

# ADA/EASD Panel Urges Caution on TZD Use

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In light of new information regarding thiazolidinediones, the American Diabetes Association and the European Association for the Study of Diabetes have updated their diabetes treatment guidelines to urge “greater caution” in the use of TZDs, particularly in patients with heart failure.

However, they did not fundamentally change last year’s original consensus algorithm, which included the thiazolidinediones as one of three possible choices—along with insulin and sulfonylureas—in patients who do not achieve hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels below 7% with the first-line therapies of lifestyle modification and metformin (Diabetes Care 2006;29:1963-72;

Diabetologia 2006;49:1711-21).

**The panel concluded that the increased risk of heart failure or fractures is not ‘of a magnitude to warrant [TZDs]’ removal’ from the treatment algorithm.**

The update, due to be published in January 2008 in both Diabetes Care and Diabetologia, also included information about sitagliptin, which was not yet approved by the Food and

Drug Administration at the time the original document was written. As monotherapy, sitagliptin is expected to decrease HbA<sub>1c</sub> by 0.5%-0.8%. It has the advantage of being weight neutral, but it also has disadvantages, including limited experience and high cost, according to the ADA/EASD panel of seven authors led by Dr. David M. Nathan, director of the Diabetes Center at Massachusetts General Hospital and professor of medicine at Harvard Medical School, Boston.

But TZDs were the main topic of the update, deemed necessary because of the enormous amount of attention that the class of drugs received during 2007, beginning with the widely publicized meta-analysis by Dr. Steven E. Nissen concluding that rosiglitazone was associated with a significant increase in the risk of myocardial infarction (N. Engl. J. Med. 2007;356:2457-71). At least four additional meta-analyses—including one from the manufacturer and one by the FDA—also called into question the safety of rosiglitazone with regard to the risk of MI, with a putative 30%-40% relative increase in risk.

However, another meta-analysis of essentially the same data found no significant increased risk of cardiovascular mortality for either rosiglitazone or pioglitazone (Lancet 2007;370:1129-36), while the interim analysis from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study revealed no significant effect on MI but did confirm the risk for heart failure (N. Engl. J. Med. 2007;357:28-38). Meanwhile, yet another meta-analysis suggested a protective effect for pioglitazone (JAMA 2007;298:1180-8).

In addition to the MI concern with rosigli-

tazone, the previously recognized risk of fluid retention and heart failure that occurs with both rosiglitazone and pioglitazone has now been quantified as approximately twofold. This information is included in a “black box” warning on the labels for both TZDs. Both drugs have also been associated with an increased risk for fractures, particularly in women. The majority of these were in the distal upper or lower limb, not the classic sites of osteoporotic fractures.

Despite these developments, the

ADA/EASD panel concluded that the data on MI for both drugs are not definitive, and that the increased risk of heart failure or fractures is not “of a magnitude to warrant their removal as one of the possible second-step medications in our algorithm,” particularly since they do have at least one advantage over either insulin or sulfonylureas: They are far less likely to cause hypoglycemia. Thus, the panel opted to compromise by urging clinicians to consider carefully whether to use TZDs

versus insulin or sulfonylureas, as well as to consider what is known about the differences between the two available TZDs.

“We are mindful of the importance of not changing this consensus guideline in the absence of definitive or compelling new data. Future updates are planned to consider further revisions of the algorithm, guided by the evidence base and clinical experience with the newer classes of glucose-lowering medication,” Dr. Nathan and the other panel members wrote. ■



\*Model is for illustrative purposes only.

#### 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.

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.

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic

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

Whether these observed differences represent true differences in the effects of Levemir, NPH insulin, and insulin glargine is not known, since these trials were not blinded and the protocols (eg, diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences in weight has not been established.

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- Less weight gain<sup>7†</sup>

**References:** 1. Meneghini LF, Rosenberg KH, Koenen C, Meriläinen MJ, Lüddeke H-J. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab*. 2007;9(3):418-427. 2. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P, for the Levemir Treat-to-Target Study Group. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care*. 2006;29(6):1269-1274. 3. Klein O, Lyngø J, Endahl L, Damholt B, Nosek L, Heise T. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. *Diabetes Obes Metab*. 2007;9(3):290-299. 4. Phillis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther*. 2006;28(10):1569-1581. 5. Data on file. Novo Nordisk Inc, Princeton, NJ. 6. Heise T, Nosek L, Rønn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. *Diabetes*. 2004;53(6):1614-1620. 7. Data on file. NDA21-536. Novo Nordisk Inc, Princeton, NJ.



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