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Newer Diabetes Treatments Drug Class Update with New Drug Evaluation: Semaglutide and Ertugliflozin

Date of Review: July 2018

Generic Name: semaglutide
Generic Name: ertugliflozin, ertugliflozin/sitagliptin, ertugliflozin/metformin

Date of Last Review: September 2017
End Date of Literature Search: 05/23/2018
Brand Name (Manufacturer): Ozempic® (Novo Nordisk)
Brand Name (Manufacturer): Steglatro™, Steglujan™, Segluromet™ (Merck & Co., Inc.)
Dossier Received: ertugliflozin (yes), semaglutide (no)

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

Purpose for Class Update:
To evaluate the safety and efficacy of semaglutide and ertugliflozin (and combinations) which were recently approved for blood glucose lowering in patients with type 2 diabetes mellitus (T2DM). High quality new evidence published since the last review will also be presented.

Research Questions:
1. In patients with T2DM, is there any new comparative evidence for non-insulin antidiabetic therapies based on surrogate efficacy outcomes (e.g., hemoglobin A1c [HbA1c]) and long-term clinically meaningful effectiveness outcomes (e.g., microvascular outcomes, macrovascular outcomes and mortality)?
2. In patients with T2DM, is there any new comparative evidence for non-insulin diabetes treatments based on harms outcomes (e.g., severe hypoglycemia, heart failure, diabetic ketoacidosis, pancreatitis, etc.)?
3. Are there subpopulations of patients with T2DM for which specific therapies may be more effective or associated with less harm?
4. What are the efficacy and harms evidence for the two new non-insulin diabetes treatments, ertugliflozin and semaglutide?

Conclusions:
- A Drug Effectiveness Review Project (DERP) update on newer diabetes therapies, three new guidelines/standards, one new randomized controlled trial and two new drug reviews were reviewed for this class update. The evidence pertains mostly to adult patients with T2DM, mildly elevated HbA1c levels, and unspecified healthcare coverage. Limitations to the evidence included short-term study duration and industry funding for a majority of the included studies.

DERP REVIEW
- The DERP review on newer diabetes medications and combinations was published in September of 2017.[1] The most clinically relevant outcomes with moderate or high quality evidence are summarized below.

Cardiovascular Outcomes

- Moderate strength of evidence was demonstrated for reduction in the composite outcome of CV death, nonfatal myocardial infarction (MI) or nonfatal stroke compared to placebo for the following therapies: empagliflozin (ARR 1.6%/NNT 63 over 3.1 years), canagliflozin (CANVAS ARR 1.4%/NNT 71 over 5.7 years and CANVAS-R ARR 1.1%/NNT 91 over 2.1 years), and liraglutide (ARR 1.9%/NNT 53 over 3.5 years).[1] For this same endpoint, the following therapies were found to produce no cardiovascular benefit and no harm compared to placebo: alogliptin, lixisenatide, semaglutide, saxagliptin, and sitagliptin.
- Cardiovascular death was reduced with empagliflozin (3.7% vs. 5.9% over 3.1 years) and liraglutide (4.7% vs. 6.0% over 3.8 years) compared to placebo based on moderate quality evidence as determined by DERP.[1] No difference in CV death was seen between treatment and placebo for saxagliptin, sitagliptin, and lixisenatide.

CLINICAL EFFICACY

HbA1c

Within Class Comparisons

- For within class comparisons DERP found that there was moderate evidence of a statistical benefit in HbA1c lowering favoring the first therapy listed in the following comparisons: daily lixisenatide vs. daily liraglutide and once-weekly exenatide vs. exenatide twice daily.[1] The difference in HbA1c lowering between the treatments was approximately 0.5% to 0.6%, suggesting benefit in patients who are close to achieving their HbA1c goal.

Between Class Comparisons

- DERP found moderate strength of evidence of significant differences between classes of antidiabetic treatments for the outcome of HbA1c lowering. Canagliflozin 300 mg decreased HbA1c by a mean difference of -0.16% (95% CI, -0.29 to -0.02) more than sitagliptin 100 mg which is unlikely to be clinically impactful. A higher percent of patients obtained a HbA1c less than 7% with empagliflozin compared to linagliptin based on moderate strength of evidence.[1] Moderate strength of evidence found no difference between empagliflozin and sitagliptin.

Newer Diabetes Medications

- DERP found moderate evidence of more HbA1c reduction with metformin compared to sitagliptin (weighted mean difference [WMD] -0.30%; 95% CI, -0.52 to -0.09). [1]

Changes in Weight

- Moderate evidence found canagliflozin, empagliflozin and dapagliflozin to cause more weight loss compared to sitagliptin ranging from 6 to 10 pounds which could be clinically impactful.[1]
- The fixed-doe combination product (FDCP) of empagliflozin/linagliptin was found to cause more weight loss compared to linagliptin.
- Metformin was associated with more weight loss, ranging from -1.2 kg to -1.7 kg, when compared to sitagliptin (moderate evidence).

