-</td>
</tr>
<tr>
<td>CRESTOR (rosuvastatin)</td>
<td>AstraZeneca Pharmaceuticals</td>
<td>08/12/2003</td>
<td></td>
</tr>
<tr>
<td>LESCOL (fluvastatin)</td>
<td>Novartis</td>
<td>12/31/1993</td>
<td></td>
</tr>
<tr>
<td>LESCOL XL (fluvastatin)</td>
<td>Novartis</td>
<td>10/06/2000</td>
<td></td>
</tr>
<tr>
<td>LIPITOR (atorvastatin)</td>
<td>Pfizer</td>
<td>12/17/1996</td>
<td></td>
</tr>
<tr>
<td>LIVALO® (pitavastatin)</td>
<td>Kowa Company</td>
<td>08/03/2009</td>
<td></td>
</tr>
<tr>
<td>MEVACOR (lovastatin)</td>
<td>Merck &amp; Co., Inc.</td>
<td>08/31/1987</td>
<td></td>
</tr>
<tr>
<td>PRAVACHOL (pravastatin)</td>
<td>Bristol Myers Squibb</td>
<td>10/31/1991</td>
<td></td>
</tr>
<tr>
<td>ZOCOR (simvastatin)</td>
<td>Merck &amp; Co., Inc.</td>
<td>12/31/1991</td>
<td></td>
</tr>
<tr>
<td>CADUET (amlodipine/atorvastatin)</td>
<td>Pfizer</td>
<td>01/30/2004</td>
<td></td>
</tr>
<tr>
<td>LIPTRUZET†</td>
<td>Watson Labs Teva</td>
<td>04/26/2017</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Manufacturer</td>
<td>FDA Approval Date</td>
<td>Generic Availability</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>(ezetimibe/atorvastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VYTORIN® (ezetimibe/simvastatin)</td>
<td>Merck &amp; Co., Inc.</td>
<td>07/23/2004</td>
<td>✔️</td>
</tr>
</tbody>
</table>

*The brand, MEVACOR, has been discontinued.
†The brand, LIPTRUZET, by Merck was discontinued in 2015. A generic formulation by Watson Labs Teva was recently approved by the FDA.

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)
## INDICATIONS

### Table 2. FDA-approved Indications

<table>
<thead>
<tr>
<th>Indications</th>
<th>Single-Entity Agents</th>
<th>Combination Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>atorvastatin</td>
<td>fluvastatin</td>
</tr>
<tr>
<td><strong>Hypertriglyceridemia</strong></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce elevated TG in patients with hypertriglyceridemia</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Treatment of adult patients with hypertriglyceridemia in combination with diet</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Primary Hypercholesterolemia and Mixed Dyslipidemia</strong></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apo B), and TG and to increase HDL-C in patients with primary hyperlipidemia or hypercholesterolemia and mixed dyslipidemia</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce total cholesterol (TC), LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other cardiovascular risk factors are present in the pediatric patient</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce elevated TG and very high LDL-C in patients with primary dysbetalipoproteinemia</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments or if such treatments are unavailable</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce TC, LDL-C, and apo B in adults with HoFH</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce LDL-C, TC, non HDL-C and apo B in children and adolescents with HoFH, as monotherapy or with other lipid-lowering therapies</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet</td>
<td>□</td>
<td>□</td>
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<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td>Prevention of CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic CVD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional CVD risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evident CHD</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td><strong>Reduce the risk of total mortality by reducing CHD deaths, nonfatal MI and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evident CHD</strong></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td><strong>Slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction &lt;40%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptomatic treatment of chronic stable angina</strong></td>
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</tr>
<tr>
<td><strong>Treatment of confirmed or suspected vasospastic angina</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment of HTN, to lower blood pressure</strong></td>
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</tr>
</tbody>
</table>

**Abbreviations:** CAD=coronary artery disease, CHD=coronary heart disease, ER=extended-release, IR=immediate-release, HTN=hypertension, MI=myocardial infarction.

§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescent girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients eight to 17 years of age.
¥For ER lovastatin, for patients at high risk; for IR lovastatin, for patients with average to moderately elevated TC and LDL-C and below average HDL-C.


Clinical Pharmacology, 2017

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.
The AFCAPS/TexCAPs trial (N=6,605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial, lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (P<0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality (Downs et al, 1998).

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N=10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial, patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of HTN and three additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (P=0.0005) (Sever et al, 2003).

Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (P=0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials (Colhoun et al, 2004; Sever et al, 2003; Sever et al, 2005).

