Pitavastatin: The Newest HMG-CoA Reductase Inhibitor

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Statins were first introduced in the 1980s as a treatment of hypercholesterolemia. They provide a remarkable array of clinical benefits, including the reduction of low-density lipoprotein cholesterol, total cholesterol, and triglycerides, and elevation of high-density lipoprotein cholesterol. The US Food and Drug Administration has recently approved a new statin—pitavastatin—for launch in 2010. In several clinical trials, pitavastatin has shown favorable clinical efficacy, a positive safety profile, and encouraging clinical experience in Japan and other parts of Asia.
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Coronary heart disease (CHD) remains a major cause of death worldwide, and despite continued improvements in cardiovascular care CHD rates remain unacceptably high.[1,2] Elevated low-density lipoprotein cholesterol (LDL-C) is an important contributor to the development of CHD; therefore, LDL-C reduction has been a mainstay of CHD prevention and treatment. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are associated with considerable reductions in LDL-C and have revolutionized the treatment of hypercholesterolemia.[3] Furthermore, results from large-scale clinical trials have shown that statins are associated with dramatic decreases in cardiovascular risk. Because of these benefits, statins have developed into first-line therapy for the overwhelming majority of patients with elevated LDL-C.[4] Statins lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis.[5] Inhibition of this enzyme in the liver results in decreased cholesterol synthesis as well as increased synthesis of LDL receptors, resulting in an increased clearance of LDL from the bloodstream.

History of Statins

In 1971, a Japanese biochemist named Akiro Endo and his colleagues were searching for new antibiotics. Because many microorganisms require cholesterol for growth, the group was hoping to identify novel factors that would inhibit the rate-limiting enzyme in cholesterol biosynthesis—HMG-CoA-reductase—to develop these compounds as antibiotics.[6] Ultimately, Endo isolated several inhibitors of HMG-CoA reductase, including one—mevastatin—from the mold *Penicillium citrinum*. This compound was found to be a potent agent for the reduction of serum cholesterol.[6] The pharmaceutical company Merck & Co. began similar research in 1976, and isolated lovastatin from the mold *Aspergillus terreus*. By 1990, 3 statins (lovastatin, pravastatin, and simvastatin) were available, and these initial agents were are all derivatives of a fungal compound.[7] In the early 1980s, it was discovered that the lactone ring of statins was the segment responsible for HMG-CoA reductase inhibition and that some of the other portions of the fungal metabolites were not required for cholesterol lowering and could be eliminated without compromising biologic activity[8,9]; thus, scientists started to play with the structure of statins, exploring the possibility of substituting noncritical portions to achieve desired biologic activities.

The synthetic statins currently available in the United States are atorvastatin, fluvastatin, and rosuvastatin (Table 1). Another synthetic statin (cerivastatin) was briefly available in the United States; however, it was withdrawn from clinical use due to excessive rhabdomyolysis rates. The chemical structures of the statins, both fungally derived and synthetic, are shown in Figure 1.

Table 1
Chemical Names of Statins and the Method of Production of Previously Released Statins in the United States

Chemical Name	Trade Name	Production Method
Pravastatin	Pravachol®	Modified fermentation
Simvastatin	Zocor®	Modified fermentation
Lovastatin	Mevacor®	Fermentation
Fluvastatin	Lescol®	Synthetic
Atorvastatin	Lipitor®	Synthetic
Rosuvastatin	Crestor®	Synthetic
Cerivastatin	Baycol®	Synthetic (no longer available)

Pravachol is manufactured by Bristol-Myers Squibb (New York, NY); Zocor is manufactured by Merck & Co. (Whitehouse Station, NJ); Mevacor is manufactured by Merck & Co.; Lescol is manufactured by Novartis (East Hanover, NJ); Lipitor is manufactured by Pfizer (New York, NY); Crestor is manufactured by AstraZeneca (Wilmington, DE); Baycol was manufactured by Bayer HealthCare (Leverkusen, Germany).

