



# **DRUG EFFECTIVENESS REVIEW PROJECT**

## **P&T Committee Brief Drug Class Review on Newer Drugs for the Treatment of Diabetes Mellitus**

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### P&T Committee Brief Disclaimer

This brief was written by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). It is a summary of certain material matters contained in the Drug Effectiveness Review Project (DERP) report "Drug Class Review on Newer Drugs for the Treatment of Diabetes Mellitus" dated August 2008, which is a product of the OR Evidence-based Practice Center at Oregon Health & Science University. You can find the original report online at the following web address:

[http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/Diabetes\\_final\\_report\\_original.pdf](http://www.ohsu.edu/ohsuedu/research/policycenter/customcf/derp/product/Diabetes_final_report_original.pdf). Although at least one of the authors of this report reviewed and commented on the brief, its content and conclusions are those of the CEBP and not those of the authors or reviewers of the DERP report. The Center is a policy resource and is not providing any legal or business advice. This Brief is subject to the information and conclusions contained in the DERP report, and readers of this Brief are advised to review the DERP report. This Brief is intended for the benefit of the participant organizations and their constituent decision-making bodies.

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P & T COMMITTEE BRIEF  
Drug Class Review on Newer Drugs for the Treatment of Diabetes Mellitus

**Background:**

Diabetes mellitus (DM) is a chronic disease of abnormal blood glucose (BG) regulation, affecting more than 20 million Americans and 2 million Canadians (approximately 7% of the population). Of those diagnosed, 90-95% have type 2 diabetes (DM2), while 5-10% have type 1 diabetes (DM1). The cause of this condition varies depending on the type: DM1 is characterized by autoimmune destruction of beta cells of the pancreas resulting in absolute insulin deficiency. On the other hand, DM2 encompasses a heterogeneous group of disorders characterized by progressive loss of beta cell function leading to variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Insulin is the treatment for DM1. Pharmacologic options for DM2 include sulfonylureas (SU), biguanides, thiazolidinediones (TZD), meglitinides, alpha-glucosidase inhibitors, and insulin. Within the last one to two years, three new antihyperglycemic agents have been approved in the United States; of these, one is currently available in Canada (see Table 1). These agents offer mechanisms of glycemic control beyond that of “traditional” oral agents and insulin by targeting alternate glucoregulatory receptors and hormones such as amylin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and dipeptidyl peptidase-4 (DPP-4). The purpose of this review is to compare the effectiveness and safety of these newer therapies for DM.

Table 1

| Active Ingredient | Trade Name | Drug Class                               | Route of Administration | Indications   |
|-------------------|------------|--|-------------------------|---|
| sitagliptin       | Januvia®   | Incretin enhancer/DPP-4 enzyme inhibitor | Oral                    | In the US: mono or adjunctive therapy (with metformin, SU, TZD) for patients with DM2 with inadequate BG control. In Canada: in combination with metformin in adults with DM2 when diet, exercise and metformin do not provide adequate BG control. |
| pramlintide*      | Symlin®    | Amylin agonist                           | Subcutaneous injection  | Adjunctive therapy for patients with DM1 or DM2 who use insulin with inadequate BG control  |
| exenatide*        | Byetta®    | Incretin-mimetic GLP-1 analog            | Subcutaneous injection  | Adjunctive therapy (with metformin, SU, TZD) for patients with DM2 with inadequate BG control   |

\*Drug not available in Canada

**Methodology:**

The Drug Effectiveness Review Project reviews all pertinent studies, and solicits and accepts public input. This is the first report on this drug class. Study eligibility is determined by pre-set criteria. Studies which did not meet these criteria with respect to study design or duration, patient population, interventions, or outcomes were excluded. Additionally, studies not in English were excluded. The quality of all included studies was appraised.

**Evidence Available:**

Searches identified 134 citations for pramlintide, 166 for sitagliptin and 324 for exenatide. Relevant information consists of 13 publications for pramlintide, 16 for exenatide and 13 for sitagliptin. Effectiveness outcome measures include mortality, quality of life (QOL), microvascular disease (renal disease, retinopathy, neuropathy), macrovascular disease [cardiovascular (CV) events, procedures and mortality; stroke; transient ischemic attack (TIA);

coronary artery disease (CAD); extremity amputation], lower extremity ulcers and hospitalization. Efficacy outcomes include glycemic control [fasting BG, post-prandial BG, glycosylated hemoglobin (hemoglobin A1c or A1c), change in weight and time to treatment failure]. Safety outcomes include adverse event (AE) rates, withdrawals due to AEs, major AEs [e.g. diabetic ketoacidosis (DKA) and hyperosmolar coma] and specific AEs (e.g. hypoglycemia, liver toxicity, gastrointestinal effects, changes in lipid concentrations, weight gain, infection, neoplasm).

**Key Questions and Findings:**

For all three drugs, no data on children were available, no studies evaluated long-term health outcomes or AEs, and no studies were longer than 52 weeks in duration.

Pramlintide

Question # 1: For children and adults with DM1 does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?

