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Newer Diabetes Medications and Combinations (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors) Drug Effectiveness Review Project Summary Report

Date of Review: September 2016 **Date of Last Review:** September 2015

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

1. What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus (T2DM)?
2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with T2DM?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) differ in efficacy/effectiveness or tolerability and frequency of adverse events?

Conclusions:

- There was insufficient evidence to make conclusions on health outcomes (macrovascular disease, microvascular disease and all-cause mortality) for *between* class comparisons of the newer diabetes medications listed in Table 1.[1]
- *Within* class comparisons of low strength evidence were available for dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Comparison of sitagliptin and saxagliptin found similar hemoglobin A1c (A1c) lowering (-1.07% and -1.34% at 24 weeks, respectively). Pooled analysis of 3 studies found exenatide XR to lower A1c to a greater extent than exenatide (weighted mean difference [WMD] -0.46%; 95% CI, -0.69 to -0.23). Other GLP-1 receptor agonists comparisons varied in A1c lowering by -0.20% to -0.33%. Risk of adverse events were similar for *within* class comparisons of DPP-4 inhibitors and for *within* class comparisons of GLP-1 receptor agonists.[1]
- In comparisons *between* DPP-4 inhibitors and GLP-1 receptor agonists, greater A1c lowering and weight loss were seen with GLP-1 receptor agonists based on low strength evidence. However, GLP-1 receptor agonists were more commonly associated with higher withdrawal rates due to adverse events (i.e., gastrointestinal effects) compared to DPP-4 inhibitors.[1]
- Moderate strength evidence found canagliflozin (a sodium-glucose cotransporter 2 (SGLT2) inhibitor) to lower A1c by -0.24% more than sitagliptin (a DPP-4 inhibitor) in one study. Two studies found the number of patients who obtained a goal A1c of less than 7% was greater with SGLT2 inhibitors compared to DPP-4 inhibitors but one study did not find any difference between the classes (low to moderate strength evidence). Rates of overall adverse events were similar *between* classes except there were higher rates of genital mycotic infections with SGLT2 inhibitors when compared to DPP-4 inhibitors.[1] Urinary tract infections and risk of hypoglycemia were similar between groups.[1]

- Metformin was found to decrease A1c more than DPP-4 inhibitors with a mean treatment difference of -0.3% to -0.6% based on moderate evidence. Small differences in weight changes favored metformin over DPP-4 inhibitors. Withdrawals due to adverse events were similar between metformin and DPP-4 inhibitors with less hypoglycemia seen in patients treated with metformin.[1]
- In one study, the GLP-1 receptor agonist dulaglutide was found to decrease A1c more than metformin with similar changes in weight and more hypoglycemia in the dulaglutide group (low strength evidence).[1]
- Low strength evidence found comparisons of SGLT2 inhibitors to have similar A1c lowering as metformin and metformin XR with more weight changes in the SGLT2 groups (mean difference -1.18 kg to -3.9 kg). Risk of adverse events and withdrawals due to adverse events were similar between groups.[1]
- Fixed-dose combinations of DPP-4 inhibitors and metformin were found to decrease A1c by a difference of -0.44% to -1.10% compared to their monotherapy components. Changes in weight were imprecise depending on the DPP-4 inhibitor studied.[1]
- Low strength of evidence found SGLT2 inhibitors plus metformin to be more effective at lowering A1c compared to their monotherapy components. Comparisons of SGLT2 inhibitor and DPP-4 combinations also demonstrated more A1c lowering compared to their monotherapy components; however, comparisons to DPP-4 monotherapy were not clinically significant (MD -0.14%; 95% CI, -0.33 to -0.06). Weight loss was similar with dual therapy and SGLT2 inhibitor monotherapy based on moderate strength of evidence.[1]
- Limited evidence was available for subgroup comparisons therefore no conclusions could be drawn.[1]

Recommendations:
- Current evidence for these agents does not support specific changes to the current Preferred Drug List (PDL).
- Recommend to continue current prior authorization (PA) criteria with minor modification to allow concurrent use of basal or bolus insulin with GLP-1 receptor agonists (Appendix 2).
- After review of comparative drug costs in the executive session, no further changes to the PDL were made.

