



July 22, 2012

Pharmacokinetic Study Results Released Evaluating Interactions Between LIVALO® (pitavastatin) and Protease Inhibitor Combination (darunavir/ritonavir) in Healthy Volunteers

Study showed no clinically significant change in blood levels for pitavastatin or protease inhibitor combination darunavir/ritonavir when co-administered

WASHINGTON, July 22, 2012 /PRNewswire/ -- Kowa Pharmaceuticals America, Inc. (Kowa Pharmaceuticals) and Eli Lilly and Company (Lilly) (NYSE: LLY) today released results from a pharmacokinetic (PK) study exploring potential drug interaction between the cholesterol medication pitavastatin (LIVALO) 4 mg and the protease inhibitor (PI) combination darunavir/ritonavir (Prezista®/Norvir®) 800mg/100mg in healthy volunteers.¹ The study, presented at the 19th International AIDS Conference in Washington, DC, found that when co-administered, the blood levels for LIVALO and each of the PIs were not significantly affected.¹ In February 2012, the PK data darunavir/ritonavir were added to the LIVALO label.

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"Examining drug interactions has been an ongoing part of product development, and we are pleased that results show no clinically significant drug interaction between pitavastatin and the protease inhibitor combination darunavir/ritonavir," said Dr. Craig Sponseller, Vice President of Medical Affairs, Kowa Pharmaceuticals America, Inc.

The current study was designed to assess the changes in pharmacokinetic parameters when pitavastatin 4 mg and darunavir/ritonavir 800mg/100mg were administered alone or in combination. Pitavastatin and darunavir/ritonavir were co-administered in 28 healthy, adult volunteers over a 16-day period. When co-administered with darunavir/ritonavir, pitavastatin peak exposure, as measured by C_{max} , decreased by 4%, while total exposure of pitavastatin, as measured by AUC_{0-T} , decreased by approximately 26%. When co-administered with pitavastatin, the C_{max} and AUC_{0-T} of darunavir increased by 6% and 3% respectively, and the C_{max} and AUC_{0-T} of ritonavir increased by 2% and 8%, respectively. These effects were not considered to be clinically significant.^{1,2}

A secondary objective of the study was to investigate the safety of pitavastatin and darunavir/ritonavir when each treatment was given alone or in combination. The majority of treatment emergent adverse events (TEAEs) were mild in severity, and no serious or severe adverse events were reported. Nineteen of 28 patients reported at least one TEAE, of which 10 were from the darunavir/ritonavir only group; 7 from the pitavastatin and darunavir/ritonavir group; 2 from the pitavastatin only group.¹

For TEAEs occurring in ≥ 2 subjects in any treatment group, the most frequently reported drug-related TEAEs were diarrhea (7.1% darunavir/ritonavir only group; 7.4% pitavastatin and darunavir/ritonavir; 3.6% pitavastatin only), headache, (10.7% darunavir/ritonavir only group; 0% pitavastatin and darunavir/ritonavir; 0% from the pitavastatin only group) and myalgia (7.1% darunavir/ritonavir only; 3.7% pitavastatin and darunavir/ritonavir group; 3.6% pitavastatin only). One subject was discontinued from the study due to maculopapular rash during treatment with darunavir/ritonavir only.¹

About LIVALO

LIVALO is a HMG-CoA reductase inhibitor indicated for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C).

Limitations of Use:

- Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.
- The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.
- LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

In addition to being launched in the U.S. in June 2010, LIVALO is also approved in Japan (2003), South Korea (2005), Thailand (2007), China (2008), European Union (2010), Taiwan (2011), Mexico (2009) and Australia (2010).

About Primary Hyperlipidemia and Mixed Dyslipidemia

Primary hyperlipidemia is defined as an elevation of cholesterol, particularly "bad" cholesterol (LDL-C), triglycerides (TG), or both. Mixed dyslipidemia is usually characterized by an elevation of LDL-C, TG, and a decrease in the "good" cholesterol (HDL-C) in the blood.