A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was terminated early (median duration 1.9 years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (P<0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (P=0.02) (Ridker et al, 2008).

Meta-analyses support the findings observed in the individual primary prevention trials (Baigent et al, 2005; CTT Collaborators et al, 2008; Mora et al, 2010; O’Regan et al, 2008; Taylor et al, 2011).

The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N=8,888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial, atorvastatin did not significantly reduce the risk of the primary composite endpoint of CHD death, nonfatal MI, or cardiac arrest with resuscitation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001) and for the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001). For the individual events, atorvastatin had a lower rate of nonfatal acute MI than simvastatin (7.2% vs. 6.0%; HR, 0.83; 95% CI, 0.71 to 0.98; P=0.02), but the treatments were no different in terms of all-cause (P=0.81) or noncardiovascular (P=0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (P<0.001) (Pedersen et al, 2005). A total of 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed peripheral arterial disease (HR, 0.7; 95% CI, 0.53 to 0.91; P=0.007) (Stoekenbroek et al, 2015).

Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD. Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (P=0.02) (Byington et al, 1995; Chan et al, 2010; Crouse et al, 2007; Furberg et al, 1994; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; Schoenhagen et al, 2006).

The majority of secondary prevention trials have evaluated the use of statins initiated three to six months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event (Briel et al, 2006; Cannon et al, 2004; de Lemos et al, 2004; Liem et al, 2002).

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N=3,086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated that when initiated in the hospital following an acute coronary syndrome (ACS), atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia after 16 weeks (P=0.048) (Schwartz et al, 2005).

Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N=4,162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on...
improvements in lipid profile). Patients who were hospitalized with an ACS within the preceding 10 days were enrolled. After two years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed >30 days after randomization, and stroke by 16% compared to pravastatin (P=0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (P=0.04) and unstable angina (P=0.02). In this trial, discontinuations due to adverse events were similar between the two treatments (P=0.11) (Cannon et al, 2004).

