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Abbreviated Class Update: Newer Diabetes Medications

Month/Year of Review: September 3013
Last Review: June 2009 (pramlintide, exenatide, sitagliptin)
March 2011 (pramlintide, sitagliptin, saxagliptin, exenatide, liraglutide)

End date of literature search: July 2013
Source: Health Resources Commission
OSU DURM

Current PDL Status:

Preferred

Drug Class	Drug
Incretin Enhancers	sitagliptin
Biguanide	metformin
Sulfonylurea (second generation)	glimepiride, glipizide, glyburide
Thiazolidinedione (TZD)	Pioglitazone
Insulin	various preparations

Non-preferred

Drug Class	Drug
Alpha-glucosidase inhibitors	acarbose, miglitol
Amylin analog	pramlintide
Dipeptidyl peptidase-4 (DPP-4) inhibitor or incretin enhancer	linagliptin, saxagliptin
Glucagon-like, peptide-1 (GLP-1) agonist or incretin mimetic	exenatide, exenatide ER, liraglutide
Insulin	various preparations
Meglitinide	nateglinide, repaglinide
Sulfonylureas (first generation)	chlorpropamide,

	tolazamide, tolbutamide
Thiazolidinedione (TZD)	**rosiglitazone**
Others - bile acid sequestrant	**colesevelam**
Others – dopamine agonist	**bromocriptine**

Research Questions:

- Are canagliflozin and/or alogliptin more effective than preferred PDL treatments for patients with type 2 diabetes mellitus (DM)?
- Are canagliflozin and/or alogliptin a safer alternative to preferred PDL treatments for patients with type 2 DM?
- Are there indications or subpopulations where canagliflozin and/or alogliptin may be more effective or safer than other available agents?
- Are there new guidelines and/or evidence that suggest that sulfonylureas should not be a preferred second-line option after metformin?

Conclusions:

- There is moderate evidence that canagliflozin is more effective than placebo in lowering glycated hemoglobin (A1C) (-0.77% to -1.06%) in type 2 DM patients. Canagliflozin treatment is associated with genital mycotic infections and hypotension. There is a concern of potential increased risk of cardiac events and fractures that needs further study.
- There is moderate evidence that alogliptin lowered A1C in type 2 DM patients by 0.4%-0.9% compared to placebo. Alogliptin is generally well tolerated but there are outstanding concerns over risk of acute pancreatitis, hepatotoxicity, hypersensitivity reactions and cardiovascular risk that need to be further delineated.
- Guidelines and systematic reviews suggest that sulfonylureas are an appropriate second-line therapy for most patients with type 2 DM. Long-term outcome data suggests that sulfonylureas may reduce the incidence of microvascular risk.

Recommendations:

- Make canagliflozin non-preferred, and prior authorize canagliflozin as a fourth –line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- Make alogliptin non-preferred and prior authorize alogliptin as a third –line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.

Reason for Review:

Newer drugs for the treatment of diabetes mellitus was reviewed by the Oregon Health Resources Commission (HRC) in June 2009[1]. Since this review additional new agents for the treatment of diabetes have been approved. In addition, National guidelines have been revised and there is a shift toward a more patient centered approach to treatment management. This review will analyze the comparative effectiveness of the newer medications for diabetes and incorporate important updates and revisions as they are related to this class since the last review. New evidence-based guidelines have been released and new systematic reviews were also updated and will be included.

Author: Kathy Sentena March 2013

Previous HRC Conclusions/June 2009:

- Evidence was insufficient to determine long term effectiveness of pramlintide when added to prandial insulin compared to conventional insulin therapy, with or without concurrent oral agents, in patients with type 2 DM.
- Evidence was insufficient to determine long term effectiveness of sitagliptin.
- No studies met inclusion criteria for exenatide.

Background:

Type 2 diabetes is a prevalent disease which affects an estimated 25.6 million people in the United States.[2] Despite a variety of treatments a significant number of patients fail to meet A1C goals and within three years of being diagnosed 50% of patients require combination therapy to control rising glucose levels. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have diabetes by 2050.[4] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with type 2 diabetes and add pharmacotherapy for persistent elevated glucose levels. Guidelines recommend a goal A1C of ≤6.5% to ≤ 7% but in all cases should be tailored according to patient specific factors, such as concomitant comorbidities.[5,6] A number of therapeutic options are available for management of glycemic variances associated with diabetes yet no agent has demonstrated clear superiority.[7] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 analogues, insulins, meglitinides, sulfonylureas, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. A1C is often used as a surrogate outcome to assess comparative efficacy of different AHA therapies, as hyperglycemia has been shown to correlate with microvascular complications and potentially macrovascular outcomes.[6] Available data is limited to short-term studies, which prevents the assessment of the durability of available AHAs to control glucose levels long-term and to compare the effectiveness of AHAs on outcomes such as microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of cardiovascular disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.[6] UKPDS data has also indicated a reduced incidence of microvascular risk with sulfonylurea and insulin therapy. TZDS, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular disease events but additional data is needed.[6] The long-term effect of many of the AHAs on complications of diabetes is unknown.

Methods:

A Medline literature search ending in July 2013 for new systematic reviews and randomized controlled trials (RCTs) for diabetic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: five clinical treatment guidelines[5,6,], four systematic reviews[8-11] and ten RCTs [19-22,25-30].

Author: Kathy Sentena March 2013

Systematic Reviews:

CADTH- Second-Line Pharmacotherapy for Type 2 Diabetes – Update[8]

A CADTH Optimal Use Report, including a systematic review and network meta-analysis (NMA), was done in July of 2013 to update their previous recommendation for AHA therapies in patients not at A1C goals despite optimal metformin use. Previous analysis and recommendations from a similar 2010 report suggest that there were no apparent differences in efficacy of AHA agents and sulfonylureas were recommended for those requiring a second-line treatment beyond metformin monotherapy. The recent update analyzed 56 trials using the GRADE evaluation method. Eight AHA classes were included: sulfonylureas, DPP-4 inhibitors, TZDs, GLP-1 analogues, basal insulin, alpha-glucosidase inhibitors, meglitinides, and biphasic insulin. Outcomes that were tracked were mortality, diabetes-related complications, A1C, body weight, hypoglycemia and severe adverse events (SAE). Changes from baseline A1C for all included AHA classes were found to be -0.64 (95% Crl: -0.91 to -0.38) to -1.06 (95% Crl: -1.32 to -0.80), with all classes significantly lowering A1C compared to metformin monotherapy. Significantly greater changes in baseline body weight (1.7 to 3.1 kg), compared to metformin monotherapy, were found for sulfonylureas, insulin (basal and biphasic), TZDs, and meglitinides. Weight neutral classes were DPP-4 inhibitors and alpha-glucosidase inhibitors. AHA agents found to cause significant weight loss compared to metformin were GLP-1 analogues. Hypoglycemia rates were significantly higher for sulfonylureas (OR 7.5), insulins (OR 4.1 to 7.0) and meglitinides (OR 8.3). Incidence of severe hypoglycemia was low for all classes (0.1% to 1.6% of total population). Severe adverse events occurred in patients at a rate of 0.7% to 9.1%, with the exception of two long-term extension trials in which SAE rates were as high as 21%. There was insufficient evidence to determine clinically important differences between the classes of AHA agents in regards to long-term complications.

CADTH- Third-Line Pharmacotherapy for Type 2 Diabetes – Update[9]

A second CADTH Optimal Use Report was done in July of 2013 to update previous recommendations for third-line treatment options for patients with diabetes. This report updates the August 2010 version, specifically including an analysis of GLP-1 analogues that were not approved at the time of previous report. The systematic review evaluated the comparative efficacy and safety of third-line AHA treatment in patients that were not reaching A1C goals on metformin and sulfonylurea therapy. This review included 41 trials of the following classes of AHA agents: alpha-glucosidase inhibitors, meglitinides, TZDs, DPP-4 inhibitors, GLP-1 analogues, basal insulin, bolus insulin, and biphasic insulin. Changes from baseline A1C were statistically significantly lower, -0.72% to -1.15%, for all classes studied except alpha-glucosidase inhibitors and meglitinides. Basal and biphasic insulin produced the greatest A1C lowering. Similar to the review of second-line agents, basal insulin, biphasic insulin, rapid acting insulin, and TZDs all produced significant increases in weight, 1.9-5.0 kg, when compared to metformin and a sulfonylurea alone. For this same comparison, DPP-4 inhibitors and alpha-glucosidase inhibitors were weight neutral and GLP-1 analogues were shown to produce significant decreases in weight (-1.6 kg, 95% Crl, -2.8 to -0.4). Data revealed uncertain results regarding meglitinides effect on weight, with a trend toward increased body weight. The risk of hypoglycemia was found to be increased for TZDs, DPP-4 inhibitors, basal insulin and GLP-1 analogues when compared to placebo when given in combination with metformin and a sulfonylurea. Active treatment comparisons showed hypoglycemia risk was highest with the insulin preparations, with basal insulin having significantly less risk of hypoglycemia compared to biphasic and bolus regimens. Severe hypoglycemia was rare, making comparisons difficult. There was insufficient data to compare the effect of the AHA classes on the occurrence of the long-term complications of diabetes.

