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New Data Showed LIVALO® (pitavastatin) 4 mg had Neutral Effects on Fasting Serum Glucose and HbA1c Levels in HIV-infected Adults with Dyslipidemia

Study results presented at ENDO 2013 Annual Meeting

SAN FRANCISCO, June 17, 2013 /PRNewswire/ -- Kowa Pharmaceuticals America, Inc. and Eli Lilly and Company (NYSE: LLY) announced results of a pre-specified safety analysis from the INTREPID (HIV-infected patients and Treatment with Pitavastatin vs. pravastatin for Dyslipidemia) trial evaluating the effect of LIVALO® (pitavastatin) 4 mg compared with pravastatin 40 mg on changes in levels of blood glucose and glycated hemoglobin (HbA_{1c}) in HIV-infected adults with dyslipidemia. INTREPID was a Phase 4, multicenter, 12-week randomized superiority study followed by a 40-week safety extension study (NCT01301066) comparing the lipid-lowering effects of pitavastatin 4 mg and pravastatin 40 mg in adults with HIV infection and dyslipidemia.¹

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The results of this pre-specified safety analysis, presented yesterday at the Endocrine Society's 95th Annual Meeting & Expo in San Francisco, CA, showed neutral effects of pitavastatin 4 mg and pravastatin 40 mg on fasting serum glucose (FSG) and HbA_{1c} levels over 12 weeks.¹

By week 12, the mean change in FSG for pitavastatin (n=109) was -0.1mg/dL and pravastatin (n=112) was 0.6 mg/dL, and the adjusted (least squares mean) change in FSG was 0.6 mg/dL for pitavastatin and 2.5 mg/dL for pravastatin with no significant differences in each treatment group (p=0.68 and 0.09, respectively). There was no significant difference between treatment groups (p=0.20).¹

The mean change in HbA_{1c} was -0.02% for pitavastatin (n=110) and -0.01% for pravastatin (n=113), and the adjusted (least squares mean) change in HbA_{1c} was 0.04% for pitavastatin and 0.05% for pravastatin with no significant differences in each treatment group (p=0.27 and 0.09, respectively). There was no significant difference between treatment groups (p=0.58). A significantly greater decrease in LDL-C over 12 weeks was noted with pitavastatin 4 mg compared with pravastatin 40 mg where the primary endpoint of mean percent change was -31.1% and -20.9%, respectively (p < 0.001), with a mean change in LDL-C of -49.4 mg/dL for pitavastatin 4 mg vs. -33.6 mg/dL for pravastatin 40 mg.¹

Studies have shown that patients living with HIV infection have increased cardiovascular disease risk factors, including dyslipidemia and glucose abnormalities.²

"We are pleased with the results of this safety analysis that showed neutrality for the maximum dose of pitavastatin 4 mg on parameters of glucose metabolism, which are consistent with our previous findings in non-HIV-infected adult populations with dyslipidemia," said Dr. Craig Sponseller, Vice President of Medical Affairs at Kowa Pharmaceuticals America, Inc.

Study investigator, Dr. Judith Aberg, Director of Virology, Bellevue Hospital Center and Director, Division of Infectious Diseases and Immunology, NYU School of Medicine, said, "Based on treatment guidelines, statins are often the first line treatment for the management of dyslipidemia when therapeutic lifestyle changes are not effective in HIV-infected patients. These results may further physician education on statin use."

About the Study

In the 12-week, Phase 4, randomized (1:1), double-blind, double-dummy, active-controlled, parallel-group study, 252 patients were randomized to receive once-daily doses of pitavastatin 4 mg or pravastatin 40 mg. Only patients who took the study drug and had both baseline and week 12 values for FSG or HbA_{1c} were included in these analyses. Mean changes from baseline to week 12 were compared between treatments using ANCOVA, with change in FSG/HbA_{1c} as the dependent variable, and treatment, site and hepatitis B and C status as independent variables.¹

About LIVALO

LIVALO is a HMG-CoA reductase inhibitor indicated 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) in adult patients with primary hyperlipidemia or mixed dyslipidemia.

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 has been approved in 33 other countries around the world as of May 2013.³

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 co-administration 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. These risks can occur at any dose level, but increase in a dose-dependent manner.

- LIVALO should be prescribed with caution in patients with predisposing factors for myopathy
- 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)
- LIVALO should be administered with caution in patients with impaired renal function, in elderly patients, or when used concomitantly with fibrates or lipid-modifying doses of niacin
- 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
- Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors coadministered with colchicine, and caution should be exercised when prescribing LIVALO with colchicine
- There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents. IMNM has not been reported with LIVALO therapy
- Advise patients to promptly report if muscle signs and symptoms persist after discontinuing LIVALO as this may be a sign of IMNM requiring immediate medical attention

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 HbA_{1c} 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 $\geq 2\%$ of patients treated with LIVALO 1 mg, 2 mg, and 4 mg, respectively, and at a rate $\geq$ 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 additional information please see the full Prescribing Information provided, or visit www.LivaloRx.com.

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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 \$572 million in Japan fiscal year ending March 2013, 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=90JPY

About Eli Lilly and Company

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

This press release contains certain forward-looking statements about LIVALO[®], a HMG-CoA reductase inhibitor indicated 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) in adult patients with primary hyperlipidemia or mixed dyslipidemia. This release reflects Lilly and Kowa's current beliefs; however, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that future study results and patient experience will be consistent with study findings to-date or that LIVALO will be commercially successful. For further discussion of these and other risks, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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

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PS 85181

¹ Data on File: Aberg J, Sponseller C, Kryzhanovskiy V, Kartman C, Thompson M. Neutral Effects of Pitavastatin 4 mg and Pravastatin 40 mg on Blood Glucose and HbA_{1c} Levels over 12 Weeks: Prespecified Safety Analysis from the INTREPID (HIV infected patients and Treatment with Pitavastatin vs pravastatin for Dyslipidemia) Phase 4 Trial. Poster presented at the Endocrine Society's 95th Annual Meeting & Expo, June 15-18 2013; San Francisco, CA.

² Lo J. Dyslipidemia and Lipid Management in HIV-infected Patients. *Current Opinion in Endocrinology and Diabetes and Obesity*. 2011; 18(2): 144—147.

³ Data on File: 05292013

SOURCE Kowa Pharmaceuticals America, Inc. and Eli Lilly and Company

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