FDA Approves Sitagliptin for Glycemic Control

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Sitagliptin phosphate, an agent in the new class known as dipeptidyl peptidase-4 inhibitors, has been approved by the Food and Drug Administration for use as monotherapy or in combination with metformin or a thiazolidinedione.

The DPP-IV inhibitors work by blocking the enzyme that breaks down the two incretin hormones glucagonlike peptide-1 and glucose-dependent insulinotropic peptide, which help regulate glucose metabolism via increased insulin release, suppressed glucagon release, and delayed gastric emptying.

Manufactured by Merck & Co. under the name Januvia, sitagliptin is a once-daily oral agent that will cost $4.86 per tablet. Another DPP-IV inhibitor, Novartis' vildagliptin (Galvus), is expected to be approved by the end of the year.

Data from three randomized, placebo-controlled phase III studies on sitagliptin were presented in September at the annual meeting of the European Association for the Study of Diabetes, in Copenhagen.

Dr. Pablo Aschner, of the Colombian Diabetes Association, Bogota, presented the findings from the 24-week monotherapy trial, in which 741 patients aged 18-75 years were randomized to daily placebo, 100 mg sitagliptin or 200 mg sitagliptin. At baseline, the entire study population had a mean hemoglobin A_{1c} of 8.0% and fasting plasma glucose of 9.6 mmol/L. At 24 weeks, the two sitagliptin doses produced statistically significant, placebo-adjusted reductions in A_{1c} of 0.79% with 100 mg and 0.94% with 200 mg, and in fasting plasma glucose of 1.0 mmol/L and 1.2 mmol/L, respectively.

Reductions in A_{1c} were greater among the patients with higher baseline A_{1c} levels, Dr. Aschner reported.

The proportion of patients achieving an A_{1c} level of less than 7.0% were 41% with 100 mg sitagliptin and 45% with 200 mg, while 18% and 20%, respectively, reached an A_{1c} below 6.5%.

Placebo-adjusted reductions in 2-hour postmeal glucose values were 2.6 mmol/L with 100 mg and 3.0 mmol/L with 200 mg sitagliptin. Improvements with sitagliptin relative to placebo also were seen in postmeal insulin and C-peptide concentrations, as well as in homeostasis model assessment–β and the ratios of insulin to glucose areas under the curve and proinsulin/insulin, suggesting improved β-cell function, he said.

A second study, presented by Dr. Avraham Karasik, of Chaim Sheba Medical Centre, Tel Hashomer, Israel, randomized 701 type 2 diabetic patients who were inadequately controlled on 1,500 mg/day or more of metformin alone to receive either placebo or 100 mg/day of sitagliptin for 24 weeks. The addition of sitagliptin to ongoing metformin therapy resulted in a significant mean placebo-subtracted reduction from baseline in hemoglobin A_{1c} of 0.65%, in fasting glucose (1.4 mmol/L), and in 2-hour postprandial glucose (2.8 mmol/L).

The proportions achieving a hemoglobin A_{1c} value of less than 7% were 47% with sitagliptin plus metformin, compared with just 18% of those receiving placebo with metformin, while 17% and 5%, respectively, reached an A_{1c} level below 6.5%, Dr. Karasik reported.

The addition of sitagliptin to metformin had no effect on body weight, nor did it increase the risk for hypoglycemia or gastrointestinal adverse events, compared with placebo, he said.

Dr. Julio Rosenstock, of the Dallas Diabetes and Endocrine Center and the University of Texas Southwestern Medical Center, Dallas, reported the findings of a third study in which 353 patients who had hemoglobin A_{1c} values between 7% and 10% while taking 30 or 45 mg/day of pioglitazone were randomized to receive the addition of placebo or 100 mg/day of sitagliptin. At 24 weeks, mean A_{1c} was 7.2% with sitagliptin, compared with 7.8% with placebo, a significant difference. The proportions achieving an A_{1c} level of less than 7% were 45% vs. 23%, while 24% vs. 5%, respectively, reached the A_{1c} targets of less than 6.5%.

There was no increase in hypoglycemia with sitagliptin, compared with placebo. The sitagliptin group reported a slightly higher incidence of abdominal pain (3.4% vs. 0), but there were no significant differences in other gastrointestinal adverse events. Mean body weight change was not different between sitagliptin and placebo when added to pioglitazone, Dr. Rosenstock reported. ■

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