Previous Conclusions:
- There is insufficient new comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for T2DM. Evidence-based recommendations in new clinical practice guidelines and a systematic review of diabetes agents from the Agency for Healthcare Research and Quality (AHRQ) support the current status of non-insulin antidiabetic therapies on the preferred drug list (PDL).[2]
- High quality evidence suggest patients on metformin, pioglitazone, metformin plus a DPP-4 inhibitor, or metformin plus a SGLT-2 inhibitor have similar rates of all-cause mortality based on one systematic review.[2]
- In patients with a history of cardiovascular (CV) disease, there is moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) can decrease risk for CV death, non-fatal myocardial infarction (MI), or non-fatal stroke versus placebo (10.5% vs. 12.1%), with a number needed to treat (NNT) of 63 over 3.1 years (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99) in patients with high cardiovascular risk. Reduction in risk is primarily driven by a 2.2% reduction in CV death (3.7% vs. 5.9%) and not non-fatal MI or non-fatal stroke.[2]
- There is high quality evidence that monotherapy with either metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU) results in similar lowering of A1c based on one systematic review.[2]
- There is moderate quality evidence that DPP-4 inhibitors lower A1c less than metformin and glimepiride.[2]
- Moderate quality evidence suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo. Evidence finds these agents to be non-inferior to placebo when a composite of CV outcomes are evaluated.[2]

- Moderate quality evidence showed a statistically significant increase in heart failure (HF) outcomes with DPP-4 inhibitors compared to placebo or active treatment.[2]
- High quality evidence suggests hypoglycemia rates are higher with SU than comparative T2DM therapy. Evidence suggests glyburide is associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).[2]
- There is low quality evidence to recommend metformin use in patients with mild to moderate kidney disease. Evidence suggests metformin is safe in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m^2) without increased risk of lactic acidosis. The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.[2]
- In December of 2014, Saxenda (liraglutide for injection) was approved for chronic weight management in addition to a reduced-calorie diet and physical activity. Treatments for weight loss are not funded by the OHP.[2]

Previous Recommendations:
- Make Byetta (exenatide) a preferred agent but subject to current PA for GLP-1 receptor agonists.
- Make Glyxambi (empagliflozin/linagliptin) non-preferred drug subject to current PA for SGLT-2 inhibitors.
- Remove clinical PA for pramlintide due to low overall utilization and current FDA-mandated Risk Evaluation Mitigation Strategy (REMS) already in place to promote safe use through education.
- Modify SGLT-2 inhibitor clinical PA criteria to require monitoring renal function every 6 months.
- Continue clinical PA criteria for all DPP-4 inhibitors and all GLP-1 receptor agonists.

Methods:
The July 2016 Drug Class Review on newer diabetes medications and combinations by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1]

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
In July 2016, DERP released a drug class update on newer diabetes medications in adults with T2DM. The report included 52 studies.[1] The review classified the amylin agonists, DDP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors as newer diabetes medications (Table 1).[1] Fixed-dose formulations and fixed-dosed regimens, administered as separate agents at the same time (defined as dual therapies), were also included. Patient characteristics were predominately middle-aged white women and men who were obese with a history of T2DM of less than 10 years and a baseline A1c of less than 9%.[1] No evidence, or insufficient evidence, was found for health outcomes (microvascular disease, macrovascular disease and all-cause mortality) comparisons *between* classes.[1]

Table 1. Newer Diabetes Medications Included in the DERP Review.[1]

Generic Name	Trade Name	Formulation
DPP-4 Inhibitors		
Sitagliptin	Januvia®	Oral
Saxagliptin	Onglyza®	Oral
Linagliptin	Tradjenta®	Oral
Alogliptin	Nesina®	Oral
GLP-1 Receptor Agonists		
Albiglutide	Tanzeum™	Injection
Dulaglutide	Trulicity®	Injection
Exenatide	Byetta®	Injection
Exenatide XR	Bydureon®	Injection
Liraglutide	Victoza®, Saxenda®	Injection
Sodium-glucose co-transporter-2 inhibitor (SGLT2)		
Canagliflozin	Invokana®	Oral
Dapagliflozin	Farxiga®	Oral
Empagliflozin	Jardiance®	Oral
Fixed Dose Combination Products (FDCPs)		
Alogliptin + Pioglitazone	Oseni	Oral
Metformin + Sitagliptin	Janumet®	Oral
Metformin + Sitagliptin XR	Janumet XR®	Oral
Metformin ER + Saxagliptin	Kombiglyze XR®	Oral
Metformin + Alogliptin	Kazano®	Oral
Metformin + Linagliptin	Jentadueto®	Oral
Metformin + Canagliflozin	Invokamet®	Oral
Metformin + Empagliflozin	Synjardy®	Oral
Metformin ER + Dapagliflozin	Xigduo XR®	Oral
Empagliflozin + Linagliptin	Glyxambi®	Oral

Within Class Comparisons:

GLP-1 Receptor Agonists

- Exenatide XR was found to be more effective at lowering A1c compared to exenatide (weighted mean difference [WMD] -0.46%; 95% CI, -0.69 to -0.23%) based on moderate evidence from 3 studies.[1]
- Single study comparisons are listed below in Table 2.

