



# **Newer Drugs for the Treatment of Diabetes Mellitus**

Draft

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Produced by:  
The Health Resources Commission  
Office for Oregon Health Policy & Research  
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## **Health Resources Commission**

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

## ***Overview***

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, a PhD, MPA and a PharmD. All meetings were held in public with appropriate notice

provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, *Newer Drugs for the Treatment of Diabetes Mellitus*, August 2008, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *"Newer Drugs for the Treatment of Diabetes Mellitus"* is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

[www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence\\_based\\_reports.shtml](http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml)

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

### ***Critical Policy***

#### *Senate Bill 819*

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

#### *Health Resources Commission*

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

### ***Clinical Overview***

Diabetes mellitus (diabetes) is a chronic and insidious disease affecting more than 20 million Americans, approximately 7% of the population.<sup>1</sup> Of those diagnosed, 90-95% have type 2 diabetes, while 5-10% have type 1 diabetes. Type 1 diabetes is characterized by autoimmune destruction of beta cells of the pancreas resulting in absolute insulin deficiency. Type 2 diabetes encompasses a heterogeneous group of disorders characterized by slow progressive loss of beta cell function and mass leading to variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Among the counterregulatory hormones, higher glucagon levels relative to insulin also plays a significant role in the pathogenesis and management of type 2 diabetes, making optimal control difficult to maintain.

The 2008 American Diabetes Association treatment guidelines recommend achieving and maintaining an A1c goal of <7% in nonpregnant patients with the caveat that less stringent goals may be appropriate for certain populations, all the while maintaining minimal hypoglycemia in order to prevent micro- and perhaps macrovascular outcomes.<sup>2</sup> Insulin is the treatment for type 1 diabetes. Pharmacologic options for type 2 diabetes have primarily included sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, and insulin. Because of the progressive nature of diabetes, practitioners and patients experience challenges in reaching and sustaining American Diabetes Association goals. In fact, it is estimated that more than 50%

of persons with type 2 diabetes will require more than one oral hypoglycemic agent after 3 years of diagnosis and approximately 70% will require combination oral therapy with or without insulin 6 to 9 years from diagnosis.<sup>3</sup>

Within the last 1 to 2 years, three new antihyperglycemic agents have been approved: pramlintide, exenatide, and sitagliptin (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), glucosedependent insulinotropic peptide (GIP), and dipeptidyl peptidase-4 (DPP-4).

Amylin is a neuroendocrine hormone co-secreted with insulin from beta cells in response to elevated blood glucose concentrations and complements the actions of insulin. GLP-1 and GIP are secreted by L- and K-type cells in the intestinal tract in response to a combination of endocrine and neural signals initiated by the entry of food into the gut. Secretion of GLP-1 and GIP enhance insulin release. Both endogenous GLP-1 and GIP are rapidly degraded by the proteolytic enzyme DPP-4.

### ***Quality of the Evidence***

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC’s ratings of “good, fair or poor” for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding
- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

### ***Weighing the Evidence***

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

## ***Scope and Key Questions***

This literature search for this review included Ovid MEDLINE®, Ovid MEDLINE® IN-Process (1950 to April Week 3, 2008), Cochrane Database of Systematic Reviews®, Cochrane Central Register of Controlled Trials®, and the Database of Abstracts of Reviews of Effects (3rd quarter 2007). In addition, the EPC searched the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technologies in Health, and the National Institute for Health and Clinical Excellence web sites for medical or statistical reviews and technology assessments. Finally, the EPC searched dossiers of published and unpublished studies submitted by pharmaceutical companies.

The purpose of this review was to compare the effectiveness and harms of newer diabetes medications for persons with diabetes mellitus. The key questions for this review were developed with input from experts in the fields of endocrinology and internal medicine. The Oregon Evidence-based Practice Center wrote preliminary key questions. The participating organizations of the Drug Effectiveness Review Project were responsible for ensuring that the scope of the review reflected the populations, drugs, and outcome measures of interest to clinicians and patients in their constituencies. The participating organizations approved the following key questions to guide this review:

### **Pramlintide: Key Questions**

1. For children and adults with type 1 diabetes does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?
2. For children and adults with type 2 diabetes 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?
3. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?

### **Exenatide: Key Questions**

1. For children and adults with type 2 diabetes does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control compared with other hypoglycemic agents as monotherapy or combined therapy?
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?
3. Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?

### **Sitagliptin: Key Questions**

1. For children and adults with type 2 diabetes does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control compared with placebo?
2. For children and adults with type 2 diabetes 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?
3. Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?

**Table 1. Characteristics of included drugs**

Drug Drug class Brand name (Manufacturer) Approval date Country	Dosage How supplied	FDA indications Mono- or combined therapy	Contraindications Precautions Pregnancy category	Dose adjustments Monitoring
<p>Pramlintide Amylinomimetic/amylin agonist Symlin® (Amylin) March 2005 US</p>	<p>DM1: Initiate at 15 mcg subQ before major meals (<math>\geq 30</math> g of carbohydrate) and titrate by 15 mcg every 3 days to 30 or 60 mcg/meal as tolerated. If nausea persists at the 45 or 60 mcg dose, may decrease to 30 mcg. DM2: Initiate at 60 mcg subQ before major meals and increase every 3-7 days to 120 mcg/meal as tolerated. If nausea persists at the 120 mcg dose, may decrease to 60 mcg. Supplied as Symlin Pen™ 60 or 120 prefilled pen, or as a 5 mL vial containing 600 mcg/mL.</p>	<p>Adjunctive therapy in DM1, DM2, adults only, who use prandial insulin and failed desired glucose control despite optimal therapy (+/- SU and/or metformin in DM2). Patients who meet any of the following criteria should NOT be considered: Poor compliance with current insulin regimen and with self-blood glucose monitoring, A1c &gt;9%, recurrent severe hypoglycemia, requires use of drugs that stimulate gastrointestinal motility, pediatric patients</p>	<p><u>Contraindications:</u> Hypersensitivity to pramlintide or its components, confirmed diagnosis of gastroparesis, hypoglycemia unawareness.</p> <p><u>Precautions:</u> Pramlintide should not be mixed with any type of insulin.</p> <p><u>Pregnancy category:</u> C</p>	<p>Decrease rapid or short-acting insulins, including fixed mix insulins (such as 70/30) by 50% to reduce the risk of hypoglycemia. Patients should monitor blood glucose and A1c frequently. Recent blood glucose monitoring data, history of hypoglycemia, current insulin regimen, and body weight should be reviewed prior to use.</p>
<p>Mechanism of action: The exact mechanism of action is unclear but it appears to affect the rate of postprandial glucose appearance by slowing gastric emptying, suppressing glucagon secretion (not normalized by insulin alone), which leads to suppression of endogenous glucose output from the liver, and regulating food intake due to centrally mediated modulation of appetite.</p>				

**Table 1. Characteristics of included drugs (continued)**

<p>Exenatide Incretin mimetic/GLP-1 analog Byetta® (Amylin) April 2005 US</p>	<p>5 mcg BID subQ before a meal, can be increased to 10 mcg BID subQ before a meal after 1 month. Supplied as 5 mcg 1.2 mL prefilled pen and 10 mcg 2.4 mL prefilled pen</p>	<p>DM2, adults only, in patients taking metformin, SU, or TZD with inadequate glycemic control Combined therapy with metformin +/- SU, SU, TZD +/- metformin</p>	<p><u>Contraindications:</u> Hypersensitivity to exenatide or any of its components <u>Precautions:</u> Not a substitute for insulin in insulin- requiring patients, type 1 diabetes, diabetic ketoacidosis, acute pancreatitis, antiexenatide antibodies, end- stage renal disease, severe renal impairment, severe gastrointestinal disease, hypoglycemia <u>Pregnancy</u> <u>category:</u> C</p>	<p>Decrease SU dose to reduce risk of hypoglycemia; monitor hypersensitivity</p>
<p>Mechanism of action: The exact mechanism is unclear but appears to have acute effects on pancreatic beta cell responsiveness to glucose and leads to insulin release only in the presence of elevated glucose concentrations. Exenatide improves fasting and postprandial glycemic control by suppressing elevated glucagon levels from alpha-cells of the pancreas, and delaying gastric emptying time while increasing the sensation of satiety by mimicking the actions of GLP-1 in the gut and through stimulation of GLP-1 receptors located in the central nervous system and vagus nerve.</p>				
<p>Sitagliptin Incretin enhancer/DPP- 4 enzyme inhibitor Januvia® (Merck) October 2006 US, Canada</p>	<p>100 mg once daily with or without food. Available as 100 mg, 50 mg, or 25 mg tablets</p>	<p>Mono- or as add- on therapy in DM2, adults only, inadequately managed on diet and exercise. Combined therapy with metformin +/- SU, SU, TZD</p>	<p><u>Contraindications:</u> Hypersensitivity to sitagliptin or its components <u>Precautions:</u> Dose adjustment is recommended in patients with renal insufficiency and failure <u>Pregnancy</u> <u>category:</u> B</p>	<p>Decrease sitagliptin dose to 50 mg if CrCl 30- 50 mL/min and decrease dose to 25 mg if CrCl &lt;30 mL/min, or on dialysis.  SU dose may need to be decreased if frequent hypoglycemia occurs.</p>
<p>Mechanism of action: Inhibits the degradation of endogenous GLP-1 and glucose-dependent insulinotropic peptide (GIP), thereby prolonging their half-lives and concentrations. It is unclear whether sitagliptin has clinically relevant effects on prolonging gastric emptying time or reducing satiety. It appears that sitagliptin may exhibit a flat dose-response curve at 100 mg/d.</p>				

Abbreviations: AMP, adenosine monophosphate; BID, twice daily; CrCl, creatinine clearance; DM1, type 1 diabetes; DM2, type 2 diabetes; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide-1; SC, subcutaneous; SU, sulfonylureas; TZDs, thiazolidinediones

## **Conclusions:**

### *Limitations of the evidence*

There were no studies that met inclusion criteria for children ( $\leq 18$  years of age) for any of the studied drugs.