IMPORTANT SAFETY INFORMATION FOR LIVALO® (pitavastatin) tablets

CONTRAINDICATIONS

LIVALO is contraindicated in patients with a known hypersensitivity to product components, in patients with active liver disease (which may include unexplained persistent elevations in hepatic transaminase levels), in women who are pregnant or may become pregnant, in nursing mothers, or in coadministration with cyclosporine.

WARNINGS AND PRECAUTIONS

Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO.

- The risk of skeletal muscle effects (e.g., myopathy and rhabdomyolysis) increases in a dose-dependent manner with advanced age (> 65 years), renal impairment, inadequately treated hypothyroidism, and in combination use with fibrates or lipid-modifying doses of niacin (> / =1 g/day).
- Concomitant administration of LIVALO with gemfibrozil should be avoided.
- LIVALO therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. LIVALO therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis; hypotension; dehydration; major surgery; trauma; severe metabolic, endocrine, and electrolyte disorders; or uncontrolled seizures).
- Advise patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, and to discontinue LIVALO if these signs or symptoms appear.

Liver Enzyme Abnormalities

Increases in serum transaminases have been reported with HMG-CoA reductase inhibitors, including LIVALO.

- It is recommended that liver enzyme tests be performed before the initiation of LIVALO and if signs or symptoms of liver injury occur.
- There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LIVALO, promptly interrupt therapy. If an alternate etiology is not found do not restart LIVALO.
- Advise patients to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.
- LIVALO should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease.

Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including LIVALO.

ADVERSE REACTIONS

In short-term controlled studies, the most frequent adverse reactions reported by > / =2% of patients treated with LIVALO 1 mg, 2 mg, and 4 mg, respectively, and at a rate > / = placebo were back pain (3.9%, 1.8%, 1.4% vs 2.9%), constipation (3.6%, 1.5%, 2.2% vs 1.9%), diarrhea (2.6%, 1.5%, 1.9% vs 1.9%), myalgia (1.9%, 2.8%, 3.1% vs 1.4%), and pain in extremity (2.3%, 0.6%, 0.9% vs 1.9%). This is not a complete listing of all reported adverse events.

For complete product prescribing information consult the current LIVALO (pitavastatin) tablet package insert which is available

at http://www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf.

LIV-RA-0044 PS77436 2/2012

About Kowa Company, Ltd. and Kowa Pharmaceuticals America, Inc.

Kowa Company, Ltd. (KCL) is a privately held multinational company headquartered in Nagoya, Japan. Established in 1894, KCL is actively engaged in various manufacturing and commercial activities in the fields of pharmaceutical, life science, information technology, textiles, machinery and various consumer products. KCL's pharmaceutical division is focused on cardiovascular therapeutics, with sales of the company's flagship product LIVALO, totaling \$530 million (14.6% market share) in Japan in the 2010 fiscal year, and was launched in the United States in June 2010.

Kowa Pharmaceuticals America, Inc. (KPA) is a pharmaceutical company specializing primarily in the area of cardiometabolic diseases. The company, started in 2001 as ProEthic Pharmaceuticals, Inc., was acquired by KCL in September of 2008. A privately held company, KPA directs its efforts towards the acquisition, licensing and marketing of pharmaceutical products.

exchange rate used \$1=85JPY

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers — through medicines and information — for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com. P-LLY

LIVALO is a registered trademark of the Kowa group of companies.

[1] Data on File: Yu C, Campbell S, et al. *Steady-state Pharmacokinetic Interactions of Darunavir/Ritonavir with Pitavastatin in Healthy Adult Volunteers*. 19th International AIDS Conference. Washington, DC. July 22-27, 2012.

[2] LIVALO [prescribing information] Montgomery, AL; Kowa Pharmaceuticals America, Inc; February 2012.

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LIV-MT-0410 PS79267

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