Figure 1. *Molecular structures of the currently available statins.*

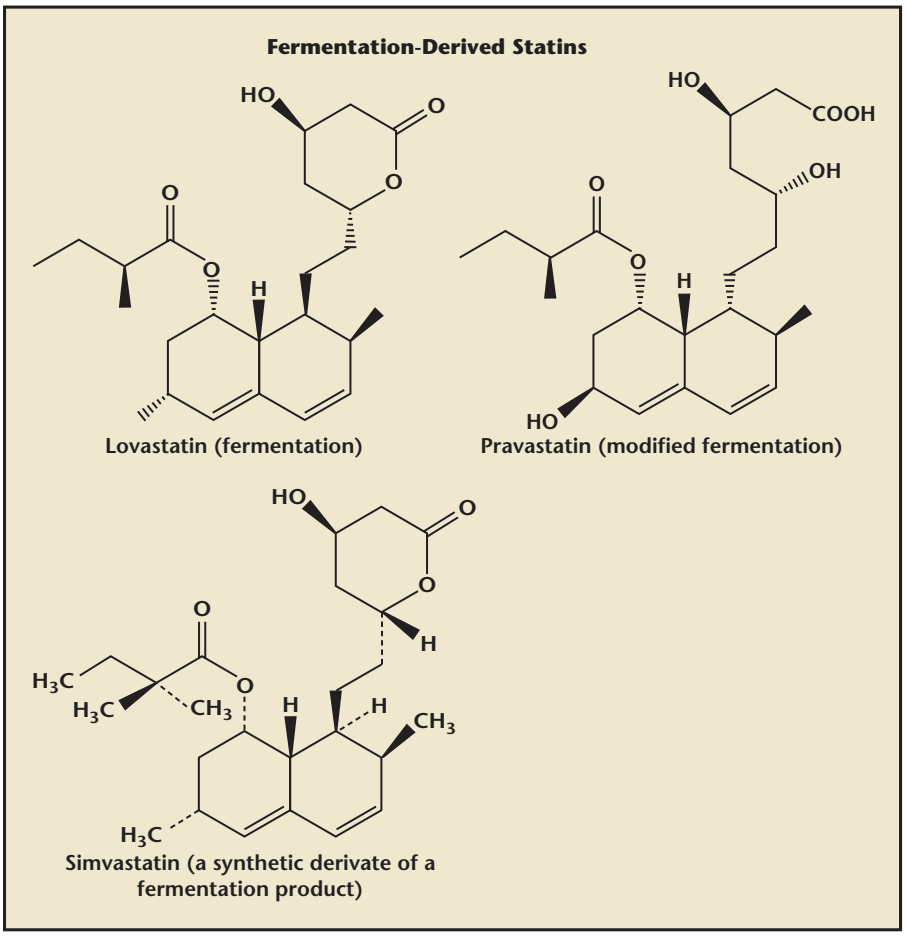
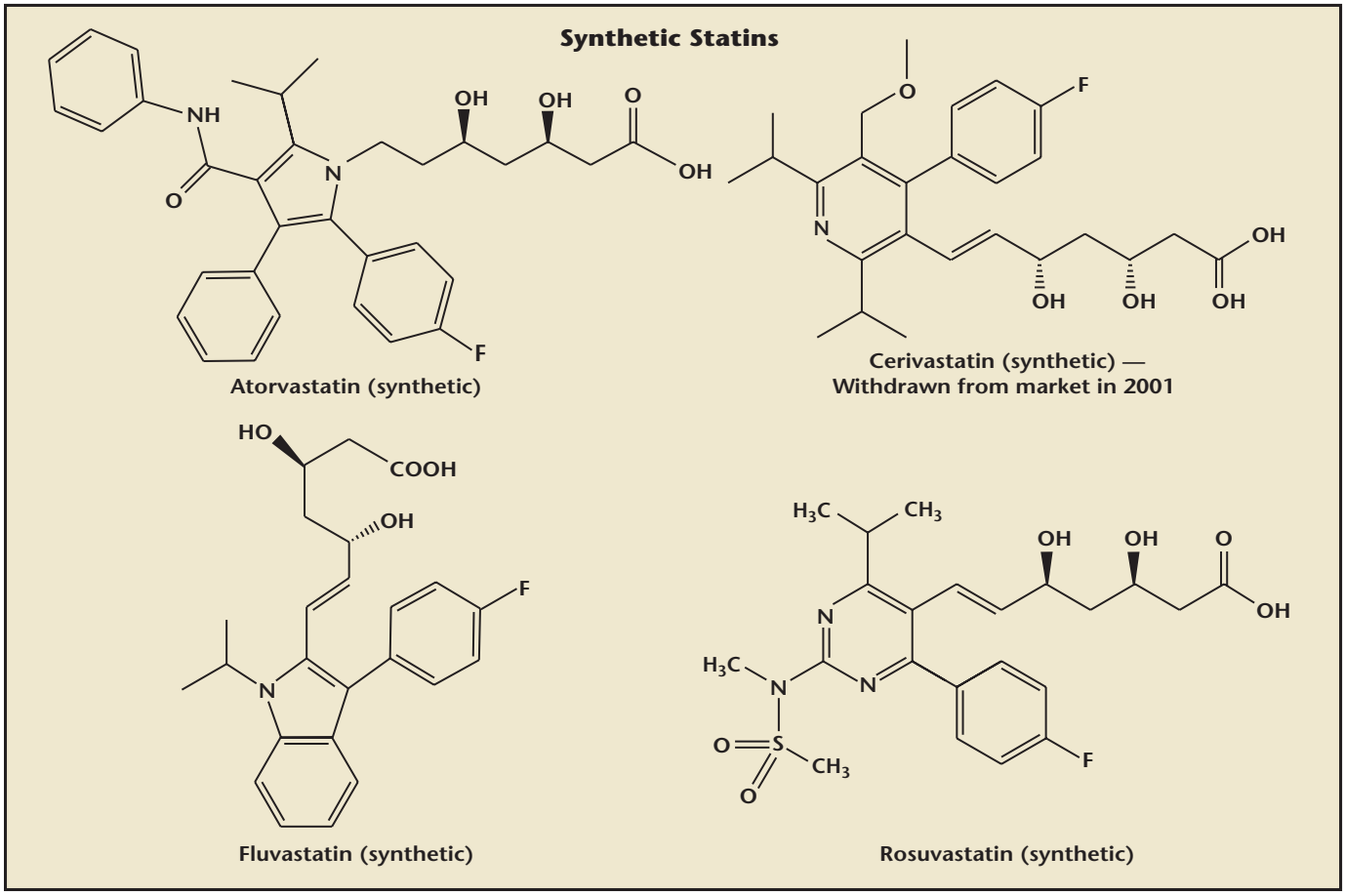