The addition of pramlintide to a *flexible-dose* insulin regimen resulted in A1c that was either slightly improved or no different when compared to placebo plus *flexible-dose* insulin regimen administered over 29 or 52 weeks. When pramlintide was added to *fixed-dose* insulin therapy, A1c decreased by 0.29% to 0.34% ( $P<0.01$ ), with no significant effect in the placebo plus *fixed-dose* insulin group at 52 weeks of follow-up. Patients receiving pramlintide in addition to insulin for 29-52 weeks lost weight (range: -0.4 to -1.3 kg) compared to those receiving placebo plus insulin, who experienced weight gain (range: +0.8 to +1.2 kg). Groups receiving pramlintide in addition to insulin therapy exhibited larger overall rates of treatment withdrawal (range across studies: 20% to 42% compared with 10% to 33%) and withdrawals due to AEs (range across studies: 5% to 20% compared with 2% to 8%) than groups receiving placebo plus insulin. AEs including nausea, vomiting, anorexia, and reduced appetite were more commonly reported with the use of pramlintide plus insulin than with the use of placebo plus insulin. Severe hypoglycemia occurred more frequently with pramlintide plus insulin during the first four weeks of treatment compared with placebo plus insulin; rates of severe hypoglycemia declined once pramlintide doses stabilized but continued to remain slightly higher than with placebo plus insulin at up to 52 weeks of follow-up.

Question #2: For children and adults with DM2 does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy with or without concurrent oral hypoglycemic agents?

Pramlintide added to *fixed-dose* insulin decreased A1c by 0.13% to 0.4% and weight by 1.1 kg to 1.85 kg at 52 weeks compared with placebo plus insulin. At 16 weeks the addition of pramlintide to insulin glargine (without prandial insulin) reduced A1c by 0.34% and weight by 2.3 kg relative to placebo plus insulin glargine used in a *flexible-dose* setting. Both pramlintide- and placebo-treated subjects exhibited similar rates of withdrawal and withdrawal due to AEs. The most commonly reported AE was nausea, which occurred more frequently with pramlintide plus insulin than with placebo plus

insulin, especially during the first four weeks of treatment and declined thereafter. Severe hypoglycemia occurred more frequently with pramlintide 150 mcg administered three times a day with insulin than with insulin plus placebo during the first 4 weeks of treatment. Rates of hypoglycemia after four weeks were similar among treatment groups.

Question #3: Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?

No studies conducted subgroup analyses evaluating whether the addition of pramlintide exhibited differential effects depending on total daily insulin dose. In one pooled analysis, patients with good but not optimal control (baseline A1c 7%-8.5%) experienced similar reductions in A1c as the populations included in the original trials without increased risk of hypoglycemia at 26 weeks. In one trial, the use of pramlintide appeared to inhibit weight gain in patients with body mass index  $\leq 23$  kg/m<sup>2</sup> while exhibiting mild weight loss for patients with body mass index  $>23$  kg/m<sup>2</sup> from baseline to week 26.

### Exenatide

Question #1: For children and adults with DM2 does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control compared with other hypoglycemic agents as monotherapy or combined therapy?

There were no studies that met inclusion criteria that compared exenatide to oral diabetes agents used as either monotherapy or combined therapy.

Question #2: For children and adults with type 2 diabetes, does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to other hypoglycemic agents compared with conventional insulin therapy?

Active-control trials compared exenatide to insulin, with both groups receiving oral diabetes agents, and demonstrated improved A1c in both treatment groups, with no significant differences between treatments. In one trial, the substitution of exenatide for insulin did not improve A1c. However, when compared to regimens of placebo plus oral diabetes agents, the use of exenatide plus oral diabetes agents improved A1c, with decrease in A1c levels ranging from -0.6% to -1.0%. Active-control studies demonstrated significant weight loss in exenatide groups compared to weight gain with insulin groups (between-group difference 4.0 to 5.5 kg). Weight also decreased with exenatide compared with placebo, but weight change was small and not statistically significant. Quality of life was examined in only one study. No significant differences were seen between exenatide administered twice a day and insulin glargine, despite higher rates of gastrointestinal AEs with exenatide.

Total number of withdrawals was less with exenatide 5 mcg twice daily than with placebo [relative risk (RR): 0.67, 95% confidence interval (CI): 0.53 to 0.85]; there was no significant difference in the total number of withdrawals between placebo and exenatide 10 mcg twice daily. Withdrawal rates due to AEs were however higher with exenatide 10 mcg twice a day than with placebo; there were no differences between treatment groups when exenatide was administered at 5 mcg twice daily. Although the

incidence of hypoglycemia was elevated with exenatide used either at 5 or 10 mcg twice a day compared with placebo, statistical significance was only reached with the 10 mcg twice daily dosage (RR 2.44, 95% CI 1.09 to 5.49). Rates of hypoglycemia were similar between insulin and exenatide groups. Nausea and vomiting were the most frequent AEs among exenatide patients; rates of these AEs were significantly higher in the exenatide group than the insulin or placebo groups. Frequency of nausea declined after the first eight weeks of therapy. There was no evidence of cardiovascular, pulmonary, hepatic, or renal AEs across studies. Rates of serious AEs were similar between treatment groups.