Cochrane- Sulphonylurea Monotherapy for Patients with Type 2 Diabetes Mellitus (Review)[10]

A systematic review of 72 trials was analyzed to compare sulfonylureas, first and second generation, with other AHAs in the treatment of type 2 diabetes. The primary outcome was all-cause mortality and cardiovascular mortality. Study durations ranged from 24 weeks to over 10 years. All studies were associated with

bias and individual comparisons were comprised of a small number of participants. First-generations sulfonylureas were associated with an increased risk of cardiovascular mortality compared to placebo (RR 2.63, 95% CI 1.32 to 5.22, p=0.006). Comparison of first-generation sulfonylureas to insulin showed no significant differences in all-cause mortality rates. When compared to insulin, first-generation sulfonylureas were not shown to increase cardiovascular mortality and were favored over alpha-glucosidase inhibitors for adverse events. Second-generation sulfonylureas were shown to not be significantly different from metformin, TZDs, insulin, meglitinides, or incretin-based therapies for the outcome of all-cause mortality. Cardiovascular mortality was not found to be different between second-generation sulfonylureas and metformin, insulin, TZDs and meglitinides. Based on data from three trials, second-generation sulfonylureas were favored over metformin for the composite outcome of non-fatal macrovascular events (RR 0.67, 95% CI 0.48 to 0.93, p=0.02). Second-generation sulfonylureas weren't found to be significantly different in adverse events compared to placebo, metformin, TZDs, alpha-glucosidase inhibitors, or meglitinides. Second generation sulfonylureas were less likely than alpha-glucosidase inhibitors to be associated with drop-outs due to adverse events. Metformin and TZDs were favored over second-generation sulfonylureas for severe hypoglycemia (RR 6.11, 95% CI 1.57 to 23.79, p=0.009). No difference was found between meglitinides and second-generation sulfonylureas in for severe hypoglycemia. Data on third-generation sulfonylureas was lacking for all-cause mortality, cardiovascular mortality and other macrovascular and microvascular outcomes. None of the outcomes met the criteria for firm RRR in a trial sequential analysis and therefore the authors concluded that additional studies are needed in order to support recommending sulfonylurea monotherapy.

Cardiovascular Safety of Sulfonylureas: A Meta-analysis of Randomized Controlled Trials[11]

The cardiovascular safety of sulfonylureas was examined in a meta-analysis by Monami, et al. This analysis included randomized trials that compared sulfonylureas to active treatment or placebo in patients with type 2 diabetes. One hundred fifteen trials were included, lasting at least 6 months in duration, with a mean duration of 70 weeks. Patients had a mean age of 56.6 years, mean duration of diabetes of 6.3 years and mean A1C of 8.4%. Types of sulfonylureas included were three second generation agents available in the United States (US) (glimepiride, glyburide, and glipizide), four first generation agents available in the US (chlorpropamide, tolazamide, tolbutamide and acetohexamide), two second generation agents not available in the US (glibenclamide, gliquidone) and one mixed generation agent not available in the US (gliclazide). The quality of the trials were accessed using Jadad parameters but no minimum score was required. The principle outcome was the incidence of major cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction (MI) and stroke, and acute coronary syndrome and/or heart failure reported as serious adverse events of sulfonylureas compared to placebo or active treatment. Secondary outcomes were fatal and non-fatal MI and stroke, all-cause and cardiovascular mortality and severe hypoglycemia.

Sulfonylureas were not found to have a significant difference in the occurrence of MACE compared to active treatment and placebo (MH-OR: 1.08 [0.86 to 1.36], p=0.52). However, sulfonylureas were found to have a significantly higher incidence of MACE compared to DPP-4 inhibitors in a subgroup analysis. The incidence of MI was not found to be different between sulfonylureas and active treatment and placebo. The analysis of 16 trials found the risk of stroke to be significantly higher with sulfonylureas (MH-OR: 1.28 [1.03 to 1.60], p=0.026). The risk of stroke was found to be significant when compared to DPP-4 inhibitors and with glimepiride (MH-OR: 4.22 [1.65 to 10.79], p=0.003). In the analysis of 88 trials, sulfonylureas were found to increase all-cause mortality significantly compared to other treatments and placebo (MH-OR: 1.22 [1.01 to 1.49], p=0.047). Cardiovascular mortality rates were not found to be significantly different between sulfonylureas and other treatments. Sulfonylureas were found to have a higher incidence of hypoglycemia when compared to metformin and placebo. The authors concluded that in general sulfonylurea treatment is not associated with a significant increase in cardiovascular risk. Limitations to this meta-analysis are the following; the inclusion of sulfonylureas not applicable to the most commonly used treatments in the US, the lack of reporting of cardiovascular events and sample size limitations.

Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitor: Meta-Analysis and Systematic Review[12]

In a recent meta-analysis and systematic review Aroda, et al, summarized the overall evidence related to incretin therapies in patients with type 2 diabetes. Exenatide, exenatide weekly, liraglutide, alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin (not available in the US) were included in the analysis. Eighty studies were included for evaluation, lasting from 12-52 weeks with the change from baseline A1C being the primary outcome. Seventy-six percent of the included studies were comparisons of combined treatments. GLP-1 were found to result in mean A1C changes of -1.1% to -1.6%. DPP-4 inhibitors were associated with decreases of -0.6% to -1.1% in A1C. Specifically, reductions from baseline in A1C were the following; alogliptin -0.70% (95% CI -0.90 to -0.50); linagliptin -0.60% (95% CI -0.80 to -0.40); saxagliptin -0.71% (95% CI -0.89 to -0.54); sitagliptin -0.70% (95% CI -0.78 to -0.63) and vildagliptin -0.98% (95% CI -1.46 to -0.52). GLP-1 analogues were associated with significant weight loss and DPP-4 inhibitors trended toward weight loss.

Oral Diabetes Medications for Adults with Type 2 Diabetes. An Update[13]

An AHRQ review was updated in March 2011 to include the benefit and harms of AHAs in patients with type 2 diabetes. The following treatments were included: metformin, second generation sulfonylureas, thiazolidinediones, meglitinides, DPP-4 inhibitors and GLP-1 agonists. Randomized controlled trials lasting 3 months or longer and enrolling at least 40 subjects were included. Studies were evaluated according to the Jadad criteria for quality and given an overall grade for the strength of evidence. The analysis found that there was a high strength of evidence that most AHA agents reduced A1C to a similar extent, approximately one percent compared to baseline values. The DPP-4 inhibitors were the only exception, which did not lower A1C as much as metformin (moderate strength of evidence). Most combination therapies were shown to decrease A1C by and additional one percent. There was high strength of evidence that metformin had beneficial effects on body weight and lipids compared to other AHAs. There was high strength of evidence that sulfonylureas were associated with a higher risk of mild-to-moderate hypoglycemia as monotherapy and when used in combination with other AHAs. There was limited data on long-term clinical outcomes for many of the AHAs.

New Guidelines:

ADA/EASD Guideline – Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach[6]

The ADA/EASD recently updated their 2008 guideline recommendations in 2012. Recommendations were based on evidence and expert opinion. Due to the complex nature of treating patients with type 2 diabetes the guideline replaced their previous algorithm of recommendations with a more patient-centered approach, which takes into consideration patient preferences and tolerances. The guideline also recommends that a variety of factors should be taken into account when considering if the patient is a candidate for more stringent or less stringent glucose control. Metformin is suggested as the most commonly recommended first-line choice. If metformin is not an option then sulfonylureas/glinides, pioglitazone or DPP-4 inhibitors are considered good options. GLP-1 analogues may be an appropriate first-line choice for those with specific weight loss concerns. AHAs not already mentioned may be appropriate for specific patients but are less commonly recommended initially to due adverse effects and modest lowering of A1C. For patients requiring a dual glucose lowering treatment, the guidelines recommend a second oral AHA, a GLP-1 analogue or basal insulin. If triple therapy is required, insulin was found to provide the most A1C lowering.

