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Pankaj *et al.*
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Review Article

Pitavastatin: A Potent Drug

Pankaj Kumar [1,*], Bharti Mangla[2], Satbir Singh[1]
Department of pharmaceutics, Advanced institute of pharmacy, Palwal, Haryana, 121102, India
Department of pharmaceutics, Jamia hamdard university, New delhi,11062, India

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ABSTRACT

Pitavastatin is a very potent drug called as HMG CoA reductase inhibitors, or "statins." Pitavastatin reduces levels of low-density lipoprotein, or LDL and triglycerides in the blood, while increasing levels of high-density lipoprotein, or HDL. Pitavastatin help to prevent heart disease and hardening of the arteries, conditions that can lead to heart attack, stroke, and vascular disease by reducing the cholesterol level. Pitavastatin is a novel, well-tolerated statin, many researchers works on this drug and proved to be very effective on human beings. Pitavastatin is available as a brand-name drug called Livalo. It's also available as a generic drug. This review article covers the pharmacology, side effects, precautions, doses from and drug interaction of Pitavastatin. Also covers the marketed formulation and recent updates on Pitavastatin.

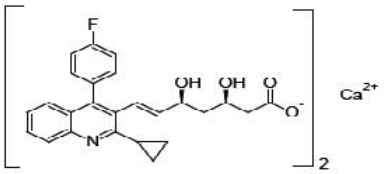
Keywords : Pitavastatin, statins, HMG CoA, lipoprotein, LDL, HDL

1. INTRODUCTION

Pitavastatin is a drug called a statin. It's used to lower LDL (bad) cholesterol and triglycerides, and increase HDL (good) cholesterol in your blood. This drug is used along with a healthy diet and other lifestyle changes to help decrease risk of a heart attack or stroke. 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. It is a synthetic lipid-lowering agent for oral administration.

Corresponding author *
Pankaj kumar*
Assistant professor, advanced institute of pharmacy, palwal
Email: pankazdagar@gmail.com

The chemical name for Pitavastatin is (+) monocalcium *bis*{(3R, 5S, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5dihydroxy-6-heptenoate}. The structural formula is:



The empirical formula for Pitavastatin is $C_{50}H_{46}CaF_2N_2O_8$ and the molecular weight is 880.98. Pitavastatin is odorless and occurs as white to pale-yellow powder. It is freely soluble in pyridine, chloroform, dilute hydrochloric acid, and tetrahydrofuran, soluble in ethylene glycol, sparingly soluble in octanol, slightly soluble in methanol, very slightly soluble in water or ethanol, and practically insoluble in acetonitrile or diethyl ether. Pitavastatin is hygroscopic and slightly unstable in light.[1]

Pitavastatin Internationally available as Livalo.[2] Each film-coated Tablet of LIVALO contains 1.045 mg, 2.09 mg, or 4.18 mg of Pitavastatin calcium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base and the following inactive ingredients such as lactose monohydrate, low substituted hydroxypropyl cellulose, hypromellose, magnesium alumino metasilicate, magnesium stearate, and film coating containing the inactive ingredients like hypromellose, titanium dioxide, triethyl citrate, and colloidal anhydrous silica. Each Tablet has"KC" debossed on one side and a code number specific to the Tablet strength on the other.

Pitavastatin calcium was discovered by Nissan chemical industries limited Japan and developed further by kowa pharmaceuticals Tokyo, Japan. This is a novel member of the medication class of statins. It is available in Japan since 2003, and is being marketed under licence in South Korea and in India. It is likely that Pitavastatin will be approved for use in hypercholesterolemia (elevated levels of cholesterol in the blood) and for the prevention of cardiovascular disease outside South and Southeast Asia as well. In the US, it has received FDA approval in 2009.[3]

Pitavastatin (LIVALO) Generic Manufacturer

Taj Pharmaceuticals Ltd. is a Pharmaceutical Generic manufacturer of Pitavastatin and manufacturer of various pharmaceutical formulations in India as shown in Table 1 and 2. Taj Pharmaceuticals Ltd. provide different pharmaceutical brands and Generic Medicines.[4]

Table: 1 Generic drug manufacturer of Pitavastatin

Sr. No.	Manufacturer	Approval date	Strength (mg)
1	Aurobindo Pharma Ltd	December 20, 2016	1,2,4
2	Orient Pharma Co. Ltd	February 3, 2017	1,2,4
4	Sawai USA	February 3, 2017	1,2,4

