U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Update to ongoing safety review of Lantus (insulin glargine) and possible risk of cancer

Safety Announcement

[1-12-2011] The U.S. Food and Drug Administration (FDA) is updating the public about its ongoing safety review of Lantus (insulin glargine) and a possible increased risk of cancer. Lantus is a long-acting modified version of human insulin (insulin analog) used to control blood sugar in patients with Type 1 and Type 2 diabetes.

In July 2009, FDA issued an Early Communication About Safety of Lantus (insulin glargine)[1] to inform the public that it was reviewing four published observational studies, three of which suggested an increased risk c cancer associated with the use of Lantus.[1-4] FDA has reviewed the four studies and has determined that the evidence presented in the studies is inconclusive, due to limitations in how the studies were designed and carried out and in the data available for analysis. These limitations prevent our ability to attribute the observed cancer risk to Lantus (see Data Summary below).

FDA has also reviewed results from a five-year randomized clinical trial, *Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin*, which compared Lantus to Neutral Protamine Hagedorn (NPH) insulin in individuals with Type 2 diabetes. The results did not show an increased risk of cancer in subjects treated with Lantus compared to those treated with NPH insulin; however, this study was not specifically designed to evaluate cancer outcomes.

FDA is continuing to work with the manufacturer of Lantus and the U.S. Department of Veterans Affairs (VA) to further evaluate the long-term risk, if any, for cancer associated with the use of Lantus.

At this time, FDA has not concluded that Lantus increases the risk of cancer. Our review is ongoing, including review of information from a current clinical trial, and the Agency will update the public when it has additional information.

- Healthcare professionals should continue to follow the recommendations in the drug label when prescribing Lantus.
- Patients should continue taking Lantus unless told otherwise by their healthcare professional.
- Patients who have concerns about using Lantus should talk to their healthcare professional.

This communication is in keeping with FDA's commitment to inform the public about its ongoing safety revie of drugs.

Additional Information for Patients

- Do not stop taking your Lantus unless told to do so by your healthcare professional.
- FDA has not concluded that Lantus increases the risk of cancer. The Agency is continuing to review this safety concern and will update the public when additional information is available.
- Talk to your healthcare professional if you have concerns about Lantus.

- Report any side effects from the use of Lantus to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- FDA has not concluded that Lantus increases the risk of cancer. The Agency is continuing to review this safety concern and will update the public when additional information is available.
- Follow the recommendations in the drug label when prescribing Lantus.
- Report adverse events involving Lantus to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

In July 2009, FDA issued an Early Communication About Safety of Lantus (insulin glargine)[2] to inform the public that it was reviewing four published observational studies, three of which suggested an increased risk c cancer associated with the use of Lantus.[1-4] FDA has completed its review of the studies and has determined that the evidence presented in these studies is inconclusive due to methodological limitations.

The duration of patient follow-up in all four studies was shorter than what is generally considered necessary t evaluate cancer risk from drug exposure. Also, the four studies provided limited information on patients' use of insulin products. Additionally, some of these studies did not take into account whether the patients used any anti-diabetic drugs before the study time period or whether there were any changes in how patients used these drugs during the study period. Furthermore, risk factors for cancer, such as smoking, family history of cancer, and obesity, may not have been adequately controlled for in these studies. This prevents our ability t attribute the observed cancer risk solely to Lantus.

In addition to the four published observational studies, FDA has reviewed results from the *Evaluation of Diabetic Retinopathy Progression in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents Plus Insulin* trial, which was a five-year, randomized trial comparing Lantus to NPH insulin in individuals with Type 2 diabetes. A post-hoc evaluation (examining the data after the trial concluded for outcomes that were not identified a priori) of the occurrence of cancer was conducted. The safety population consisted of over 500 patients per treatment arm with a median exposure of approximately five years. The overall occurrence of all cancers was 5.8% in the Lantus arm versus 9.3% in the NPH insulin arm. The odds ratio for all cancers was 0.60 (95% Confidence Interval 0.36, 0.99). The results did not support an increased risk of cancer associated with Lantus in comparison to NPH insulin; however, the study was not designed or powered to evaluate cance outcomes and these outcomes were not verified in medical records or reviewed by cancer experts.

FDA continues to work with the manufacturer of Lantus and other scientists to further evaluate the safety of Lantus. The manufacturer's ongoing Outcome Reduction with Initial Glargine Intervention (ORIGIN) clinical trial has been amended to adjudicate (have a panel of experts in cancer evaluate) all cases of cancer occurring during the trial. The ORIGIN trial is designed to determine if treatment with Lantus to reduce fastin plasma glucose to 95 mg/dL or less would reduce the incidence of cardiovascular events in patients with pre-diabetes or early diabetes versus standard care. An interim review of the data by an independent data monitoring committee did not show evidence of a signal for increased cancer risk. Results from the ORIGIN trial are expected at the end of 2011.

FDA is aware that the manufacturer plans to conduct three epidemiological studies to further evaluate cancer risk associated with the use of Lantus. Results from the epidemiological studies are expected by the end of June 2011.

FDA is also working with the VA to decide whether to use the VA's patient database to further evaluate any potential cancer risk with Lantus.

FDA will communicate important new data on this issue when they become available.

References

1. Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. *Diabetologia*. 2009;52:1732-44.

2. Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. *Diabetologia*. 2009;52:1745-54.
3. Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia*. 2009;52:1755-65.
4. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009;52:1766-77.

Related Information

- Information for Lantus (insulin glargine)[3]
- Early Communication About Safety of Lantus (insulin glargine)[4]
  7/1/2009

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