

Drug Class Review

Newer Drugs for the Treatment of Diabetes Mellitus

**Final Report
Executive Summary**

August 2008

The Agency for Healthcare Research and Quality has not yet seen or approved this report.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Diabetes mellitus (diabetes) is a chronic and insidious disease affecting more than 20 million Americans, approximately 7% of the population. Of those diagnosed, 90% to 95% have type 2 diabetes, while 5% to 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.

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. Within the last 1 to 2 years, 3 new antihyperglycemic agents have been approved: pramlintide, exenatide, and sitagliptin. 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).

Scope and Key Questions

The purpose of this review was to compare the effectiveness and harms of newer diabetes medications for persons with diabetes mellitus. 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?

Study inclusion and exclusion criteria

Included populations

- Adults and children
- Type 1 and type 2 diabetes mellitus

Excluded populations

- Gestational diabetes and Type 1 and type 2 diabetes mellitus in pregnancy

Subgroups of interest

- Demographic characteristics (age, race, and sex)
- Concomitant medications and drug-drug interactions
- Comorbidities such as obesity and cardiovascular disease
- History of hypoglycemic episodes
- Baseline A1c
- Drug specific-subgroups: pramlintide, renal insufficiency; exenatide, renal insufficiency; and sitagliptin, renal and hepatic insufficiency

Included health outcomes

- All-cause mortality
- Microvascular disease: chronic kidney disease including renal dialysis, renal transplantation, and end-stage renal disease; retinopathy including proliferative retinopathy and blindness; and peripheral neuropathy
- Macrovascular disease: cardiovascular events, cardiovascular mortality, stroke or transient ischemic attack, coronary heart disease, cardiovascular procedures, and extremity amputation
- Other complications of diabetes: lower extremity ulcers
- Quality of life including treatment satisfaction
- Other: hospitalization and medical visits related to diabetes care

Included intermediate outcomes

- Glycemic control: fasting glucose, post-prandial glucose, and A1c
- Change in weight
- Time to treatment failure

Included safety and harms outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Major adverse events including but not limited to diabetic ketoacidosis and non-ketotic hyperosmolar coma
- Specific adverse events including but not limited to hypoglycemia, liver toxicity, liver function abnormalities, gastrointestinal effects, adverse changes in lipid concentrations, and weight gain
- Adverse events specific to drug class: DPP-4 inhibitors, infection and neoplasm including cancer; amylinomimetics, neoplasm including cancer

Included study designs

- All studies (efficacy, effectiveness, and harms) were required to have ≥ 12 weeks of follow-up, the minimum study duration needed to adequately assess change in glycemic control.
- Studies evaluating health outcomes: randomized controlled trials of cross-over or parallel group design, good-quality systematic reviews, observational studies reporting health outcomes such as: cohort studies with a comparison group and case-control studies.
- Studies evaluating intermediate outcomes: randomized controlled trials of cross-over or parallel group design and good-quality systematic reviews
- Studies evaluating harms: randomized controlled trials, controlled clinical trials, population-based comparative cohort studies focused on adverse events, case-control studies, reports from voluntary adverse event reporting systems, and good-quality systematic reviews

METHODS

To identify relevant citations we searched 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) using search terms for included drugs, indications, and study designs. Electronic database searches were supplemented by hand searches of reference lists of included studies and reviews. In addition, we searched the U.S. 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, we searched dossiers of published and unpublished studies submitted by pharmaceutical companies.

All potentially relevant full-text articles identified from literature searches were assessed for inclusion. Data abstracted from included trials were study design, setting, population characteristics, eligibility and exclusion criteria, interventions, comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. Dual assessment by independent reviewers was used for all processes and disagreements were resolved by consensus.

We assessed the internal validity (quality) of trials based on the predefined criteria. We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis.

Original Drug Effectiveness Review Project reports are independently reviewed and commented upon by three to five peer reviewers and are posted for a two-week public comment period prior to finalization of the report. Public comments are discussed with the Drug Effectiveness Review Project participating organizations and then a determination is made as to what revisions are appropriate.