SAFETY SUMMARY

- Statins are contraindicated in documented hypersensitivity to the agent, unexplained elevations in serum transaminases, active liver disease, and patients who are pregnant or nursing.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1 to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation, however, myopathy can sometimes take the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria. Rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All statins can increase hepatic transaminase levels and creatinine kinase.
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (Wiggins et al, 2016).
- The 2016 scientific statement written by the American Heart Association (AHA) stated that the risk for interactions between statins and other cardiovascular drugs may be unavoidable for heart patients, but it can be reduced with proper clinical management. A review of all of the medications that statin-treated patients are taking should be done at each patient visit, so that potential drug interactions can be identified early. Some key recommendations include:
  - Concomitant use of lovastatin, pravastatin, or simvastatin with gemfibrozil should be avoided. When gemfibrozil is used with other statins, a lower statin dose should be utilized.
  - A non-CYP3A4-metabolized statin should be used in combination with verapamil and diltiazem (calcium channel blockers). The dose of lovastatin or simvastatin should be limited to 20 mg daily or less when given with the calcium channel blocker amlodipine.
  - The concomitant use of cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided with lovastatin, simvastatin, and pitavastatin, as the combination could be potentially harmful.
  - Numerous other drug interactions are listed, many of which require dose adjustment of statin therapy or drug level monitoring (e.g. digoxin) (Wiggins et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form: Strength</th>
<th>Usual Recommended Dose</th>
<th>Other Dosing Considerations</th>
<th>Administration Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Entity Agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atorvastatin</td>
<td>Tablet: 10 mg, 20 mg, 40 mg, 80 mg</td>
<td>Hyperlipidemia: Tablet: initial, 10 to 40 mg once daily; maintenance, 10 to 80 mg/day</td>
<td>After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly.</td>
<td>May be administered with or without food. Tablets may be taken at any time during the day.</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage Form: Strength</td>
<td>Usual Recommended Dose</td>
<td>Other Dosing Considerations</td>
<td>Administration Considerations</td>
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<tr>
<td>-----------</td>
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<tr>
<td>fluvastatin</td>
<td>Capsule: 20 mg, 40 mg Extended-release tablet: 80 mg</td>
<td>Hypercholesterolemia (including HeFH and nonfamilial) and mixed dyslipidemia in adults: Capsule: 40 mg once daily or 40 mg twice daily Extended-release tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily Extended-release tablet: 80 mg once daily</td>
<td>After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly.</td>
<td>Capsules should be taken in the evening if dosed once daily. If 80 mg/day is used, it should be administered in two divided doses (immediate-release capsule). May be administered with or without food. Tablets may be taken at any time during the day (extended-release tablet). Tablets should be swallowed whole. (extended-release tablet).</td>
</tr>
<tr>
<td>lovastatin</td>
<td>Extended-release tablet: 20 mg, 40 mg, 60 mg Tablet: 10 mg, 20 mg, 40 mg</td>
<td>Hyperlipidemia: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day Prevention of CVD: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day</td>
<td>Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.</td>
<td>Extended-release tablet should be taken at bedtime. Extended-release tablets should be swallowed whole. Immediate-release tablet should be taken with an evening meal.</td>
</tr>
<tr>
<td>pitavastatin</td>
<td>Tablet: 1 mg, 2 mg, 4 mg</td>
<td>Hyperlipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day</td>
<td>After initiation and/or upon titration, lipid levels should be May be administered with or without food.</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage Form: Strength</td>
<td>Usual Recommended Dose</td>
<td>Other Dosing Considerations</td>
<td>Administration Considerations</td>
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<td>--------------</td>
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</tr>
<tr>
<td>pravastatin</td>
<td>Tablet: 10 mg* 20 mg 40 mg 80 mg</td>
<td>Hyperlipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily</td>
<td>After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly.</td>
<td>Tablets may be taken at any time during the day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention of CVD: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pediatric patients: Ages eight to 13 years old: 20 mg once daily Ages 14 to 18 years old: 40 mg once daily</td>
<td>Max dose in patients taking cyclosporine is 20 mg/day. Max dose in patients taking clarithromycin is 40 mg/day.</td>
<td></td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>Tablet: 5 mg 10 mg 20 mg 40 mg</td>
<td>Hyperlipidemia: Tablet: initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg/day</td>
<td>After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly.</td>
<td>May be administered with or without food. Tablets may be taken at any time during the day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce TC, LDL-C and apo B in patients with HoFH: Tablet: initial, 20 mg once daily; Ages seven to 17 years: Tablet: 20 mg once daily</td>
<td>Dosing in Asian patients: initial, 5 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged eight to less than 10 years: Tablet: maintenance, 5 to 10 mg/day Aged 10 to 17 years: Tablet: maintenance, 5 to 20 mg/day</td>
<td>Max dose is 5 mg once daily when used with cyclosporine and 10 mg once daily when used with gemfibrozil, atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir.</td>
<td></td>
</tr>
</tbody>
</table>
| simvastatin  | Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg | Hyperlipidemia: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day | After initiation and/or upon titration, lipid levels should be analyzed after four weeks and Dos as of May 18, 2017 MG-U/YP-U/DB Page 10 of 27

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form: Strength</th>
<th>Usual Recommended Dose</th>
<th>Other Dosing Considerations</th>
<th>Administration Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>lowering treatments or if such treatments are unavailable: Tablet: 40 mg once daily</td>
<td>dosage adjusted accordingly.</td>
<td>myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose should be restricted to patients who have been taking the 80 mg dose chronically without evidence of muscle toxicity.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention of CVD: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day</td>
<td>Dose should be decreased by 50% if initiating lomitapide. Simvastatin dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically (e.g. for 12 months or more) without evidence of muscle toxicity) while taking lomitapide. Max dose is 10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 20 mg/day when used with amiodarone, amlodipine, or ranolazine.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged 10 to 17 years: Tablet: initial, 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day</td>
<td>dosage adjusted accordingly.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently.</td>
<td>After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly.</td>
<td>May be administered with or without food. Tablets may be taken at any time during the day.</td>
</tr>
</tbody>
</table>

**Combination Products**

| Combination Products | Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg | Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently. The usual starting dose for amlodipine is 5 mg daily and for atorvastatin 10 to 20 mg daily. The maximum dose is | After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. | May be administered with or without food. Tablets may be taken at any time during the day. |