Question #3: Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?

In one pooled analysis, exenatide was equally efficacious in reducing A1c in patients over and under 65 years of age, and rates of hypoglycemia were similar between these two age groups. There were no other data on subgroups.

### Sitagliptin

Question #1: For children and adults with DM2 does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control compared with placebo?

When compared with placebo, sitagliptin 100 mg/day monotherapy over 12-24 weeks significantly lowered A1c (pooled effect, between-group change -0.81%) in patients inadequately controlled on diet and exercise. Though formal statistical analyses were not conducted for glipizide or metformin monotherapy compared with sitagliptin monotherapy, it appears that sitagliptin may be comparable to glipizide and metformin in lowering A1c based on estimated magnitude of difference between groups.

Sitagliptin's effects on fasting BG and postprandial BG were moderate compared with placebo whether used as monotherapy [pooled estimates of fasting BG -24.4 mg/dL (-1.3 mmol/l) postprandial BG -54.5 mg/dL (-3.0mmol/l)] or as adjunctive therapy [range of between-group difference for fasting BG -18 to -35 mg/dL (-1.0 to -1.9 mmol/l); postprandial BG -35 to -50 mg/dL (-1.9 to -2.7mmol/l)]. Weight generally decreased for both sitagliptin-treated and placebo-treated patients (range for change in weight from baseline: sitagliptin -0.1 kg to -0.6 kg compared with placebo -0.7 kg to -1.1 kg); however, subjects randomized to sitagliptin lost less weight compared with placebo. The rates for total withdrawal were slightly lower with sitagliptin than compared with placebo (pooled RR 0.69, 95% CI 0.55-0.88) and withdrawal rates due to AEs were not significantly different between the treatment groups.

Question #2: For children and adults with DM2 does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control as monotherapy compared with other hypoglycemic agents or when added as part of combined therapy?

In patients inadequately controlled on metformin, the addition of sitagliptin was as effective as the addition of glipizide or rosiglitazone in lowering A1c at the end of 18 and 52 weeks. Patients receiving glipizide or rosiglitazone gained weight compared with patients on sitagliptin who lost weight during the course of the trial. In patients

inadequately controlled on two oral hypoglycemic agents, the addition of sitagliptin lowered A1c by about 0.6% compared with a 0.3% increase in A1c with placebo plus two oral hypoglycemic agents administered over 24 weeks. In patients inadequately controlled on diet and exercise, initial 24 week treatment with a combination of sitagliptin and metformin lowered A1c by 1.4% to 1.9% compared with a reduction of 0.66% with sitagliptin monotherapy or a reduction ranging from 0.82% to 1.13% with metformin monotherapy. Adjunctive therapy with sitagliptin also did not negatively affect weight, particularly in persons taking metformin; however, small increases in weight were seen when sitagliptin was added to a SU or TZD. The more commonly reported AEs across treatment groups were hypoglycemia, nausea, vomiting, diarrhea, and abdominal pain. Overall, sitagliptin appeared to be well-tolerated.

Question #3: Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?

Seven trials reported no significant differences in A1c based on subgroups defined by age, sex race, and body mass index. However, data on file from one trial showed that Hispanic patients exhibited the largest decline in A1c from baseline (placebo-corrected difference: -1.04%) followed by White patients (placebo-corrected difference: -0.69%). Two trials showed larger reductions in A1c in patients with baseline A1c  $\geq 9\%$  compared in patients with baseline A1c  $< 8\%$ . Four trials did not detect any significant differences in A1c based on baseline A1c. One trial showed that patients with  $\leq 3$  years' duration of diabetes had greater reduction in A1c than patients with  $> 3$  years duration of diabetes.

### **Conclusion:**

For all drugs in this report, no evidence is available on children or on long-term outcomes beyond 52 weeks. For pramlintide, no improvement in A1c for patients with DM1 was found when used in conjunction with *flexible-dosed* insulin compared to placebo, although there was slight improvement when used in conjunction with *fixed-dose* insulin. In this population, the use of pramlintide resulted in a slight decrease in weight, and higher rates of withdrawals and AEs than placebo. For patients with DM2, pramlintide resulted in slight improvement in A1c and slight decrease in weight compared to placebo in patients using either *flexible* or *fixed-dose* insulin. Withdrawal rates were similar, although pramlintide patients experienced more nausea, vomiting and hypoglycemia. For exenatide, improvements in A1c were similar between DM2 patients inadequately controlled on oral hypoglycemic agents taking exenatide and those taking insulin, with both drugs being more effective than placebo. No difference in QOL between the two regimens was found. Frequency of withdrawals varied depending on dose and comparator; patients taking exenatide had more hypoglycemia, nausea and vomiting than those on placebo. For sitagliptin, there was improvement in A1c compared to placebo in both diet controlled DM2 patients and those on two oral diabetes agents. For patients inadequately controlled with metformin, the addition of sitagliptin improved A1c similarly to the addition of glipizide or rosiglitazone. When used as monotherapy or combination therapy, sitagliptin resulted in moderate improvement in both fasting and post-prandial BG compared to placebo; withdrawals due to AEs were not significantly different from placebo.