RESULTS

Pramlintide

We identified 134 citations from our literature search. Six randomized controlled trials (with 1 companion paper) and 4 pooled analyses fulfilled inclusion criteria. No comparative cohort or case-control studies reporting long-term benefits or harms were identified. In the FDA Medical and Statistical Reviews, 6 relevant trials were identified, of which 4 were published and already included in our review. The remaining 2 trials could not be found in the published literature. No good quality systematic reviews of pramlintide were identified for inclusion.

Summary of Evidence for Pramlintide

Type 1 diabetes

No data on children were reported, although children were eligible for study enrollment, and no studies evaluated long-term health outcomes or adverse events. No studies were longer than 52 weeks in duration.

A1c was either slightly improved or no different with the addition of pramlintide 30 or 60 mcg/meal to a flexible-dose insulin regimen compared with placebo plus flexible-dose insulin regimen over 29 weeks (between-group difference: 0.0%) and 52 weeks (between-group difference: 0.27%, *P* value not reported) of treatment. However, when pramlintide 60 mcg 3 or 4 times a day was added to fixed-dose insulin therapy, A1c decreased from baseline by 0.29% to 0.34% ($P < 0.01$), with no significant effect in the placebo group (0.04%) at 52 weeks of follow-up.

Patients randomized to receive pramlintide in addition to insulin lost slightly more weight from baseline (range: -0.4 to -1.3 kg) than compared with those receiving placebo plus insulin in a fixed- or flexible-dose setting, who experienced slight weight gain (range: +0.8 to +1.2 kg) over 29 and 52 weeks. Groups receiving pramlintide in addition to fixed- or flexible-dose insulin therapy exhibited larger overall rates of withdrawal (range across studies: 20% to 42% compared with 10% to 33%) and withdrawals due to adverse events (range across studies: 5% to 20% compared with 2% to 8%) than groups receiving placebo plus insulin.

Adverse events including nausea, vomiting, anorexia, and reduced appetite were more commonly reported with the use of pramlintide plus insulin than with placebo plus insulin. Severe hypoglycemia occurred more frequently with pramlintide plus insulin during the first 4 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.

Type 2 diabetes

Children and adolescents ≤ 18 years were not included in any of the published studies on effectiveness, efficacy, or harms and no studies evaluated long-term health outcomes or adverse events. No studies were longer than 52 weeks in duration.

Pramlintide 90 mcg or 120 mcg added to fixed or stable doses of insulin decreased A1c by 0.13% to 0.4% and weight by 1.1 kg to 1.85 kg (placebo-corrected differences) at 52 weeks compared with placebo and insulin. At 16 weeks the addition of pramlintide to glargine (without

prandial insulin) reduced A1c by 0.34% and weight by 2.3 kg (placebo-corrected differences) relative to placebo plus glargine in a flexible-dose setting.

Both pramlintide- and placebo-treated subjects exhibited similar rates of withdrawal and withdrawal due to adverse events. The most commonly reported adverse event was nausea, which occurred more frequently with pramlintide plus insulin than with placebo plus insulin, especially during the first 4 weeks of treatment and declined thereafter. Severe hypoglycemia occurred more frequently with pramlintide 150 mcg 3 times a day when added to insulin than with insulin plus placebo during the first 4 weeks of treatment. Rates of hypoglycemia after 4 weeks were similar among treatment groups.

Pramlintide summary evidence table

Type 1 diabetes

Type 1 diabetes	Quality of evidence	Conclusion
Key Question 1. For children and adults with type 1 diabetes, does pramlintide differ in efficacy, effectiveness, and in harms for achieving glycemic control when added to prandial insulin compared to conventional insulin therapy?		Evidence in children is lacking.
Effectiveness	No available data	-Data are insufficient to determine long-term effectiveness of pramlintide. -No studies assessed long-term health outcomes and none were > 52 weeks in duration.
Efficacy	Pramlintide with titratable insulin (flexible schedule) -Fair, 2 RCTs	Pramlintide with titratable insulin -Evidence on FPG and time to treatment failure is lacking. -One trial showed no significant differences in A1c lowering between those receiving pramlintide+insulin and placebo+insulin (in a setting where insulin was titrated to achieve prespecified glycemic targets) at the end of 29 weeks. -In contrast, one trial showed a small improvement in A1c by 0.27% (placebo-corrected) with pramlintide + insulin compared with placebo + insulin over 52 weeks. -Two trials showed small reductions in total daily insulin dose with those on pramlintide+insulin than compared with those on placebo+insulin (range: 3-12% decrease compared with 0-1% increase). Clinical significance is yet to be determined. -Pramlintide-treated subjects showed more weight loss than insulin-treated subjects, but this was not clinically significant (range: -0.4 kg to -1.3 kg compared with +0.8 kg to +1.2 kg) at 29 or 52 weeks.