Evidence on Harms

- Liraglutide was associated with a higher incidence of withdrawal due to adverse events compared to sitagliptin (RR 3.28; 95% CI, 1.81 to 5.93).[1]

New Drugs

Semaglutide:

- A CV outcomes study found semaglutide to be noninferior to placebo based on a phase 3, double-blind, double-dummy, noninferiority, randomized trial of fair quality lasting a mean duration of 2.1 years in patients with CV disease or at high risk of CV disease (60 years or older and at least 1 CV risk factors).[2] The incidence of the primary composite outcome (CV death, nonfatal MI or nonfatal stroke) occurred in 6.6% of patients treated with semaglutide compared to 8.9% of patients treated with placebo (HR 0.74; 95% CI, 0.58 to 0.95; P<0.001 for noninferiority). In a subgroup analysis in patients with only CV risk factors (primary prevention patients), there was no benefit over placebo of semaglutide therapy and also no benefit over placebo seen in patients from only US treatment sites (HR 0.84; 95% CI 0.57 to 1.34). Results are most applicable to patients with a history of CV disease, kidney disease or both. Primary outcome analysis was done on the intention to treat (ITT) population which can bias results toward no difference between groups in trials with a noninferiority design. Semaglutide patients were found to have better glucose control compared to placebo (HbA1c mean difference -1.0%), which may have influenced study results. The trial was not powered to determine statistical superiority between semaglutide and placebo and was funded by industry.
- Semaglutide efficacy was demonstrated in six trials studying HbA1c reduction from baseline over 30-56 weeks.[3–8] Noninferiority trials of fair quality compared semaglutide to active comparisons; sitagliptin, insulin glargine, exenatide ER and dulaglutide.[3–6] Estimated HbA1c treatment differences (ETD) between semaglutide and active treatments were -0.38% to -1.06%, proving noninferiority and superiority. Differences in HbA1c between semaglutide compared to placebo ranged from –1.35% to -1.75%.[7,8] Semaglutide was associated with greater weight loss, up to approximately 4 kg more than active treatment comparisons (P<0.05). Adverse events were similar to other glucagon-like peptide-1 receptor agonists (GLP-1 RAs), with gastrointestinal related adverse events being the most common. Semaglutide was associated with an increased risk for diabetic retinopathy complications compared to placebo (3% versus 1.8%, respectively; HR 1.76; 95% CI, 1.11 to 2.78), which has not been demonstrated with other GLP-1 RAs.[2]

Ertugliflozin:

- Ertugliflozin was recently approved as monotherapy and in combination with sitagliptin and metformin.[9] Placebo controlled studies found HbA1c lowering similar to other sodium-glucose cotransporter-2 (SGLT-2) inhibitors with lowering of up to -0.9%.[10–13] An active treatment comparisons with glimepiride demonstrated noninferiority for ertugliflozin 15 mg (estimated treatment difference [ETD] 0.1%; 95% CI, -0.0 to 0.2) but not at the lower dose of 5 mg.[14] Combination ertugliflozin and sitagliptin were found to be more effective than monotherapy components.[15]
- Genital and urinary tract infections were associated with ertugliflozin use, which is similar to other SGLT-2 inhibitors. An increased risk of lower limb amputations with ertugliflozin in at-risk patients was demonstrated across the phase 3 trials; 1 (0.1%) in non-ertugliflozin treated patients, 3 (0.2%) in the ertugliflozin 5 mg group and 8 (0.5%) in the ertugliflozin 15 mg group.[9]

Randomized Controlled Trial

- A CV safety study comparing exenatide extended release (ER) to placebo, in patients with T2DM and CV disease (70% of participants) and those at high risk of CV disease (30%), found exenatide ER to be no more harmful or effective in CV risk reduction than placebo based on an incidence of the primary endpoint of 11.4% in exenatide ER treated patients compared to 12.2% for placebo (HR 0.91: 95% CI, 0.83 to 1.00; P<0.001 for noninferiority and P=0.06 for superiority).[16]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended for the non-insulin class of antidiabetic therapies based on review of efficacy and safety data.
- Add new formulations to existing prior authorization (PA) criteria.

- The Committee also recommended to remove amylin analogs from the list of agents required to try and fail (or have contraindications to) prior to approval in the SGLT-2 Inhibitors PA criteria.
- After evaluation of comparative drug costs in executive session, no changes to the PDL were recommended.