## **Pramlintide**

### *Type 1 Diabetes*

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

1. Data are insufficient to determine long term effectiveness of Pramlintide in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy.
2. Pramlintide + insulin treated patients had an increased incidence of nausea, vomiting and anorexia than insulin treated patients.

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

1. There were no subgroup analyses conducted on age, race, gender, or total daily insulin dose.

### *Type 2 Diabetes*

Key Question 2 For children and adults with type 2 diabetes 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?

1. Data are insufficient to determine long term clinical effectiveness of pramlintide in Type 2 Diabetes when added to prandial insulin compared to conventional insulin therapy with or without concurrent oral agents.

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

1. No subgroup analyses were conducted on age, race, gender or total daily insulin usage.

## **Exenatide**

Key Question 1 For children and adults with type 2 diabetes does exenatide differ in efficacy, effectiveness, or harms in achieving glycemic control compared with other hypoglycemic agents as monotherapy or combined therapy?

1. No studies meeting inclusion criteria examined exenatide as monotherapy or combined therapy for long term health outcomes.
2. Nausea and Vomiting were more common in exenatide vs. insulin groups.

Key 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?

1. No studies met inclusion criteria for this question.
2. Nausea and vomiting were more common in exenatide vs. insulin groups.

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

1. No good or fair quality studies met inclusion criteria for this question.

### **Sitagliptin**

Key Question 1 For children and adults with type 2 diabetes does sitagliptin differ in efficacy, effectiveness, or harms in achieving glycemic control compared with placebo?

1. Data are insufficient to determine the long term clinical effectiveness of sitagliptin.
2. No studies provided evidence on benefits or harms for follow-up periods longer than 52 weeks.
3. There was no evidence of increased adverse events for sitagliptin vs. placebo.

Key Question 2 For children and adults with type 2 diabetes 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?

1. Data are insufficient to determine the long term clinical effectiveness of sitagliptin.
2. No studies provided evidence on benefits or harms for follow-up periods longer than 52 weeks.
3. Sitagliptin had lower rates of abdominal pain, nausea, vomiting and diarrhea than metformin.
4. Sitagliptin and metformin as monotherapy as in combination have a lower incidence of hypoglycemia than glipizide.

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

1. There is insufficient data to determine differences in treatment effect for subgroups based on gender, age, race, and BMI.

## **Supporting Evidence**

### **Pramlintide**

*Key Question 1. For children and adults with type 1 diabetes, does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?*

No data on children were reported, although children were eligible for study enrollment in 2 included trials.

No studies evaluated long-term health outcomes or adverse events and none were longer

than 52 weeks in duration.

### Flexible-dose Insulin

In a fair-quality trial the addition of pramlintide 30 mcg or 60 mcg 3 or 4 times a day with meals to a flexible-dose insulin regimen did not significantly improve A1c (-0.5% compared with -0.5%). The comparison group was patients receiving a combination of short- and long-acting insulin plus placebo adjusted to achieve specified glycemic targets over 29 weeks.<sup>13</sup> According to the study investigators, a greater percentage of pramlintide-treated patients who self-monitored blood glucose concentrations achieved post-prandial glucoses below the American Diabetes Association targets for all three meals compared with those on insulin plus placebo (breakfast: 68% compared with 51%; lunch: 71% compared with 61%; dinner: 70% compared with 58%,  $P < 0.0001$  for each meal compared with placebo). Pramlintide-treated patients lost slightly more weight than insulin-only patients (-1.3 kg compared with +1.2 kg).

Pramlintide-treated patients also exhibited slightly larger reductions in total daily insulin doses (-12% of total daily dose from baseline) than patients using insulin plus placebo (+1% of total daily dose from baseline) by the end of 29 weeks. In the initial 4 weeks of treatment however, more pramlintide-treated patients decreased their prandial insulin doses than patients on insulin plus placebo (-28% of prandial insulin compared with -8% of prandial insulin). During the remainder of the trial, patients in both treatment arms required dose increases to their basal insulin regimen (pramlintide, +3% compared with placebo, +10%). Patients were mainly middle-aged and white and had long-standing type 1 diabetes. Mean baseline A1c was 8.1%. A 30%-50% reduction in mealtime insulin was recommended before starting pramlintide to avoid hypoglycemic events.

A patient survey examined whether subjects in this study *believed* that pramlintide added to insulin provided marked benefits compared with placebo plus insulin.<sup>19</sup> A significantly greater proportion of subjects receiving pramlintide believed their study medication provided them with more control over their blood sugar, weight, appetite, and ability to function than compared with those in the insulin plus placebo arm. However, more pramlintide-treated patients believed their study medication “had side effects that would keep me from using it on a long-term basis” relative to those randomized to the placebo plus insulin arm.

### Stable insulin dosing

The addition of pramlintide 60 mcg 3 or 4 times a day with meals to fixed or stable background insulin therapy improved A1c by 0.25% and 0.34% compared with 0.04% improvement in the insulin plus placebo group over 52 weeks of therapy.<sup>15</sup> A greater proportion of pramlintide treated patients achieved the A1c goal of <7% at “any time” and exhibited small decline in total daily insulin doses over the study duration (3-6% decrease in total daily dose of insulin from baseline compared with 0% change). Pramlintide-treated subjects also demonstrated nominal weight loss from baseline (-0.5 kg at 52 weeks,  $P < 0.05$ ), which was not seen with placebo (+0.8 kg at 52 weeks,  $P > 0.05$ ). This trial was rated fair-poor quality because of high withdrawal rates (>35% in all treatment arms This trial began with a 90 mcg dose arm, which was removed from efficacy analysis when another trial (identified as study #137-117 in FDA reviews) revealed an adverse tolerability profile associated with this 90 mcg dose.

Specific reasons for “intolerability” with the 90 mcg dose could not be found in either study #137-117 in the FDA documents or from this trial by Ratner and colleagues. Only general sweeping statements were made by Ratner and colleagues: there was 2-fold increase in nausea, vomiting, anorexia and 4-fold increase in severe hypoglycemia event rates associated with pramlintide across the doses compared with placebo. Study #137-117 could not be found in a peer-reviewed publication.

### Harms

Patients receiving pramlintide in addition to insulin had greater rates of withdrawal due to all causes and withdrawal due to adverse events than patients receiving placebo plus insulin. This was found with both fixed- and flexible-dose insulin. No included trial reported deaths or listed rare adverse events. There were no significant cardiac, hepatic, renal, or drug-related idiosyncratic adverse events observed in any treatment arm.

### *Hypoglycemia*

During the first 4 weeks of treatment severe hypoglycemia occurred more frequently with pramlintide plus insulin than with insulin plus placebo, with both fixed and flexible insulin regimens. The rate of severe hypoglycemia declined once pramlintide doses were stabilized and not being titrated; however, at weeks 26-52 [14, 15](#) and weeks 0-29 [13](#) the rate of severe hypoglycemia associated with pramlintide was still slightly higher than placebo (event rates 0.42 to 1.10 compared with 0.30 to 0.52) (Table 5). Only 1 trial (Edelman 2006) specifically reported in the methods section that a 30-50% reduction in prandial insulin was allowed before the use of pramlintide. Even in this study, pramlintide-treated patients exhibited slightly higher rates of severe hypoglycemia than compared with insulin plus placebo-treated patients. No trials reported the overall incidence of mild to moderate hypoglycemic episodes. All 3 trials predefined the term “severe hypoglycemia” to mean: those requiring either assistance of another person, the administration of glucagon, or the administration of intravenous glucose.

### *Nausea and vomiting*

A significant proportion of pramlintide-treated patients experienced nausea during the trials: Across trials overall rates of nausea for pramlintide groups ranged from 46% to 95%; for placebo groups, 12% to 36%. Specifically, patients who did not tolerate pramlintide 60 mcg also frequently experienced nausea with the 30 mcg dose, and the highest reported rates of nausea (95%) were in subjects who received 30 mcg 3 times a day. [13](#) Higher rates of nausea were reported with pramlintide 90 mcg 3 times a day [15](#) than with lower dosages in the same trial.