NICE Guideline – Type 2 Diabetes: Newer Agents[14]

A short clinical guideline was produced in May of 2009 to update current NICE guidelines on recommendations for therapy for elevated glucoses in patients with type 2 diabetes. An evidence based, clinical pathway outlines preferences for 1st, 2nd and 3rd line therapies with exceptions for each based on specific patient characteristics. In general metformin is considered the first-line therapy, sulfonylureas as the preferred second-line treatment option and insulin is

recommended third line. DPP-4 inhibitors (only sitagliptin approved at the time of the guideline) are to be considered second-line in patients with a high risk of hypoglycemia (or the consequences), or for those whom a sulfonylurea or metformin is not tolerated or contraindicated. For those unable to use insulin, DPP-4 inhibitors are also recommended as a third-line treatment. TZDS are recommended as second-line agents in patients who are at elevated risk of hypoglycemia (or the consequences) or if they are not candidates for metformin or sulfonylurea therapy. TZDs are to be considered third-line in patients unable to use insulin. GLP-1 analogues (only exenatide approved at the time of guideline) are recommended as third-line agents if patient weight is of particular concern. Long-acting insulins (insulin detemir and insulin glargine) were recommended, in lieu of preferred first line NPH, if patient requires a caregiver for injections and use of a long-acting insulin would decrease injections to once-daily, decrease hypoglycemia, or patient would require multiple doses of NPH in addition to oral AHAs.

* This guideline was also updated in 2010 to include the suspension of marketing of rosiglitazone by the European Medicines Agency due to the risks of treatment exceeding benefit and again in 2011 to due to new recommendations on the risk of bladder cancer with pioglitazone.

AACE Guidelines – American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013 Consensus Statement[5]

AACE recently updated guidelines for comprehensive diabetes management and hyperglycemia treatment algorithm in 2013. Recommendations for pharmacotherapy are similar to the previous 2009 algorithm and use A1C to guide treatment selection.[5,14] Monotherapy is recommended for those patients with A1C <7.5%, with metformin being the agent of choice for initial therapy. Alternatives to metformin are GLP-1 analogues, DPP-4 inhibitors and alpha-glucosidase inhibitors. Other agents that are options but should be used with caution are TZDs, sulfonyulureas/glinides and SGLT2s. Dual therapy is recommended for patients with an A1C $\geq$7.5% or for those unable to obtain their goal A1C on monotherapy. Metformin in combination with a second agent is preferred or any combination with complimentary mechanisms of action. GLP-1 analogues and DPP-4 inhibitors are recommended as the preferred dual pharmacotherapy options (with metformin), followed by TZDs, SGLT2s and basal insulin, all which should be used with caution. Additional potential combination therapy includes (in order of preference): colesevelam, bromocriptine, alpha-glucosidase inhibitors and sulfonylureas/glinides. For patients with an A1C >8%, a third AHA may be considered. GLP-1 analogues are preferred, followed by TZDs, SGLT2s, basal insulin, DPP-4 inhibitors, colsevelam, bromocriptine, alpha-glucosidase inhibitors and sulfonylureas/glinides. For patients with an A1C >9.0% insulin is recommended.

IDF Guidelines- Global Guideline for Type 2 Diabetes[16]

In 2012 the International Diabetes Federation (IDF) updated its 2005 guidelines for the treatment and management of diabetes. Recommendations were made based on available evidence and expert opinion. Metformin was recommended as initial therapy. For second-line therapy sulfonylureas are recommended with other options including alpha-glucosidase inhibitor, DPP-4 inhibitors, TZD or meglitinides. Insulin (basal or pre-mix) or a third oral agent is recommended third-line. Other third-line options are alpha-glucosidase inhibitors, DPP-4 inhibitors, TZD or a GLP-1 analogue. Insulin is recommended as the only fourth-line agent.

ACP Guideline – Oral Pharmacological Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From the American College of Physicians[17]

This 2012 Guideline provides recommendations for AHAs based on comparative efficacy and safety for the outcomes of A1C, lipids, weight, all-cause mortality, cardiovascular and cerebrovascular morbidity, retinopathy, nephropathy, neuropathy, hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, server allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision and gastrointestinal side effects. Additional data on safety and effectiveness of subgroups was also studied. Trial quality was rated via Jadad and the overall evidence was graded using the GRADE system. Metformin is recommended first-line for most patients based on high quality evidence but no specific second-line therapy is suggested.

One hundred and four trials were used for the A1C comparison of medications used for the treatment of type 2 diabetes. Comparison of monotherapy treatments showed similar A1C lowering across the groups, average of 1%, with the exception of metformin compared to DPP-4 inhibitors. Metformin was shown to decrease A1C to a greater extent than DPP-4 inhibitors by a mean difference of -0.37% (moderate quality of evidence). Combination therapy was shown to be more effective than monotherapy with the metformin and sulfonylurea combination producing the largest mean decrease (-1.0%), metformin and DPP-4 inhibitors with a -0.69 men decrease and metformin with a TZD with a -0.66 mean decrease. There was insufficient evidence provided on GLP-1 analogue combination therapy (moderate to high quality evidence). Moderate to high quality evidence demonstrated that metformin therapy resulted in more weight loss compared to TZDs, sulfonylureas and DPP-4 inhibitors. Metformin was also had the most favorable effect on low density lipoprotein (LDL) compared to TZDs, sulfonylureas and DPP-4 inhibitors (moderate-high quality of evidence). TZDs had them most effect on increasing high density lipoprotein (HDL) compared to metformin and sulfonylureas. Metformin was favored with moderate quality of evidence over sulfonylureas and for decreasing triglyceride (TG) levels. For many of the long-term outcomes only low-quality or insufficient evidence was available for analysis. Nephropathy rates (based on albumin levels) were the only long-term outcomes with moderate quality of evidence, in which pioglitazone was shown to decrease urinary albumin ratio to a greater extent than metformin.

Severe hypoglycemia rates were similar across treatment groups. Sulfonylureas were shown to increase mild and moderate hypoglycemia rates compared to metformin, TZDS, DPP-4 inhibitors, GLP-1 analogues and meglitinides based on low to high quality evidence. Combination therapy with metformin and a sulfonylureas also was shown to increase hypoglycemia compared to combinations containing TZDs. Moderate quality of evidence from observational studies favored metformin over sulfonylureas and sulfonylureas over TZDs for risk of congestive heart failure (CHF). Combination therapy of TZD and sulfonylureas doubled the risk of CHF compared to metformin and sulfonylurea combination therapy. There was high quality of evidence that sulfonylureas were associated with less fracture risk than TZDs.

New Safety Alerts:

Pioglitazone and Bladder Cancer- FDA Safety Review[18]

In August of 2011 the FDA issued label changes to be made to pioglitazone prescribing information detailing the findings of a potential increased risk of bladder cancer when the drug is used beyond one year. The FDA made these recommendations based on a five year interim analysis of a 10 year epidemiological study which found no increased risk in bladder cancer overall but there was an increased risk in those whom had been taking pioglitazone for the longest time and at the highest doses. The FDA recommends against using pioglitazone in those with active bladder cancer and cautions against its use in those with a history of bladder cancer.

Incretin Mimetic Drugs and Pancreatitis/Pre-cancerous Findings in the Pancreas[19]

In March of 2013 the FDA announced that it is investigating the findings of a potential risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia) in patients with type 2 diabetes taking incretin mimetic type drugs (exenatide, liraglutide, sitagliptin, saxagliptin, alogliptin, and linagliptin). Current labeling includes warnings of acute pancreatitis with these agents. There is no conclusive link of pancreatic cancer and incretin mimetics. The FDA is involved in ongoing evaluations to gain additional information.

New Primary Literature:

New Drug Evaluation- Canagliflozin (Invokana ®)[20]

FDA Indications:
Canagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor, which is a new class of AHAs. SGLT2 inhibitors work by preventing reabsorption of glucose by the kidney and increaseing urinary glucose excretion. This results in mild osmotic diuresis and net calorie loss. Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. Canagliflozin is not to be used for the treatment of type 1 diabetes or diabetic ketoacidosis.[18]

Clinical Efficacy Data (see evidence table below):
Canagliflozin was studied in over 10,000 patients in multiple trials as monotherapy and in combination with other agents (metformin, sulfonylurea, metformin and sulfonylurea, metformin and TZD and insulin). Active treatment comparisons were between canagliflozin and sitagliptin and canagliflozin and glimepiride. At this time only four trials have been published and available to be critically evaluated. In all studies the primary endpoint was the change in baseline A1c at specified durations. Important secondary endpoints were percent of subjects obtaining an A1c <7.0%, fasting plasma glucose levels, and percent change in body weight.