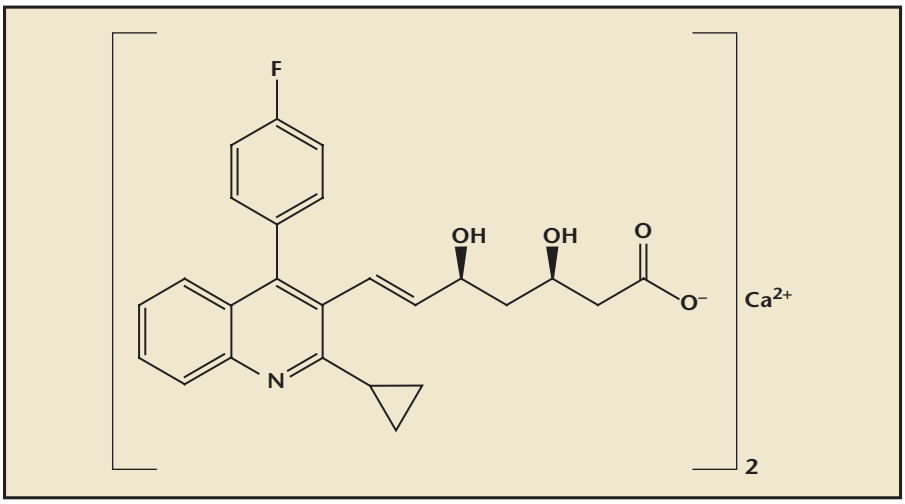
Figure 1. *(continued)*



Pitavastatin: The Newest Statin

Pitavastatin, a lipophilic, synthetic statin, is the newest addition to the statin drug class, joining atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin (Figure 2). The drug was approved by the US Food and Drug Administration (FDA) in 2009, and is expected to launch in the United States in 2010. Pitavastatin has been available in Japan since 2003 and is also available in South Korea, Thailand, and China. The FDA approval states that pitavastatin is indicated as an adjunctive therapy to diet to reduce elevated total cholesterol, LDL-C,

