Pitavastatin Calcium: Clinical Review of a New Antihyperlipidemic Medication

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ABSTRACT

Background: Pitavastatin calcium is a new addition to the class of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") approved for use in the United States for the treatment of primary hyperlipidemia and mixed dyslipidemia.

Objective: The purpose of this review was to evaluate the literature related to the medicinal chemistry, pharmacology, pharmacokinetic properties, clinical efficacy, and tolerability of pitavastatin in the treatment of hyperlipidemia.

Methods: A search of MEDLINE, EMBASE, and the Journal Archive for English-language literature was conducted for articles published through January 2011 using the following search terms: *itavastatin, Livalo, nisvastatin, NK 104,* and *pitavastatin*. Articles were reviewed if they pertained to the clinical efficacy, pharmacology, pharmacokinetic properties, or tolerability of pitavastatin. Clinical trials were systematically included in the analysis of clinical efficacy if they used a randomized design to study the effects of the drug on hyperlipidemia, hypercholesterolemia, or heart disease. Trials were excluded if they did not signify the statin used, did not pertain to clinical efficacy, or enrolled <20 patients.

Results: A total of 16 studies were identified and reviewed for clinical efficacy. Based on findings from pharmacokinetic studies, pitavastatin may be given at any time of the day, with or without food. The drug had a mean plasma elimination $t_{1/2}$ of 12 hours, is expected to be associated with minimal drug–drug interactions because it is not metabolized by the cytochrome P450 3A4 isozyme, and is primarily excreted unchanged in the bile with little renal elimination. Clinical trials described the effects of pitavastatin on cholesterol, high-sensitivity C-reactive protein (hs-CRP), and progression of atherosclerosis. Pitavastatin at doses of 1 to 4 mg/d was reported to be associated with reductions in LDL-C of 38% to 44% and in triglycerides of 14% to 22%, and with increases in HDL-C of 5% to 8% (all, $P < 0.05$). Overall, the effect of pitavastatin on cholesterol was comparable to those of atorvastatin and simvastatin at low to intermediate doses. Studies on the effects of pitavastatin on cardiovascular outcomes were lacking. The adverse-events (AE) profile of pitavastatin compared favorably with those of other available statins. AEs included gastrointestinal symptoms (0.7%–2.2%), myopathies (0.3%–1.1%), and elevated hepatic enzyme concentrations (0.0%–8.8%).

Conclusions: Based on the findings from previously published clinical trials, pitavastatin is an effective lipid lowering agent and is another therapeutic option of currently available statins. (*Clin Ther*. 2011;33:1023–1042) © 2011 Elsevier HS Journals, Inc. All rights reserved.

Key words: cholesterol, HMG-CoA reductase inhibitors, Livalo, low-density lipoprotein, pitavastatin, statins.

INTRODUCTION

Medications used for the treatment of hyperlipidemia are numerous, but no class of drugs is as widely prescribed or as heavily studied as those that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase ("statins"). In 2007 and 2008, lipid-modifying agents were the top class of prescribed drugs in the United States, and atorvastatin calcium was the most-dispensed prescription medication in 2009, accounting for $5.7 billion in annual sales.[1,2] The reasons for extensive use of statins is their favorable efficacy and safety profiles and their benefit in reducing the risk for cardiovascular events (CVEs) and death in patients with or without established cardiovascular disease (CVD). They are also the recommended first-line treatment for hyperlipidemia and for the prevention of

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Table I. Statins approved by the US Food and Drug Administration.

Generic Name	Brand Name	Approval Date
Lovastatin*	Mevacor® (Merck & Co., Inc., Rahway, New Jersey)	8/31/1987
Pravastatin sodium*	Pravachol® (Bristol-Myers Squibb Company, New York, New York)	10/31/1991
Simvastatin*	Zocor® (Merck & Co., Inc.)	12/23/1991
Fluvastatin sodium*	Lescol® (Novartis Pharmaceuticals Corporation, East Hanover, New Jersey)	12/31/1993
Atorvastatin calcium	Lipitor® (Pfizer Inc, New York, New York)	12/17/1996
Cerivastatin sodium	Baycol® (Bayer Pharmaceuticals Corporation, West Haven, Connecticut)	6/26/1997 (Withdrawn 2001)
Rosuvastatin calcium	Crestor® (AstraZeneca Pharmaceuticals LP, Wilmington, Delaware)	8/12/2003
Pitavastatin calcium	Livalo® (Kowa Pharmaceuticals America, Inc., Montgomery, Alabama)	8/9/2009

*Became available as a generic in January 2011.

CVD by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III).[3] Pitavastatin calcium is the statin most recently approved by the US Food and Drug Administration and is the seventh statin available in the United States (**Table I**). It has been used in the Japanese market since its approval there in 2003, and also has approval for use in South Korea, Thailand, and China.

The purpose of this review was to evaluate the available literature related to the medicinal chemistry, pharmacology, pharmacokinetic properties, clinical efficacy, and tolerability of pitavastatin in the treatment of hyperlipidemia.

METHODS

For clinical efficacy, MEDLINE and EMBASE were systematically searched for English-language randomized trials published from 1990 through January 2011, using the terms *itavastatin, Livalo, nisvastatin, NK 104,* and *pitavastatin.* Trials were included for analysis of clinical efficacy if they studied the effects of pitavastatin on hyperlipidemia, hypercholesterolemia, or CVD. Articles were excluded if they did not signify the statin used, did not pertain to clinical efficacy, or enrolled <20 patients. Due to the large number of Japanese published articles, the database Journal Archive was also searched using the same key terms. This database contains English translations of articles pertaining to the pharmacology and pharmacokinetic properties of pitavastatin that were unavailable from other databases. Articles from all 3 databases relating to the pharmacology, pharmacokinetic properties, or tolerability of pitavastatin were reviewed for inclusion in the review.

RESULTS

Study Selection

A total of 361 citations were identified from the electronic search of MEDLINE and 854 citations from EMBASE. Restricting the search to randomized trials resulted in 34 trials from MEDLINE and 46 trials from EMBASE. Articles were limited to 14 trials from MEDLINE and 13 trials from EMBASE following the application of the exclusion criteria. Eliminating for duplicates found in both databases, a total of 16 trials were identified for inclusion in the review of clinical efficacy (**Figure 1**). Additional trials related to the medicinal chemistry, pharmacology, pharmacokinetic properties, and tolerability were included nonsystematically in the review from the original search results.

Medicinal Chemistry

The chemical name of pitavastatin is (+)monocalcium *bis*{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}, and