CANATA-M was a poor to fair quality, phase III trial comparing canagliflozin 100mg and 300mg daily to placebo in 584 patients for 26 weeks.[21] Patients in the main study had a mean HbA1c of 8.0% and a mean duration of diabetes of 4.3 years. A substudy of patients with elevated glucose concentrations was also conducted and included patients with a mean HbA1c of 10.6% and duration of diabetes of 4.9 years. The primary endpoint was the change in baseline HbA1c at week 26. An important secondary endpoint was the percent of patients achieving HbA1c <7%. Canagliflozin 100mg and canagliflozin 300mg both reduced HbA1c to a greater extent than placebo, -0.77, -1.03 and 0.14%, respectively ($p<0.001$ for both comparisons). There were also a greater percentage of patients that obtained a HbA1c <7% compared to placebo, with a NNT of 2-4. Patients in the high glycemic substudy also experienced greater HbA1c lowering compared to placebo. The lack of blinding details as it relates to patients, caregivers and outcomes assessors limits the ability to determine the likelihood of bias represented in the results. Description of randomization methodology was also lacking.

A 52 week, head to head comparison of canagliflozin 300 mg and sitagliptin 100 mg, on background metformin and sulfonylurea therapy, was studied in the CANTATA-D2 trial.[22] This was a fair quality, phase III, DB, RCT of 755 patients with type 2 diabetes whom were previously inadequately controlled on metformin and sulfonylurea therapy. Included patients had a mean duration of diabetes of 9.2 years with a mean A1C of 8.1%. The primary endpoint was change in baseline A1C at week 52. Canagliflozin was shown to be noninferior and superior to sitagliptin with A1C changes of -1.03% and -0.66%, respectively. Improvements in FPG, body weight and systolic blood pressure were significantly greater with canagliflozin compared to sitagliptin. When A1C changes were analyzed according to baseline A1C subgroups, the greatest difference was shown in those with the highest baseline A1cs ($\geq$9.0%). The overall discontinuation rate was high (38.5%) and occurring in 44% of the sitagliptin group and 33% in the canagliflozin group. Last observation carried forward imputation was used to provide results for missing data. This method may introduce assessment bias especially in circumstances such as in this study where there was a higher percentage of drop out in the active comparator group (sitagliptin) which assumes no change, potentially overestimating the true treatment effect of canagliflozin.

In a small fair quality, phase III, PC, RCT canagliflozin 100mg and 300mg was studied for 26 weeks in patients with type 2 diabetes and chronic kidney disease (eGFR $\geq$30 and <50 ml/min /1.73 m^2).[23] Patients were a mean age of 69 years old with a baseline A1C of 8.0% and eGFR of 39 ml/min/1.73m^2. Canagliflozin 100mg and

300mg decreased A1C to a greater extent than placebo, -0.33%, -0.44% and -0.03%, respectively ($p<0.05$). Reduction in FPG were also greater for canagliflozin but not significantly so.

Recently, a trial was published on the use of canagliflozin, 100mg and 300mg daily, compared to glimepiride, 6-8 mg daily, in patients (n=1452) uncontrolled on metformin (CANTATA-SU).[24] This was a fair quality, phase III, DB, randomized, non-inferiority trial lasting 52 weeks. The mean patient age was 57 years with a mean baseline A1C of 7.8%. As with the other studies, the primary endpoint was the change from baseline in A1C. Canagliflozin 100 mg and 300mg were shown to be non-inferior to glimepiride and canagliflozin 300 mg was shown to be superior to glimepiride. A1C changes were -0.82%, - 0.93%, -0.81% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively. The percent of patients obtaining an A1C <7% was similar between groups. Both canagliflozin groups were associated with significant decreases in body weight compared to the glimepiride group.

FDA approval summary documents for canagliflozin noted that the efficacy of canagliflozin is attenuated as renal function declines.[24] FDA statements include the need for future research related to the risk of cardiovascular events and fracture risk, which were shown to be increased in canagliflozin groups but correlation to canagliflozin treatment is not definitive and studies are ongoing.[25]

Clinical Safety[20]:
The most common adverse effects associated with canagliflozin were fatigue, female genital mycotic infections, urinary tract infections, increased urination and male genital mycotic infections. Hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration as a result of osmotic diuresis with potential decreases in intravascular volume have also been associated with canagliflozin treatment. Patients at increased risk of osmotic diuresis were those over 75 years of age, use of loop diuretics and moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2). Dose-related increases in serum creatinine were also noted. Slightly higher rates of hypoglycemia were experienced in canagliflozin groups compared to placebo and were more common when canagliflozin was combined with insulin or sulfonylureas.

Lab abnormalities were seen in patients randomized to canagliflozin, including hemoglobin elevations and dose-related increases in potassium, magnesium and phosphate. Changes in LDL levels of 4.4 mg/dL (4.5%) in the canagliflozin 100mg group and 8.2 mg/dL (8.0%) in the 300mg group were demonstrated.

Conclusion: Canagliflozin is has been shown to be modestly effective in lowering A1C as monotherapy and in combination with other AHA agents, with A1C lowering from -0.63% to -1.06%. Canagliflozin is unlikely to cause hypoglycemia as monotherapy and has demonstrated positive effects on FPG, BP, HDL and body weight while negatively impacting LDL levels. The use of canagliflozin in patients with chronic renal failure has been shown to be effective, but efficacy is attenuated with declining renal function. There is insufficient evidence to determine the impact of canagliflozin therapy on cardiovascular risk and fractures.

New Drug Evaluation- Alogliptin (Nesina ®), Alogliptin + Pioglitazone (Oseni ®) and Alogliptin + Metformin (Kazano®)

FDA Indications:
Alogliptin is a DPP-4 inhibitor available as a single agent and in combination with pioglitazone (Oseni) and metformin (Kazano).[26,27,28] Alogliptin and its combination products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM. Alogliptin should not be used for

the treatment of type 1 diabetes or diabetic ketoacidosis. Alogliptin differs from currently offered agents by being more selective and potent at inhibiting the DPP-4 enzyme but the clinical relevance of this is unknown.

Clinical Efficacy Data (see evidence table below):

Alogliptin 12.5 mg and 25 mg have been extensively studied in many trials. Due to lack of details on randomization, treatment allocation, blinding and high attrition rates not all studies were able to be adequately evaluated for internal and external validity and are therefore not included in the evidence table. Alogliptin studies were of similar design, enrolling patients 18-80 years with A1C of 7-10% (except for alogliptin and insulin trial, which patients had an A1C $\geq$8%) for 26 weeks with a 4-week run-in period.[29-34] The primary endpoint was the change in A1C from baseline at week 26 or 52. Key secondary endpoints were: changes in fasting plasma glucose, number of patients obtaining an A1C <7.0% and changes in baseline body weight.

Nauke, et al studied aloglitptin 12.5 mg and 25mg with metformin compared to placebo in patients with a baseline A1C of 8% and mean age of 55 years.[29] Change in A1C was -0.6% for both alogliptin groups compared to a placebo decrease of -0.1%, p<0.001 for both groups. Results were similar when alogliptin was studied with pioglitazone in a study by Prately, et al.[30] Patients were allowed to continue background metformin and/or sulfonylurea. Decreases in baseline A1C for alogliptin 12.5 mg and alogliptin 25 mg were -0.66% and 0.8%, respectively, compared to a placebo A1C increase of 0.19%. Smaller but still significant A1C changes were shown in a trial by Pratley, et al that compared alogliptin 12.5 mg and 25 mg to placebo with background glyburide therapy.[31] Decrease from baseline A1C were -0.38% for alogliptin 12.5 mg and -0.52% for alogliptin 25 mg compared to placebo 0.01% (p<0.001 for both groups). A poor-fair study by Rosenstock, et al found A1C decreases for alogliptin significantly more than placebo when patients were on background insulin therapy with or without metformin.[32] Changes from baseline A1C were -0.13%,-0.63%, -0.71% for placebo, alogliptin 12.5 mg and alogliptin 25 mg, respectively. Defronzo, et al compared alogliptin 12.5 mg and 25 mg to placebo and pioglitazone 15, 30 and 45 mg, as well as the combination of alogliptin 12.5 mg and all pioglitazone doses and alogliptin 25 mg and all pioglitazone doses.[33] Decreases in A1C were greater for alogliptin and pioglitazone combination therapy compared to pioglitazone alone ($p\leq0.001$ for all groups). Changes from baseline A1C were similar for alogliptin 12.5 mg and pioglitazone 15 mg (-0.7%) and for alogliptin 25 mg and pioglitazone 30mg (-0.9%). The combination of alogliptin and pioglitazone was superior to pioglitazone alone with decreases in A1C ranging from -1.25% to -1.6%. Changes in fasting plasma glucose and percent of subjects obtaining an A1C <7% were significantly more for alogliptin 25mg compared to placebo in all studies. A study of alogliptin 25mg, metformin (≥1500 mg) and pioglitazone 30mg (A/M/P) was compared to pioglitazone 45mg and metformin (≥1500mg) (P/M).[34] At week 52 least squares mean change from baseline in A1C were significantly greater for the A/M/P compared to P/M, -0.70% and -0.29% (p<0.001), respectively. Significantly more patients were able to achieve an A1C of ≤7%, with a NNT of 8.