Table 2. Within Class Comparisons of GLP-1 Receptor Agonists.[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Liraglutide 1.8 mg once daily vs. exenatide 10 mcg twice daily	26 weeks	A1c lowering	MD -0.33%; 95% CI, -0.47 to -0.18; P<0.0001	Low
Exenatide 5-10 mcg twice daily vs. Dulaglutide 0.75 mg or 1.5 mg once weekly	26 weeks	A1c <7%	Exenatide: 52% Dulaglutide 0.75 mg: 66% (P < 0.001) Dulaglutide 1.5 mg: 78% (P < 0.001)	Low
Albiglutide 30-50 mg once weekly vs. Liraglutide 0.6 to 1.8 mg once daily	32 weeks	A1c lowering A1c <7%	Albiglutide: -0.79% Liraglutide: -0.99% RR 1.23; 95% CI, 1.06 to 1.42	Low Low
Abbreviations: A1c – hemoglobin A1c; MD – mean difference				

- Liraglutide was associated with more weight loss than dulaglutide and albiglutide. Exenatide and dulaglutide 1.5 mg had similar weight loss with a difference of -0.24 kg. Dulaglutide 0.75 mg was associated with more weight loss compared to exenatide (mean difference [MD] 1.27 kg; P<0.001).[1]
- No difference in adverse events or withdrawals were found in within class comparisons of GLP-1 receptor agonists.[1]
- Evidence was imprecise for the incidence of gastrointestinal (GI) effects with dulaglutide and exenatide. One trial showed less GI effects with dulaglutide 0.75 mg compared with exenatide; however, higher strengths of dulaglutide were not found to have any differences in incidence of GI adverse events compared to exenatide.[1]

DPP-4 Inhibitors

- Sitagliptin and saxagliptin were associated with similar A1c lowering (-0.62% and -0.52% over 18 weeks and -1.07% and -1.34% over 24 weeks, respectively).[1]
- Low strength evidence did not find differences in adverse events or withdrawals between the different DPP-4 inhibitors in studies lasting 18 to 24 weeks. Hypoglycemia rates were higher with saxagliptin compared to sitagliptin (3.2% vs. 2.8%, respectively).[1]

Between Class Comparisons

DPP-4 Inhibitors vs. GLP-1 Receptor Agonists

- Low strength evidence for comparisons between DDP-4 inhibitors and GLP-1 receptor agonists comes from 8 trials. Specific comparisons are presented in Table 3. Overall, more A1c lowering was seen with GLP-1 receptor agonists compared to DPP-4 inhibitors.[1]

Table 3. Between Class Comparisons between DPP-4 Inhibitors vs. GLP-1 Receptor Agonists.[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Exenatide XR vs. sitagliptin 100 mg*	26 weeks	A1c lowering	WMD -0.48; 95% CI -0.69 to -0.26	Low
Exenatide 10 mcg vs. sitagliptin 100 mg	24 weeks	A1c lowering	No difference	Insufficient
Liraglutide 1.2-1.8 mg vs. sitagliptin 100 mg	26 weeks	A1c lowering	Liraglutide 1.2 mg: -1.24% Liraglutide 1.8 mg: -1.5% Sitagliptin: -0.6% L1.2 vs. S: - 0.34% (95% CI, -0.51 to -0.16; p<0.0001) L1.8 vs. S: - 0.60% (95% CI, -0.77t o -0.43; p<0.001)	Low
Liraglutide 1.2 mg vs. sitagliptin 100 mg	24 weeks	A1c lowering	Liraglutide: -1.4% Sitagliptin: -1.3%	Low
Albiglutide 30 mg vs. sitagliptin 100 mg	104 weeks	A1c lowering	Albiglutide: -0.63% Sitagliptin: 0.28% P<0.001	Low
Liraglutide 1.2 mg vs. saxagliptin 5 mg	24 weeks	A1c lowering	Liraglutide: -1.5% Saxagliptin: -1.23%	Low
Dulaglutide 0.75 mg vs. sitagliptin 100 mg Dulaglutide 1.5 mg vs. sitagliptin 100 mg	104 weeks	A1c <7%	Dulaglutide 0.75: 45% Dulaglutide 1.5: 54% Sitagliptin: 31% D 0.75 vs. S: RR 1.44 (95% CI, 1.17 to 1.77) D 1.5 vs. S: RR 1.75 (95% CI, 1.44 to 2.12)	Low
*Pooled data Abbreviations: A1c – hemoglobin A1c; WMD – weighted mean difference				