Figure 2. *The chemical structure of pitavastatin.*



apolipoprotein B, and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hyperlipidemia or mixed dyslipidemia. Pitavastatin will be available in doses of 1 mg, 2 mg, and 4 mg.[10]

Clinical Studies With Pitavastatin

Phase I Studies

Several studies examining the safety and pharmacokinetics of pitavastatin have been performed. In 1 such study, pitavastatin was given to 40 volunteers at doses of 0.5 mg, 1 mg, 2 mg, 4 mg, and 8 mg, along with placebo. In addition, the 2-mg dose of pitavastatin was given under both fasting and nonfasting conditions in a crossover design.[11] In another study, a placebo-controlled, single-blind, 7-day repeated administration study, pitavastatin at a dose of 4 mg was given to 9 volunteers.[11] These studies determined that (1) maximum plasma concentration and area under the curve (AUC) of pitavastatin and its lactone were correlated with the administered pitavastatin dose; (2) the AUC of pitavastatin was decreased only 17% by food intake; (3) urinary excretion of pitavastatin was no more than 3% of administration; and (4) minimum plasma concentration of pitavastatin and its lactone reached steady state after administration on day 3 or 4.

The dose range for pitavastatin is 1 to 4 mg orally once daily at any time of the day with or without food.

Based on these results, it was determined that pitavastatin doses of 1 mg, 2 mg, and 4 mg were safe. Thus, the dose range for pitavastatin is 1 to 4 mg orally once daily at any time of the day with or without food. The recommended starting dose is 2 mg and the maximum dose is 4 mg. Because doses of pitavastatin $>$ 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies, the FDA approval states that the 4-mg once daily dosing of pitavastatin should not be exceeded.[10]

Phase II Studies

The efficacy and safety of pitavastatin were further evaluated in several phase II studies. In one study, pitavastatin was administered at 4 mg/d for 8 weeks in 34 hyperlipidemic patients.[12] The results showed that serum LDL-C fell by 46%, serum TG fell by 42%, and HDL-C rose by approximately 8%. In another phase II study, pitavastatin was administered at 1 mg, 2 mg, or 4 mg once daily for 12 weeks to 273 hyperlipidemic patients.[13] These results revealed that LDL-C fell by 34% at the 1-mg dose, LDL-C fell by 42% at the 2-mg dose, and LDL-C fell by 47% at the 4-mg dose.

Phase III Studies: Comparative Studies With Other Statins

Pitavastatin versus pravastatin. At least 3 comparative studies with pitavastatin and other statins have been performed. One study compared pitavastatin, 2 mg/kg/d, to pravastatin, 10 mg/kg/d.[14] This study found that LDL-C fell by 38% in the pitavastatin-treated group, as compared with 18% in the pravastatin-treated group, a statistically significant difference.[14] The percentage reductions of serum TG by pitavastatin and pravastatin were 23% and 20%, respectively, and the HDL-C increase was 4 mg/dL and 5 mg/dL, respectively, for pitavastatin and pravastatin. In this study, there were also 124 patients in the pitavastatin-treated group and 109 patients in the pravastatin-treated group that were included in a safety analysis. This analysis found that there were no serious adverse events in either group.

Pitavastatin versus simvastatin. Another comparative study conducted was an 8-week, multicenter, prospective, randomized, open-label trial comparing the efficacy and safety of pitavastatin, 2 mg/d, versus simvastatin, 20 mg/d, in Korean patients with hypercholesterolemia.[15] Serum LDL-C fell by 38.2% in the pitavastatin-treated group and 39.4% in the simvastatin-treated group. Among patients with baseline TG values $>$ 150 mg/dL, TG fell by 29.8% in the pitavastatin group and 17.4% in the simvastatin group. HDL-C rose by 8.3% in the pitavastatin group and 3.6% in the simvastatin group. None of these differences was statistically significant.

