

**Important safety news surrounding Levemir® [insulin detemir (rDNA origin) injection] focusing on meta-analysis of clinical studies assessing the incidence of cancer diagnosis**



XXXX X, 2009

Dear Health Care Provider:

Recently, the European Association for the Study of Diabetes (EASD) conducted its annual meeting in Vienna, Austria, where one of the primary topics was the question surrounding the relationship between insulin therapy and cancer. New clinical data presented at the meeting demonstrated no increased incidence of cancer in patients treated with Levemir® [insulin detemir (rDNA origin) injection] compared with patients treated with human insulin (NPH insulin), when comparing rates of diagnosis.<sup>1</sup> The clinical significance of in vitro activation of the insulin-like growth factor 1 receptor (IGF-1R) has not been established. Studies have shown that IGF-1R may play an important role in the progression and development of certain types of human cancer.<sup>2</sup> Levemir® has been shown to have a low affinity for IGF-1R relative to both Lantus® (insulin glargine [rDNA origin] injection) and human insulin.<sup>3,4</sup>

The consensus from the meeting is that while any link with Lantus® and cancer is still inconclusive, the potential issue requires further attention. To date, these additional studies have focused primarily on Lantus®; Levemir® has not been the subject of such investigations. Continued research is required to draw more definitive conclusions.

Patient safety is very important to Novo Nordisk, and we value your trust and confidence in our products and company. Novo Nordisk remains committed to taking a safe approach to developing and maintaining our insulin analog portfolio.

### **Indications and usage**

Levemir® is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

### **Important safety information**

Levemir® is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

- For the past 20 years, Novo Nordisk insulin analogs have been tested for IGF-1R binding in the early research phase. Only insulin analogs with a binding ratio between the insulin and IGF-1 receptors similar to or better than that of human insulin have been accepted for further development or commercialization<sup>1,5</sup>
- Novo Nordisk insulin analogs have been studied in multiple randomized, controlled trials and are monitored for any safety signals through rigorous postmarketing safety surveillance. Furthermore, Novo Nordisk has not identified any cancer signals for any of its 3 insulin analogs during extensive clinical development programs and in postmarketing safety surveillance
- In vitro studies have been conducted on IGF-1R affinity of insulin analogs.<sup>3,4</sup> Levemir® was shown to have a low affinity to IGF-1R relative to human insulin (16% ± 1% vs 100%). The IGF-1R affinity of insulin glargine was 641% ± 51% vs 100% for human insulin. In a separate study, not sponsored by Novo Nordisk, the IGF-1R affinity of insulin glargine was 551%, compared with 100% for human insulin<sup>4</sup>
- A recently published meta-analysis sponsored by Novo Nordisk assessed the relative risk of cancer diagnosis during clinical treatment with Levemir®. It compared the incidence of cancer diagnosed in patients treated with Levemir® during clinical treatment with that of patients treated with either human insulin or Lantus®<sup>1</sup>
  - When comparing rates of diagnosis, there was no increased incidence of cancer in patients treated with Levemir® compared with patients treated with human insulin. The nonstratified odds ratio between Levemir® and human insulin in this meta-analysis was 2.44 (95% confidence interval 1.01-5.89;  $P < 0.05$ ) versus 1.47 between Levemir® and Lantus® (95% confidence interval 0.55-3.94;  $P = NS$ ).<sup>1</sup> The estimated ORs were significantly in favor of Levemir®<sup>1</sup>

— **Study design**

Dejgaard et al. *Diabetologia*, 2009

- Of the 95 Novo Nordisk–sponsored, randomized, open-label, clinical trials, 21 trials met criteria for inclusion in this individual data meta-analysis
  - 16 trials compared the incidence of cancer diagnosis during the trials in patients treated with Levemir® with that of patients treated with human insulin (NPH insulin)
  - Levemir® and insulin glargine were compared in 5 of the 21 trials in the meta-analysis. These results were not considered in the meta-analysis
- Inclusion criteria applied:
  - Levemir® used in one of the treatment arms
  - NPH insulin or insulin glargine used as the comparator
  - Trial had a duration of at least 12 weeks
  - Commercial formulation of Levemir® used
- Cancer incidence was not a predefined end point of the individual trials. Incidence was calculated from the databases on all adverse events from the included studies

In recent news regarding the new study, Professor David Russell-Jones of the Royal Surrey County Hospital, United Kingdom, a speaker at the EASD meeting stated:

*The new experimental and clinical data confirm that Levemir® has an excellent safety profile and is not associated with any increase in the incidence of cancer when compared to human insulin.<sup>6</sup>*

**Important safety information**

**Levemir® should not be diluted or mixed with any other insulin preparations.**

**Hypoglycemia is the most common adverse effect of all insulin therapies, including Levemir®. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Levemir® is not to be used in insulin infusion pumps. Any change of insulin dose should be made cautiously and only under medical supervision. Concomitant oral antidiabetes treatment may require adjustment.**

**Needles and Levemir® FlexPen® must not be shared.**

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir® from other intermediate or long-acting insulin preparations. The dose of Levemir® may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 4% of patients in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation. Less common but more serious are severe cases of generalized allergy, including anaphylactic reaction, which may be life threatening.

Please see accompanying Prescribing Information.

Patient safety remains our priority. As a world leader in insulin therapy, Novo Nordisk is continually dedicated to people with diabetes. For more information on Novo Nordisk products, please contact Novo Nordisk Customer Care at 800-727-6500 or visit **NovoNordisk-US.com**.

Kind regards,

**Alan Moses, MD**

VP, Global Chief Medical Officer

If you do not want to be included in future mailings or communications from Novo Nordisk or would like to stop use of your information by Novo Nordisk, please call 800-727-6500 or contact us at:

Novo Nordisk Inc.  
100 College Road West  
Princeton, NJ 08540

**References:** **1.** Dejgaard A, Lynggaard H, Råstam J, Krogsgaard Thomsen M. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. *Diabetologia*. 2009;52(12):2507-2512. **2.** Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer*. 2004;4(7):505-518. **3.** Kurtzhals P, Schäffer L, Sørensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes*. 2000;49(6):999-1005. **4.** Kohn WD, Micanovic R, Myers SL, et al. pI-shifted insulin analogs with extended in vivo time action and favorable receptor selectivity. *Peptides*. 2007;28(4):935-948. **5.** Gammeltoft S, Hansen BF, Dideriksen L, et al. Insulin aspart: a novel rapid-acting human insulin analogue. *Expert Opin Investig Drugs*. 1999;8(9):1431-1442. **6.** Novo Nordisk data on file, presented at the EASD on October 1, 2009.

Lantus® is a registered trademark of sanofi-aventis U.S. LLC.

FlexPen® and Levemir® are registered trademarks of Novo Nordisk A/S.  
© 2009 Novo Nordisk Inc.

139902

December 2009