Type 1 diabetes	Quality of evidence	Conclusion
	<p>Pramlintide with fixed or stable doses of insulin -Fair-Poor, 1 RCT (relevance: Low)</p>	<p>Pramlintide with fixed or stable insulin -Pramlintide produced small reductions in A1c (placebo-corrected: 0.21% to 0.30%) and weight (-1.3 kg) compared with a fixed doses of placebo plus insulin over 52 weeks.</p>
<p>Harms</p>	<p>-Fair-Poor</p>	<p>For both groups: -Studies beyond 52 weeks in duration evaluating harms are lacking.</p> <p>-More pramlintide-treated patients withdrew due to adverse effects than insulin-treated patients (5-20% compared with 2-8%).</p> <p>-In general, adjunctive therapy with pramlintide was associated with higher rates of severe hypoglycemia during the initial 4 weeks than insulin alone (event rate: 0.46 to 3.78 compared with 0.42 to 1.04). In one trial where patients were allowed to decrease prandial insulin by 30-50%, rates of severe hypoglycemia were still slightly higher for those on pramlintide+insulin than compared with those receiving placebo+insulin.</p> <p>-There was significantly greater incidence of nausea, vomiting, and anorexia associated with pramlintide therapy than insulin therapy. Two trials mentioned that most of these events occurred within 4 weeks of therapy, however, no actual data were available to verify the statement.</p>
<p>Key Question 2. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?</p>	<p>-Poor (post hoc analyses and selective outcome reporting)</p>	<p>-No subgroup analyses were conducted on age, sex, race, or total daily insulin usage.</p> <p>-One study showed patients with baseline A1c <8% exhibited similar reductions in A1c than the total population.</p> <p>-One study showed the use of pramlintide prevented weight gain in normal weight populations (BMI < 23 kg/m²) and assisted weight loss in overweight and obese patients (BMI > 23 kg/m²).</p>

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial glucose; RCT, randomized controlled trial.

Pramlintide summary evidence table

Type 2 diabetes

Type 2 diabetes	Quality of evidence	Conclusions
Key Question 1. For children and adults with type 2 diabetes, does pramlintide differ in efficacy, effectiveness, and in harms for achieving glycemic control when added to prandial insulin compared to conventional insulin therapy?		No evidence in children.
Effectiveness	No available data	-Data were insufficient to determine long-term effectiveness of pramlintide. -No studies assessed long-term health outcomes and none were > 52 weeks in duration.
Efficacy		-Evidence on FPG and time to treatment failure was lacking.
	Pramlintide added to titratable doses of insulin glargine with or without oral agents -Fair, 1 RCT	Added to titratable insulin glargine with or without oral agents -Addition of pramlintide to a glargine-only regimen lowered A1c by 0.36% (placebo-corrected values) more than those receiving placebo+glargine over 16 weeks. -Small weight loss was observed with pramlintide, while minimal weight gain was seen with glargine. The results were not clinically significant (-1.6 kg compared with +0.7 kg) over 16 weeks. -Patients in both treatment groups required dose increases to their insulin regimens. There was no significant differences between the groups at the end of 16 weeks (change from baseline: +11.7 units compared with +13.1 units).
	Added to fixed or stable doses of insulin with or without oral agents -Fair-Poor, 2 RCTs (relevance: Low)	Added to fixed or stable doses of insulin with or without oral agents - Pramlintide lowered A1c by 0.13%-0.4% compared with placebo (placebo-corrected) over 52 weeks. -Pramlintide-treated patients had larger weight loss than patients not on pramlintide, but these results were not clinically significant (-0.5 to -1.25 kg compared with +0.6 kg) over 52 weeks.
Harms	-Fair-Poor	-Studies beyond 52 weeks in duration evaluating harms are lacking. -There were no significant differences in withdrawal rates between