Data as of May 18, 2017 MG-U/YP-U/DB

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form: Strength</th>
<th>Usual Recommended Dose</th>
<th>Other Dosing Considerations</th>
<th>Administration Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>amlodipine 10 mg daily and atorvastatin 80 mg daily.</td>
<td>pressure goals. In general, wait seven to 14 days between titration steps. Titration may proceed more rapidly if clinically warranted, provided the patient is assessed frequently.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients requiring large LDL-C reductions (&gt;45%) should initiate atorvastatin therapy at 40 mg once daily.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ezetimibe/atorvastatin</td>
<td>Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg</td>
<td>Usual starting dose: 10/10 mg or 10/20 mg once daily. Usual dose range is 10/10 mg to 10/80 mg once daily.</td>
<td>After initiation or titration of doses, lipid levels may be analyzed after two or more weeks.</td>
<td>Tablets may be taken at any time of the day. May be administered with or without food.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May initiate at 10/40 mg once daily for patients requiring a larger LDL-C reduction (&gt; 55%).</td>
<td>For patients taking clarithromycin, itraconazole, saquinavir + ritonavir, darunavir + ritonavir, or fosamprenavir alone or with ritonavir: Do not exceed 10/20 mg once daily.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HoFH: 10/40 mg or 10/80 mg once daily.</td>
<td>For patients taking nelfinavir: Do not exceed 10/40 mg once daily.</td>
<td></td>
</tr>
<tr>
<td>ezetimibe/simvastatin</td>
<td>Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg</td>
<td>Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 10/10 or 10/20 mg once</td>
<td>After initiation and/or upon titration, lipid levels should be analyzed within two or more weeks and dosage adjusted accordingly. Decrease dose</td>
<td>May be administered with or without food. Tablets should be taken in the evening. Due to the increased risk of myopathy,</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage Form: Strength</td>
<td>Usual Recommended Dose</td>
<td>Other Dosing Considerations</td>
<td>Administration Considerations</td>
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<td>------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>daily; maintenance, 10/10 to 10/40 mg/day</td>
<td>of VYTORIN by 50% if initiating lomitapide. VYTORIN dosage should not exceed 10/20 mg once day (or 10/40 mg once daily for patients who have previously taken simvastatin 80 mg once day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. Max dose is 10/10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 10/20 mg/day when used with amiodarone, amlodipine, or ranolazine.</td>
<td>particularly during the first year of treatment, use of the 10/80 mg dose should be restricted to patients who have been taking the 10/80 mg dose chronically.</td>
<td></td>
</tr>
</tbody>
</table>

*S*Pravachol 10 mg is no longer available, however, generic pravastatin 10 mg remains available. *Clinical Pharmacology, 2017.*

**SPECIAL POPULATIONS**

**Table 4. Special Populations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population and Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>Elderly</td>
</tr>
<tr>
<td></td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger</td>
</tr>
<tr>
<td></td>
<td>Pregnancy Category X</td>
</tr>
<tr>
<td>Drug</td>
<td>Population and Precaution</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td></td>
<td>Elderly</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.</td>
</tr>
<tr>
<td>lovastatin</td>
<td>No dosage adjustment required in the elderly. The initial starting dose of lovastatin extended-release should not exceed 20 mg/day (ALTOPREV).</td>
</tr>
<tr>
<td>pitavastatin</td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.</td>
</tr>
<tr>
<td>Drug</td>
<td>Population and Precaution</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Elderly</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>pravastatin</td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.</td>
</tr>
<tr>
<td>simvastatin</td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.</td>
</tr>
<tr>
<td>Drug</td>
<td>Population and Precaution</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combination Products</strong></td>
<td></td>
</tr>
<tr>
<td>amlodipine/atorvastatin</td>
<td>Safety and efficacy in elderly patients have not been established.</td>
</tr>
<tr>
<td>ezetimibe/atorvastatin</td>
<td>The maximum dosage limit is 10/80 mg once daily for most patients.</td>
</tr>
<tr>
<td>ezetimibe/simvastatin</td>
<td>No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients; prescribe with caution.</td>
</tr>
</tbody>
</table>

* Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA’s Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.


CONCLUSION

- Statins are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.
- The fixed-dose combination products (CADUET [amlodipine/atorvastatin], ezetimibe/atorvastatin, and VYTORIN [ezetimibe/simvastatin]) are indicated for use when dual therapy is appropriate.
Statins decrease LDL-C according to the intensity of statin used and TG by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease TG and increase HDL-C by varying levels.

All products in this review are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL-C lowering is required, initial treatment with a statin is recommended.

In 2004, the National Cholesterol Education Program (NCEP) published guidelines on the Implications of Recent Clinical Trials for the NCEP Adult Treatment Panel III, which stated the following:

- When LDL-C lowering drug therapy is employed in high-risk or moderately-high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels.
- Standard statin doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products such as bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols.
- When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the statin dose may need to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals.
- Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins.
- In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent.
- For the treatment of HeFH, LDL-C lowering drugs should be initiated in young adulthood. Statins are considered first-line therapy Two-drug and sometimes three-drug therapy may be needed (Grundy et al, 2004).


