Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Abbreviated Class Update: Diabetes Medications

Month/Year of Review: September 2014
Last Class Update: September 2013
PDL Classes: See Appendix 2

End date of literature search: August 2014
Source: OSU DURM

Research Questions:

- Is there any new comparative evidence for diabetes treatments?
- Is there any new evidence about comparative harms among the available diabetes treatments?
- Are there subpopulations of patients with diabetes for which a specific diabetes therapy may be more effective or associated with less harm?

Conclusions:

- A recent systematic review found insufficient evidence to compare health outcomes of the newer diabetes medications and combinations. Intermediate endpoints, including hemoglobin A1c (HbA1c) and weight, found low strength of evidence (SOE) that exenatide XR weekly was superior to exenatide daily, liraglutide was superior to exenatide and sitagliptin, exenatide was superior to sitagliptin, and canagliflozin was similar in efficacy to metformin. In a comparison between metformin and dapagliflozin there was low SOE of a trend favoring dapagliflozin for HbA1c lowering, but it was not deemed clinically significant, -.11% and -.12%, respectively. There was moderate SOE that metformin was superior to linagliptin, alogliptin and sitagliptin. The addition of metformin to alogliptin, linagliptin or sitagliptin resulted in greater glucose lowering than monotherapy dose comparisons.[1]
- In a phase 4, placebo-controlled, randomized trial of over 16,000 patients there was moderate evidence that saxagliptin therapy neither conferred a cardiovascular risk or benefit compared to placebo (HR 1.00 (95% CI, 0.89 to 1.12, P<0.001 for noninferiority). Only small benefits in HbA1c were seen with saxagliptin compared to placebo at 2 years, 7.5% vs. 7.8%, respectively. Hospitalization rates in patients with heart failure were found to be higher in those patients treated with saxagliptin (HR 1.27 [95% CI, 1.07 to 1.51, P=0.007]).[2]
- A systematic review and meta-analysis on sodium-glucose cotransporter 2 (SGLT2) inhibitors, including canagliflozin and dapagliflozin, demonstrated HbA1c lowering when compared to placebo (mean difference -0.66% [95% CI, -0.73% to -0.58%]) and to active comparators (mean difference -0.06% [95% CI, -0.18% to 0.05%]). The most common adverse events were urinary infections (odds ratio, 1.42 [95% CI, 1.06 to 1.90)] and genital tract infections (odds ratio, 5.06 [95% CI, 3.44 to7.45]).[3]
- Oral hypoglycemic scan summary from the Drug Effectiveness Review Project (DERP) found limited new evidence since the last review; no further review or research needed.[4]

Recommendations:

- The current PA criteria (Appendix 1) align with the conclusions of a recent systematic review by the Drug Effectiveness Review Project. No changes to the PDL are recommended.
- Continue to require a prior authorization for saxagliptin therapy. No changes to the PDL are recommended.
- Evidence on SGLT2 inhibitors supports the current PA criteria. Dapagliflozin should be added to the criteria and made non-preferred. No changes to the PDL are recommended.
- There is no new evidence on the comparative efficacy/effectiveness or safety for the oral hypoglycemic PDL class. Evaluate comparative costs in executive session

Reason for Review:

Therapies for the treatment of diabetes were reviewed in September of 2013. Annual class review updates allow for the incorporation of new literature and ensure prior recommendations are current and accurate. This review will analyze the comparative effectiveness of the newer medications for diabetes, including a recent report from the DERP, and incorporate important updates and revisions as they are related to this class since the last review. There was also a recent DERP Scan for the oral hypoglycemic class.[4]

Previous Conclusions and Recommendations:

- There is moderate evidence that canagliflozin is more effective than placebo in lowering HbA1C (-0.77% to -1.06%) in patients with type 2 DM. Designate canagliflozin as non-preferred. Canagliflozin will be available as a fourth–line treatment option for patients unable to tolerate or have contraindications to metformin, sulfonylurea therapy and other third-line treatments.
- There is moderate evidence that alogliptin lowered HbA1C in patients with type 2 diabetes by 0.4%-0.9% compared to placebo. Make alogliptin a non-preferred treatment. Alogliptin is available by PA as a third–line treatment option for patients unable to tolerate or have contraindications to metformin and/or sulfonylurea therapy.
- 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. Sulfonylurea therapies should be considered a preferred second-line treatment option for patients without contraindications or tolerance issues.