Type 2 diabetes	Quality of evidence	Conclusions
		<p>pramlintide+insulin and placebo+insulin treated patients.</p> <p>-Both pramlintide+insulin and placebo+insulin groups exhibited similar rates of mild-moderate hypoglycemia.</p> <p>-More pramlintide+insulin treated patients had greater incidence of severe hypoglycemic events during the first 4 weeks of treatment than those receiving placebo+insulin.</p> <p>-Incidence of nausea was significantly greater for pramlintide + insulin than placebo+insulin treated patients. One trial reported data that showed most events occurring within 4 weeks of therapy.</p> <p>-Headache was reported at a slightly higher rate in patients receiving pramlintide+insulin compared with those receiving placebo+ insulin. It is unknown whether these events were associated with hypoglycemia.</p> <p>-Neither vomiting nor anorexia was reported.</p>
<p>Key Question 2. Are there subgroups of patients for which pramlintide is more or less suitable than other hypoglycemic agents?</p>	<p>-Poor (post hoc analyses with selective outcome reporting)</p>	<p>-No subgroup analyses were conducted on age, sex, race, or total daily insulin usage.</p> <p>- Black patients may have slightly larger treatment effects with pramlintide than White or Hispanic patients.</p> <p>-The incidence of nausea had no impact on observed weight loss with pramlintide.</p> <p>- Markedly obese subjects (BMI ≥ 35 kg/m²) had the largest reduction in weight (2-3 kg) but only 1%-2% achieved clinically significant weight loss of $\geq 10\%$ of body weight.</p> <p>-Patients with higher baseline A1c ($>8.5\%$) had larger treatment effects than patients with baseline A1c $\leq 8.5\%$.</p>

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial glucose; RCT, randomized controlled trial.

Exenatide

We identified 4 randomized controlled trials that compared exenatide with conventional insulin therapy, with both groups receiving oral diabetes agents. In addition we identified 4 placebo-controlled trials, 5 single-arm open-label extension studies of exenatide, one single-arm retrospective cohort study, and two relevant systematic reviews. 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.

Summary of Evidence for Exenatide

Efficacy

Active-control trials compared exenatide to insulin, with both groups receiving oral diabetes agents, and demonstrated improved A1c in both treatment groups (range change in A1c exenatide 10 mcg twice daily -1.0% to -1.4%; range insulin -0.9% to -1.4%), with no significant differences between treatments. The substitution of exenatide for insulin did not improve A1c in either group. However, A1c improved more with exenatide than with placebo, both added to various oral agents. Between-group difference (exenatide minus placebo) for 5 mcg twice daily was -0.6% (95% CI -0.8 to -0.4%) and for 10 mcg twice daily was -1.0% (95% CI -1.2 to -0.8%).

Active-control studies demonstrated significant weight loss in exenatide groups compared to weight gain with insulin (between-group difference 4.0 to 5.5 kg). Compared with placebo, weight decreased progressively with exenatide combined with oral agents, but the weight change was small (pooled between group difference: exenatide 5 mcg twice daily, -0.51 kg, 95% CI -0.89 to -0.13; exenatide 10 mcg twice daily, -1.25 kg, 95% CI -1.90 to -0.61).

No study examined children or adolescents with type 2 diabetes.

Effectiveness

Quality of life was examined in only one study. No significant differences were seen between exenatide dosed twice a day and insulin glargine, despite higher rates of gastrointestinal adverse effects with exenatide.

Adverse effects

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. Withdrawal rates due to adverse events were higher with exenatide 10 mcg twice a day than with placebo and there were no differences between treatment groups at the 5 mcg twice daily dosing.

The incidence of hypoglycemia was elevated with exenatide 5 and 10 mcg twice a day compared with placebo but was significant only for the higher dosage (relative risk 2.44, 95% CI 1.09 to 5.49). Rates of hypoglycemia were greatest in subjects taking a sulfonylurea and exenatide compared with placebo plus exenatide. Rates of hypoglycemia were similar between insulin-treated and exenatide groups.

