

Vytorin Cut Cardiac Risk in Kidney Disease

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DENVER – A once-daily combination of ezetimibe 10 mg and simvastatin 20 mg reduced the risk of major atherosclerotic events in patients with chronic kidney disease by 16.5%, according to a randomized, placebo-controlled trial funded by the drug's maker, Merck.

However, the combination (trade name Vytorin) did not slow progression to end-stage renal disease in the trial or significantly impact mortality.

The “trial results provide clear evidence that lowering cholesterol with [Vytorin] reduces the risk of major atherosclerotic events,” in patients with chronic kidney disease, said Dr. Colin Baigent, Oxford University professor of epidemiology, and the lead investigator

of the Study of Heart and Renal Protection (SHARP) trial. He presented the study results at the meeting.

Merck will seek Food and Drug Administration approval for Vytorin use in chronic kidney disease (CKD) patients based on the SHARP trial results, the company said.

In SHARP, 4,650 patients with CKD were randomized to Vytorin, and 4,620 to placebo. The median duration of therapy

was 4.9 years. The mean age at baseline was 62 years, and patients had no revascularization or MI histories; 23% had diabetes, and 15% had vascular disease.

About a third of the patients started the trial on dialysis; the remainder had a baseline average estimated glomerular filtration rate of 26.5 mL/minute per 1.73 m².

The average LDL cholesterol at enrollment was 108 mg/dL. Midway through the trial, Vytorin lowered LDL cholesterol by an average of 32 mg/dL.

Major atherosclerotic events – coronary death, MI, nonhemorrhagic stroke, or revascularization – occurred in 11.3% (526) of patients in the Vytorin group, and in 13.4% (619) of patients in the placebo group. That translated to a significant 16.5% risk reduction among Vytorin users, results similar to previous statin studies in other populations, Dr. Baigent noted.

The rate of treatment compliance was about two-thirds among patients in both the placebo and Vytorin arms of the trial. “With full compliance, we would be likely to reduce the risk of vascular events by about a quarter,” he predicted.

However, lowering patients' LDL did not affect progression to end-stage renal disease, which developed in about a third of patients in each arm: 33.9% of the treatment group, and 34.6% of the controls.

Cancer was also on the minds of investigators during the trial, due to reports about possible carcinogenicity associated with use of ezetimibe (trade name Zetia). The FDA concluded in December 2009 that “it is unlikely that Vytorin or Zetia increases the risk of cancer or cancer-related death,” and the SHARP results supported the assertion.

There were 438 cancers diagnosed and 150 cancer deaths in the Vytorin group, compared with 439 cancers diagnosed and 128 cancer deaths in the placebo group. The differences were nonsignificant.

Overall, cardiac, renal, and vascular-related deaths were less frequent in Vytorin users, but nonvascular deaths were more frequent. As with cancer deaths, however, the differences between the groups were small and not significant.

Similarly, there were no significant differences in myopathy, rhabdomyolysis, liver dysfunction, pancreatitis, or gallstone complications between groups.

The study largely “confirms what we already know” – that statins benefit kidney patients, said nephrologist Pablo Pergola, clinical associate professor of medicine at the University of Texas Health Science Center, San Antonio.

Dr. Pergola was curious, however, about what role, if any, ezetimibe may have played in the outcomes.

“My guess is it's not something special ezetimibe is doing,” Dr. Baigent said. “It's lowering LDL cholesterol in the same way statins do.”

Dr. Baigent and Dr. Pergola said they have no conflicts of interest. Dr. Baigent added that the trial was run independently of Merck, and that he and his colleagues do not accept payments from the pharmaceutical industry, other than the costs of attending scientific meetings. ■

• *Insulin initiation and intensification of glucose control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

• *Lipodystrophy*

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration* (2.1)].

• *Weight gain*

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

• *Peripheral Edema*

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

• *Allergic Reactions*

Local Allergy

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

• *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [See *Patient Counseling Information* (17) in the full prescribing information]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

7. DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during

LANTUS®

(insulin glargine [rDNA origin] injection) solution for subcutaneous injection

organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [see *Clinical Studies* (14) in the full prescribing information]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [see *Dosage and Administration* (2.3) and *Clinical Studies* (14) in the full prescribing information]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [See *Warnings and Precautions* (5.3)].

10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

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