Background:

Type 2 diabetes is a prevalent disease which affects an estimated 25.6 million people in the United States.[5] 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.[6] 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.[7,8] A number of therapeutic options are available for management of glycemic variances associated with diabetes.[9] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, insulins, meglitinides, sulfonylureas, thiazolidinediones (TZD), bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Author: Kathy Sentena 8/22/2014 3:18 PM

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, A1C, severe adverse events (SAE) and hypoglycemia rates. Hemoglobin 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.[8] 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.[8] 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.[8] The long-term effect of many of the AHAs on complications of diabetes is unknown.

Methods:

A Medline literature search ending in August 2014 for new systematic reviews and randomized controlled trials (RCTs) for diabetic treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Drug Effectiveness Review Project (DERP), 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, and will be limited to head to head trials.

Systematic Reviews:

DERP – Drug Class Review: Newer Diabetes Medications and Combinations

The Drug Effectiveness Review Project (DERP) reviewed newer antihyperglycemic treatments; amylin agonists, DPP-4 inhibitors, GLP-1 analogs, SGLT2 inhibitors (including dapaliflozin), and drug combinations in individuals with type 2 diabetes and in those with type 1 diabetes for pramlintide only.[1] This streamlined report includes comparisons of head-to-head studies between the classes of newer diabetes medications and newer diabetes medications compared to metformin. Comparisons of the newer diabetes agents to pioglitazone or sulfonylureas were not included. Patients on background therapy with insulin or other oral medications were allowed if the study met other eligibility criteria. Thirty trials met the inclusion criteria, all were randomized controlled trials. The intermediate outcomes, HbA1c and weight, were analyzed in all trials. Health outcomes were rarely reported and a majority of trial durations were 6 months or less. The comparative evidence is presented below.

Within Class Comparisons

Exenatide XR vs. Exenatide

A meta-analysis of three trials found low SOE that exenatide XR weekly lowered HbA1c to a greater extent than twice daily exenatide (WMD -0.46%l 95% CI, -0.69 to -0.23). No differences were found in their effect on weight. Injection site reactions were higher in the exenatide weekly group (moderate SOE).[1]

Liraglutide vs. Exenatide

Liraglutide 1.8 mg daily was compared to exentatide 10 µg twice daily in 464 patients and found to have greater HbA1c lowering (between-group difference: -0.33%; 95% CI, -0.47 to -0.18) based on low SOE. Minor hypoglycemia was higher in the exenatide group (RR 0.55; 95% CI, 0.34 to 0.88). Effect on weight was not different between the groups.[1]

Sitagliptin vs. Saxagliptin
One trial of unknown quality was found to be insufficient to determine the comparative efficacy or harms between sitagliptin and saxagliptin.[1]

Separate Class Comparisons
Exentatide XR vs Sitagliptin
Exenatide XR was found to be more effective than sitagliptin 100mg at lowering HbA1c in a pooled data analysis of two trials (n=753) (WMD -0.48; 95% CI, -0.69 to -0.26) (low SOE). Exenatide was also associated with more weight loss compared to sitagliptin (WMD -1.32; 95% CI, -1.87 to -0.76) based on low SOE. Nausea, vomiting and diarrhea were higher in with exenatide XR compared to sitagliptin.[1]

Liraglutide vs. Sitagliptin
One trial of 665 patients found liraglutide 1.2mg and liraglutide 1.8mg to be more effective than sitagliptin 100mg in mean HbA1c reduction, -0.34 and -60%, respectively (low SOE). More nausea was reported with liraglutide than with sitagliptin.[1]

Canagliflozin vs. Sitagliptin
Canagliflozin 100mg and 300mg was compared to sitagliptin and no differences in HbA1c lowering were seen based on low SOE. Canagliflozin (100mg and 300ng) was associated with more weight loss than sitagliptin (low SOE). Women allocated to canagliflozin were found to have a higher incidence of genital mycotic infections compared to sitagliptin in one trial (low SOE).[1]