Nausea and vomiting were the most frequent adverse events among exenatide-treated patients, and rates of these symptoms were significantly higher in the exenatide group than the insulin or placebo groups. Nausea declined after the first 8 weeks of therapy and there was no

evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies. Rates of serious events were similar between treatment groups.

Subgroups

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 defined by demographic or other characteristics.

Exenatide summary evidence table

Type 2 diabetes	Quality of evidence	Conclusion
Key Question 1. For children and adults with type 2 diabetes, does exenatide differ in:		No study examined children or adolescents with type 2 diabetes. No study examined exenatide as monotherapy.
Efficacy and effectiveness for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy?	Placebo-controlled trials, both groups receiving oral diabetes agents Glycemic control: Fair quality, 4 RCTs	A1c improved more with exenatide than with placebo, both added to various oral agents: between-group difference (exenatide minus placebo): 5 mcg BID: -0.6% (95% CI -0.8 to -0.4%); 10 mcg BID -1.0% (95% CI, -1.2 to -0.8%)
	Weight change: Fair quality, 4 RCTs	Weight decreased progressively with exenatide combined with oral agents and compared with placebo, but weight change was small (pooled between group difference: exenatide 5 mcg twice daily, -0.51 kg, 95% CI -0.89 to -0.13; exenatide 10 mcg twice daily, -1.25 kg, 95% CI -1.90 to -0.61).
	Health outcomes: No data	No study examined health or quality-of-life outcomes. Exenatide was not compared with other active drugs except insulin.
Efficacy and effectiveness for achieving glycemic control when added to other hypoglycemic agents compared to conventional insulin therapy?	Active-controlled trials, both groups receiving oral diabetes agents Glycemic control: Fair quality, 3 RCTs	A1c improved in both treatment groups with no significant differences between treatments. The substitution of exenatide for insulin did not improve A1c in either group.
	Weight change: Fair quality, 3 RCTs	Exenatide produced significant weight loss compared to weight gain with insulin (difference 4-5.5 kg).
	Health outcomes: Poor quality, 1 RCT	Quality of life was examined in only one study, with no significant differences between exenatide and insulin glargine despite higher rates of gastrointestinal adverse effects with exenatide.
Harms for achieving glycemic control when compared to other hypoglycemic agents as monotherapy or combined therapy?	Nausea: Good quality, 7 RCTs	Total withdrawal rates were higher with exenatide than with insulin treatment or placebo.
	Hypoglycemia: Good quality, 7 RCTs	Withdrawal rates due to adverse events were higher with exenatide 10 mcg BID
	Severe, long-term, or idiosyncratic	

Type 2 diabetes	Quality of evidence	Conclusion
<p>Harms for achieving glycemic control when added to other hypoglycemic agents compared to conventional insulin therapy?</p>	<p>adverse events: Fair, most data from less than 30-week follow-up.</p>	<p>than with placebo; there was no difference between treatment groups for 5 mcg BID.</p> <p>Nausea and vomiting were the most frequent adverse events and rates were significantly higher in the exenatide group than with insulin or with placebo. Nausea persisted in 8% of subjects after 2 years (1 study).</p> <p>The incidence of hypoglycemia was elevated with exenatide 5 and 10 mcg BID compared with placebo (both groups received oral agents), but was significant only for the higher dosage. Hypoglycemia rates were similar between insulin-treated and exenatide groups.</p> <p>There was no evidence of cardiovascular, pulmonary, hepatic, or renal adverse effects across studies, and rates of serious events were similar between treatment groups.</p>
<p>Key Question 2. Are there subgroups of patients for which exenatide is more or less suitable than other hypoglycemic agents?</p>	<p>Poor quality, 1 subgroup analysis</p>	<p>One study showed exenatide improved A1c to a similar degree in persons over and under 65 years of age. There were no other data on subgroups of interest.</p>

Abbreviations: BID, twice daily; RCT, randomized controlled trial.

Sitagliptin

We identified 166 citations by various methods of literature searching. Eleven randomized controlled trials and 2 systematic reviews fulfilled inclusion criteria. No comparative cohort or case-control studies were identified reporting either long-term benefits or adverse events. In the FDA Medical and Statistical Reviews we identified 10 relevant trials, of which 7 were published in peer-reviewed journals. One of the trials identified from the FDA Reviews was not included because it did not meet inclusion criteria; the 3 remaining trials (study #P10X1, P014, and P014X1) could not be found in the medical literature.

