

# Controlled-Release Zileuton in Pipeline for Asthma

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SALT LAKE CITY — A controlled-release formulation of the oral 5-lipoxygenase inhibitor zileuton proved safe and effective in asthma patients in a pivotal phase III clinical trial, Dr. Leonard Bielory reported at the annual meeting of the American College of Chest Physicians.

Zileuton is available only in an immediate-release formulation marketed as

Zyflo, dosed at 600 mg four times daily. Zileuton controlled-release (CR) will offer the greater convenience of b.i.d. dosing, noted Dr. Bielory, professor of medicine at New Jersey Medical School, Newark.

The double-blind study involved 613 patients with chronic asthma at 76 U.S. sites who were randomized to 12 weeks of zileuton CR tablets at 1,200 mg b.i.d., zileuton, or placebo.

From a mean baseline forced expiratory volume in 1 second (FEV<sub>1</sub>) of 58.5%

predicted, FEV<sub>1</sub> rose by 4% in patients on zileuton CR, significantly better than with placebo.

In terms of safety end points, the most significant finding was that alanine transaminase elevations of at least three times the upper limit of normal occurred in 2.5% of patients on zileuton CR, 2.1% on zileuton, and 0.5% on placebo. In all cases, the abnormal liver function tests resolved while patients remained on their study drug or within 43 days of its discontinuation.

The incidence of all other adverse events in the zileuton CR group was similar to placebo.

Zileuton, the only 5-lipoxygenase inhibitor approved by the Food and Drug Administration, is contraindicated in patients with active liver disease or baseline elevated liver function tests. The product labeling recommends periodic liver function testing. Critical Therapeutics, the study sponsor, filed for marketing approval of zileuton CR with the FDA last summer. ■

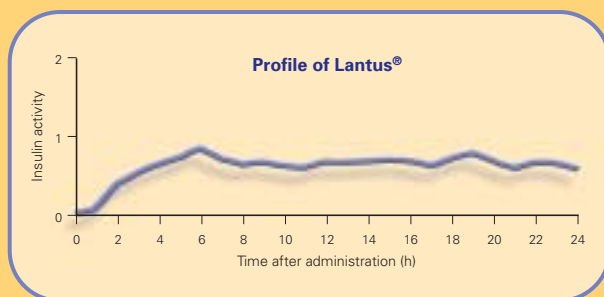
## Lantus®: the #1-prescribed insulin for good reason

### The #1 priority for people with diabetes-related hyperglycemia is to reduce blood glucose and A1C.<sup>1</sup>

Over the past 5 years, physicians like you have turned to Lantus® in steadily increasing numbers to do just that.\* Why? Because 5 years ago when you were wishing for a basal insulin that mimicked the way physiologic basal insulin works, Lantus® came along. It was then, and is still, the only once-daily, 24-hour basal insulin with no pronounced peak.<sup>2</sup> The result? Millions of prescriptions have been written for Lantus®.\* Lantus®, along with diet, exercise, and prandial and/or oral agents, allows patients to benefit from a full 24 hours of glucose lowering. Studies have shown Lantus® is associated with a low rate of hypoglycemia and has a neutral effect on weight.<sup>2-4</sup>

### Lantus® closely mimics physiologic basal insulin secretion.<sup>5,6</sup>

Physiologic basal insulin is secreted continuously over 24 hours, at a rate of approximately 0.5 IU/h, to meet between-meal and overnight glucose-regulating requirements and to suppress excess hepatic glucose production.<sup>6</sup> Past attempts at creating an insulin to mimic this profile have resulted in agents that have wide variability in their absorption and length of effect. Lantus® demonstrates a low rate of variability in its action, with a relatively flat, predictable profile after only 1 injection that lasts for a full 24 hours.<sup>2,7,8</sup> Additionally, in a crossover study of healthy volunteers, no differences in absorption rates were observed whether Lantus® was injected into the leg, arm, or abdomen.<sup>2,9</sup>



Physiologic basal profile means patients are better able to plan when to eat—because they don't have to contend with insulin peaks.<sup>6</sup> That can help patients by not requiring them to eat or snack at a specific time to balance a peak. In fact, Lantus® is associated with a low rate of hypoglycemia. It also has a neutral effect on weight.

### Lantus®, a basal insulin for patients with diabetes, has the features you want. It's what you've told us.

It's what you've shown us by making Lantus® the #1-prescribed insulin.

Lantus® is the only once-daily, 24-hour basal insulin with no pronounced peak, and it closely mimics physiologic basal insulin secretion.<sup>2</sup>

It's tried. It's trusted. And it's there for you as you help

more and more patients with diabetes toward control of blood glucose.

We thank you for letting Lantus® help.

Once-Daily  
24-HOUR  
**LANTUS®**  
insulin glargine [rDNA origin] injection

### Important Safety Information

Lantus® is indicated for once-daily subcutaneous administration, at the same time each day, for the treatment of adult and pediatric patients (6 years and older) with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

**LANTUS® MUST NOT BE DILUTED OR MIXED WITH ANY OTHER INSULIN OR SOLUTION. If mixed or diluted, the solution may become cloudy, and the onset of action/time to peak effect may be altered in an unpredictable manner.**

Lantus® is contraindicated in patients hypersensitive to insulin glargine or the excipients.

**Hypoglycemia is the most common adverse effect of insulin, including Lantus®. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin type and/or regimen should be made cautiously and only under medical supervision. Concomitant oral antidiabetes treatment may need to be adjusted.**

Other adverse events commonly associated with Lantus® include the following: lipodystrophy, skin reactions (such as injection-site reaction, pruritus, rash), and allergic reactions.

**Please see brief summary of prescribing information on adjacent page.**

\*Based on PNRx. IMS Health. National Prescription Audit Plus™. September 2003 – December 2005.

References: 1. American Diabetes Association. *Diabetes Care*. 2005;28(suppl 1):S4-S36. 2. Lantus Prescribing Information. 3. Data on file, sanofi-aventis U.S. LLC (CSR HOE901/5001). 4. Data on file, sanofi-aventis U.S. LLC (CSR HOE901/5024). 5. Nathan DM. *N Engl J Med*. 2002;347:1342-1349. 6. Guthrie R. *Clin Diabetes*. 2001;19:66-70. 7. Scholtz HE, Pretorius SG, Wessels DH, Becker RHA. *Diabetologia*. 2005;48:1988-1995. 8. Fanelli CG, Pampanelli F, Porcellati P, et al. Poster presented at: 38th Annual Meeting of the European Association for the Study of Diabetes (EASD); September 1-5, 2002; Budapest, Hungary. 9. McKeage K, Goa KL. *Drugs*. 2001;61:1599-1624.