

Triple-Drug Pill May Reduce Blood Pressure

VITALS

Major Finding: After 12 weeks, 66% of blacks and 72% of nonblacks reached a target BP goal of less than 140/90 mm Hg and 23% of blacks and 29% of nonblacks reached a target of less than 120/80 mm Hg by taking a pill combining three different medications, compared with those who took dual-combination therapies for 12 weeks.

Data Source: A phase III, randomized, parallel-group study of 2,492 adults with moderate to severe hypertension.

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BY HEIDI SPLETE

FROM A MEETING SPONSORED BY
THE INTERNATIONAL SOCIETY ON
HYPERTENSION IN BLACKS

WASHINGTON — A triple-combination pill including 40 mg olmesartan, 10 mg amlodipine, and 25 mg hydrochlorothiazide significantly improved diastolic and

systolic blood pressure in black and non-black adults with moderate to severe hypertension, based on data from 2,492 patients in an investigational study.

Dr. Suzanne Oparil of the University of Alabama at Birmingham and her colleagues reviewed data from patients in TRINITY, a randomized, phase III parallel-group study conducted at 317 clinical sites in the United States and Puerto Rico.

The primary measure of effectiveness was a significant reduction in seated diastolic blood pressure after 12 weeks of daily treatment, and the secondary measure was a significant reduction in systolic blood pressure over the same period, Dr. Oparil said at the meeting.

Patients were randomized to receive one of four treatment protocols: 40 mg olmesartan, 10 mg amlodipine, and 25 mg hydrochlorothiazide (HCTZ); 40 mg olmesartan and 10 mg amlodipine; 40 mg olmesartan and 25 mg HCTZ; and 10 mg amlodipine and 25 mg HCTZ.

All treatment regimens yielded significant improvements in both systolic and diastolic blood pressure compared with baseline measures, but the triple-drug combination reduced seated diastolic blood pressure by an average of 20.8 mm Hg in black patients and 21.8 mm Hg in nonblack patients, which was significantly greater than the reductions in each of the three dual-therapy combinations.

The triple-drug combination also significantly reduced systolic blood pressure in blacks and nonblacks, with average reductions of 37.1 mm Hg and 38.9 mm Hg, respectively, both of which were significantly greater than the reductions in each of the three dual-therapy combinations.

In addition, 66% of blacks and 72% of nonblacks with a target blood pressure goal of less than 140/90 mm Hg were able to reach their goal on the triple-combination regimen, as were 23% of blacks and 29% of nonblacks with a target blood pressure goal of less than 120/80 mm Hg. The percentages in the triple-combination group were significantly higher than those in any of the dual-therapy groups.

The researchers excluded pregnant or lactating women and individuals with severe renal insufficiency, uncontrolled diabetes, uncontrolled hypertension, and a history of significant cardiac disease. The baseline demographics were similar across all groups, and the mean age of the patients was 54 years. Approximately 15% of the study population had controlled diabetes, and about 63% were obese.

The results suggest that the triple-drug therapy is equally effective for controlling high blood pressure in patients of different ethnic groups, the researchers noted.

The drug, marketed as Tribenzor, was approved by the Food and Drug Administration last month. One other triple-combination antihypertensive drug that includes amlodipine, valsartan, and HCTZ (Exforge HCT) was approved in 2009. ■

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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- *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