Summary of Evidence for Sitagliptin

Children and adolescents ≤ 18 years were not included in any of the published studies on effectiveness, efficacy, or harms and no studies provided data on benefits or harms for follow-up periods longer than 52 weeks.

When compared with placebo, sitagliptin 100 mg/day monotherapy significantly lowered A1c (pooled effect, between-group change -0.81%, 95% CI -0.94% to -0.67%) in patients inadequately controlled on diet and exercise over 12 to 24 weeks. 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 1 g/day in lowering A1c based on estimated magnitude of difference between groups. However, in patients inadequately managed 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 managed on 2 oral hypoglycemic agents, the addition of sitagliptin lowered A1c by about 0.6% compared with an increase in A1c of 0.3% with placebo plus 2 oral hypoglycemic agents over 24 weeks.

In patients inadequately controlled on diet and exercise, treatment with initial combination of sitagliptin and metformin 1-2 g/day lowered A1c by about 1.4% to 1.9% from baseline compared with sitagliptin monotherapy (-0.66%) or metformin monotherapy 1-2 g/day (-0.82% to -1.13%) at 24 weeks.

Sitagliptin's effects on fasting plasma glucose and postprandial glucose were moderate compared with placebo whether used as monotherapy (pooled estimates of fasting plasma glucose -24.4 mg/dL, 95% CI -1.6 to -1.1 mg/dL; postprandial glucose -54.5 mg/dL, 95% CI -3.6 to -2.4 mg/dL) or as adjunctive therapy (range of between-group difference for fasting plasma glucose -18 to -35 mg/dL; postprandial glucose -35 to -50 mg/dL). 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 than compared with placebo. 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 sulfonylureas, pioglitazone, or rosiglitazone.

The more commonly reported adverse events across treatment groups were hypoglycemia, nausea, vomiting, diarrhea, and abdominal pain. Overall, sitagliptin appeared to be well-tolerated. There were 20 reports of severe hypoglycemia in 2 of 9 trials, mostly in patients taking glipizide (90%). 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 due to adverse events were not significantly different between the treatment groups (pooled RR 0.76, 95% CI 0.33-1.73).

Sitagliptin summary evidence table

Type 2 diabetes	Quality of evidence	Conclusion
Key Question 1. For children and adults with type 2 diabetes, does sitagliptin differ in efficacy, effectiveness, and in harms when compared to placebo, when compared to other hypoglycemic agents as monotherapy, or when added to other hypoglycemic agents?		Evidence in children is lacking.
Effectiveness	No available data	-No studies assessed long-term health outcomes and none were > 52 weeks in duration.
Efficacy		-Evidence on time-to-treatment-failure is lacking.
	Monotherapy compared with placebo	Monotherapy compared with placebo -Sitagliptin significantly improved A1c, FPG,

Type 2 diabetes	Quality of evidence	Conclusion
	<p>-Fair, 5 RCTs</p>	<p>and PPG relative to placebo.</p> <p>Pooled data for the above: A1c: -0.81% (95% CI, -0.94 to -0.67) FPG: -24.4 mg/dL (95% CI, -29.5 to -19.3) PPG: -54.5 mg/dL (95% CI, -65.5 to -43.5)</p> <p>-Sitagliptin-treated patients lost slightly less weight compared with placebo-treated patients (range: -0.1 to -0.6 kg compared with -0.7 to -1.1 kg; pooled: +0.62 kg (95% CI, +0.36 to +0.89)</p>
	<p>Monotherapy compared with an oral hypoglycemic agent -Fair, 2 RCTs</p>	<p>Monotherapy compared with an oral hypoglycemic agent-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 1 g/d in lowering A1c based on qualitative evaluation of the magnitude of difference between groups. Additional trials are needed to verify the findings.</p> <p>Ranges for sitagliptin monotherapy compared with glipizide and metformin monotherapies: A1c: -0.54% to -0.66% compared with -0.8% to -1.1% FPG: -18 mg/dL compared with -25 to -29 mg/dL PPG: -48 to -59 mg/dL compared with -53 to -78 mg/dL</p> <p>-Weight remained unchanged for sitagliptin while weight gain (+0.9 kg) occurred for those on glipizide. Weight loss occurred with metformin by about 1 kg.</p>
	<p>Combined therapy compared with placebo -Fair, 4 RCTs</p>	<p>Combined therapy compared with placebo -The addition of sitagliptin to one or two oral hypoglycemic agents was more effective for glycemic control than the addition of placebo.</p>
	<p>Combined therapy compared with oral hypoglycemic agents -Fair-Poor, 1 RCT</p>	<p>Combined therapy compared with oral hypoglycemic agents -There was no difference in A1c between regimens that included the addition of sitagliptin or glipizide to metformin. Sitagliptin-treated patients experienced slightly more weight loss (-1.5 kg) than compared with weight gain seen in glipizide-treated patients (+1.5 kg).</p> <p>-There were no significant differences in the reduction in A1c for those on sitagliptin or rosiglitazone added to metformin monotherapy (between-group difference: -0.06%, 95% CI -0.25 to +0.14%) at 18 weeks.</p>
<p>Harms</p>		<p>-Studies beyond 52 weeks in duration evaluating harms are lacking.</p>