Overall, adverse reactions occurred in 15.4% of the patients in the pitavastatin group and 37.3% of the patients in the simvastatin group, a statistically significant difference; however, there were no serious adverse reactions in either group.

Pitavastatin versus atorvastatin. Another study comparing pitavastatin with atorvastatin was conducted in India, Denmark, Russia, and Spain.[16] This was a 12-week, multicenter, prospective, randomized, double-blind trial comparing the efficacy and safety of pitavastatin, 2 to 4 mg/d, with atorvastatin, 10 to 20 mg/d, in patients with hypercholesterolemia or combined dyslipidemia. Pitavastatin, 2 to 4 mg/d, decreased serum LDL-C by 37.9% and 44.6%, respectively, which was comparable with the LDL-C reductions with atorvastatin, 10 to 20 mg/d (37.8% and 43.5%, respectively).

Table 2
Lipoprotein Effects of Currently Available Statins

Drug	Daily Dose (mg)	Lipoprotein Effects			
		TC	LDL-C	HDL-C	TG
Atorvastatin	10–80	↓29%–45%	↓39%–60%	↑5%–9%	↓19%–37%
Fluvastatin	20–80	↓17%–27%	↓22%–36%	↑3%–11%	↓12%–25%
Lovastatin	10–80	↓16%–32%	↓21%–32%	↑2%–8%	↓6%–27%
Pravastatin	10–80	↓16%–27%	↓22%–37%	↑2%–12%	↓11%–24%
Rosuvastatin	5–40	↓33%–46%	↓45%–63%	↑8%–14%	↓10%–35%
Simvastatin	5–80	↓19%–36%	↓26%–47%	↑8%–16%	↓12%–33%
Pitavastatin	1–4	↓23%–31%	↓32%–43%	↑5%–8%	↓15%–19%

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
Data abstracted from package inserts.[25-31]

There were also no other significant differences in any other lipid parameters. The lipid effects of the currently available statins, abstracted from their respective product information, are presented in Table 2.

Studies in Special Populations

Patients with familial hypercholesterolemia. The clinical efficacy of pitavastatin, 2 to 4 mg/d, was assessed in 30 patients with heterozygous familial hypercholesterolemia. At a dose of 2 mg/d, LDL-C levels of patients on pitavastatin fell by 40%, and at 4 mg/d LDL-C levels fell by 48%. There were no adverse events noted.[17]

Patients with type 2 diabetes. Pitavastatin was administered to 34 patients with type 2 diabetes mellitus and dyslipidemia at a dose of 2 mg/d for 8 weeks. No significant changes were noted in the fasting blood glucose, indicating that pitavastatin does not significantly affect glycemic status.[18]

Clinical Outcomes Trials

Noninvasive measure of atherosclerosis. The Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndromes (JAPAN-ACS) study was a prospective, randomized, open-label, parallel group, multicenter study conducted in Japan.[19,20] A total of 307 patients with ACS undergoing intravascular ultrasound (IVUS)-guided percutaneous coronary intervention were randomized and 252 patients had evaluable IVUS examinations at baseline as well as at the 8- to 12-month follow-up. Participants were randomized to receive pitavastatin, 4 mg/d, or atorvastatin, 20 mg/d, and the effect on the coronary plaque volume as detected by IVUS was the outcome. Plaque volume was reduced by 16.9% (± 13.9%) in the pitavastatin group and 18.1% (± 14.2%) in the atorvastatin group, a nonsignificant difference.

Two additional large clinical trials, the Japan Prevention Trial of Diabetes by Pitavastatin in Patients With Impaired Glucose Tolerance (J-PREDICT) and the pitavastatin heart failure study (PEARL Study) are ongoing. Because no hard cardiovascular outcomes trials have yet been reported with pitavastatin, the FDA approval notes that the effect of pitavastatin on cardiovascular morbidity and mortality has not been determined.

Safety and Tolerability of Pitavastatin

Drug Metabolism

Pitavastatin is to a minor extent metabolized by CYP2C9 and to an even lesser extent by CYP2C8. The major metabolite in human plasma is a lactone, which is formed via an ester-type pitavastatin glucuronide. The principal route of elimination is glucuronidation via liver glucuronosyltransferase with subsequent formation of this pitavastatin lactone.