Severe nausea was much less common than nausea overall, ranging between 5.8% and 8.5% for pramlintide plus insulin and 0.7% to 1.7% for placebo plus insulin across studies. [13-15](#)

More than 10% of patients randomized to pramlintide plus insulin experienced vomiting, compared with rates of up to 8.0% with placebo plus insulin. Severe vomiting occurred in up to 2% of patients taking pramlintide compared with 0.4% to 0.7% taking placebo. [13-15](#) Of note, 2 of 3 placebo-controlled trials [14, 15](#) reported that most cases of nausea and vomiting tended to occur within 2-4 weeks of treatment but no actual data were provided to verify these statements.

### *Anorexia or reduced appetite*

Rate of anorexia was significantly more frequent with pramlintide plus insulin (11%-18% across trials) than with placebo plus insulin (approximately 2%). Severe anorexia occurred in <2% of pramlintide patients and no placebo patients. [14,15](#)

### *Other adverse events*

One trial reported sinusitis at a rate of 14.0% with pramlintide and 8.8% with placebo ( $P>0.05$ ). [13](#)

### *Key Question 3. Are there subgroups of patients with type 1 diabetes for which pramlintide is more or less suitable than other hypoglycemic agents?*

There was insufficient evidence to perform subgroup analyses based on age, sex, race, ethnicity, or baseline A1c in individual studies.

One randomized controlled trial conducted subgroup analyses that were not all prespecified, and one post hoc pooled-analysis was identified. [15, 22](#) Results from these hypothesis-generating analyses should be used with caution. Further prospective research with larger sample sizes will need to be conducted to verify these findings.

### ***Total daily insulin dose***

No studies conducted subgroup analysis evaluating whether pramlintide exhibited differential effects depending on total daily insulin dose.

### ***Stable insulin dose***

A1c outcomes were reported for a subgroup with stable insulin dosing ( $\pm 10\%$  change in total insulin dose from baseline over 52 weeks). [15](#) Change in A1c was -0.59% with pramlintide 60 mcg 3 times a day and -0.57% with dosing 4 times a day. These reductions were significantly larger than those noted in the entire study group of -0.29 to -0.34%; however, generalizability of using fixed doses of insulin is limited in clinical practice.

### ***Baseline body mass index***

Pramlintide appeared to inhibit weight gain in patients with baseline body mass index  $\leq 23$  kg/m<sup>2</sup> while producing mild weight loss for patients with body mass index  $> 23$  kg/m<sup>2</sup> (baseline to week 26). [15](#) Data at 52-week follow-up were not reported.

### ***Baseline A1c < 8%***

Data from 3 studies that included patients with baseline A1c between 7% and 8.5% receiving pramlintide 30 mcg or 60 mcg were pooled and reported in a separate publication. [22](#) Two of the 3 studies were identified and included in our review. [14, 15](#) The third study was in abstract form and was excluded. The pooled publication reported results up to 26 weeks. In this subgroup, the pooled change in A1c was -0.3% and the change in weight was -1.6 kg (both placebo-corrected; both  $P<0.0009$ ). There was no overall increased risk in hypoglycemia. The improvement in A1c in this pooled subgroup analysis was similar to the change in A1c noted for all subjects (across a range of A1c) in the original studies. Thus, it appears that patients with good but not optimal baseline A1c

of 7%-8.5% experienced similar degrees of A1c reduction as the populations included in the original trials, with no increased risk of hypoglycemia at 26 weeks.

### ***Applicability to general populations with type 1 diabetes***

The methods for recruiting study subjects were not reported in these trials, and subjects likely represent a highly selected population: Primarily white, middle-aged men and women with mean baseline A1c ranging from 8.1% to 9.0% and diabetes of 16 to 21 years duration. None of the patients had significant cardiovascular or renal disease or problems with gastrointestinal motility. Data regarding baseline comorbidities, disease severity, and existing microvascular disease such as retinopathy or neuropathy were not reported. The population included highly motivated subjects who were willing to add 2 to 4 injections to their daily regimen and who rigorously self-monitored blood glucose over the course of the study. Study settings were not reported.

*Key Question 2. For children and adults with type 2 diabetes, does pramlintide differ in efficacy, effectiveness, or harms in achieving glycemic control when added to prandial insulin compared with conventional insulin therapy?*

Children and adolescents  $\leq 18$  years were not included in any of the published studies on effectiveness, efficacy, or harms.

No studies evaluated long-term health outcomes or adverse events and none were longer than 52 weeks in duration.

### ***Dose-ranging study***

The addition of pramlintide to fixed-dose insulin, with or without oral hypoglycemic agents (metformin or sulfonylureas), improved A1c by 0.3% to 0.4% and weight loss by 1.5 to 2.4 kg (placebo-corrected values)<sup>17</sup> in a population with poorly controlled (A1c 9.0-9.3%) type 2 diabetes. No significant differences in A1c were observed between those randomized to pramlintide 75 mcg (-0.5%) or 150 mcg (-0.6%) treatment arms at 52 weeks; the largest reductions in A1c (almost 1%) occurred at week 13. A greater percentage of patients taking pramlintide achieved an A1c goal of  $<7\%$  at “any time” during the study than compared with patients taking placebo. Both placebo and pramlintide-treated patients required increases in their total daily insulin doses during the 52 weeks (change in total daily dose from baseline for pramlintide compared with placebo: pramlintide: +8 to +11% compared with placebo: +15%, *P*-value, not reported). This trial was rated fair-poor quality based on a high withdrawal rate (~30%) which were similar for placebo, pramlintide 30 mcg and 75 mcg groups. Those randomized to pramlintide 150 mcg dose exhibited largest rates of total withdrawal and withdrawal due to adverse events (37.5% and 18%).

### ***Stable insulin dosing***

During the course of this one fair-quality trial,<sup>16</sup> results from another study (identified as study #137-123 in the FDA reviews) found that pramlintide 60 mcg was less effective than compared with higher doses. As a result, efficacy and safety information from the 60 mcg arm were excluded from this trial, though safety results should have been reported. The addition of pramlintide 90 mcg or 120 mcg to fixed or stable doses of insulin with or

without oral hypoglycemic agents (metformin or sulfonylureas) gave slightly larger improvements in A1c and weight at 52 weeks than patients randomized to placebo plus fixed dose insulin (placebo-corrected values for A1c: 90 mcg: -0.13%, 120 mcg: -0.4% and for weight: 90 mcg: -1.1 kg; 120 mcg: -1.85 kg).<sup>16</sup> Effect on A1c was greatest at 26 weeks for both pramlintide groups ( $P<0.05$  compared with placebo) and persisted only with the 120 mcg arm at 52 weeks (change in A1c from baseline -0.62%,  $P<0.05$ ). No dose adjustments of baseline insulin or oral hyperglycemic agents were implemented during the study and no specific glycemic targets were reported. Approximately 20-27% of all randomized patients were taking oral hypoglycemic agents at baseline.

### ***Flexible basal insulin dosing***

In contrast to the previous study, this short-term fair-quality trial <sup>18</sup> evaluated pramlintide as a pre-meal medication in conjunction with glargine (without prandial insulin) with or without oral hypoglycemic agents (metformin, sulfonylureas, and/or thiazolidinediones). The comparison group was patients on flexible-dose glargine plus placebo. At 16 weeks, the addition of pramlintide to glargine reduced A1c by 0.36% and induced weight loss of 2.3 kg (placebo-corrected values) relative to placebo plus glargine. Pramlintide-treated patients also exhibited larger reductions in post-prandial glucose (change from baseline: -24.4 mg/dL  $\pm$  3.6 mg/dL compared with -0.4 mg/dL  $\pm$  3.0 mg/dL,  $P<0.0001$ ). There were no significant differences between pramlintide-treated and placebo-treated groups for those achieving A1c  $<7\%$  (54% compared with 45%) and no significant differences in changes in total daily insulin dose (change from baseline: +11.7 units compared with +13.1 units) following 16 weeks of treatment. Glargine, a basal insulin without pronounced peak effects, was allowed to be adjusted during the study to achieve prespecified fasting glucose targets once pramlintide doses were stabilized. Patients had diabetes of 10 to 11 years' duration. At baseline A1c was moderately elevated at 8.5%, and patients were using insulin glargine 48 to 54 units per day, with 50% of patients concomitantly taking  $\geq 2$  oral hypoglycemic agents and 89% taking at least 1 oral agent.

### ***Harms***

Pramlintide-plus-insulin and placebo-plus-insulin groups had similar rates of withdrawal due to all causes and withdrawal due to adverse events. There was no evidence of cardiac, hepatic, renal, or drug-related idiosyncratic adverse events in patients in any treatment arm of the three randomized controlled trials identified for this review and no deaths were reported.

### ***Hypoglycemia***

Pramlintide-plus-insulin and placebo-plus-insulin groups experienced similar rates of mild-to moderate hypoglycemia,<sup>17, 18</sup> but pramlintide-treated patients experienced more episodes of severe hypoglycemia. Severe hypoglycemia occurred most with pramlintide 120 mcg during the first 4 weeks of therapy (0.9 events/patient-year compared with 0.3 events/patient-year with placebo).<sup>16</sup> The incidence of severe symptoms declined with continued use of pramlintide, and rates were similar to placebo for weeks 4-26 and 26-52.<sup>16</sup> All 3 trials predefined the term "severe hypoglycemia" to mean: those requiring

either assistance of another person, the administration of glucagon, or the administration of intravenous glucose.