Table 2: Pitavastatin Generic Drug Price

Serial no.	Brand Name	Name of manufacturer	Active constituents	Package unit	Price/10 Tablets	Generic
1	Pivasta (1mg) Tablet	Zydus Cadila Healthcare Ltd.	Pitavastatin(1 mg)	10 Tablets	48.50	Yes
2	Pivasta (2mg) Tablet	Zydus Cadila Healthcare Ltd.	Pitavastatin(2mg)	10 Tablets	85.10	Yes
3	Flovas (1 mg)	IPCA Laboratories Ltd.	Pitavastatin(1 mg)	10 Tablets	90	Yes
4	Flovas (2 mg)	IPCA Laboratories Ltd.	Pitavastatin(2 mg)	10 Tablets	150	Yes
6	Pitava (1mg)	Zydus Cadila Healthcare Ltd.	Pitavastatin(2 mg)	10 Tablets	90	Yes
7	Pitava (1mg)	Zydus Cadila Healthcare Ltd.	Pitavastatin(2 mg)	10 Tablets	150	Yes

HPLC method of Pitavastatin

Some researchers developed the method of HPLC of Pitavasatin as shown the given Table 3: [5]

Table 3: HPLC Method of Pitavastatin

Mobile phase	Acetic acid: Acetonitrile 35:65 (%, v/v),
Flow rate	1 ml/min
Column	C18 (250 x 4.60), 5 µ particle size
Wavelength	245 nm

2. RECENT UPDATES ON PITAVASTATIN

Pitavastatin significantly reduced the LDL-C levels and was well tolerated when administrated at a usual adult doses in 14 male children 10-15 years of age with heterozygous FH. Pitavastatin is a promising therapeutic agent for pediatric dyslipidemia with few safety concerns.[6]

Pitavastatin used to demonstrate the applicability of a bottom-up approach to predict transporte rmediated disposition in sandwich-cultured human hepatocytes (SCHH), allowing for the estimation of transporter contributions. Anna Vild hede et al successfully simulate transporter-mediated processes in a complex system such as SCHH at the level of individual transport proteins using a bottom-up approach. [7]

Dyslipidemia as a risk factor of cardiovascular disease is common especially in HIV-infected patients who are using protease inhibitors (PIs) including atazanavir. Pitavastatin has less drug-drug interactions and demonstrable efficacy in decreasing lipid levels in non HIV infected individuals. [8]

HMG-CoA reductase inhibitor, Pitavastatin, on macrophage miRNAs in the presence and absence of oxidized-LDL, a hallmark of a pro-atherogenic milieu. Pitavastatin can differentially modulate miRNA in the presence of ox-LDL and results provide the evidence that net effect on

cholesterol homeostasis is mediated by a network of miRNAs. [9]

Soichi Kurioka1et al suggest that combination therapy of Pitavastatin and Sitagliptin may have a kidney protective effect in patients with type 2 diabetes with hypercholesterolemia.[10]

Hiroaki Satoh et al suggest that Pitavastatin has beneficial effects on insulin sensitivity in an insulin-resistant state. [11]

Thus, although future trials are required to assess the impact of pitavastatin treatment on CV morbidity and mortality, studies suggest that pitavastatin will play an important role in the future management of dyslipidaemia and in the overall reduction of CV risk.[12]

Pitavastatin calcium is a BCS class 2 drug having low solubility. Some researcher found that their solubility and bioavailability were enhanced by the formulation of self-micro-emulsifying drug delivery system (SMEDDS) of Pitavastatin calcium.[19]

3. PHARMACOLOGY OF PITAVASTATIN [13]

Pharmacodynamics, Pharmacokinetics of pitavastatin as shown in Table 4

Table 4: Pharmacodynamics, Pharmacokinetics of pitavastatin

Indication	Pitavastatin is used to lower serum levels of total cholesterol, LDL-C, apolipoprotein B, and triglycerides, and raise levels of HDL-C for the treatment of dyslipidemia.
Pharmacodynamics	Bioavailability (51%), Tmax.1 hour; Pitavastatin was absorbed in the small intestine but very little in the colon. Cmax decreases by 43%, if Pitavastatin is taken with a fatty meal
Mechanism of action	Pitavastatin is lipid-lowering agent that works to control the synthesis of cholesterol via competitive inhibition of the liver enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.
Absorption	Bioavailability (51%), Tmax.1 hour; Pitavastatin was absorbed in the small intestine but very little in the colon. Cmax decreases by 43%, if Pitavastatin is taken with a fatty meal
Metabolism	Metabolized by liver, undergoes glucuronidation by uridine 5-diphosphate glucuronosyl transferases (UGT1A3 and UGT2B7) to form the major circulating metabolite.
Route of elimination	79% in feces and 15% excreted in urine
Half life	Plasma elimination half-life = 12 hours
Clearance	23.6 L/h
Toxicity	Myalgia, back pain, diarrhea, constipation and pain in extremity
Dosage Forms	Livalo is the calcium salt of Pitavastatin Zypitamag is the magnesium salt of Pitavastatin
Volume of distribution	148 L
Protein binding	99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein.