Because pitavastatin is only minimally metabolized by CYP isozymes,[21,22] it might be expected to be associated with fewer incidences of drug interactions.[23] A large-scale, long-term, prospective postmarketing surveillance study of pitavastatin, called the Livalo Effectiveness and Safety (LIVES) Study, analyzed the incidence of adverse reactions for concomitantly administered medications with pitavastatin. This study found no increase in the incidence of adverse reactions with any of the concomitantly administered drugs.[24]

Clinical Trials

In clinical trials, pitavastatin at doses of 1, 2, and 4 mg has been well tolerated, with a safety profile comparable with that of other statins. An analysis of 8 different clinical trials revealed that adverse drug reactions occurred in 5.6% of the subjects (50/886 subjects), but none of the events individually occurred at a rate higher than 1%. Abnormal laboratory values were noted in 18.8% of the subjects (167/886 subjects). The most common laboratory abnormalities were increased serum γ-glutamyl transpeptidase (GTP) in 5.3%, increased serum creatine phosphokinase (CPK) in 4.6%, increased serum alanine aminotransferase (ALT) in 3.6%, and increased serum aspartate aminotransferase (AST) in 3.2% of the cases. These event rates were felt to be similar to the rates observed for the statins already available on the market.

Severe adverse reactions occurred in 0.9%, and adverse reactions leading to drug discontinuation occurred in 2.8% of patients. Again, these rates were felt to be similar to the rates observed for the statins already available on the market.

Postmarketing Surveillance

The LIVES Study, evaluated the safety and efficacy of pitavastatin in 19,925 patients during clinical use in Japan.[24] Adverse drug reactions were observed in 2069 of the 19,925 patients (10.4%), and most of the adverse drug reactions were classified as mild. Common adverse drug reactions were elevated CPK (2.74%), elevated ALT (1.79%), elevated AST (1.50%), myalgia (1.08%), and elevated γ-GTP (1.00%). Treatment with pitavastatin resulted in a significant reduction in serum LDL-C (29.1%). The peak LDL-C reduction occurred within 4 weeks of treatment initiation and then reached a plateau. In patients with abnormal baseline serum TG levels and serum HDL-C, pitavastatin decreased the serum TG by 22.7% and increased serum HDL-C by 19.9%.

Conclusions

Statins were first introduced in the 1980s as a treatment for hypercholesterolemia, and since their introduction they have been shown to provide a remarkable array of clinical benefits. Because of their remarkable safety and efficacy profile, it seems certain that statins will remain a valuable and essential part of the lipid-lowering landscape for some time to come. There are currently 6 FDA-approved and marketed statins in the United States, with the 7th and newest FDA-approved statin ready for launch in 2010. Pitavastatin is the newest statin and it has shown favorable clinical efficacy, a positive safety profile, and encouraging clinical experience in Japan and other parts of Asia. The role that it will play in the US lipid-lowering landscape is unknown, but will soon be seen with its launch in 2010. ■

Dr. Watson reports that she has received honoraria from Abbott Laboratories, AstraZeneca, Kowa Co., Merck & Co., and Pfizer.

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Main Points

- Elevated low-density lipoprotein cholesterol (LDL-C) is an important contributor to the development of coronary heart disease (CHD); therefore, LDL-C reduction has been a mainstay of CHD prevention and treatment. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are associated with considerable reductions in LDL-C and have revolutionized the treatment of hypercholesterolemia.
- Pitavastatin, the newest drug in the statin class, was recently approved by the US Food and Drug Administration for launch in 2010, and will be available in doses of 1 mg, 2 mg, and 4 mg.
- In numerous clinical trials pitavastatin proved highly efficacious in the reduction of LDL-C and total cholesterol and triglycerides, and in the elevation of high-density lipoprotein cholesterol. In some Phase III comparative clinical studies, it proved more effective than other currently available statin drugs and had fewer adverse effects.
- A large-scale, long-term, prospective postmarketing surveillance study of pitavastatin analyzed the incidence of adverse reactions for concomitantly administered medications with pitavastatin and found no increase in the incidence of adverse reactions with any of the concomitantly administered drugs.

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