#### *Nausea*

The incidence of mild-to-moderate and severe nausea was significantly higher with pramlintide 75, 90, 120, and 150 mcg than with placebo plus insulin. Only 1 trial reported actual results showing that most events occurred within the first 4 weeks of treatment.<sup>16</sup> When metformin use was stratified in one trial, its addition to pramlintide plus insulin appeared to have no significant effect on nausea compared with the larger study population.<sup>16</sup> These trials did not report vomiting or anorexia.

#### *Headache*

Higher rates of headache were reported with pramlintide (15% and 17%) than with placebo (8%).<sup>16</sup> In another trial<sup>17</sup> rate of headache was similar among treatment groups, ranging from 13.2% in the placebo-plus-insulin group to 19.1% with pramlintide 75 mcg 3 times a day plus insulin. None of the studies provided enough information to determine whether there were any correlations between the incidence of headaches and hypoglycemic events.

#### *Other adverse events*

No trials reported any treatment-emergent adverse events occurring with a frequency of more than 2%-5%. Overall adverse events occurring with a frequency of  $\geq 10\%$  with a minimum 5 percentage point difference between pramlintide- and placebo-treated patients comprised sinusitis, retinal disorder, inflicted injury, and injection site reactions.<sup>16, 17</sup>

Higher incidence of retinal disorder was reported with pramlintide 150 mcg than with lower pramlintide doses and placebo.<sup>17</sup> The authors performed detailed medical reviews of these patients with reported retinal disorder and concluded that the increased incidence was likely attributable to preexisting conditions that were not documented at the time of screening.

*Key Question 3. Are there subgroups of patients with type 2 diabetes for which pramlintide is more or less suitable than other hypoglycemic agents?*

#### ***Age, sex, total daily insulin dose, and prior use of oral hypoglycemic agents***

None of the randomized controlled trials conducted subgroup analyses evaluating whether pramlintide had differential effects in these populations.

#### ***Race and ethnicity***

A post hoc analysis<sup>23</sup> of two 52-week trials<sup>16, 17</sup> pooled subjects of various ethnic groups. Black and Hispanic patients tended to have higher baseline A1c (9.2%-9.7%) than white patients (8.9%-9.1%). Pramlintide produced larger reductions in A1c and weight from baseline in black patients (0.7%, 4.1 kg) than white patients (0.5%, 2.4 kg) and Hispanic patients (0.3%, 2.3 kg). Changes in total daily insulin requirement and baseline oral hyperglycemic use were not different among the different races and ethnicities.

### ***Nausea and weight loss and effects of weight on A1c***

Weight loss experienced with pramlintide 90 or 120 mcg appeared to be independent of nausea, as weight loss was similar in patients never experiencing nausea (90 or 150 mcg, -1.1 to -1.5 kg) and patients experiencing nausea at anytime (90 or 150 mcg, -0.3 to -2.0 kg).<sup>16</sup> In addition, improvements in A1c observed with pramlintide appeared to be independent of weight lost or gained during the trial (subjects who gained weight, change in A1c -0.29% to -0.53%; subjects who lost weight, change in A1c -0.22% to -0.58%). A pooled analysis<sup>24</sup> of overweight and obese patients also evaluated whether weight loss associated with pramlintide 120 mcg was influenced by nausea. Like the other, this post hoc subgroup analysis suggested that weight loss was independent of nausea (change in weight in group reporting “never nausea,” -1.3 kg; “nausea at anytime,” -1.9 kg). None of the studies explored to see if there were any correlations between anorexia and weight loss.

### ***Overweight and obese patients***

A post hoc analysis<sup>24</sup> pooled data from two randomized controlled trials comparing pramlintide 120 mcg with placebo when both were added to insulin. At 26-week follow-up overweight and obese (body mass index > 25 kg/m<sup>2</sup>) patients receiving pramlintide showed greater reductions in A1c and weight than similar patients receiving placebo. Approximately 2% of overweight and obese patients on pramlintide plus insulin achieved weight loss of ≥10% change from baseline compared with 0% in those on placebo plus insulin. Markedly obese patients (baseline body mass index 35-40 kg/m<sup>2</sup> and >40 kg/m<sup>2</sup>) had the greatest weight loss (-2.4 kg and -3.2 kg, respectively).

### ***Baseline A1c***

When patients were stratified by baseline A1c,<sup>18</sup> at 16 weeks patients with baseline A1c > 8.5% who received pramlintide plus insulin glargine showed larger improvements in A1c, fasting plasma glucose, and postprandial glucose than patients receiving placebo plus glargine (pramlintide change in A1c -1.19%, fasting plasma glucose -44.4 mg/dL, postprandial glucose -23 mg/dL, and weight -1.0 kg compared with placebo plus glargine A1c -0.69%, fasting plasma glucose -18.4 mg/dL, postprandial glucose +3.2 mg/dL, weight +1.1 kg). Among subjects with lower baseline A1c (≤ 8.5%), improvements in A1c and weight were also larger in pramlintidetreated patients than those who took placebo plus glargine.

Another post hoc analysis<sup>25</sup> pooled data from two trials at 26-week follow-up and examined patients with baseline A1c of 7.0% to 8.5%. Pramlintide plus insulin was better than placebo plus insulin for A1c (placebo-corrected change in A1c -0.43,  $P<0.0009$ ) and weight (placebo-corrected change in weight -2.0 kg,  $P<0.0003$ ).

### ***Applicability to general populations with type 2 diabetes***

No included trial evaluated the effects of pramlintide in patients whose type 2 diabetes was inadequately managed on combination prandial and basal insulin therapy with or without oral agents. Two studies evaluated pramlintide in patients using fixed-dose insulin. One trial used flexible dosing for insulin glargine only. Hence, results have

limited applicability to the broader population using more commonly prescribed insulin regimens.

FDA-approved dosage of pramlintide for type 2 diabetes includes initial therapy of 60 mcg/meal and maintenance therapy of 120 mcg/meal. Only 2 trials examined the 120 mcg dosage.<sup>16, 18</sup> The third included trial was a dose-ranging study that did not use a 120 mcg dose but did include a 75 mcg dose which may be used in clinical practice.<sup>17</sup> Overall, patients included in these 3 trials represent a highly selected population: mainly white, middle-aged men and women with mean baseline A1c between 8.5% and 9.3% and diabetes of 11-13 years' duration. None of the patients had significant pulmonary, cardiovascular, renal, neurologic, or hematologic diseases or problems with gastrointestinal motility. The study populations probably included highly motivated subjects who desired to achieve optimal glycemic control through the additional 2-4 injections added to their usual regimens of insulin and oral hypoglycemic agent over 16-52 weeks of participation in a trial. Study setting also was not reported in any of the included trials.

### Exenatide

No studies that met our inclusion criteria compared exenatide to oral diabetes agents used as either monotherapy or combined therapy in adults. We found no studies of exenatide in children.

*Key Question 1 and 2. For children and adults with type 2 diabetes, does exenatide differ in efficacy, effectiveness, and in harms for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy? Or when added to other hypoglycemic agents compared to conventional insulin therapy?*

### Systematic Reviews

Two systematic reviews of exenatide met our inclusion criteria.<sup>41,42</sup> Amori and colleagues<sup>41</sup> published a high-quality review of published and unpublished English-language studies of FDA-approved and unapproved DPP-4 inhibitors (sitagliptin and vildagliptin) and GLP-1 analogs including exenatide. These reviewers derived the following pooled estimates of change from baseline for exenatide compared with placebo (both groups combined with various oral diabetes agents): A1c -1.01% (95% CI -1.18% to -0.84%), fasting plasma glucose -27 mg/dL (95% CI -34 to -20 mg/dL), and weight -1.44 kg (95% CI -2.13 to -0.75 kg).

When exenatide was compared with various insulin regimens, the following pooled estimates of change from baseline for exenatide compared with insulin were noted: A1c -0.06% (95% CI -0.22% to 0.10%), fasting blood glucose 13 mg/dL (95% CI -16 to 41 mg/dL), and weight -4.8 kg (95% CI -6.0 to -3.5 kg). Weight loss was dose-dependent and progressive, with no apparent plateau by week 30. Severe hypoglycemia was rare (5/2781 patients who used exenatide) and occurred only when combined with sulfonylurea use. The risk ratio for mild to moderate hypoglycemia with exenatide compared with placebo was 2.3 (95% CI 1.1 to 4.9). Dose-dependent nausea and vomiting were the most frequently reported adverse events with exenatide (risk ratio

nausea compared with any other treatment 2.9 (95% CI 2.0 to 4.2). Withdrawal rates due to gastrointestinal effects were higher with exenatide (4%) than with placebo. The second review<sup>42</sup> was poor quality and so was not included in our review.