4. DOSAGE FORMS & STRENGTHS

Livalo is the calcium salt of pitavastatin

Zypitamag is the magnesium salt of pitavastatin[14]. Different dose ranges of Pitavastatin for various disease as shown in the Table5

Table 5: Different dose ranges of Pitavastatin for various disease.

Disease	Initial dose	Maintenance dose	Maximum dose
Hyperlipidemia patients	2 mg orally once a day	1 mg to 4 mg orally once a day	4 mg/day
Dyslipidemia	2 mg orally once a day	1 mg to 4 mg orally once a day	4 mg/day
Renal Dose Adjustments Moderate to severe renal dysfunction	1 mg orally once a day		2 mg orally once a day
Liver Dose Adjustments	Maximum dose: 1 mg orally once a day		2 mg orally once a day
Dialysis	1 mg orally once a day		Maximum dose: 2 mg orally

5. PITAVASTATIN MARKETED FORMULATIONS

The available marketed formulations of Pitavastatin as shown in Figure 1 and 2

Fig 1: Plastic Bottle container packaging of Pitavastatin Tablets 2mg[15,16]

Fig 2: Pitavastatin Calcium Tablets strip packaging[17]

6. PITAVASTATIN TABLET COMMON SIDE EFFECTS

Pitavastatin Tablet has number of side effects which lead to cause major problems as shown in Table 6.

Table 6: The side effects of Pitavastatin

Common Side Effects of Pitavastatin	• Back Pain • Constipation • Diarrhea • Muscle Aches • Pain in your Arms or Legs
Pitavastatin serious side effect	• Muscle problems. Symptoms can include: o Severe Muscle Pain o Muscle Tenderness o Muscle Weakness • Kidney problems. Symptoms can include: o Tiredness o Confusion o Nausea o Shortness of Breath o Swelling of Legs, Ankles, Or Feet o Decreased Urination • Liver problems. Symptoms can include: o Jaundice o Itching o Pain in The Upper/Right Side of The Stomach Area o Nausea o Vomiting o Loss of Appetite o Dark-Colored Urine o Pale-Colored or Dark, Tarry Stools o Tiredness o Bruising Easily

7. PITAVASTATIN DRUG INTERACTIONS

Pitavastatin may interact with other drugs as shown in Table 7.Some medications that have known interaction with Livalo [18]

Table 7: Drug Interactions of Pitavastatin

Antigout Agents	Colchicine (Colcrys)
Blood Thinners	Warfarin (Coumadin, Jantoven
Drugs For HIV/AIDS Especially Protease Inhibitors	Amprenavir (Agenerase) Atazanavir (Reyataz) Darunavir (Prezista) Fosamprenavir (Lexiva) Indinavir (Crixivan) Lopinavir And Ritonavir (Kaletra) Nelfinavir (Viracept) Saquinavir (Fortovase, Invirase) Ritonavir (Norvir) Tipranavir (Aptivus)
Antigout Agents	sildenafil (Revatio, Viagra)
Fibrates	Fenofibrate (Antara,Lofibra, Tricor, Triglide) Gemfibrozil (Lopid)
Immunosuppresive Agents	Cyclosporine (Gengraf, Neoral, Sandimune)
Nutritional Supplements	Niacin (Niacor, Nicolar)
Antibiotics	Clarithromycin (Biaxin) Daptomycin (Cubicin) Erythromycin Rifampin Telithromycin (Ketek)
Antilipidemic Agents (Statins)	Atorvastatin (Lipitor) Fluvastatin (Lescol, Lescol XL) Lovastatin (Altoprev, Mevacor) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor) Other Antilipidemic Preparations Such as Advicor, Caduet, Juvisyn, Vytorin, And Simcor

8. CONCLUSION

This review article shows that Pitavastatin, a potent drug used for lowering LDL cholesterol level, without affecting glycemic control in patients with diabetes, as seen often atorvastatin group. Across the studies, Pitavastatin consistently produces a clinically significant increase in HDL-C. By contrast, other statins show inconsistent results on HDL-C. Thus, Pitavastatin may be more suitable for the treatment of hyperlipidemia in patients with type-2 diabetes. Pitavastatin has been shown to have no effect on the plasma glucose levels, which makes it a favorable drug for patients with type-2 diabetes. Pitavastatin generic version available in market and Indian company also manufacturing this potent drug. Various clinical trials occurring on Pitavastatin for its safety, efficacy with other statins on different group of patients. In future, this drug become very useful

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