- There was consistently more weight loss with GLP-1 receptor agonists compared to DPP-4 inhibitors.[1]
- Exenatide XR was associated with more withdrawals due to adverse events than sitagliptin 100 mg and more GI effects based on low strength evidence.[1]
- Liraglutide 0.9 mg, 1.2 mg and 1.8 mg were associated with an increased incidence of any adverse event versus comparators (moderate strength evidence). More withdrawals due to adverse events and GI events were found with linagliptin compared to sitagliptin 100 mg (59% vs. 48%, respectively).[1]
- Low strength evidence found albiglutide 30 mg and sitagliptin 100 mg to have similar rates of adverse events and withdrawals. However, albiglutide was associated with more nausea (12% vs. 7%) and diarrhea (15% vs. 9%).[1]
- Sitagliptin and dulaglutide were found to have similar rates of hypoglycemia and withdrawals due to adverse events. However, low strength of evidence found dulaglutide to have an increased incidence of GI adverse events (35% vs. 17%).[1]

DPP-4 Inhibitors vs. SGLT2 Inhibitors

- A systematic review found canagliflozin 300 mg to be more effective at A1c lowering than sitagliptin 100 mg (MD -0.24%; 95% CI, -0.40 to -0.09) based on moderate strength of evidence.[1]
- A pooled analysis of 2 studies that compared canagliflozin 100 mg to sitagliptin 100 mg found low strength of evidence that canagliflozin was associated with a higher incidence of patients who obtained a goal A1c of less than 7% (RR 1.20; 95% CI, 1.07 to 1.33).[1]
- Comparison of empagliflozin and sitagliptin did not find any difference in A1c lowering; however, more weight loss was found in the empagliflozin group (pooled data from 2 studies) based on moderate strength of evidence.[1]
- Moderate strength of evidence from pooled data of 2 studies that empagliflozin 25 mg improves the chance of obtaining an A1c less than 7% compared to linagliptin 5 mg (OR 3.3; 95% CI, 1.9 to 4.6). Results were similar for empagliflozin 10 mg compared to linagliptin 5 mg.[1]
- Dapagliflozin 10 mg was found to be similar in efficacy to saxagliptin 5 mg in one small study based on low strength evidence.[1]
- Adverse events and withdrawals due to adverse events were similar between canagliflozin 300 mg and sitagliptin 100 mg, between empagliflozin 25 mg and sitagliptin 100 mg, and between dapagliflozin and sitagliptin 100 mg.[1]
- Moderate strength evidence found canagliflozin to be associated with increased risk for genital mycotic infections (RR 4.20; 95% CI, 2.51 to 7.03). Hypoglycemia rates were similar based on low strength of evidence.[1]
- Genital mycotic infections were 4-times more common with empagliflozin compared to sitagliptin (3.5% vs. 0.7%). Dapagliflozin was also found to have increased genital mycotic infections compared to saxagliptin (6% vs. 0.6%; RR 9.83, 95% CI, 1.27 to76).[1]

Newer Diabetes Medications Compared with Metformin

DPP-4 Inhibitors vs. Metformin

- 12 studies compared DDP-4 inhibitors to metformin. Metformin was found to be more effective in A1c lowering compared to DPP-4 inhibitors (Table 4).[1]

Table 4. Between Class Comparisons between DPP-4 Inhibitors and Metformin[1]

Comparators	Trial Duration	Outcome	Result1	Strength of Evidence
Metformin 2000 mg* vs. linagliptin 5 mg	24 weeks	A1c lowering	MD -0.60%; 95% CI, -0.32 to -0.88%	Moderate
Metformin 2000 mg* vs. alogliptin 12.5 mg	26 weeks	A1c lowering	MD -0.55%; 95% CI, -0.29 to -0.81%	Moderate
Metformin 2000 mg vs. sitagliptin 100 mg^	24-52 weeks	A1c lowering	WMD -0.30%; 95% CI -0.52 to -0.09%	Moderate
* Metformin given as 1000 mg twice daily ^ Pooled analysis Abbreviations: A1c – hemoglobin A1c; MD – mean difference; WMD – weighted mean difference				