DPP-4 vs. Metformin
Eight trials compared a DPP-4 inhibitor to metformin. Half of the trials were sitagliptin and metformin comparisons. One study of linagliptin and alogliptin and two saxagliptin studies were included. Metformin 1000 mgs or more was found to be more effective than linagliptin 5 mg, alogliptin 25 mg and sitagliptin 100 mg (between-group differences range from -0.30% to -0.60%) (moderate SOE). When "uptitration" of metformin (patients not at goal on submaximal doses of metformin) were compared to saxagliptin, no difference in efficacy was found based on low SOE. The addition of saxagliptin resulted in more hypoglycemia events compared to metformin alone (low SOE). Adverse events for the DPP-4 inhibitors and metformin were similar between groups except for the incidence of diarrhea, which was higher for metformin compared to alogliptin and sitagliptin (low SOE). Greater weight reduction was found with metformin 1000 mg per day when compared head-to-head with DPP-4 inhibitors.[1]

GLP-1 Analogs vs. Metformin
Exentatide and exenatide XR were compared to metformin in two studies, however there was insufficient evidence to compare efficacy.[1]

Dapagliflozin vs. Metformin

In a comparison between dapagliflozin and metformin, no difference in HbA1c lowering was found. There was a trend favoring dapagliflozin but it was not deemed clinically significant (-.11% and -.12%). Low SOE found dapagliflozin to be associated with more weight loss than metformin. Rates of hypoglycemia and nausea were similar between groups (low SOE).[1]

Fixed Dose Combination/Dual Therapy Product Comparisons

Alogliptin plus Metformin

There was moderate SOE that alogliptin plus metformin was more effective, HbA1c lowering of -0.44% to -0.99%, than monotherapy for all dose comparisons. Similar changes in weight were observed for all groups (moderate SOE).[1]

Linogliptin plus Metformin

The combination of linagliptin plus metformin was shown to lower HbA1c more than component therapy of each. Differences in HbA1c lowering ranged from -0.50% to -1.10%. The combination of linagliptin 2.5 mg and metformin 1000 mg twice daily was found to cause greater weight loss than linagliptin 5 mg daily (low SOE).[1]

Sitagliptin plus Metformin

Sitagliptin 100 mg plus metformin 2000 mg daily was associated with greater HbA1c reductions compared to metformin monotherapy in a meta-analysis of two trials of short duration (WMD -0.60 %; 95% CI, -0.75 to -0.45). No differences in weight reductions between the groups were seen.[1]

Vasilakou, et al- Sodium-Glucose Cotransporter 2 Inhibitors for Type 2 Diabetes

A systematic review and meta-analysis was performed on the new AHA class sodium-glucose cotransporter 2 (SGLT2) inhibitors.[3] Forty five placebo-controlled and 13 active comparator studies of canagliflozin 100 or 300mg (12 trials), dapagliflozin 5 or 10 mg (21 trials), ipragliflozin (8 trials), empagliflozin (3 trials), luseogliflozin (2 trials), tofogliflozin (1 trial), ertugliflozin (1 trial), and remogliflozin (1 trial). Of the agents studied canagliflozin and dapagliflozin are the only US approved SGLT2 inhibitors. In the active comparator studies, SGLT2 inhibitors were compared to metformin (6 studies), sitagliptin (5 studies), and sulfonylureas (2 studies). The majority of studies lasted between 12-26 weeks.