Type 2 diabetes	Quality of evidence	Conclusion
	<p>Monotherapy compared with placebo -Fair, 5 RCTs</p>	<p>Monotherapy compared with placebo -Fewer sitagliptin-treated patients than placebo-treated patients withdrew due to adverse events.</p> <p>-There was no statistically significant difference in the risk of hypoglycemia between sitagliptin and placebo groups (pooled relative risk 1.21, 95% CI 0.42 to 3.5).</p> <p>- There were no statistically significant differences between sitagliptin monotherapy and placebo in the risk of abdominal pain, nausea, vomiting, or diarrhea.</p> <p>Pooled relative risks: Abdominal pain: RR 1.17, 95% CI 0.54-2.52 Nausea: RR 1.56, 95% CI 0.53-4.57 Vomiting: pooled RR 0.65, 95% CI 0.18-2.4 Diarrhea: RR 1.26, 95% CI 0.64-2.25</p>
	<p>Monotherapy compared with an oral hypoglycemic agent -Fair, 2 RCTs</p>	<p>Monotherapy compared with an oral hypoglycemic agent -Sitagliptin and metformin had a lower incidence of hypoglycemia than glipizide.</p> <p>-Sitagliptin had lower rates of abdominal pain, nausea, vomiting, and diarrhea than metformin.</p>
	<p>Combined therapy compared with placebo -Fair, 4 RCTs</p>	<p>Combined therapy compared with placebo - Regimens that included sulfonylurea ± sitagliptin exhibited greater risk of hypoglycemia than therapies without sulfonylurea.</p> <p>-Combination therapies of sitagliptin with sulfonylurea, thiazolidinedione, and metformin had slightly greater rates of abdominal pain, nausea, vomiting, and diarrhea than the individual oral hypoglycemic agents as monotherapy.</p>
	<p>Combined therapy compared with oral hypoglycemic agents -Fair-Poor, 1 RCT</p>	<p>Combined therapy compared with oral hypoglycemic agents -Sitagliptin added to metformin had lower rates of hypoglycemia than glipizide added to metformin.</p> <p>- Sitagliptin + metformin versus glipizide + metformin showed minimal difference in the incidence of abdominal pain, nausea, vomiting, and diarrhea.</p>
<p>Key Question 2. Are there subgroups of patients for which sitagliptin is more or less suitable than other hypoglycemic agents?</p>	<p>-Fair-Poor</p>	<p>-In general, it appears that there are no significant differences in treatment effect based on age, sex, BMI, race. Data on file from 1 trial showed that Hispanic patients showed slightly larger reductions in A1c than White or "Other" patients.</p>

Type 2 diabetes	Quality of evidence	Conclusion
		- Patients with higher baseline A1c $\geq 9\%$ tended to exhibit larger treatment effects than patients with baseline A1c $< 8\%$. - Patients with < 3 years' duration of diabetes tended to exhibit larger treatment effects than those with > 3 years' duration of diabetes.

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; PPG, postprandial glucose; RCT, randomized controlled trial.

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