- Metformin 1000 mg (twice daily) was associated with greater weight loss compared to linagliptin 5 mg (MD -0.70 kg; 95% CI, -0.11 to -1.29%) but differences are unlikely to be clinically significant. Greater weight loss was also found with metformin in a comparison to alogliptin and sitagliptin.[1]

- Meta-analysis of 2 trials found no difference in A1c between increasing the dose of metformin (in patients on submaximal doses) compared to adding saxagliptin 5 mg (WMD -0.31, 95% CI, -0.74 to 0.13) based on low strength of evidence.[1]
- Up-titration of metformin was associated with greater weight loss compared to the addition of saxagliptin 5 mg with a between group difference of -0.9 kg.[1]
- Metformin compared to linagliptin, alogliptin, and saxagliptin all had similar risk of withdrawals due to adverse events.[1]
- Hypoglycemia rates were higher with linagliptin and saxagliptin compared with metformin.[1]

GLP-1 Receptor Agonists vs. Metformin

- Low strength of evidence from one trial found dulaglutide 1.5 mg resulted in more patients obtaining an A1c less than 7% compared to metformin (RR 1.16; 95% CI, 1.01 to 1.34) with no difference in weight change between the groups.[1]
- Hypoglycemia was more common with exenatide compared to metformin (12% vs. 3.2%, respectively; $p<0.05$). Similar rates of withdrawals due to adverse events were seen with exenatide XR and metformin.[1]
- Low strength of evidence found dulaglutide and metformin have similar risk of overall adverse events and withdrawals due to adverse events.[1]

SGLT2 Inhibitors vs. Metformin

- Comparisons between dapagliflozin and metformin found more A1c lowering with dapagliflozin (WMD -0.12%, 95% CI, -0.16 to -0.08%). A second trial found similar results when comparing dapagliflozin to metformin XR (WMD -0.11%, 95% CI, -0.11 to -0.0%5). Changes in A1c are too small to be clinically significant.[1]
- A meta-analysis of 2 studies found dapagliflozin 5 mg resulted in greater weight loss compared to metformin XR 1,500-2,000 mg/day (WMD -1.18 kg; 95% CI, -1.86 to -0.26).[1] Dapagliflozin 10 mg, as compared to metformin 1,500-2,000 mg, was also associated with more weight (WMD -1.3 kg; 95% CI, -1.8 to -0.7 kg).[1]
- Empagliflozin and canagliflozin comparisons to metformin found similar A1c reduction and number of patients who obtained an A1c of less than 7% based on low strength of evidence. More weight loss was experienced in the empagliflozin group compared to metformin in trials of 52 weeks duration. Canagliflozin was also associated with more weight loss compared to metformin (-3.9 kg vs. -2.1 kg, respectively).[1]
- Metformin XR, dapagliflozin 5 mg, and dapagliflozin 10 mg had overall similar incidence of adverse events or withdrawals due to adverse events based on low strength of evidence. Low strength evidence of metformin compared to empagliflozin 25 mg also found similar risks of overall adverse events or withdrawals due to adverse events.[1]

Fixed-dose Combination Products or Dual Therapy

- Greater A1c lowering was found when dual therapy (individual medications taken together) or fixed-dose combinations were initiated in patients not controlled on metformin monotherapy compared to component monotherapy.[1]