A majority of studies were found to have a high risk of publication bias due to incomplete outcome data and use of last-observation-carried-forward (LOCF) methodology, which can overstate results. For most efficacy outcomes the evidence was graded as low. Studies of placebo-controlled trials showed SGLT2 inhibitors to lower A1c (mean difference, -0.66% [95% CI, -0.73% to -0.58%]).[3] Comparison of SGLT2 inhibitors versus active treatments also slightly favored SGLT2 inhibitors (mean difference -0.0.6% [95% CI -0.18% to -0.05%]). SGLT2 inhibitors as add-on treatment also demonstrated A1c lowering (WMD, -0.61%, 95% CI -0.69% to -0.53%). SGLT2 inhibitors were found to have similar lowering as other AHAs when used as monotherapy or as add-on treatment in studies included in the analysis. Changes in A1c seen with dapagliflozin compared to placebo were -0.59% (95% CI, -0.67% to -0.50%) and for canagliflozin -0.78% (95% CI, -0.90% to -0.66%). Changes in body weight from baseline favored SGLT2 inhibitors compared to placebo (WMD -1.74 kg, 95% CI -2.03 to -1.45 kg) and percent change (WMD -2.27%, 95% CI, -2.73% to -2.02%).[3] Comparison in body weight changes with active comparators demonstrated only small weight reductions favoring SGLT2 inhibitors. Greater blood pressure reductions were seen with SGLT2 inhibitors compared to placebo and active control, -3.77 mmHg and –4.45 mmHg, respectively. SGLT2 inhibitors were associated with an increased risk of genital and urinary tract infections. Hypoglycemia risk was similar to other treatments. There was insufficient evidence on cardiovascular outcomes and mortality. Dapagliflozin was shown to have a higher incidence of bladder and breast cancer compared to control, however, data is insufficient to draw firm conclusions.

Author: Kathy Sentena 8/22/2014 3:18 PM

New Guidelines:

IDF – Managing Older People with Type 2 Diabetes Global Guideline
In response to the need for specific advice for older individuals with diabetes the International Diabetes Foundation (IDF) released a global guideline in 2013.[10] Recommendations include glucose and management targets that are individualized and based on patient's functional status and comorbidities (established CVD, history and risk of hypoglycemia, and presence of microvascular complications).

Treatment selection should be based on the overall risk-to-benefit ratio to the patient.[10] First-line therapy, in patients without contraindications, is metformin. Sulfonylureas are recommended for those unable to take metformin, however, glyburide/glibenclamide should be avoided due to risk of hypoglycemia. DDP-4 inhibitors may be considered if an economically viable option for the patient. For patients with an unpredictable eating schedule and those with postprandial hyperglycemia, glinides maybe an appropriate choice.

For second-line treatment, sulfonylureas are recommended and DPP-4 inhibitors can also be considered.[10] Long-acting basal insulin is appropriate in patients who cannot tolerate or have contraindications to oral agents. Third line treatments include: triple oral therapy, basal or pre-mixed insulins and GLP-1 agonists. If patients are still not meeting glycemic goals in triple therapy then switching one of the oral agents to a different class, initiating basal or pre-mixed insulin, using GLP-1 agonists, changing to or adding insulin if on a GLP-1 agonists or maximizing current insulin regimen is recommended. Basal insulin, long-acting insulin or once or twice daily premixed insulin should be used in patients requiring further glucose lowering.

NICE – Dapagliflozin in Combination Therapy for Treating Type 2 Diabetes
A 2013 technology report on the use of dapagliflozin in combination with other AHA was created by the National Institutes for Health and Care Excellence (NICE).[11] Five, good-quality, randomized controlled trials were included in the analysis. Recommendations were to consider the use of dapagiflozin with metformin if there is a significant risk of hypoglycemia and if there are contraindications to a sulfonylurea. Dapagliflozin could also be considered as an addition to sulfonylurea therapy if metformin is contraindicated or not tolerated. Dapagliflozin and insulin in combination is a recommended option for type 2 diabetes patients. The combination of dapagliflozin and insulin is also recommended. Using dapaglifozin as a third agent, with metformin and a sulfonylurea, is not recommended at this time.

NICE – Canagliflozin in Combination Therapy for Treating Type 2 Diabetes
A 2014 technology report form NICE reported on the evidence of six, good-quality, randomized controlled trials on the use of canagliflozin.[12] Canagliflozin is recommended as dual therapy when sulfonylureas are contraindicated or not tolerated and in patients at significant risk of hypoglycemia. Canagliflozin use may also be considered in patients taking metformin and a sulfonylurea or metformin and pioglitazone as part of a three-drug regimen. The use of canagliflozin and insulin may also be an appropriate treatment option.