Evaluation of efficacy data for alogliptin was limited by high drop out rates that were highest in the study using alogliptin and insulin together (47%) and ranged from 11-40% in other studies. In the alogliptin and insulin trial, high attrition rates can be attributed to a large number of patients requiring hyperglycemic rescue, which was determined by A1C at 12 weeks compared to FPG. An additional concern with data analysis in light of data imputation due to drop outs is the sustained efficacy of alogliptin out to 52 weeks. True efficacy is difficult to determine due to high drop out rates and differing rates of attrition between alogliptin and placebo groups which introduce selection and attrition bias.

Clinical Safety:

The adverse effects that alogliptin therapy is most commonly associated with are; nasopharyngitis, headache, upper respiratory infection and urinary tract infections. Studies showed that alogliptin was weight neutral and hypoglycemia rates were similar to placebo. Discontinuations due to adverse effects were low (2% to 5%). Studies of alogliptin were found to be associated with a higher incidence of serious cardiovascular events compared to placebo. This increase may

be due to study design and implementation, however, the association can not be ruled out and is being further evaluated. Additional FDA post marketing study requirements are a cardiovascular outcomes trial (EXAMINE study), an enhanced pharmacovigilance program to monitor for liver abnormalities, serious cases of pancreatitis and severe hypersensitivity reactions as well as three pediatric studies.[35] Combination products, Oseni and Kazano, carry black box warnings due to congestive heart failure risk with pioglitazone and lactic acidosis risk with metformin.[27,28]

Conclusion

Alogliptin is a moderately effective agent to treat glucose abnormalities in patients with type 2 DM as monotherapy and as a combination product. Placebo adjusted mean FPG changes from baseline ranged from -4 to -28 and mean A1C reductions were 0.4%-0.6% for alogliptin monotherapy compared to placebo, with the 25mg alogliptin dose being only slightly more effective than the 12.5 mg dose.[34] Alogliptin does not appear to have any advantages over currently available DPP-4 inhibitors and is associated with similar adverse reactions (infections, skin reactions, hepatoxicity, hypersensitivity reactions, pancreatitis and renal safety issues).[26,35] Alogliptin has been shown to be weight neutral with a low risk of hypoglycemia. Additional studies are needed to determine safety and efficacy of chronic use as randomized trial durations were limited to 52 weeks.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1.) Microvascular Outcomes
2.) Macrovascular Outcomes
3.) Hypoglycemic Episodes
4.) Adverse Effects leading to discontinuation

Primary Study Endpoints:

1.) Changes in HbA1c
2.) Changes in weight

Evidence Table

CANTATA-M[21]

Stenlöf, et al Phase III, RCT, DB, PC 17 Countries	1. Canagliflozin 100mg QD (C100) 2. Canagliflozin 300mg QD (C300) 3. Placebo QD (P)	Mean Age (main study): 55 Mean Age (substudy): 49 Female: 55% Main study baseline A1C: 8.0% Substudy baseline A1C: 10.6% **Inclusion**: Patients 18-80 years with type 2 DM with the either of the following: not on a AHA with A1C of ≥7.(and ≤10.0% or on AHA monotherapy (except PPARγ) or metformin plus sulfonylurea combination therapy with A1C of ≥6.5 and ≤9.5% at screening and A1C ≥7 and ≤10.0% and FPG of <150 mmol/L at week -2. Substudy: A1C of >10.0 and ≤12.0% at screening or week -1 and FPG ≤19.4 mmol/l at week -1. **Exclusion**: FPG >15 mmol/l during pre-treatment phase (or >19.4 mmol/l for the substudy), type 1 DM, hereditary glucose-galactose malabsorption, primary renal glucosuria or CV disease, tx with other SGLT2	Main Study: 1. 195 2. 197 3. 192 Sub-study: 1. 47 2. 44	26 weeks	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.77% C300: -1.03% P: 0.14% LS Mean Change C100: -0.91% (95% CI -1.1 to -0.7, p<0.001) LS Mean Change C300: -1.16% (95% CI -1.3 to -1.0, p<0.001) <u>Fasting Plasma Glucose:</u> C100: -1.5 mmol/l (27 mg/dl) C300: -1.9 mmol/l (34 mg/dl) P: 0.5 mmol/l (9 mg/dl) LS Mean Change C100: -2.0 mmol/l (95% CI -2.3 to -1.6, P<0.001) LS Mean Change C300: -2.4 mmol/l (95% CI -2.8 to -2.0, p <0.001) <u>Subjects reaching A1C <7.0%:</u> C100: 44.5% C300: 62.4% P: 20.6% P<0.001 for both doses <u>Changes in Baseline body weight:</u> C100: -2.5 kg (2.8%) C300: -3.4kg (3.9% P: -0.5 kg (-0.6%) LS Mean Change C100: -2.2% (95% CI -2.9 to -1.6, p<0.001)	NA NA C100 ARR: 24 NNT: 4 C300 ARR: 42 NNT: 2 NA	<u>Urinary tract infection:</u> C100: 14 (7.2%) C300: 10 (5.1%) P: 8 (4.2%) <u>Males genital mycotic infection:</u> C100: 2 (2.5%) C300: (5.6%) P: 0 <u>Female genital mycotic infection:</u> C100: 10 (8.8%) C300: 8 (7.4%) P: 4 (3.8%) <u>Hypoglycemia:</u> C300: 3.6% C100: 3.0% P: 2.6% <u>Withdrawal due to Adverse Events:</u> C100: 6 (3.1%) C300: 4 (2.0%) P: 2 (1.0%)	NA NA NA NA	**Quality Rating: Poor-Fair** **Internal Validity: RofB** Selection: not described Performance: double-blind treatment design was stated but no details on blinding were provided Detection: details were not provided Attrition: mITT analysis was used with LOCF fo missing data. Overall 13.1% discontinued treatment prior to 26 weeks **External Validity** Recruitment: recruited from 17 countries Patient Characteristics: almost half of patients had prior exposure to glucose lower therapy, but HbA1c lowering was similar regardless of prior treatment. Patients with mild to moderate renal impairment were included. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

CANTATA-D2[22]									
Schern-thaner, et al Phase III, RCT, DB, active control, non-inferiority trial 17 countries	1. Canagliflozin 300 mg (C300) 2. Sitagliptin 100 mg (S100) * Both groups on background metformin and sulfonylurea	Age: 56 years Female: 43.5% Main study baseline A1C: 8 % Male: 56% <u>Inclusion:</u> Subjects 18 years and older, type 2 diabetes diagnosis, on stable doses or adjustment period of metformin (1500-2000mg dose) and sulfonylurea (at least half of maximum labeled dose) therapy and A1C ≥7.0% and ≤ 10.5%. <u>Exclusion</u>: Prior AHA therapy other than metformin and sulfonylurea up to 12 weeks prior to study enrollment, type 1 diabetes, uncontrolled hypertension, cardiovascular disease and eGFR <55 mL/min/1.73m^2.	1. 378 2. 378	52 weeks with 2 week prior single-blind placebo run-in	<u>Change from Baseline in A1C at 52 weeks :</u> C300: -1.03% S100: -0.66% LS means: -0.37 (95% CI -0.50 to -0.25) noninferiority and superiority was achieved <u>Fasting Plasma Glucose:</u> C300: -1.7 mmol/l (29 mg/dl) S100: -0.3 mmol/l (2.2 mg/dl) LS Mean Change: -1.3 mmol/l P<0.001 LS Mean Change C300: -2.4 mmol/l (95% CI -2.8 to -2.0, p <0.001) <u>Subjects reaching A1C <7.0%:</u> C300: 47.6% S100: 35.3% <u>Changes in Baseline body weight:</u> C300: -2.3 kg (-2.5%) S100: 0.1 kg (0.3%) LS Mean Change: -2.8%, p<0.001	NA NA NA	<u>Urinary tract infection:</u> C100: 15 (4.0%) S100: 10 (5.6%) <u>Males genital mycotic infection:</u> C300: 19 (9.2%) S100: 1 (0.5%) <u>Female genital mycotic infection:</u> C300: 26 (15.3%) S100: 7 (4.3%) <u>Severe Hypoglycemia:</u> C300: 4.0% S100: 3.4% <u>Withdrawal due to Adverse Events:</u> C300: 20 (5.3%) S100: 11 (2.9%)	NA NA NA NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. High and different levels of attrition may have affected the ability to maintain randomization. Performance: Study was double-blind with study personnel remaining blinded to treatment allocation. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Potential for bias due to only 39% of patients completed 52 week study, most withdrawals due to rescue therapy. **External Validity:** Recruitment: 140 centers in 17 countries. Patient Characteristics: Patients with almost 10 years of diabetes and moderate A1cs were included. Not studied in newly diagnosed and those with cardiovascular disease. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
Canagliflozin and Chronic Kidney Disease[23]									
Yale, et al Phase III, DB,	1. Canagliflozin 100mg (C100)	Age: 69 yrs Female: 36-46% Baseline A1C: 8.0% Baseline eGFR: 39	1. 90	26 weeks with 2 week single-blind placebo run-in	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.33% C300: - 0.44%	NA	<u>Urinary tract infection:</u> C100: 5 (5.6%) C300: 7 (7.9%)	NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via