### Active-control trials

Four open label studies compared exenatide 10 mcg twice a day to insulin therapy (various regimens). All studies used concurrent sulfonylurea and/or metformin in addition to the study treatment regimes. Three of these trials were fair-quality noninferiority studies,<sup>27, 28, 30</sup> and one was a fair-to-poor-quality exploratory substitution study.<sup>26</sup>

### Efficacy and effectiveness

Heine and colleagues<sup>27</sup> compared once-daily glargine to exenatide twice daily over 26 weeks of follow-up in a noninferiority study, with both groups receiving metformin and a sulfonylurea. Reductions in A1c were 1.11% in both groups (between-group difference 0.017%, 95% CI -0.123 to 0.157%). Fasting plasma glucose decreased in both treatment groups, with a greater reduction with insulin glargine (change in the insulin glargine group - 51.5 md/dL and in the exenatide group -25.7 md/dL; between-group  $P < 0.001$ ). Weight increased in the insulin glargine group throughout the trial, with progressive reduction in the exenatide group (weight change -2.3 kg with exenatide, +1.8 kg with insulin glargine; between-group difference -4.1 kg, 95% CI -4.6 to -3.5 kg).

Quality of life was assessed in this trial.<sup>27, 29</sup> A per protocol analysis of 455 of 549 original trial patients revealed no significant differences between the two treatments for measures of symptoms, quality of life, vitality, and treatment satisfaction despite an additional injection daily and gastrointestinal adverse events with exenatide.

Another noninferiority study<sup>30</sup> also compared exenatide 10mcg twice daily to insulin glargine, with both groups continuing pre-study single oral agents. Change in A1c at 16 weeks was identical in the two treatment arms (-1.36%, SE 0.09%, within group  $P < 0.001$ ). Both exenatide and insulin glargine reduced A1c by a similar amount in patients with baseline A1c  $\geq 9\%$  (approximate change -1.8%) and  $< 9\%$  (change -0.9%).<sup>30</sup>

A third non-inferiority study<sup>28</sup> compared exenatide twice daily with biphasic insulin aspart in patients poorly controlled on sulfonylurea and metformin. The change in A1c was similar between groups (change with exenatide -1.04%, change with insulin aspart -0.89%; between group difference -0.15%, 95% CI -0.32 to 0.01%). Exenatide patients lost weight while insulin-treated patients gained weight (between-group difference -5.4 kg, 95% CI -5.9 to -5.0 kg). Fasting serum glucose decreased in both groups (insulin aspart -1.7 mmol/L; exenatide -1.8 mmol/L).

The fourth active-control trial<sup>26</sup> examined persons with type 2 diabetes who were already using insulin and sulfonylurea and/or metformin. In this small (N=51), exploratory RCT, exenatide 5 and then 10 mcg twice daily was substituted for insulin, while oral agents were continued. Specific glycemic goals were not set. A1c did not change significantly in either group ( $P > 0.05$ ) and there was no significant between-group difference in A1c at 12-week follow-up. Exenatide patients noted a decrease in weight (mean weight change -4.2 kg, SD 3.0 kg,  $P < 0.001$ ), in contrast to the insulin group (mean weight change +0.5 kg, SD 1.7,  $P < 0.001$ ). This study was rated fair-poor quality because of its high and

differential withdrawal rate and lack of reporting methods for randomization and allocation.

#### Adverse effects

Total withdrawals in the exenatide group ranged from 12.0% to 21.3% and in the comparison group from 0% to 10.1% in the four active-controlled trials. [26-28, 30](#) Withdrawals due to adverse events for the exenatide group ranged from 8% to 15% and were less than 1% in the comparison groups. Nausea and vomiting were the most frequent adverse events among exenatide-treated subjects, and rates of these symptoms were significantly higher in the exenatide group than in groups using insulin glargine [27, 30](#) or other insulin routines, [26, 28](#) with rates of nausea ranging from 33% to 57% in the exenatide groups compared with <1 to 9% with the comparison group receiving insulin. Overall hypoglycemia rates were similar between groups treated with insulin and with exenatide. [27, 28, 30](#) Hypoglycemia was particularly common when exenatide (39%) or insulin (38%) was combined with sulfonylurea and/or metformin; [26](#) 79% of hypoglycemia cases were associated with sulfonylurea. In a study comparing exenatide and titrated insulin glargine, [30](#) the overall rate of hypoglycemia with exenatide (14.7%) was not statistically different than that with insulin glargine (25.2%). In subgroup analysis of this study, however, the rate of hypoglycemia in patients who received metformin and exenatide was 2.6% as compared with 17.4% in those receiving insulin glargine ( $P=0.010$ ), whereas the rates of hypoglycemia in patients taking sulfonylureas was similar with exenatide (30.0%) and insulin glargine (34.5%).

#### *Placebo-controlled trials*

We identified 4 large, multicenter, fair-quality placebo-controlled trials [31-34](#) of exenatide as combination therapy. Overall, study subjects were fairly homogeneous. Subjects were similar in age (mean 53 to 57 years) and sex (52 to 60% male) with some variation in race and ethnicity. Mean baseline A1c ranged from 7.9% to 8.6% and mean duration of diabetes from 4.9 to 9.4 years.

#### Efficacy and effectiveness

Three very similar studies with overlapping authors compared exenatide to placebo, with both treatment groups taking oral hypoglycemic agents. [31-33](#) Kendall and colleagues [33](#) randomized patients to exenatide 5 mcg or 10 mcg or placebo twice daily over 30 weeks. Patients continued their pre-study metformin and a sulfonylurea. A1c decreased in the exenatide arms and steadily increased with placebo (placebo-adjusted change in A1c for exenatide 5 mcg, -0.8%; 10 mcg, -1.0%;  $P<0.001$  for both treatment groups versus placebo). Weight decreased progressively in both exenatide arms, more so than in the placebo arm (weight change -1.6 kg, SE 0.2 kg in both exenatide groups; -0.9 kg, SE 0.2 kg with placebo).

In a similarly designed study Buse and colleagues [31](#) compared exenatide to placebo in patients taking a sulfonylurea. A1c improved in both treatment groups (A1c change with exenatide 5 mcg, -0.46%; 10 mcg, -0.86%) while increasing slightly in the placebo group (between-group  $P\leq 0.0002$ ). Weight decreased more in the exenatide groups (weight change -1.6 kg, SE 0.3) than in the placebo group (weight change -0.6 kg, SE 0.3 kg). DeFronzo and colleagues [32](#) performed a similar study except that all subjects were taking

metformin. The researchers noted very similar improvements in A1c with exenatide 10 mcg (A1c change -0.78%, SE 0.1%) compared with placebo (A1c change 0.08%, SE 0.10%) and also a similar decrease in weight with exenatide.

In a fourth placebo-controlled trial, subjects who were inadequately controlled with a thiazolidinedione (with or without metformin), were randomized to exenatide 10 mcg twice daily or placebo.<sup>34</sup> Exenatide improved A1c (mean between-group difference -0.98, 95% CI -1.21 to -0.74%) and fasting glucose (mean between-group difference -30.5 mg/dL, 95% CI -40.0 to -21.1 md/dL). Exenatide reduced weight but placebo did not (between-group difference -1.51 kg, 95% CI -2.15 to -0.88).

In several placebo-controlled trials of exenatide combined with oral agents, patients with a baseline A1c more than 9.0% achieved greater reductions in A1c than subjects with baseline less than 9.0%.<sup>31, 33, 36</sup> Weight reductions were greater in persons who had higher body mass index at baseline.<sup>35, 38</sup>

These studies were sufficiently homogeneous to obtain pooled estimates of effect. When compared with placebo, exenatide 5 mcg twice daily produced a significant decrease in A1c (pooled effect -0.59, 95% CI -0.79 to -0.40,  $P < 0.00001$ ).<sup>31-33</sup> A larger improvement in A1c was noted with exenatide 10 mcg twice daily (pooled effect versus placebo -0.97, 95% CI -1.16 to -0.79,  $P < 0.00001$ ).<sup>31-33</sup> Significant improvements were also noted in fasting plasma glucose with exenatide 10 mcg twice daily compared with placebo (pooled effect -1.50 mmol/L, 95% CI -1.85 to -1.15,  $P < 0.00001$ ).<sup>31-33</sup>

When compared with placebo, exenatide produced a significant decrease in weight (pooled effect exenatide 5 mcg twice daily, -0.51 kg, 95% CI -0.89 to -0.13,  $P = 0.009$ ; exenatide 10 mcg twice daily, -1.25 kg, 95% CI -1.90 to -0.61,  $P = 0.0001$ ).<sup>31-34</sup>

Statistical tests for heterogeneity were not significant ( $P > 0.05$ ) for all glycemic control and weight outcomes.

#### *Adverse effects*

Based on pooled estimates across the four placebo-controlled trials, total withdrawals were less with exenatide 5 mcg twice daily than with placebo (relative risk 0.67, 95% CI 0.53 to 0.85); there was no significant difference between placebo and exenatide 10 mcg twice daily.

Withdrawals due to adverse effects were greater with exenatide 10 mcg twice daily than with placebo, however, with no significant difference between exenatide 5 mcg twice daily and placebo. There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups. One study reported one subject who withdrew from the exenatide group because of chest pain and a second subject because of an injection site reaction.<sup>34</sup> Two additional treatment-group patients in this study had serious adverse events (chest pain and allergic alveolitis) which did not necessitate study withdrawal.