Table 5. Fixed-dose Combinations or Dual Therapy Product Comparisons for DPP-4 Inhibitors[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Alogliptin 12.5 mg/pioglitazone 30 mg* vs. pioglitazone 30 mg Alogliptin 25 mg/pioglitazone 30 mg* vs. pioglitazone 30 mg Alogliptin 25 mg/pioglitazone 30* mg vs. alogliptin 25 mg	26 weeks	A1c lowering	Alo 12.5/Pio: -1.56% vs. Pio: -1.15% (P<0.05) Alo 25/Pio: -1.71% vs. Pio: -1.15% (P<0.05) Alo 25/Pio: - 1.71% vs. Alo: -0.96% (P<0.05)	Low
Alogliptin 12.5 mg/metformin 500 mg twice daily† vs. alogliptin 25 mg daily Alogliptin 12.5 mg/metformin 500 mg twice daily† vs. metformin 500 mg twice daily Alogliptin 12.5 mg/metformin 1000 mg twice daily† vs. alogliptin 12.5 mg daily Alogliptin 12.5 mg/metformin 1000 mg twice daily† vs. metformin 1000 mg daily	26 weeks	A1c lowering	Alo/Met: -1.22% vs. Alo: -0.52% (P<0.001) Alo/Met: -1.22% vs. Met: -0.65% (P<0.001) Alo/Met: -1.55% vs. Alo: -0.56% (P<0.001) Alo/Met:-1.55% vs. Met: -1.11% (P<0.001)	Moderate
Linagliptin 2.5 mg/metformin 500 mg twice daily* vs. linagliptin 5 mg once daily Linagliptin 2.5 mg /metformin 500 mg twice daily* vs. metformin 500 mg twice daily Linagliptin 2.5 mg/metformin 1000 mg twice daily* vs. linagliptin 5 mg daily Linagliptin 2.5 mg/metformin 1000 mg twice daily* vs. metformin 1000 mg twice daily	26 weeks	A1c lowering	MD -0.70%; 95% CI, -0.98 to -0.42 MD -0.60%; 95% CI, -0.88 to -0.32 MD -1.10%; 95% CI, -1.38 to -0.82 MD -0.50%; 95% CI, -0.78 to -0.22	Moderate Moderate Moderate Moderate
Linagliptin 5 mg/metformin 1500 to 2000 mg once daily* vs. linagliptin 5 mg daily	24 weeks	A1c lowering	MD -0.8%; 95% CI, -1.1 to -0.5%	Moderate
Sitagliptin 100 mg/metformin 1000 mg versus metformin^*†	24-104 weeks	A1c lowering	WMD -0.60%; 95% CI, -0.75 to -0.45	Moderate

^ Pooled data
* Dual therapy
† Fixed-dose combination
Abbreviations: A1c – hemoglobin A1c; MD – mean difference; WMD – weighted mean difference

- Moderate evidence found alogliptin 12.5 mg/metformin 1000 mg resulted in greater weight reductions than alogliptin 12.5 mg twice daily.[1]
- Low strength of evidence found imprecise results for linagliptin plus metformin versus comparators for weight changes. One study found no differences while a second study found evidence for greater weight loss in the combination group.[1]
- Weight changes were similar between sitagliptin/metformin compared to component monotherapy.[1]
- Low strength of evidence found withdrawal rates due to adverse events ranged from 1.8% to 9.6% with fixed-dose alogliptin/metformin and dual therapy of metformin and alogliptin. Metformin at the highest doses were found to be associated with higher rates of hypoglycemia.[1]
- Withdrawal rates due to adverse events and adverse events were similar between fixed-dose linagliptin and metformin and dual therapy with linagliptin and metformin.[1]
- Sitagliptin and metformin dual therapy and fixed-dose treatment were associated with similar rates of adverse events and low incidence of hypoglycemia.[1]

SGLT2 Inhibitor Combinations

Table 6. Dual Combination Product Comparisons for SGLT2 Inhibitors.[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Canagliflozin 100 mg/metformin vs. metformin Canagliflozin 300 mg/metformin vs. metformin Canagliflozin 100 mg/metformin vs. canagliflozin 100 mg Canagliflozin 300 mg/metformin vs. canagliflozin 300 mg	26 weeks	A1c lowering	MD -0.46%; 95% CI, -0.66 to -0.27 MD -0.48%; 95% CI, -0.67 to -0.28 MD -0.40%; 95% CI, -0.59 to -0.21 MD -0.36%; 95% CI, -0.56 to -0.17	Low
Empagliflozin 25 mg/linagliptin 5 mg vs. linagliptin 5 mg Empagliflozin 25 mg plus/linagliptin 5 mg vs. empagliflozin 5 mg	24 weeks	A1c lowering	MD -0.41%; 95% CI, -0.61 to -0.22 MD -0.14%; 95% CI, -0.33 to -0.06	Moderate

- In canagliflozin/metformin comparisons, combination therapy resulted in more weight loss compared to metformin monotherapy, with differences that ranged from -1.2 kg to -2.0 kg based on low strength evidence.[1]
- Empagliflozin 25 mg plus linagliptin 5 mg resulted in more weight loss compared to linagliptin alone (MD -1.2 kg; 95% CI, -2.2 to -0.2 kg). However, combination therapy compared to empagliflozin alone resulted in similar weight loss. Results were similar for empagliflozin 10 mg and linagliptin 5 mg compared to their monotherapy components.[1]
- Empagliflozin and linagliptin fixed-dose therapy compared to their monotherapy components did not find any differences in rates of adverse events, withdrawals due to adverse events or hypoglycemia risk based on low strength of evidence.[1]