New Safety Alerts:

FDA to Review Heart Failure Risk with Diabetes Drug Saxagliptin (marketed as Onglyza and Kombiglyze XR)

In February of 2014 the FDA announced that they will be investigating heart failure associated with saxagliptin.[13] The FDA action was in response the SAVOR-TIMI 53 trial[2] in New England Journal of Medicine (NEJM), presented below, which showed an increased risk of hospitalizations for heart failure in those patients randomized to saxagliptin.

New Primary Literature:

Saxagliptin and Cardiovascular Outcomes

In order to further define the risks and benefits of saxagliptin therapy on cardiovascular outcomes, a phase 4, placebo-controlled, good quality, randomized controlled trial was conducted in 16,492 patients in the SAVOR-TIMI 53 trial.[2] Patients were randomized in a 1:1 fashion to saxagliptin 5 mg daily (patients with an estimated glomerular filtration rate [GFR] of ≤50 ml/minute received saxagliptin 2.5mg daily) or placebo for median of 2.1 years. Majority of patients were male (67%) and were a mean age of 65 years. The mean HbA1c was 8% and median duration of diabetes was 10 years. To be eligible for study participation patients had to have type 2 diabetes and history of established cardiovascular disease or multiple risk factors for vascular disease. Other treatments for diabetes and cardiovascular disease were permitted, however, the use of incretin-based therapy currently or within the previous 6 months was not allowed. The primary efficacy and safety endpoint was the composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal ischemic stroke. Key secondary endpoints were the primary composite endpoint and hospitalization for heart failure, coronary revascularization, or unstable angina.

There is moderate SOE that saxagliptin was not superior but was non-inferior to placebo for the incidence of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal ischemic stroke (HR: 1.00 (95% CI, 0.89 to 1.12, P<0.001 for noninferiority).[2] For the secondary endpoint of the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, coronary revascularization or heart failure was found to be similar between saxagliptin and placebo, 12.8% and 12.4%, respectively (HR: 1.02 [95%CI, 0.94 to 1.11, P=0.66). The results for the primary and secondary endpoints in the saxagliptin groups were similar for patients with heart failure and without. Saxagliptin was associated with more hospitalizations for heart failure compared to placebo (HR1.27 [95% CI, 1.07 to 1.51, P=0.007). Hemoglobin A1c levels were significantly lower in patients treated with saxagliptin compared to placebo at year 1 (7.6% vs 7.9%), year 2 (7.5% vs. 7.8%) and end of the treatment period (7.7% and 7.9%).

Hypoglycemia was more in common in patients treated with saxagliptin compared to placebo and major hypoglycemia occurred in 2.1% of saxagliptin patients and 1.7% of placebo treated patients (P=0.047). The rate of pancreatitis was similar between groups (0.3%). The risk of pancreatic cancer was higher in the placebo group (n=12) compared to saxagliptin (n=5). Overall discontinuation rates were slightly lower with saxagliptin versus placebo, 18.4% and 20.8%, respectively.[2]

In patients with type 2 diabetes, saxagliptin therapy was associated with no cardiovascular benefit or risk. Hemoglobin A1c reductions favored saxagliptin but the change was small and clinical significance is unknown. The optional use and titration of other medications for diabetes could account for small differences in HbA1c between the groups but also raises the question if the benefit of saxagliptin is worth the potential for additional adverse events. Saxagliptin association with an increased risk of hospitalizations in patients with heart failure needs to be further investigated.

Drug Class Scans

Author: Kathy Sentena 8/22/2014 3:18 PM

The DERP Scan was used to identify any new comparative research that has emerged since the last P&T review.[4] There is limited new evidence since the last review; no further review or research needed.

Previous research found the following:

- There is no clinically significant difference between any of the agents in these two drug classes (oral sulfonylureas and non-sulfonylurea secretagogues) in their ability to lower hemoglobin HbAlc.
- There is no statistically significant difference between glyburide and chlorpropamide in the progression or occurrence of clinically relevant outcomes with the exception of retinopathy. Patients on glyburide had greater risk reduction of progression of retinopathy than those on chlorpropamide.
- There is insufficient evidence on other sulfonylureas and nonsulfonylureas secretagogues to identify a difference in progression or occurrence of clinically relevant outcomes.
- Chlorpropamide has a less favorable adverse effect profile compared to glyburide. There is no difference in safety or adverse effect profiles for other oral sulfonylureas and non-sulfonylureas secretagogues. Glimepiride, glipizide, glyburide, micronized glyburide and repaglinide do not differ in safety or adverse effect profile. No evidence exists for evaluation of tolbutamide, tolazamide or nateglinide.