Nausea, vomiting, and diarrhea were significantly more frequent with treatment at both dosages than in the placebo group. Nausea declined after 8 weeks of treatment, although the statistical significance of the trend was not reported.<sup>31-34</sup> There was no correlation between change in body weight and duration<sup>32, 33</sup> or severity<sup>35</sup> of nausea. When the incidence of nausea remained stable, body weight continued to decrease.<sup>39</sup>

Hypoglycemia and nausea were much more common in the exenatide groups in a study by Buse and colleagues (no episodes of severe hypoglycemia [requiring third party

assistance] were noted),<sup>31</sup> where all subjects received a sulfonylurea, than in the other three placebo-controlled studies. Rates were particularly high with 10 mcg twice daily dosing. These high rates lead to heterogeneity of the data across studies. Excluding this study from the pooled effect still produced statistically a significant increase in hypoglycemia (RR 1.88, 95% CI 1.29 to 2.75) and nausea (RR 2.28, 95% CI 1.86 to 2.80), but with statistically homogeneous data (chi-square for heterogeneity  $P < 0.05$ ). High rates of hypoglycemia were also noted in a placebo-controlled trial where all subjects received metformin plus a sulfonylurea.<sup>33</sup> The risk of hypoglycemia was not increased compared with placebo when all subjects received a thiazolidinedione<sup>34</sup> or metformin.<sup>32</sup>

None of these studies included in this report noted cases of acute pancreatitis, however, from the date of the drug's approval through December 2006, the FDA received 30 domestic reports of acute pancreatitis in patients who received exenatide.<sup>44</sup> Median age of patients was 60 years and daily doses ranged from 10-20 mcg. The median time to onset of the symptoms was 34 days (range 4 to 300 days). Median amylase value was 384 IU/L and median lipase value 545 IU/L. Seventy percent of patients required hospitalization. A majority of affected patients (90%) had other risk factors for pancreatitis, including alcohol use or hypertriglyceridemia.

### ***Cohort studies***

We examined adverse events in cohort studies of exenatide. All of the open label extension studies assessed exenatide 10 mcg twice daily. In these studies, investigators included only subjects who had previously completed a prior study and several studies<sup>35, 38, 39</sup> excluded patients who had received placebo.

An open-label extension study of three of the placebo-controlled primary trials<sup>31-33</sup> included in this report was published in multiple publications with overlapping or identical populations.<sup>35, 36, 38, 39, 45</sup> These publications represented a pooled synthesis of patients continuing in an open-label extension beyond the original 30-week trial comparing exenatide 5 mcg or 10 mcg twice daily to placebo. Subjects from both the placebo and treatment groups were invited to continue on 10 mcg twice daily along with their existing metformin and/or sulfonylurea regimens for a 2-year<sup>36</sup> and then 3-year<sup>45</sup> period. Mild-to-moderate nausea was the most frequently reported adverse event, and 3% of subjects withdrew over the extension period (30 weeks to 2 years) because of nausea. Eight percent of subjects continued to complain of nausea after 2-years of follow-up. Hypoglycemia (of any severity) occurred at a rate of 1 case in 1010 person-years of exenatide treatment. There were no cardiovascular, pulmonary, hepatic, or renal effects attributed to treatment.

Adverse events in subjects completing 3-year follow-up of the open label extension of these three placebo-controlled trials<sup>45</sup> included mild-to-moderate nausea (59%) (5% of subjects withdrew due to nausea over the 3 years), and hypoglycemia (40%) with 2 of 527 subjects withdrawing because of hypoglycemia. Weight progressively decreased over the follow-up period (change from baseline -5.3kg, SE 0.4). A1c reductions seen at 12 weeks were sustained at 3 years (A1c change -1.0%, SE 0.1%). This study population was a select group: only approximately half (46%) of subjects originally enrolled in the

three primary trials enrolled in the open-label extension. Of subjects enrolled, only 54% completed the 2-year follow-up and 41% the 3-year follow-up.

An unrelated open-label, extension study<sup>37</sup> (“Study B”) of a 28-day trial reported that nausea and vomiting were the most common adverse effects with exenatide 10 mcg twice daily for 26 weeks, but incidence rates were not reported. Approximately ¾ of subjects also received metformin; the other ¼ received diet and exercise only.

A retrospective chart review<sup>40</sup> of 200 patients who had used exenatide noted that 13% discontinued treatment due to side effects, including nausea (8%), urticaria (2%), and hypoglycemia (0.5%).

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

Only one publication examined subgroups based on demographic characteristics. A pooled analysis<sup>36</sup> of three placebo-controlled trials reported that reductions in A1c were not related to age and that hypoglycemia was not more frequent in subjects  $\geq 65$  years of age. No primary study examined the efficacy or effectiveness of exenatide in subgroups defined by age or other characteristics.

#### Applicability of efficacy, effectiveness, and safety data to general diabetes populations

The studies identified for this review are rather homogeneous, relatively small, and may be rather selected, thus applicability to broader diabetes populations may be limited. Study subjects were homogeneous across studies for age, sex, and baseline A1c in both the placebo and active-controlled trials. Significant comorbidities were excluded in the three placebo-controlled studies reporting that characteristic<sup>31-33</sup> and comorbidities were not mentioned in three of the four active-controlled trials.<sup>26, 28, 30</sup>

The number of potential study subjects who did not tolerate twice daily injections and who were therefore not included in the study was usually not reported. Open label extension studies were of highly selected populations who completed the primary study and who volunteered to continue (or start if on placebo) exenatide.

#### **Sitagliptin**

Children and adolescents  $\leq 18$  years were not included in any of the published studies on effectiveness, efficacy, or harms.

No studies provided data on benefits or harms for follow-up periods longer than 52 weeks.

#### **Systematic Reviews**

Amori and colleagues<sup>41</sup> published a high-quality systematic review of FDA approved and unapproved GLP-1 analogues (exenatide, linaclotide) and DPP-4 inhibitors (sitagliptin [8 studies] and vildagliptin [12 studies]). Sitagliptin and vildagliptin (examined together) lowered A1c, fasting plasma glucose, and postprandial glucose when used as either monotherapy or add-on therapy compared with placebo, with or without additional oral hypoglycemic agents. When sitagliptin and vildagliptin were compared with other active oral hypoglycemic agents, the DPP-4 inhibitors were slightly less effective in reducing A1c (pooled weighted mean difference in A1c: 0.21%, 95% CI 0.02

to 0.39; I<sup>2</sup>= 66%). The results were pooled from 4 trials, 3 of which evaluated vildagliptin and included patients with baseline A1c of 8.7%. Sensitivity analyses regarding baseline A1c or other areas of potential heterogeneity were not reported. Small increases in weight were also observed with sitagliptin when compared with placebo. When compared with glipizide or pioglitazone, sitagliptin had a more favorable weight profile. Metformin was the only comparator medication that exhibited weight loss. Both DPP-4 inhibitors were generally well tolerated; severe hypoglycemia was reported in only two patients receiving DPP-4 inhibitors across the included studies. No differences in risk of mild-to moderate hypoglycemia or gastrointestinal adverse events were reported when sitagliptin and vildagliptin were compared to placebo. Results for sitagliptin and vildagliptin were not examined individually; vildagliptin is also not yet approved in the United States.

### ***Sitagliptin monotherapy***

#### *Sitagliptin compared with placebo*

Five fair-quality trials ranging from 12-24 weeks in duration compared sitagliptin 100 mg/d to placebo.<sup>46, 47, 52, 53, 55</sup> Patients randomized to receive sitagliptin 100 mg/d showed significant reductions in A1c (placebo-corrected change 0.81%, 95% CI -0.94% to -0.67%) and fasting plasma glucose (placebo-corrected change 24.4 mg/dL, 95% CI -29.5 to -19.3 mg/dL), while placebo-treated patients generally showed worsening glycemic control.

For patients who volunteered to participate in a meal-tolerance test, sitagliptin lowered postprandial glucose relative to placebo (placebo-corrected change 54.5 mg/dL, 95% CI -65.5 to -43.5 mg/dL). A greater proportion of patients receiving sitagliptin than placebo reached the A1c goal of <7%, although 9%-21% of subjects on sitagliptin required the use of a second medication.

Weight generally decreased in both treatment arms (range for change from baseline: sitagliptin -0.1 to -0.6 kg compared with placebo -0.7 to -1.1 kg). Overall, however, subjects randomized to sitagliptin lost slightly less weight than subjects randomized to placebo (weighted mean difference: 0.62, 95% CI 0.36-0.89).

Mean baseline A1c was 7.6%-8.9% and mean duration of diabetes was 4-5 years.

#### *Sitagliptin compared with an active agent*

In 2 fair-quality trials that evaluated sitagliptin 100 mg/d, active treatment arms of glipizide 5-20 mg/d or metformin 1000-2000 mg/d were included in the studies.<sup>52, 53</sup> Although statistical analyses were not reported for these comparisons, based on qualitative analysis of the magnitude of difference between groups, it appears that sitagliptin may be comparable to these oral hypoglycemic agents in lowering A1c, fasting plasma glucose, and postprandial glucose (with the possible exception of metformin 2g/d). Additional trials are needed to verify the findings and the results should be considered with caution.