Subgroup Analysis

- Gender had no influence on risk of genital mycotic infections in studies that compared SGLT2 inhibitors and DPP-4 inhibitors.[1]
- Use of albiglutide and sitagliptin in patients with renal impairment found A1c lowering was greater with albiglutide compared to sitagliptin (-0.83% vs. -0.52%, respectively) with no difference in risk of adverse reactions, withdrawals due to adverse events or hypoglycemia (after controlling for sulfonylurea use).[1]

New Safety Alerts

In August 2015, the FDA issued a warning that DPP-4 inhibitors (saxagliptin, sitagliptin, linagliptin, and alogliptin) may cause severe and disabling joint pain.[3] The warning prompted labeling changes for the DPP-4 inhibitor prescribing information. Symptoms appeared 1 day to years after initiation of a DPP-4 inhibitor. Upon discontinuation of the DPP-4 inhibitor, symptom resolution occurred in a month or less. Recurrence of joint pain was noted in some patients resuming therapy with the same or another DPP-4 inhibitor.

A FDA safety warning was issued in May 2016 for the increased risk of leg and foot amputations with canagliflozin.[4] The warning is a result of increased amputations associated with canagliflozin use during an ongoing clinical trial in which initial results suggest the risk of amputations over a 1-year period were 7/1,000 for canagliflozin 100 mg; 5/1,000 for canagliflozin 300 mg; and 3/1,000 patients treated with placebo. The FDA is continuing to investigate this association.

In June of 2016, the FDA issued warnings of acute kidney injury (AKI) for 2 SGLT2 inhibitors, canagliflozin and dapagliflozin.[5] One hundred and one cases of AKI, some cases requiring hospitalization and dialysis, have been identified. Acute kidney injury occurred within 1 month of starting the drug in approximately half of the cases. Patients with conditions that may predispose them to increased risk of AKI should be evaluated before starting canagliflozin or dapagliflozin. Co-morbidities include decreased blood volume; chronic kidney disease; heart failure; and use of some common medications (i.e., diuretics, ACE inhibitors, ARBs and NSAIDs). Renal function tests are recommended before initiating therapy and should be rechecked periodically throughout therapy.

New Formulations or Indications

<u>Jentadueto XR (linagliptin and metformin)</u>

This fixed-dose combination of linagliptin and metformin was originally approved in 2012 and then approved as an extended-release formulation in 2016.[6] The combination can be given once a day in doses of up to 5 mg linagliptin and 2000 mg metformin. Four double-blind, randomized, placebo-controlled studies of the once daily formulation (given as separate medications) were used for FDA approval. In a 24-week study of treatment-naïve patients with high baseline A1c (mean 9.9%), metformin 1500-2000 mg daily and linagliptin 5 mg daily decreased A1c -2.9% from baseline compared to linagliptin and placebo with a -2% decrease (MD -0.8%; 95% CI, -1.23% to -0.45%; $p<0.0001$). A second 24-week study added linagliptin 5 mg or placebo to patients with uncontrolled A1c levels on metformin at a dose of at least 1500 mg per day. Linagliptin and metformin were found to decrease A1c more than placebo and metformin (MD -0.6%; 95% CI, -0.8% to -0.5%). The number of patients who achieved an A1c goal of less than 7% was also higher in the linagliptin and metformin group compared to the placebo and metformin group (26% and 9%, respectively). No differences in weight loss were observed between the groups. In a 104-week non-inferiority study, linagliptin 5 mg or glimepiride 1-4 mg per day was added to patients with uncontrolled glycaemia despite metformin therapy.[6] The linagliptin/metformin combination was less effective in lowering A1c compared to glimepiride/metformin with a mean difference in A1c at week 52 and week 104 of 0.2% (95% CI, 0.1% to 0.3%). The fourth study was a 24-week comparison of linagliptin 5 mg, metformin and a sulfonylurea compared to placebo, metformin and a sulfonylurea. Change in A1c favored the linagliptin group compared to the placebo combination (MD -0.6%; 95% CI, -0.7% to -0.5%). Twenty-nine percent of patients in the linagliptin group obtained an A1c less than 7% compared to 8% in the placebo combination group. Body weight changes were not significantly different between groups. Nasopharyngitis and diarrhea were more commonly experienced (≥5%) in the linagliptin/metformin group compared to placebo.[6]

Randomized Controlled Trials

No additional randomized controlled trials provided evidence to prompt changes to current policy.