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
3.) Composite of cardiovascular death, MI or ischemic stroke

Evidence Table

Study Design	Drug Regimen/ Duration	Patient Population	N	Outcomes/Efficacy Results (CI, p-values)	ARR/NNT	Safety Results (CI, p-values)	ARR/NNH	Quality Rating

SAVOR-TIMI[2] Scirica B, et al Phase 4, RCT, DB, PC Countries	1. Saxagliptin 5mg daily (S)* 2. Placebo daily (P) * Saxagliptin dose was reduced to 2.5 mg daily if estimated GFR was ≤50 ml/min	Mean Age: 65 years Female: 33% Baseline A1C: 8.0% **Inclusion**: Patients with type 2 DM, HbA1C of ≥6.5 and ≤12.0% and a history of cardiovascular disease or multiple risk factors for vascular disease. **Exclusion**: currently receiving or had received in the previous 6 months a incretin-based therapy, end-stage renal disease with dialysis, renal transplant or elevated serum creatinine (>6.0 mg/dL)	Main Study: 1. 828 2. 8212	2.1 years median follow-up	<u>Composite of cardiovascular death, MI or ischemic stroke :</u> S: 613 (7.3%) P: 609 (7.2%) HR 1.00 (95% CI, 0.89 to 1.12, P=0.99 for superiority, P<0.001 for non-inferiority <u>Cardiovascular death, MI, ischemic stroke, hospitalization for unstable angina, coronary revascularization or heart failure:</u> S: 1059 (12.8%) P: 1034 (12.4%) HR: 1.02 (95% CI, 0.94 to 1.11, p=0.66) <u>Hospitalizations due to heart failure:</u> S: 289 (3.5%) P: 228 (2.8%) HR 1.27 (95% CI, 1.07 to 1.12, p=0.007) <u>A1c levels at 2 years:</u> S: 7.5% P: 7.8% P<0.001 <u>Changes in Baseline body weight at 2 years:</u> S: 87.3 kg P: 87.8 kg P=0.46	NA NA ARR: 0.7% NNH: 1,428 NA NA	<u>Major Hypoglycemia</u> S: 177 (2.1%) P: 140 (1.7%) P=0.047 <u>Pancreatitis:</u> S: 24 (0.3%) P: 21 (0.3%) P=0.77	ARR: 0.4% NNH: 2,500 NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: randomization done via central computerized telephone or web-based system Performance: study was conducted in blinded fashion with matched placebo control. Detection: data analysis done independently o sponsors with blinded adjudication of event. Attrition: ITT analysis was used and 97% of patients completed trial. **External Validity** Recruitment: Not stated. Patient Characteristics: majority of patients ha established atherosclerotic disease, hypertension and dyslipidemia. Outcomes: primary outcome was appropriate health outcome for this population.

[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, A1c- hemoglobin A1c, MI-myocardial infarction

References:

1. Feltner C, Wines R, Simon J, et al. Drug class review: Newer diabetes medications and combinations. Prepared by the RTI-UNC Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health and Science University. Portland, OR. 2014.
2. Scirica B, Bhatt D, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2013;369:1317-26. Doi:10.1056/NEJMoal1307684.
3. Vasilakou D, Karagiannis T, Athanasiasou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159:262-274.
4. Thakurta, S. Drug Effectiveness Review Project: Drug Class Review on Oral Hypoglycemics. Preliminary Scan Report #6. May 2014.
5. National Diabetes Information Clearinghouse (NDIC). National Diabetes Statistics. NIH Publication. Accessed July 2, 2013. Accessed at: http://www.diabtetes.niddk.nih.gov/dm/pubs/statistics/#Diagnosed20
6. Centers for Disease Control and Prevention Press Release. Number of Americans with Diabetes Projected to Double or Triple by 2050. 2010. Accessed July 23, 13. Available at: http://www.cdc.gov/media/pressrel/2010/r101022.html.
7. ACCE Guidelines. American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013 Consensus Statement. Endocr Pract. 2013;19(Suppl 2).
8. Inzucchi S, Bergenstal R, Buse J, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Diabetes Care 2012; 35:1364-1379.
9. Nathan D, Buse J, Davidson M, et al. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2008;31:1-11.
10. International Diabetes Federation. Managing Older People with Type 2 Diabetes Global Guideline. 2013. Accessed on July 28, 2014. Available at: http://www.idf.org/sites/default/files/IDF-Guideline-for-older-people-T2D.pdf.
11. National Institute for Health and Care Excellence (NICE). Dapagliflozin in combination therapy for treating type 2 diabetes. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jun. 61 p. (Technology appraisal guidance; no.288).
12. National Institute for Health and Care Excellence (NICE). Canagliflozin in combination therapy for treating type 2 diabetes. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jun. (Technology appraisal guidance; no.315).
13. Food and Drug Administration Drug Safety Communication. FDA to Review Heart Failure Risk with Diabetes Drug Saxagliptin (marketed as Onglyza and Kombiglyze XR). Accessed July 29, 2014. Available at: http://www.fda.gov/drugs/drugsafety/ucm385287.htm

APPENDIX 1: Current PA Criteria

Incretin Enhancers (DPP-4 Inhibitors)

Initiative:

- Optimize correct use that corresponds to National Guidelines of incretin enhancers.

Length of Authorization:

Up to 12 months

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org.

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.
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: *9/23/14 (HM/KS), 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

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

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.
3. Has the patient tried and failed other third-line treatments for diabetes or have contraindications to third-line treatments?	Yes: Approve for up to 12 months.	No: Deny. Require 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.

P&T / DUR Action: *9/23/14 (KS), 9/26/13 (KS)*
Revision(s):
Initiated: *9/26/13*

Incretin Mimetics (GLP-1 Analog)

Initiative:

- **To optimize the correct use of insulin mimetics.**

Length of Authorization:

Up to 12 months

Requires PA:

- **Non-preferred drugs**

Preferred Alternatives:

Preferred alternatives listed at www.orpdl.org

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. www.orpdl.org	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Renal disease or renal dysfunction	**Yes:** Go to #**4.**	**No:** Pass to RPH; Deny (medical appropriateness). **Recommend trial of metformin or sulfonylurea. See**

- Known hypersensitivity - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity - Increased risk of hypoglycemia		**below for metformin titration schedule.**
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 12 months	**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: *9/23/14 (KS), 9/26/13(KS), 3/17/11 (KS), 4/26/12 (KS)*
Revision(s): *1/31/12 (KS)*
Initiated:

Appendix 2 – Preferred Drug List Classes and Drug Status

Incretin Enhancers (DPP-4 Inhibitors and SGLT2 Inhibitors)

Brand	Generic	FormDesc	PDL
JANUMET	SITAGLIPTIN PHOS/METFORMIN HCL	TABLET	Y
JANUVIA	SITAGLIPTIN PHOSPHATE	TABLET	Y
FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	TABLET	N
INVOKANA	CANAGLIFLOZIN	TABLET	N
JENTADUETO	LINAGLIPTIN/METFORMIN HCL	TABLET	N
KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	TABLET	N
NESINA	ALOGLIPTIN BENZOATE	TABLET	N
ONGLYZA	SAXAGLIPTIN HCL	TABLET	N
TRADJENTA	LINAGLIPTIN	TABLET	N
JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	TBMP 24HR	N
KOMBIGLYZE XR	SAXAGLIPTIN HCL/METFORMIN HCL	TBMP 24HR	N
OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	TABLET	N

Incretin Mimetics (GLP-1 Analog)