In one trial, patients randomized to glipizide gained approximately 1 kg from baseline compared with a slight increase in weight from baseline (0.4 kg) for those on sitagliptin.<sup>52</sup> In another trial<sup>53</sup> patients on metformin observed slightly larger reductions

in weight by about 1 kg from baseline than no change in weight experienced by those receiving sitagliptin.

### ***Sitagliptin as Add-on therapy***

#### *Sitagliptin or placebo added to one oral hypoglycemic agent*

Three fair-quality randomized controlled trials<sup>49, 56, 57</sup> assessed the effects of sitagliptin added to background therapy of “failed” treatment with metformin, pioglitazone, or glimepiride. Mean baseline A1c ranged from 8.0% to 8.4% with 6.1-8.0 years’ duration of diabetes. Approximately 60% of patients were on more than 1 oral hypoglycemic agent, while 30% were on more than 2 oral agents. Patients were considered to have “failed” therapy with metformin, pioglitazone, or glimepiride at screening or after 10-19 weeks of dose stabilization and if A1c was between 7-10% or 7.5-10.5%. Patients also entered 2-week single-blind, placebo run-in periods prior to randomization.

The addition of sitagliptin to metformin, pioglitazone, or glimepiride appears to show larger reductions in A1c and fasting plasma glucose compared with the addition of placebo over 24 weeks. A larger proportion of sitagliptin-treated patients also achieved the A1c goal of <7% than placebo-treated patients (approximately 11%-47.0% compared with 9%-23.0%). Subjects who received placebo and glimepiride showed worsening glycemic control, while placebo-treated subjects on metformin or pioglitazone had slight improvements or no change in A1c from baseline. Weight gain generally was seen in patients taking pioglitazone or glimepiride, with or without the addition of sitagliptin. Patients randomized to metformin lost weight by 0.6 kg to 0.7 kg ( $P<0.017$  and  $P<0.0001$  compared with baseline).

One fair quality randomized trial<sup>51</sup> studied the effects of sitagliptin or placebo added to ongoing metformin therapy. Unlike the other studies, this trial evaluated the effects of sitagliptin in patients with worse glycemic control (baseline A1c between 8-11%). These patients were on metformin and diet and exercise for 6 weeks, had baseline A1c between 8-11%, and had  $\geq 85\%$  adherence to their regimens during a 2-week, placebo run-in period. No patients were naïve to oral hypoglycemic agents and approximately 50% were already taking metformin monotherapy or combination oral therapy at baseline. The addition of sitagliptin to ongoing metformin therapy was more effective than placebo plus metformin at lowering A1c (placebo-corrected difference: -1.0%, 95% CI -1.4 to -0.6%) and fasting plasma glucose (placebo-corrected difference: -25.2 mg/dL, 95% CI -37.8 to -12.6 mg/dL) over 30 weeks. Further evaluation of the data showed that the largest magnitude of A1c lowering was present in patients with the highest baseline A1c between 10-11%. Postprandial glucose levels at 18 weeks were also lower with sitagliptin plus metformin than placebo plus metformin (placebo-corrected difference: -54 mg/dL, 95% CI -75.6 to -34.2 mg/dL) measurements at 30 weeks however, were not determined by the investigators. Overall, a significantly larger proportion of sitagliptin-treated patients achieved A1c <7% than placebo treated patients ( $P<0.001$ ) and also needed less rescue therapy over the study duration ( $P<0.001$ ). Both treatment groups exhibited weight loss of -0.5 kg over 30 weeks.

#### *Sitagliptin or glipizide added to metformin*

One fair-to-poor-quality trial compared the effects of adding either sitagliptin 100 mg/d or glipizide 5-20 mg/d in patients with inadequate glycemic control on metformin.<sup>54</sup> Glycemic control was considered inadequate if the metformin dose was  $\geq 1500$  mg/d with baseline A1c 6.5-10% at initial screening or after several weeks of stabilizing the metformin dose prior to a 2-week single-blind, placebo run-in period before randomization. Over 52 weeks the 2 study groups showed no significant differences in treatment effects for A1c, fasting plasma glucose, or proportion of patients achieving A1c  $<7\%$  from one another. The only significant difference between treatment groups was in the change in weight. Sitagliptin-treated subjects experienced slightly more weight loss (-1.5 kg) compared with a small weight gain (+1.1 kg) seen in glipizide-treated subjects. Most patients had low baseline A1c (mean 7.5%) and an average of 5.8 years' duration of diabetes. More than 70% of patients were on oral monotherapy while approximately 30% were on two oral agents at baseline.

This trial was rated fair-poor mainly because the withdrawal rate exceeded 30%. Of the 374 patients who withdrew, more sitagliptin-treated patients withdrew due to lack of efficacy than glipizide-treated patients (86 patients compared with 58 patients). Main reason for withdrawal due to lack of efficacy was because of prespecified fasting plasma glucose and/or A1c criteria as per study protocol. Also, patients who withdrew due to lack of efficacy had more severe hyperglycemia at baseline (A1c 8.6%) than those who completed the trial (7.5%).

#### *Sitagliptin or rosiglitazone or placebo added to metformin monotherapy*

Another fair quality trial<sup>50</sup> assessed the effects of sitagliptin, rosiglitazone, or placebo added to regimens of metformin monotherapy over 18 weeks. Prior to randomization patients had to have inadequate glycemic control (A1c 7-11%) and had to be taking metformin at stable doses  $\geq 1500$  mg/d for at least 10 weeks before entering a 2-week run-in period. The mean duration of diabetes for included patients was 4.9 years with mean baseline A1c of 7.7%. In these patients, the addition of sitagliptin or rosiglitazone to metformin was significantly more effective than the addition of placebo to metformin at lowering A1c ( $P \leq 0.001$ ). The placebo-corrected LS mean change from baseline was -0.51% (95% CI, -0.70 to -0.32%) for sitagliptin, and was -0.57% (95% CI, -0.76 to -0.37%) for rosiglitazone. Also, comparisons between sitagliptin and rosiglitazone were conducted and showed no statistically significant differences in lowering A1c (between-group difference: -0.06%, 95% CI -0.25 to 0.14). Similarly, there were no significant differences between sitagliptin-treated and rosiglitazone-treated patients in the proportion achieving A1c  $<7\%$  (55% compared with 63%; between-group difference 8%, 95% CI, -6 to 22%). Slightly larger reductions in fasting plasma glucose (between-group difference: -12.8 mg/dL, 95% CI, -22.6 to -3.0 mg/dL) and 2-hour postprandial glucose measurements (between-group difference: -15.9 mg/dL, 95% CI, -31.6 to -0.3) were observed with those randomized to rosiglitazone than compared with those on sitagliptin. Changes in weight were not assessed in this trial.

#### *Sitagliptin or placebo added to two existing oral hypoglycemic agents*

One fair-quality trial evaluated the addition of sitagliptin or placebo in patients whose glycemia was inadequately controlled on glimepiride 4-8 mg/d alone or glimepiride plus metformin 1500-3000 mg/d.<sup>49</sup> In patients already on glimepiride plus metformin, the

addition of sitagliptin improved A1c by 0.89% (95% CI -1.1 to -0.68%), fasting plasma glucose by 20.7 mg/dL (95% CI -31.7 to -9.7 mg/dL), and postprandial glucose by 37.1 mg/dL (95% CI -62.7 to -11.6 mg/dL) over 24 weeks of treatment. More sitagliptin-treated patients than placebo-treated patients also achieved the A1c goal of <7% ( $P<0.001$ ). Weight, however, increased slightly (+0.4 kg, 95% CI -0.1 to 0.9 kg) with sitagliptin relative to placebo; whereas, placebo-treated patients showed more weight loss (-0.7 kg, 95% CI -1.4 to -0.1 kg). In this trial, mean baseline A1c was 8.3%, average duration of diabetes was 8.8 years, and approximately 35% of subjects had an A1c <8%. More than 95% of patients were also taking combination oral hypoglycemic agents at baseline and were considered to have failed this regimen either at screening or after several weeks of dose-stabilization of glimepiride and metformin before participating in a 2-week placebo run-in phase prior to randomization.

*Initial treatment with a combination of sitagliptin plus metformin compared with placebo*

Unlike other trials, this study compared initial combination therapy of sitagliptin plus metformin to placebo, sitagliptin monotherapy, and metformin monotherapy in subjects who were inadequately controlled only on diet and exercise.<sup>53</sup> As in the placebo-controlled monotherapy trials, patients in this study were taken off prior oral hypoglycemic agents and put through a diet and exercise run-in phase in addition to a 2-week single-blind placebo run-in period before enrollment. Approximately 50% of patients were taking oral hypoglycemic agents at baseline, implying that the remainder was medication naive. Mean A1c was between 8.7% and 8.9% and duration of diabetes was less than 5 years (Table 22). In all treatment arms metformin was titrated to increase tolerability. The initial use of sitagliptin 100 mg/d plus metformin 2000 mg/d significantly improved A1c, fasting plasma glucose, postprandial glucose, weight, and proportion of patients achieving A1c <7% compared with sitagliptin plus metformin 1000 mg/d, placebo alone, sitagliptin monotherapy, or metformin monotherapy over 24 weeks (Table 22). In general, patients in all but 1 treatment arm showed weight loss (-0.6 kg to -1.3 kg,  $P=0.01$  and  $P<0.001$  from baseline). Weight was unchanged for patients on sitagliptin monotherapy (0 kg) (weight data obtained from manufacturer).