PC	2. Canagliflozin 300mg (C300) 3. Placebo (P)	ml/min/1.73 m^2 Mean duration of DM: 16.3 years Inclusion: Type 2 diabetes, stage 2 chronic kidney disease (eGFR ≥30 and <50 ml/min/1.73 m^2, ≥25 years old, A1C ≥7.0 and ≤10.5%, not on AHA therapy or on stable regimen for ≥8 weeks Exclusion: FPG >15.0 mmol/l, type 1 diabetes, renal disease requiring treatment, and cardiovascular diseases or disorders.	2. 89 3. 90		P: -0.03% LS Mean Change C100: -0.30% (95% CI -0.5 to -0.1, p<0.05) LS Mean Change C300: -0.40% (95% CI -0.6 to -0.2, p<0.001) Fasting Plasma Glucose: C100: -0.83 mmol/l (15 mg/dl) C300: -0.65 mmol/l (12 mg/dl) P: -0.03 mmol/l (0.5 mg/dl) LS Mean Change C100: -0.85 mmol/l (95%CI -1.6 to -0.1) p-value not calculated since C300 not SS LS Mean Change C300: -0.67 mmol/l (95% CI -1.4 to -0.1, not SS) Subjects reaching A1C <7.0%: C100: 27.3% C300: 32.6% P: 17.2% Changes in Baseline body weight: C100: -1.2 kg (1.2%) C300: -1.4kg (1.5%) P: -0.3 kg (-0.3%) LS Mean Change C100: -	 NA NA	P: 5 (5.6%) Males genital mycotic infection: C100: 1 (1.7%) C300: 1 (2.1%) P: 0 Female genital mycotic infection: C100: 1 (1.3%) C300: 1 (2.4%) P: 0 Severe Hypoglycemia: C300: 4 (4.7%) C100: 1 (1.2%) P: 1 (1.1%) Withdrawal due to Adverse Events: C100: 4 (4.4%) C300: 2 (2.2%) P: 5 (5.6%)	 NA NA NA	interactive voice-response system. Performance: double-blind treatment design was stated but no details on blinding were provided. Detection: details were not provided Attrition: mITT analysis was used with LOCF for missing data. Overall 12.9% discontinued treatment prior to 26 weeks **External Validity:** Recruitment: from 89 centers in 19 countries. Patient Characteristics: Most patients (98%) were on background AHA therapy, 74% of these were on insulin. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.

					1.6% (95% CI -2.3 to -0.8) LS Mean Change C300: -1.8% (95% CI -2.6 to -1.0)				
CANTATA-SU[24]									
Cefalu, et al Phase III, DB, non-inferiority, RCT 157 centers and 19 countries	1. Canagliflozin 100mg (C100) 2. Canagliflozin 300mg (C300) 3. Glimepiride 6-8mg (G) * All patients on background metformin	Age: 57 yrs Male: 52% Baseline A1C: 7.8% Mean duration of DM: 6.6 years <u>Inclusion:</u> Type 2 diabetes, 18 80 years old, A1C ≥7.0 and ≤9.5%, and stable metformin dose for at least 10 weeks. <u>Exclusion:</u> History of severe hypoglycemia requiring treatment, FPG ≥15 mmol/L, (eGFR <55 ml/min/1.73 m^2, SrCr ≥124 µmol/L for men or SrCr ≥115 µmol/L for women or TZD in prior 16 weeks.	1. 483 2. 485 3. 482	52 weeks with 2-week placebo run-in period	<u>Change from Baseline in A1C at 26 weeks :</u> C100: -0.82% C300: - 0.93% G: -0.81% LS Mean Change C100: -0.01% (95% CI -0.11 to -0.09) C100 non-inferior to glimepiride LS Mean Change C300: -0.12% (95% CI -0.22 to -0.02) C300 superior to glimepiride (no p-value given) <u>LS Mean Change in Fasting Plasma Glucose:</u> C100: -1.35 mmol/l (24 mg/dl) C300: -1.52 mmol/l (27 mg/dl) G: -1.02 mmol/l (18 mg/dl) <u>Subjects reaching A1C <7.0%:</u> C100: 54% C300: 60% G: 56% p-value not given <u>Changes in Baseline body weight:</u>	NA NA NA NA	<u>Urinary tract infection:</u> C100: 31 (6%) C300: 31 (6%) G: 25 (5%) <u>Males genital mycotic infection:</u> C100: 17 (7%) C300: 20 (8%) G: 3 (1%) <u>Female genital mycotic infection:</u> C100: 26 (11%) C300: 34 (14%) G: 5 (2%) <u>Severe Hypoglycemia:</u> C300: 3 (<1%) C100: 2 (<1%) G: 15 (3%) <u>Withdrawal due to Adverse Events:</u> C100: 25 (5%) C300: 32 (7%) G: 28 (6%)	NA NA NA NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Study was double-blind. Detection: Investigators and local sponsor personnel were blinded to treatment assignment. Attrition: mITT analysis was used with LOCF for missing data. Overall attrition was 18-22% with similar rates between the groups. **External Validity:** Recruitment: 157 centers in 17 countries. Patient Characteristics: Patients had an approximate 7 year history of diabetes who were predominately white. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

					C100: -3.7 kg (4.2%) C300: -4.0kg (4.7%) G: 0.7 kg (1%) P<0.0001 for both doses				
ALOGLIPTIN PLUS METFORMIN[29]									
Nauk, et al Phase III, PC, DB, RCT	1. Alogliptin 12.5mg (A12.5 2. Alogliptin 25mg (A25) 3. Placebo * All on background metformin (>1500mg) therapy	Mean Age: 54-56 years Male: 47-54% Baseline A1C: 7.9-8.0% Inclusion: 18-80 years, type 2 diabetes, A1C 7-10%, BMI 23-45 kg/m^2, stable metformin dose. Exclusion: Current AHA treatment other than metformin, abnormal labs, heart disease, glucocorticoid or weight loss drug use.	1. 213 2. 210 3. 104	26 weeks with 4 week single-blind run-in period	<u>Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.6% A25: -0.6% P: -0.1 P<0.001 for both <u>Fasting Plasma Glucose LS mean change:</u> A12.5: -19 mg/dl A25: -17 mg/dl P: 0.0 mg/dl P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 110 (52%) A25: 92 (44%) P: 19 (18%) P<0.001 <u>LS Mean differences in Baseline body weight compared to placebo:</u> A12.5: -0.0 kg (95% CI -0.7 to 0.7) A25: -0.3 kg (95% CI -0.9 to 0.4)	NA NA A12.5 ARR: 34 NNT: 3 A25 ARR: 26 NNT: 4 NS	<u>Upper Respiratory Infection:</u> A12.5: 68 (32%) A25: 5 (2%) P: 7 (7%) <u>Withdrawal due to Adverse Events:</u> A12.5: 7 (3%) A25: 4 (2%) P: 1 (1%)		**Quality Rating: Poor-fair** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice-response system. Performance: Double-blind design but no details provided. Detection: Details on outcome assessment not described. Attrition: FAS analysis with LOCF. Attrition rates ranged from 17-31%. **External Validity:** Recruitment: Patients were from 115 sites in 15 countries. Patient Characteristics: Patients were predominately white, a mean duration of diabetes of 6 years and mean metformin dose of ~1850mg. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.
ALOGLIPTIN PLUS PIOGLITAZONE[30]									
Prately, et al	1. Alogliptin 12.5 mg (A12.5)	Mean Age: 55 yrs. Mean baseline A1C 8.0%	1. 2. 9081	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.66%		<u>Hypoglycemia:</u> A12.5: 5.1% A25: 7.0% P: 5.2%		**Quality Rating: Fair** **Internal Validity: RofB** Selection: Randomization was done via