These guidelines established four statin benefit groups: (1) individuals with clinical ASCVD (2) individuals with primary elevations of LDL–C >190 mg/dL (3) individuals with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD, and (4) individuals aged 40 to 75 years without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%

Intensity of statin therapy (high, moderate, and low) is the new goal of treatment in the benefit groups for use in primary and secondary prevention of ASCVD.

A new cardiovascular risk tool, based on pooled cohort equations, has been created to estimate absolute 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke). The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals without clinical ASCVD or diabetes and LDL–C 70 to 189 mg/dL to guide the initiation of statin therapy. For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type-1 and type-2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with clinical ASCVD or with LDL–C ≥190 mg/dL who are already in a statin benefit group, it is not necessary to estimate 10-year ASCVD risk (Stone et al, 2013).

Statins are the primary medications to utilize for ASCVD risk reduction according to the 2013 guidelines, which focus on treatments proven to reduce ASCVD and not comprehensive lipid management.

The 2015 AHA Scientific Statement on Familial Hypercholesterolemia (FH) recommends aggressive pharmacological treatment for patients with HeFH beginning at age eight to 10 years. Pharmacological treatment may also be considered in younger patients (less than eight years of age) with extreme elevation of LDL-C or those with other major risk factors suggesting very premature CVD. In HeFH pediatric patients, LDL-C goals are not well defined; however, treatment is recommended based on LDL-C levels and not based on genetic abnormalities or other clinical features. In adult patients with HeFH, the initial goal is to reduce LDL-C by 50% and treatment with a high-intensity statin (rosuvastatin or atorvastatin) is recommended. If LDL-C levels remain above goal after three months, then ezetimibe may be added. If LDL-C continues to be above goal after three months of two-drug therapy, then the addition of a PCSK9 inhibitor, bile acid sequestrant, or niacin can be considered. In patients with HoFH, lipid-lowering
therapy should be initiated as soon as possible, with statins providing a 10 to 25% reduction in LDL-C (Gidding et al, 2015).

- The 2016 United States Preventative Services Task Force (USPSTF) recommendations for preventive statin use for Primary Prevention of Cardiovascular Disease in Adults recommends the following:
  - Adults without a history of CVD should use a low- to moderate-dose statin for the prevention of CVD events and mortality when the following criteria are met: (1) they are aged 40 to 75 (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, hypertension, or smoking (3) they have a calculated 10-year risk of a cardiovascular risk of 10% or more.
  - Although statin use may be beneficial for the primary prevention of CVD in some adults with a 10-year cardiovascular risk of <10%, the benefits are likely smaller. A low- to moderate-dose statin may be offered to certain adults without a history of CVD when all of the following criteria are met: (1) they are aged 40 to 75 years (2) they have one or more CVD risk factor (3) they have a calculated 10-year risk of a cardiovascular event of 7.5 to 10%.
  - There is insufficient evidence to assess the balance of benefits to risks of initiating a statin for the primary prevention of CVD and mortality in patients ≥76 years without a history of MI or stroke (US Preventative Task Force, 2016).

- Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.

- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.

- Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD.

- No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.

- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatinine kinase.

- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.

- There is insufficient evidence to support that one statin is safer or more efficacious than another statin.

### Table 5. Advantages and Disadvantages of Statins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Amlodipine | • Available generically as a single entity product and as a co-formulation with atorvastatin  
• Only antihypertensive that is co-formulated with a statin (atorvastatin) | • Associated with drug-drug interactions                                      |
| Atorvastatin | • Available generically both alone and in combination with ezetimibe  
• Has been documented to have more potency in cholesterol-lowering than certain other statins  
• Cardiovascular outcomes studies support the use of the 80 mg strength in certain populations (e.g., as secondary | • Associated with drug-drug interactions through the CYP3A4 isoenzyme system |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>Has been shown to be effective as an adjunctive lipid lowering agent when added to a statin</td>
<td>Co-formulated with simvastatin and atorvastatin in generic formulations. Not considered as a first-line agent for the management of hyperlipidemia</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Available generically</td>
<td>Associated with drug-drug interactions through the CYP2C9 isoenzyme system</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Available generically</td>
<td>Associated with drug-drug interactions through the CYP3A4 isoenzyme system</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Available generically</td>
<td>Effect on cardiovascular morbidity and mortality has not been determined</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Available generically</td>
<td>Not associated with drug-drug interactions through the CYP isoenzyme system</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Available generically</td>
<td>Has been documented to have more potency in cholesterol-lowering than certain other statins</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Available generically both alone and in combination with ezetimibe</td>
<td>Associated with drug-drug interactions through the CYP3A4 isoenzyme system</td>
</tr>
</tbody>
</table>

REFERENCES


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