### **Harms**

In 5 trials with data suitable for meta-analysis, total withdrawals and withdrawals due to adverse events were lower among patients randomized to sitagliptin monotherapy than patients receiving only placebo (relative risk for total withdrawals 0.69, 95% CI 0.55-0.88; relative risk for withdrawal due to adverse events 0.76, 95% CI 0.33-1.73). Patients on sitagliptin monotherapy also had lower rates of total withdrawal relative to patients on glipizide, who experienced more hypoglycemic events. When compared with metformin, however, sitagliptin was associated with a greater attrition rate, mainly due to withdrawal of consent, violations of protocol, and abnormalities in laboratory. The rate of total withdrawals was also higher in patients whose add-on therapy was sitagliptin than in patients using monotherapy metformin, pioglitazone, or glimepiride.

The most commonly reported adverse events were hypoglycemia, abdominal pain, nausea, vomiting, and diarrhea. A total of 5 deaths occurred in 3 trials over 24-52 weeks. None was considered to be related to study interventions; 3 were sudden cardiac deaths, 1

was secondary to trauma, and 1 was related to chronic obstructive pulmonary disease and interstitial lung disease.

#### *Rare adverse events*

Five of the 10 randomized controlled trials reported adverse events. In those 5 trials adverse events occurring in at least 4% of study subjects included: upper respiratory tract infections, headache, influenza, nasopharyngitis, and urinary tract infection. Four studies<sup>46, 49, 54, 57</sup> reported small increases ( $\leq 10\%$  from baseline) in mean white blood cell count, mainly an increase in absolute neutrophil count, in regimens with sitagliptin compared to regimens without. These increases appeared early and remained stable throughout the duration of the studies. No other trials provided data on changes in white blood cell count with sitagliptin.

#### *Hypoglycemia*

Two studies<sup>52, 54</sup> documented 20 cases of severe hypoglycemia, mostly associated with glipizide (90%) rather than with sitagliptin. In 1 trial 3 patients on glipizide monotherapy discontinued treatment. In the other trial 8 patients receiving glipizide plus metformin required non-medical, third-party assistance compared with 1 patient taking sitagliptin added to metformin. Seven patients taking glipizide plus metformin experienced severe symptoms requiring medical assistance compared with 1 patient receiving sitagliptin plus metformin. The remaining six studies reported no cases of severe hypoglycemia. There was no statistically significant difference in the overall risk of mild to moderate hypoglycemia between sitagliptin and placebo (pooled relative risk 1.21, 95% CI 0.42 to 3.5). The rate of mild-to-moderate hypoglycemia increased slightly when sitagliptin was added to glimepiride (7.6% compared with 2.8%) or pioglitazone (1.1% compared with 0%).

#### *Abdominal pain, nausea, vomiting, and diarrhea*

There were no statistically significant differences between sitagliptin monotherapy and placebo in the risk of abdominal pain (pooled RR 1.17, 95% CI 0.54-2.52)<sup>46, 47, 53</sup>, nausea (pooled RR 1.56, 95% CI 0.53-4.57)<sup>46, 47, 53</sup>, diarrhea (pooled RR 1.26, 95% CI 0.64-2.25)<sup>46, 47, 53</sup>, and vomiting (pooled RR 0.65, 95% CI 0.18-2.4).<sup>46, 47, 53</sup> Compared with metformin monotherapy, sitagliptin was associated with lower incidence of abdominal pain, nausea, vomiting, and diarrhea. Combination therapy of sitagliptin plus glimepiride, metformin, or pioglitazone had  $<6\%$  incidence of abdominal pain, nausea, vomiting, and diarrhea; these results were not significantly different from their comparisons.

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

There was insufficient evidence to perform subgroup analyses based on age, sex, race, ethnicity, baseline A1c, or other characteristics at the study level. Subgroup data not available in publications were supplemented by data provided by the manufacturer. The results from this section should be considered with caution until larger prospective trials evaluating these populations verify the findings.

### ***Age, sex, race, body mass index, and prior use of oral hypoglycemic agents***

Four published trials<sup>47, 48, 50, 51</sup> reported no significant differences in changes in A1c based on subgroups defined by age, sex, race, and BMI. Data on file from 3 additional trials (Rosenstock 2006, Aschner 2006, Hermansen 2007)<sup>58</sup> also showed similar findings.

Data on file on one trial (Charbonnel 2006)<sup>58</sup> showed a significant interaction between treatment effect and race for those on sitagliptin monotherapy and placebo. Hispanic patients experienced the largest decline in A1c (placebo-corrected difference in A1c from baseline: -1.04%, 95% CI -1.38 to -0.70%) followed by White patients (placebo-corrected difference: in A1c from baseline: -0.69%, 95% CI -0.84 to 0.55%), and Other patients (placebo-corrected difference in A1c from baseline: -0.44%, 95% CI, -0.82 to -0.07%). Of the 5 studies (Scott 2007, Hermansen 2007, Nonaka 2008, Charbonnel 2006, Goldstein 2007)<sup>58</sup> that stratified groups by prior oral hypoglycemic agent use, only 1 trial (Goldstein 2007)<sup>58</sup> showed a large numerical difference in treatment effect. Patients who were not taking an oral hypoglycemic agent prior to this trial experienced greater decline in A1c across all treatment arms compared with patients who were using oral agents before enrolling into the study. For instance, the change in A1c from baseline for “no prior oral agent use” for sitagliptin versus placebo was -1.11% compared with -0.13% compared with -0.26% compared with +0.52% for those “treated with prior oral agents.” Between-group difference calculations were not conducted.

### ***Baseline A1c***

Subgroup information stratified by baseline A1c were found in 10 of 11 trials. Some data were available from the 9 published studies<sup>46-51, 53, 54, 56</sup> and additional information from 4 of these trials (Scott 2007, Charbonnel 2006, Nauck 2006, Scott 2008) were obtained from data on file.<sup>58</sup>

Four trials (Charbonnel 2006, Hermansen 2006, Nonaka 2008, Raz 2006) found no significant differences in the change in baseline A1c among those in the following subgroups:

<7.5%, <8%, 8-8.9%, >7.5%, ≥8.5%, and ≥9%. One trial<sup>46</sup> showed significant interaction ( $P<0.001$ ) in the change in A1c stratified by baseline A1c <8% and ≥9%. In patients with baseline A1c ≥9%, placebo-corrected reductions of -1.52% were observed for sitagliptin 100mg/d compared with about -0.6% decrease in those with baseline A1c <8%. Data from Goldstein, et al. were obtained from data on file<sup>58</sup> which also showed consistent findings for sitagliptin 100 mg/d compared with placebo. For this study, interaction analyses were not conducted (change from baseline for baseline A1c <8%: placebo-corrected difference: -0.52% compared with -0.96%,  $P$ -value, not reported). Results observed in the remaining trials (Rosenstock 2006, Goldstein 2007, Scott 2008, Raz 2008) assessing sitagliptin as add-on therapy, were generally similar in showing larger numerical reductions in A1c for those with higher baseline A1c.

### ***Duration of diabetes***

One trial<sup>47</sup> reported a potential interaction between median baseline duration of diabetes and A1c effects in patients randomized to sitagliptin 100 mg compared with placebo. Patients with diabetes of ≤ 3 years' duration had significantly greater reductions in A1c

than patients who had diabetes for > 3 years (placebo-corrected mean change A1c for  $\leq$  3years -0.90%, 95% CI -1.21% to -0.60% compared with mean change A1c for > 3years -0.28%, 95% CI -0.59 to +0.20).

Subgroup information in another trial (Goldstein 2007) were found from data on file.<sup>58</sup> Evaluation of the data on sitagliptin versus placebo showed similar results to Raz, et al. (change from baseline for  $\leq$  3 years: sitagliptin, -0.89% compared with +0.07% compared with those with <3 years: -0.40% compared with +0.35%); however, between-group differences were not conducted. Also, when mean duration of diabetes were assessed for those on sitagliptin plus metformin 1 g/day, results between those with  $\geq$ 3 years duration and < 3 years duration were not significantly different. The change from baseline for those with  $\leq$  3 years duration diabetes was: sitagliptin plus metformin 1 g/day, -1.59% compared with +0.07% compared with those with <3 years: -1.24% compared with +0.35%).

#### ***Applicability to general diabetes populations***

Patients enrolled in the 10 trials represented a highly selected population: primarily white, middle-aged, obese adults with moderately elevated baseline A1c (< 9%) and diabetes for less than 10 years. These populations were further selected during long dose-stabilization and run-in periods, where only persons with > 75% adherence to placebo went on to randomization. Moreover, these trials did not provide sufficient baseline information on comorbidities and other characteristics and laboratory values that would enable inference about the applicability of study findings to general diabetic populations. The available data appear to be limited to persons with diabetes without related comorbidities and who are highly motivated.