References:

1. Selph S, Blazine I, Guttmann-Bauman I, et al. Drug Class Review Newer Diabetes Medications and Combinations. Update #2 Report Draft for Final Approval prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University, Portland, Oregon, July 2016. Available with membership in the Drug Effectiveness Review Project.
2. Drug Utilization Research and Management Group. Class Update: Non-insulin Antidiabetic Agents. Oregon Pharmacy and Therapeutics Committee. Available at: http://www.orpdl.org/durm/meetings/meetingdocs/2015_09_24/archives/2015_09_24_DiabetesClassUpdatesARCHIVED.pdf. Accessed August 3, 2016.
3. Food and Drug Administration. FDA warns that DPP-4 inhibitors for type 2 diabetes may cause severe joint pain. FDA Safety Communication. August 28, 2015. Available at: http://www.fda.gov/drugs/drugsafety/ucm459579.htm. Accessed August 3, 2016.
4. Food and Drug Administration. Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate. FDA Safety Communication. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm. Accessed August 8, 2016.
5. Food and Drug Administration. FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farixiga, Xigduo XR). FDA Drug Safety Communication. June 14, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm505860.htm. Accessed on August 3, 2016.
6. Jentadueto XR. Ridgefield CT, Boehringer Ingelheim Pharmaceuticals, Inc. May 2016.

Appendix 1: Current Status on Preferred Drug List

GLP-1 RECEPTOR AGONISTS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-CUT	PEN INJCTR	BYETTA	EXENATIDE	Y
SUB-CUT	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-CUT	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-CUT	PEN INJCTR	TRULICITY	DULAGLUTIDE	N

DPP-4 INHIBITORS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	JANUMET	SITAGLIPTIN PHOS/METFORMIN HCL	Y
ORAL	TABLET	JANUVIA	SITAGLIPTIN PHOSPHATE	Y
ORAL	TABLET	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	N
ORAL	TABLET	JENTADUETO	LINAGLIPTIN/METFORMIN HCL	N
ORAL	TABLET	KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	N
ORAL	TABLET	NESINA	ALOGLIPTIN BENZOATE	N
ORAL	TABLET	ONGLYZA	SAXAGLIPTIN HCL	N
ORAL	TABLET	OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	N
ORAL	TABLET	TRADJENTA	LINAGLIPTIN	N
ORAL	TBMP 24HR	JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	N
ORAL	TBMP 24HR	KOMBIGLYZE XR	SAXAGLIPTIN HCL/METFORMIN HCL	N

SGLT-2 INHIBITORS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TABLET	SYNJARDY	EMPAGLIFLOZIN/METFORMIN HCL	N

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All GLP-1 receptor agonists

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

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 with increasing doses, 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. 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*. 2008; 31;1-11.

P&T/DUR Review: *9/16 (KS); 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *10/15; 2/15; 1/14*

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):

- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 12 months

Requires PA:

- All DPP-4 inhibitors

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient tried and failed metformin and a sulfonylurea, or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #4	**No:** Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months

Initiating Metformin

5. 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.
6. 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).
7. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
8. The maximum effective dose can be up to 1,000 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*. 2008; 31;1-11.

P&T/DUR Review: *9/16 (KS); 9/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *10/15; 1/15; 9/14; 1/14; 2/13*

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):

- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 6 months

Author: Sentena Date: September 2016

Requires PA:

- All SGLT-2 inhibitors

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of T2DM?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed metformin and a sulfonylurea, have contraindications to these treatments or is requesting a SGLT-2 inhibitor to be used with metformin and a sulfonylurea? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Has the patient tried and failed (unable to maintain goal A1c) all of the following drugs, or have contraindications to all of these drugs? 1. Insulin 2. Thiazolidinedione 3. DPP-4 inhibitor 4. GLP-1 receptor agonist 5. Amylin analog	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.

Renewal Criteria		
1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 6 months

Initiating Metformin

9. 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.
10. 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).
11. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
12. 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*. 2008; 31;1-11.

P&T Review: *9/16 (KS); 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *2/3/15; 1/1/14*