Prior Review Summary and Policy Recommendations

- Evidence supports the use of metformin for initial therapy in patients with T2DM requiring medication to reach HbA1c goals.[17,18] There is no universal recommendation for the optimal second line antidiabetic therapy, as most second-line therapies lower HbA1c to a similar extent.[19] Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the use of a sulfonylureas (SU) in patients who require additional glucose lowering in addition to metformin.[18] National Institute for Health and Care Excellence (NICE) recommends the addition of a SU, pioglitazone, DPP-4 inhibitor or SGLT-2 based on efficacy and safety data.[17] Much attention is also focused on the CV effects of antidiabetic treatments and some guidance advocates use of specific therapies in patients with atherosclerotic cardiovascular disease (ASCVD).[20] Most newer therapies have shown a neutral impact on composite CV endpoints. Small benefits have been demonstrated for canagliflozin, empagliflozin and liraglutide; however, reductions compared to placebo have only ranged from 1.1% to 1.9% and trials have had many limitations, including: lack of CV benefit in North American populations, lack of transparency on cause of CV death, industry funding and only applicable to patients at high risk or history of CV disease, average age of 63-64 years and on multiple other antidiabetic and cardioprotective treatments.[21–23] For these reasons the evidence from these studies doesn't apply to a large proportion of patients with T2DM. Additionally, adverse events need to be considered when choosing antidiabetic treatment. Serious adverse events include the following: an increased risk of amputations in T2DM patients at high CV risk or history of CV disease treated for with canagliflozin or ertugliflozin compared to placebo, increased risk of hospitalization due to heart failure when compared to placebo with saxagliptin and alogliptin, increased risk of ketoacidosis with SGLT-2 inhibitors, increased risk of retinopathy complications with semaglutide compared to placebo, potential increase in pancreatitis with dipeptidyl peptidase 4 (DPP-4) inhibitors and GLP-1 RAs, exacerbation of heart failure and increased risk of bone fracture with thiazolidinediones (TZD) and increased risk of hypoglycemia with SU compared to other active treatments.[2,17,18,24]
- Antidiabetic therapies were last reviewed in September of 2017 which resulted in no changes to the PDL or PA criteria. Current Oregon Health Plan (OHP) fee-for-service policy for non-insulin antidiabetic treatment allows for metformin, SUs and TZDs for use without restriction (**Appendix 1**). DPP-4 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are options after trials of metformin and SU or contraindications to these drugs as outlined in the PA criteria in **Appendix 6**. The DPP-4 inhibitor, sitagliptin, is also a preferred drug but requires that patients meet specific clinical PA criteria. SGLT2 inhibitors are available as last-line therapy as described in the clinical PA criteria.

Background:

Approximately 287,000 adult Oregonians have T2DM. It is estimated that over 38,000 of these patients are OHP members.[25] OHP paid $106 million in direct medical claims for diabetes and diabetes-related complications in 2012. The overall cost to the state is estimated at $3 billion a year. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have T2DM by 2050.[26] Despite a variety of treatment options, a significant number of patients fail to meet HbA1c goals within 3 years of being diagnosed and 50% of patients require combination therapy to control their disease.[27,28]

Underlying characteristics that lead to hyperglycemia and T2DM are insulin resistance and impaired insulin secretion. While evidence has shown the importance of lifestyle modifications, such as diet and exercise changes, antidiabetic treatments are necessary for treatment of hyperglycemia associated with T2DM in most patients.[29] Pharmacotherapy improves hyperglycemia by increasing glucose uptake, increasing glucose secretion and/or increasing insulin sensitivity. Goal glucose levels are dependent upon patient characteristics, such as age and comorbidities; however, guidelines recommend a goal HbA1c of less than 7% for most patients but a range of less than 6.5% to less than 8% may be appropriate.[30,31] Classes of non-insulin antidiabetic agents currently available are: alpha-

glucosidase inhibitors, biguanides, DPP-4 inhibitors, GLP-1 RAs, insulins, meglitinides, SGLT-2 inhibitors, SUs, TZDs, bile acid sequestrants, dopamine-2 agonists and amylin mimetics. Current evidence and guidelines recommend metformin a first line treatment in most patients with T2DM.[17,30,32,33] There is no consensus on a universally recognized second-line treatment and therefore, selection should be dependent on degree of glucose lowering required to assist in obtaining goal HbA1c levels, patient specific characteristics including comorbidities and harms of therapy. [17,30,32,33]

Important outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, HbA1c, severe adverse events and hypoglycemia rates. Hemoglobin A1C is often used as a surrogate marker to assess comparative efficacy of different antidiabetic therapies, as hyperglycemia is associated with increased microvascular complications, and possibly macrovascular outcomes as well. A clinically relevant change in HbA1c is considered to be ≥0.3%.[19] Available data for most new drugs are limited to short-term studies, which prevents the assessment of the durability of most antidiabetic treatments to control glucose levels long-term and to directly compare their impact on microvascular and macrovascular complications.

