

# New Incretin Therapies Require Thoughtful Use

BY SHERRY BOSCHERT  
San Francisco Bureau

SAN FRANCISCO — The new incretin mimetic exenatide and the incretin enhancer sitagliptin both have unique properties that need to be taken into account when prescribing them, American Diabetes Association president Dr. John B. Buse said at a meeting sponsored by the association.

Injections of exenatide (Byetta) were approved in 2005 as adjunctive therapy for patients with type 2 diabetes. Orally administered sitagliptin (Januvia) was approved in 2006 for use as monotherapy or in combination with metformin or thiazolidinedione for patients with type 2 diabetes.

Dr. Buse has received research funds from Amylin Pharmaceuticals and from Eli Lilly & Co., which market exenatide. He is an adviser and speaker for those companies and for Merck & Co., which markets sitagliptin.

Incretin augments glucose-stimulated insulin secretion by intestinally derived peptides. Exenatide and sitagliptin augment the incretin pathway, which appears to be attenuated in type 2 diabetes. The incretin effect is composed mainly of the peptides glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide-1 (GLP-1), which normally get inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Exenatide is a GLP-1 receptor analogue that's resistant to DPP-4 degradation and slows gastric emptying. Sitagliptin selectively inhibits DPP-4, giving the incretin enzymes a longer half-life to enhance their effects.

"We don't have long-term safety and efficacy data" for these drugs "like we do with the other four classes of medications for diabetes mellitus," Dr. Buse cautioned.

During a question-and-answer session, Dr. Buse discussed several aspects of the use of these drugs.

► **Combining them with insulin.** "I think this is a very exciting combination," he said, though the combination is not adequately studied in clinical trials. "It's something that at our center we use with some regularity." Sparse data on five patients treated for 5 days with exenatide and insulin at his institution are buried in a larger study published in 2001, said Dr. Buse, professor of medicine at the University of North Carolina, Chapel Hill.

He warned against combining exenatide with rapid-acting insulin. That idea is "fraught with problems, at least from a theoretical basis," Dr. Buse said, "and is something that I'd be exceptionally cautious about doing."

► **Fitting exenatide into the diabetes care algorithm.** Experts are wondering whether exenatide might be a reasonable alternative to sulfonylureas or glitazones. Decisions on whether to include exenatide in treatment algorithms will depend "on whether we have data demonstrating its long-term safety and efficacy, and what the effects are on  $\beta$ -cell biology," he said.

► **Analyzing the implications of rhinorrhea as a side effect of sitagliptin.** Studies of sitagliptin persistently show an elevated but low rate of rhinorrhea—around 11%, compared with 7% in placebo groups—and few other side effects. The drug affects

chemokine levels, which has raised concerns that perhaps the rhinorrhea is "a hint that there are immune effects that we haven't been able to measure yet," he said.

► **Predicting which type 2 diabetes patients of long duration will respond to these agents.** Because exenatide dramatically increases GLP-1 levels, "my guess is that virtually anybody would respond" to it, though it's unclear whether the level of response would justify two injections daily and a cost of around \$200 per day, he

said. Sitagliptin produces more modest increases in GLP-1 levels. "I just don't know what the effects would be in a patient who has severely impaired  $\beta$ -cell function," Dr. Buse said.

► **Considering the drugs' use in bariatric surgery patients, about which data are lacking.** "Part of the benefit of bariatric surgery is you actually increase the levels of GLP-1 and perhaps other incretin hormones, so it's an intriguing notion," Dr. Buse said. "The concern with exenatide

would be the nausea from the surgery plus the nausea from the exenatide may be getting somebody in a bad place."

► **Predicting potential effects on gastroparesis patients.** The clinical trials excluded patients with chronic, serious GI issues, "so we don't really know" the answer, he said. For some patients with intermittent "gastroparesis," exenatide may limit their eating and help them feel better, "but it's something you want to be very cautious with," he said. ■



Visit [novomedlink.com](http://novomedlink.com)  
to access  
Interactive Learning Programs.

## QUICK MEAL. QUICK INSULIN.

To get fast glucose control, add NovoLog®

For patients not at goal on basal insulin, NovoLog:

- Mimics the body's normal mealtime insulin response<sup>1</sup>
- Provides significantly better mean PPG\* levels than regular human insulin<sup>2</sup>
- Offers convenient mealtime dosing in the patient-preferred FlexPen®<sup>3,4</sup>

NovoLog is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

### Important safety information

NovoLog has a more rapid onset and shorter duration of action than regular human insulin. Because of the fast onset of action, the injection of NovoLog should be immediately followed by a meal. Because of the short duration of action of NovoLog, patients with diabetes also require a longer-acting insulin to maintain adequate glucose control. NovoLog is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog or one of its excipients. Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog. Any change in insulin should be made cautiously and only under medical supervision.

Please see brief summary of Prescribing Information on adjacent page.

Call 1-800-727-6500 or visit [novolog.com](http://novolog.com).



\*PPG = postprandial plasma glucose.  
FlexPen and NovoLog are registered trademarks of Novo Nordisk A/S.  
© 2007 Novo Nordisk Inc. 132693 July 2007



NovoLog®  
Insulin aspart (rDNA origin) injection  
Rapid, Flexible control™