Phase III, RCT, DB, PC 125 sites	2. Alogliptin 25 mg (A25) 3. Placebo (P) * All on background pioglitazone ± metformin and/or sulfonylurea	Inclusion: type 2 DM, BMI 23-45 kg/m2, A1C 7-10%, ≥ 3 mo. of stable dose TZD with or without metformin or sulfonylurea Exclusion Criteria: Heart disease, abnormal lab values, uncontrolled HTN, and use of other AHAs.			A25: -0.80% P: 0.19% P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 87 (44.2%) A25: 98 (49.2%) P: 18 (18.2%) p=≤ 0.016 for both <u>LS Mean Changes in Baseline body weight from placebo:</u> A12.5: 0.42 kg A25: 0.05 kg P: not given		<u>Upper Respiratory Infection:</u> A12.5: 11 (5.6) A25: 10 (5.0) P: 5 (5.2) <u>Withdrawal due to Adverse Events:</u> A12.5: 6 (3.0%) A25: 6 (3.0%) P: 3 (3.1%)		automated, interactive voice response system. Baseline characteristics were well matched. Performance: Double-blind design but no details were provided. Detection: Blinding of outcomes assessors was not described. Attrition: Patient results were included for those with baseline and at least one post-baseline measurement with LOCF for missing data. Overall attrition was 12%. **External Validity:** Recruitment: Patients from 125 sites. Patient Characteristics: Study participants had few comorbidities, predominantly white and middle-aged. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN PLUS GLYBURIDE[31]									
Pratley, et al Phase III, RCT DB, PC 124 centers and 16 countries	1. Alogliptin 12.5 mg (A12.5) 2. Alogliptin 25 mg (A25) 3. Placebo (P) * All on background glyburide (5-10mg or greater)	Age: 57 years Female: 45-50% Mean Baseline A1C 8.1% Inclusion Criteria: 18-80 years old, type 2 DM, A1C 7-10% and sulfonylurea therapy ≥3 months Exclusion Criteria: Use of AHA therapy within 3 months of study, BMI <23 or >45 kg/m^2, abnormal lab values, heart disease, use of weight loss drugs, oral glucocorticoids and bosentan within 3 months.	1. 203 2. 198 3. 99	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.38% A25: -0.52% P: 0.01% P<0.001 for both <u>Subjects reaching A1C <7.0%:</u> A12.5: 60 (29.6%) P: 18 (18.2%) p= 0.057 A25: 69 (34.8%) P: 18 (18.2%) p=0.008 <u>Changes in Baseline body weight:</u> A12.5: 0.60 kg A25: 0.68 kg P: -0.20 kg	NA NS ARR: NNT: NA	<u>Hypoglycemia:</u> A12.5: 32 (15.8%) A25: 19 (19.6%) P: 11 (11.1%) <u>Upper Respiratory Infection:</u> A12.5: 4 (2.0%) A25: 5 (2.5%) P: 6 (6.1%) <u>Withdrawal due to Adverse Events:</u> A12.5: 5 (2.5%) A25: 4 (2.0%) P: 2 (2.0%)		**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patients randomized according to a permuted block schedule other methodology was not described. Baseline characteristics were well matched. Performance: limited to double-blind designation, details not provided. Detection: no details were provided. Attrition: Levels of attrition ranged from 25-37%, patients with baseline and post-baseline measurement(s) were included with LOCF applied to missing data. **External Validity:** Recruitment: Included patients from 16 countries and 124 centers. Patient Characteristics: Patients were predominately white without significant co-morbidities including heart disease and reduced renal function. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.

ALOGLIPTIN AND INSULIN[32]									
Rosenstock, et al Phase III, RCT DB, PC 110 sites and 13 countries	1. Alogliptin 12.5 mg (A12.5) 2. Alogliptin 25 mg (A25) 3. Placebo (P) * On background insulin therapy ± metformin	Mean Age:55 years Female: 65-85% Mean A1c: 9.3% Inclusion: Patients 18-80 years, A1C ≥8%, BMI 23-45 kg/m^2 and on insulin with or without metformin Exclusion: heart disease, retinopathy, diabetic gastroparesis, cancer, use of other AHAs, weight loss drugs or glucocorticoids.	1. 131 2. 129 3. 130	26 weeks with 4 week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A12.5: -0.63% A25: -0.71% P: -0.13% P<0.001 for both <u>Mean FPG decrease from baseline:</u> A12.5: 0.1 mmol/l (2 mg/dl) A25: -0.6 mmol/l (11 mg/dl) P: 0.3 mmol/l (5.4 mg/dl) <u>Changes in Baseline body weight:</u> A12.5: 0.60 kg A25: 0.7 kg P: 0.6 kg	NA NA NA	<u>Hypoglycemia:</u> A12.5: 26.7% A25: 27.1% P: 24% <u>Any Infection/Infestation</u> A12.5: 43 (33%) A25: 38 (30%) P: 40 (30.1%) <u>Withdrawal due to Adverse Events:</u> A12.5: 1 (0.8%) A25: 6 (4.7%) P: 4 (3.1%)	NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patients randomized with an automated interactive voice response system using a randomization schedule generated before study initiation. Performance: Limited to double-blind designation, details not provided. Detection: no details were provided. Attrition: Analysis was based on FAS. Attrition rates were high; 58% for placebo, 37% for A12.5 and 40% for A25. **External Validity:** Recruitment: Included patients from 13 countries and 110 centers. Patient Characteristics: Patients attended weekly visits to discuss diet and exercise. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN AND PIOGLITAZONE[33]									
DeFronzo, et al Phase III, DB, PC, DD, RCT 20 countries 327 study sites	1. Alogliptin 12.5 mg (A12.) 2. Alogliptin 2 mg (A25) 2. Pioglitazone 15 mg (P15) 3. Alogliptin 12.5 mg + pioglitazone 15mg (A12.5/P) 4. Alogliptin 2 mg + pioglitazone	Mean Age: 54 years Female: 51.1% Baseline mean A1C 8.5% Inclusion: Patients 18-80 years, type 2 DM, AIC 7.5 -11%, failed metformin monotherapy, normal labs, BMI 23-45 kg/m^2 Exclusion: use of glucocorticoids, weight loss drugs, abnormal labs and heart disease	1. 164 2. 163 3. 164 5. 164	26 weeks with 4-week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks for alogliptin monotherapy :</u> A12.5: -0.7% A25: -0.9% P: -0.1% <u>LS Mean Change from Baseline in A1C at 26 weeks for alogliptin/pioglitazone combination therapy :</u> P15/P: -0.7% P15/A12.5: -1.3% P15/A25: -1.25 P30/P: -0.9%	NA	<u>Any hypoglycemia for pooled groups:</u> Pioglitazone groups: 8 (2.1%) A12.5/all pioglitazone doses: 4 (1.0%) A25/all pioglitazone doses: 6 (1.5%) <u>Any Infection/Infestation for pooled groups:</u> Pioglitazone groups: 26.6% A12.5/all pioglitazone doses: 25.1% A25/all pioglitazone	NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Patient randomization details not described. Performance: Limited to double-blind designation, details not provided. Detection: No details provided. Attrition: Attrition rates ranged from 11-46%, with the highest rate in the placebo group. Treatment attrition ranged from 11-28%. FAS with LOCF were used for missing data. **External Validity:** Recruitment: Patients were recruited from 20 countries and 327 sites. Patient Characteristics: Patients were predominately white with the mean duration

	15mg (A12.5/P) 5. Pioglitazone 30 mg (P30) 6. Pioglitazone 30 mg + alogliptin 12.5 mg (P30/A12.5) 7. Pioglitazone 30 mg + alogliptin 25 mg (P30/A25) 8. Pioglitazone 45 mg (P45) 9. Pioglitazone 45 mg + alogliptin 12.5 mg (P45/A12.5) 10. . Pioglitazone 45 mg + alogliptin 25 mg (P45/A25) 11. Placebo (P Alogliptin 25mg + pioglitazone 30mg (A25/P)				P30/A12.5: -1.4% P45/P: -1.0 P45/A12.5: -1.5% P45/A25: -1.6% p≤0.001 for pioglitazone vs. combination therapies (all groups) <u>Subjects reaching A1C <7.0%:</u> All pioglitazone doses: 118 (30.5%) A12.5/all pioglitazone doses: 213 (54.6%) A25/all pioglitazone doses: 218 (55.9%) P<0.001 for all groups compared to pioglitazone alone <u>Changes in Baseline body weight for pooled groups:</u> Pioglitazone groups: 1.5 kg A12.5/P groups: 1.8 kg A25/P groups: 1.9 kg P-value: NS	A12.5/P ARR: 24.1% NNT: 4 A25/P ARR: 25.4 NNT: 4	doses: 30.8% <u>Withdrawal due to Adverse Events:</u> Pioglitazone groups: 11 (2.8%) A12.5/all pioglitazone doses: 6 (2.1%) A25/pioglitazone doses: 6 (1.5%)	NA	of diabetes of 6 years. Outcomes: The accepted surrogate outcome of A1C was used for efficacy measure.
ALOGLIPTIN VS INCREASED PIOGLITAZONE DOSE[34]									