Brand	Generic	FormDesc	PDL
BYDUREON	EXENATIDE MICROSPHERES	VIAL	N
BYDUREON PEN	EXENATIDE MICROSPHERES	PEN INJCTR	N
BYETTA	EXENATIDE	PEN INJCTR	N
SYMLINPEN 120	PRAMLINTIDE ACETATE	PEN INJCTR	N
SYMLINPEN 60	PRAMLINTIDE ACETATE	PEN INJCTR	N
TANZEUM	ALBIGLUTIDE	PEN INJCTR	N
VICTOZA 2-PAK	LIRAGLUTIDE	PEN INJCTR	N
VICTOZA 3-PAK	LIRAGLUTIDE	PEN INJCTR	N

Thiazolidinediones

Brand	Generic	FormDesc	PDL
ACTOS	PIOGLITAZONE HCL	TABLET	Y
PIOGLITAZONE HCL	PIOGLITAZONE HCL	TABLET	Y
ACTOPLUS MET	PIOGLITAZONE HCL/METFORMIN HCL	TABLET	N
AVANDAMET	ROSIGLITAZONE/METFORMIN HCL	TABLET	N
PIOGLITAZONE-METFORMIN	PIOGLITAZONE HCL/METFORMIN HCL	TABLET	N
ACTOPLUS MET XR	PIOGLITAZONE HCL/METFORMIN HCL	TBMP 24HR	N
AVANDARYL	ROSIGLITAZONE/GLIMEPIRIDE	TABLET	
DUETACT	PIOGLITAZONE HCL/GLIMEPIRIDE	TABLET	
PIOGLITAZONE-GLIMEPIRIDE	PIOGLITAZONE HCL/GLIMEPIRIDE	TABLET	

Oral Hypoglycemics

Brand	Generic	FormDesc	PDL
FORTAMET	METFORMIN HCL	TAB ER 24	Y
METFORMIN HCL ER	METFORMIN HCL	TAB ER 24	Y
GLUCOPHAGE XR	METFORMIN HCL	TAB ER 24H	Y
METFORMIN HCL ER	METFORMIN HCL	TAB ER 24H	Y
AMARYL	GLIMEPIRIDE	TABLET	Y
DIABETA	GLYBURIDE	TABLET	Y
GLIMEPIRIDE	GLIMEPIRIDE	TABLET	Y
GLIPIZIDE	GLIPIZIDE	TABLET	Y
GLUCOPHAGE	METFORMIN HCL	TABLET	Y
GLUCOTROL	GLIPIZIDE	TABLET	Y
GLYBURIDE	GLYBURIDE	TABLET	Y
METFORMIN HCL	METFORMIN HCL	TABLET	Y
MICRONASE	GLYBURIDE	TABLET	Y
RIOMET	METFORMIN HCL	SOLUTION	N
GLIPIZIDE ER	GLIPIZIDE	TAB ER 24	N
GLIPIZIDE XL	GLIPIZIDE	TAB ER 24	N
GLUCOTROL XL	GLIPIZIDE	TAB ER 24	N
GLUMETZA	METFORMIN HCL	TABERGR24H	N
CHLORPROPAMIDE	CHLORPROPAMIDE	TABLET	N
GLIPIZIDE-METFORMIN	GLIPIZIDE/METFORMIN HCL	TABLET	N
GLUCOVANCE	GLYBURIDE/METFORMIN HCL	TABLET	N
GLYBURIDE MICRONIZED	GLYBURIDE,MICRONIZED	TABLET	N
GLYBURIDE-METFORMIN HCL	GLYBURIDE/METFORMIN HCL	TABLET	N
GLYNASE	GLYBURIDE,MICRONIZED	TABLET	N
NATEGLINIDE	NATEGLINIDE	TABLET	N
PRANDIMET	REPAGLINIDE/METFORMIN HCL	TABLET	N
PRANDIN	REPAGLINIDE	TABLET	N
REPAGLINIDE	REPAGLINIDE	TABLET	N
STARLIX	NATEGLINIDE	TABLET	N
TOLAZAMIDE	TOLAZAMIDE	TABLET	N
TOLBUTAMIDE	TOLBUTAMIDE	TABLET	N
ACARBOSE	ACARBOSE	TABLET	
GLYSET	MIGLITOL	TABLET	
PRECOSE	ACARBOSE	TABLET	