Bosi, et al Phase III, PG, DB, RCT	1. Alogliptin 25 mg (A/P/M)* 2. Pioglitazone 15 mg (P/M)* * All patients were on metformin (≥1500mg or maximum tolerated dose and pioglitazone 30mg	Mean Age: 55 yrs. Female: 49% Inclusion: Patients 18-80 year type 2 DM, systolic BP <160 mm Hg diastolic BP <100 mm Hg, A1C ≥ 7.0 and ≤ 10.0% on metformin and pioglitazone 2 months prior or A1C 7.5% on metformin and other AHA and later A1C ≥ 7.0 and ≤ 10.0% after switching to metformin and pioglitazone for 16 weeks and BMI 23-45 kg/m^2 Exclusion: Elevated BP, heart disease or any other severe disease.	1. 404 2. 399	52 weeks with 4-week run-in	<u>LS Mean Change from Baseline in A1C at 26 weeks :</u> A/P/M: -0.70% P/M: -0.29% P<0.001 <u>Mean FPG decrease from baseline:</u> A/P/M: -0.8 mmol/l (14.4 mg/dl) P/M: -0.2 mmol/l (3.6 mg/dl) P<0.001 <u>Subjects reaching A1C <7.0%:</u> A/P/M: 33.2% P/M: 21.3% P< 0.001 <u>Changes in Baseline body weight:</u> A/P/M: 1.10 kg P/M: 1.60 kg P=0.071	NA NA ARR: 11.9% NNT: 8 NA	<u>Hypoglycemia:</u> A/P/M: 16 (4.0%) P/M: 6 (1.5%) <u>Upper Respiratory Tract Infection:</u> A/P/M: 29 (7.2%) P/M: 16 (4.0%) <u>Withdrawal due to Adverse Events:</u> A/P/M: 12 (3%) P/M: 16 (4.0%)	NA NA NA	**Study Rating: Poor to Fair** **Internal Validity: RofB** Selection: Randomization methods were unclear, no details were provided. Performance: Double-blind design but no details were provided. Detection: Final analysis investigators blinded to interim analysis results but unknown if allocation was concealed. Attrition: Attrition rates in the alogliptin group were 30% and 40% in the pioglitazone group, this includes patients removed from study to due hyperglycemia rescue. A per protocol analysis was used with LOCF for missing data. **External Validity:** Recruitment: Patients were recruited from multiple sites and countries. Patient Characteristics: Patients were predominately white with a 7 year history of diabetes. Outcomes: The accepted surrogate outcome o A1C was used for efficacy measure.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis, FAS- full analysis set
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: AHA = antihyperglycemic agent, PPARγ = peroxisome proliferator-activated receptor-γ, FPG = fasting plasma glucose, A1c- hemoglobin A1c

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Appendix 1: Drug Information

NDE: Canagliflozin[18]

Pharmacology: Canagliflozin works by inhibiting the SGLT2, which is responsible for reabsorbing glucose that is filtered by the kidney. Inhibition of SGLT2 causes less glucose reabsorption and lowers the renal threshold for glucose which causes urinary glucose excretion.

Table 1. Pharmacokinetics[18]

Parameter	Canagliflozin
Half-life	10.6-13.1 hours

Metabolism	*O*-glucuronidation
Elimination	33% renal and 52% hepatic
Renal Dose Adjustment	In patients with an eGFR of 45 to <60 mL/min/1.73 m^2 dose should be limited to 100mg daily In patients with a eGRF of 45 mL/min/1.73 m^2 or less canagliflozin is not recommended
Hepatic Dose Adjustment	No adjustment is recommended for patients with Child-Pugh class A-B hepatic impairment Canagliflozin is not recommend for patients with Child-Pugh class C hepatic impairment

Contraindications/Warnings[18]:

- **Contraindications:** Canagliflozin should not be used in patients with a history of severe hypersensitivity to canagliflozin, severe renal impairment or end-stage renal disease (ESRD).
- **Warning:** Hypotension has been associated with canagliflozin treatment. Caution is advised and correction of volume status and hypovolemia in patients with renal impairment, the elderly, and low systolic blood pressure or on diuretics, ARBs, or ACE inhibitors is recommended. It is recommended that renal function be monitored throughout treatment.

Dose[18]

It is recommended that canagliflozin be started at 100mg with the first meal of the day, with the option of increasing the dose to 300mg once daily if tolerated. See table for renal and hepatic dosing.

NDE: Alogliptin[22]

Pharmacology: Alogliptin is a DDP-4 inhibitor which slows the inactivation of incretin hormones by the DPP-4 enzyme. Incretin hormones cause insulin release and subsequent glucose lowering.

Table 1. Pharmacokinetics[22]

Parameter	Alogliptin
Half-life	21 hours
Metabolism	60-70% excreted unchanged in the urine
Elimination	76% renal and 13% hepatic

Renal Dose Adjustment	In moderate renal impairment (CrCl ≥30 to <60 mL/min) 12.5 mg once daily is recommended In severe renal impairment (CrCl ≥15 to <30 mL/min)/ESRD (CrCl <15 mL/min or dialysis) 6.25 mg once daily is recommended
Hepatic Dose Adjustment	No adjustment is recommended for patients with Child-Pugh class A-B hepatic impairment Alogliptin has not been studied in patients with Child-Pugh class C hepatic impairment

Contraindications/Warnings[22]:

- **Contraindications:** Alogliptin should not be used in patients with a history of severe hypersensitivity to alogliptin.
- **Warning:** Cases of acute pancreatitis have been reported and patients with signs of pancreatitis should discontinue therapy. There have been postmarketing reports of serious hypersensitivity reactions and hepatic failure with alogliptin. To minimize hypoglycemia, consider lowering the dose of insulin secretagogues or insulins when combining with alogliptin.

Dose[18]

It is recommended that alogliptin be taken as a 25mg tablet daily. See table for renal and hepatic dosing recommendations.

APPENDIX 2:
Suggested PA Criteria

Incretin Mimetics

Initiative: To optimize the correct use of insulin mimetics.

Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Exenatide (Byetta®) and Liraglutide (Victoza®), Exenatide Extended-Release (Bydureon®)

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity	**Yes:** Go to #**4.**	**No:** Pass to RPH; Deny (medical appropriateness). **Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.**

- Increased risk of hypoglycemia		
4. Is the patient currently taking insulin?	**Yes:** Go to #5	**No:** Approve for up to 1 year.
5. Is the patient requesting exentatide (Byetta) and is taking insulin glargine?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPH; Deny (medical appropriateness). The safety and efficacy of other insulin formations and GLP-1 Agonists have not been studied.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

DUR Board Action: *9/26/13(KS), 3/17/11 (KS), 4/26/12 (KS)*
Revision(s): *1/31/12 (KS)*
Initiated:

Incretin Enhancers

Initiative:

- Optimize appropriate prescribing of incretin enhancers.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- Sitagliptin (Januvia®)
- Sitagliptin/metformin (Janumet®)
- Saxagliptin (Onglyza®)
- Saxagliptin/metformin (Kombiglyze XR®
- Linagliptin (Tradjenta®)
- Linagliptin/metformin (Jentadueto®)
- Alogliptin (Nesina®)
- Alogliptin/metformin (Kazano®)
- Alogliptin/pioglitazone (Oseni®)

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.

Approval Criteria		
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Go to #3.	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
3. Is the request for sitagliptin (Januvia®) or sitagliptin/metformin (Janumet®)?	Yes: Approve for up to 12 months.	No: Recommend trial of preferred incretin enhancers (sitagliptin or sitagliptin/metformin).

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

P&T / DUR Action: *9/26/13 (KS), 4/26/12 (KS), 3/17/11 (KS)*
Revision(s):
Initiated: *7/16/12, 1/1/12*

Sodium-Glucose Co-Transporter 2 (SGLT2)

Initiative:

- Optimize appropriate prescribing of SGLT2s.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- Canagliflozin (Invokana®)

Covered Alternatives:

Preferred alternatives listed at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.
2. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? Contraindications include: • Renal disease or renal dysfunction • Known hypersensitivity to therapies • Acute or chronic metabolic acidosis • Patients at increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) • Increased risk of hypoglycemia	Yes: Go to #3	No: Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Approval Criteria		
3. Has the patient tried and failed other third-line treatments for diabetes?	Yes: Approve for up to 12 months.	No: Recommend a trial of third-line agents.

Initiating Metformin

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical Management of Hyperglycemia in Type 2 Diabetes; A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care 31;1-11, 2008.

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