In 2008, the FDA started requiring that CV risk of antidiabetic therapies be evaluated. Cardiovascular studies have been published for each of the newer classes of antidiabetic therapies; however, definitive conclusions on class effects of benefits and harms have yet to be determined. Additionally, limitations of the evidence in CV studies, such as limited applicability to patients with CV disease or at high risk of CV disease, as well as small benefits of treatment prevent universal recommendations of antidiabetic therapies with suggestive CV benefit. A comparison table of effectiveness and harms can be found in **Appendix 5**.

Abbreviated Drug Utilization Evaluation:
Quarterly costs for antidiabetic therapies are driven by newer drugs from the SGLT-2, GLP-1 RA and DPP-4 classes, which have increased 5% since the last update. Metformin, SUs and TZDs account for 94% of claims but only 5% of the cost overall. Utilization of preferred antidiabetic therapies is 98% for metformin, SU and TZDs and 31% for newer therapies, with the inclusion of SGLT-2 inhibitors which have no preferred treatments within the class.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
<u>DERP – Newer Diabetes Medication and Combinations</u>
In September 2017 DERP released a review on newer medications for patients with type 2 diabetes.[1] Newer diabetes medications were defined as: amylin agonists, DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors. Twenty-six trials, 3 observational studies and 4 systematic reviews were included. Most of the

evidence comes from patients who are white, middle-aged, obese, 10 year or less history of diabetes and HbA1c baseline levels of less than 9%. Placebo run-in periods were required for many trials which can bias results in favor of patients who will be adherent to therapy. Evidence based on retrospective cohort trials, indirect comparisons, open-label extension studies or with limited applicability to OHP FFS patients were not included for reasons outlined in the Drug Use Research and Management (DURM) methods. Secondary endpoints that were not statistically or clinically significantly different between therapies were excluded.

Cardiovascular Trials

Evidence for the CV effect of newer diabetes medications was studied for SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 agonists (**Table 1**).[1] All the trials but the semaglutide trial have been previously presented in diabetes class updates. Therefore, only the semaglutide CV trial will be presented in detail. The following characteristics were similar for all trials:

- Trials were placebo controlled
- Patients had established CV disease or multiple CV risk factors
- Mean age was 61-66 years
- One-third of patients were women
- Baseline HbA1c ranged from 7.2% to 9.7%
- Patients had a 7-14 year history of diabetes
- All trials allowed additional glucose lowering drugs
- Six of eight trials were considered good quality. The LEADER and CANVAS trials were considered fair quality.

Table 1. Comparison of CV Outcomes Across Drug Trials.[1]

Author, Year **Trial Name** **Drug** **Number of Patients**	**Population**	**CV Death, Nonfatal MI, or Nonfatal Stroke**	**CV Death**
SGLT2 inhibitors			
Zinman, 2015 EMPA-REG OUTCOME Empagliflozin 7,020	Established CV disease HbA1c: 8.1 Duration of diabetes: NR	Event rate (3.1 y FU): 10.5% vs. 12.1% HR 0.86 (95% CI, 0.74 to 0.99) *moderate strength of evidence*	Event rate (3.1 y FU): 3.7% vs. 5.9% HR 0.62 (95% CI, 0.49 to 0.77) *moderate strength of evidence*
Neal, 2017 CANVAS and CANVAS-R Canagliflozin 10,142	History of CV disease (age ≥30 years) or ≥ 2 CV disease risk factors HbA1c: 8.2 Duration of diabetes :13.5 y	Both trials (combined FU of 2.4 y): HR 0.86 (95% CI, 0.75 to 0.97) CANVAS (5.7 y FU): Event rate: 15% vs. 16% *moderate strength of evidence* CANVAS-R (2.1 y FU): Event rate: 5.5% vs. 6.6% *moderate strength of evidence*	Event rate (combined FU of 2.4 y): 4.6% vs. 4.3% HR 0.87 (95% CI, 0.72 to 1.06) *low strength of evidence*
DPP-4 Inhibitors			

White, 2013 EXAMINE Alogliptin 5,380	Recent acute coronary syndrome HbA1c: 8.0 Duration of diabetes: 7.2 y	Event rate (1.5 y FU): 11.3% vs. 11.8% HR 0.96 ($\leq$ 1.16); P = 0.32 *moderate strength of evidence*	Event rate (1.5 y FU): 4.1% vs. 4.9% HR 0.85 (95% CI, 0.66 to 1.10) *low strength of evidence*
Scirica, 2013 SAVOR-TIMI 53 Saxagliptin 16,492	Established CV disease (age ≥ 40 years) or ≥ 2 CV disease risk factors HbA1c: 8.0 Duration of diabetes: 10 y	Event rate (2 y KM): 7.3% vs. 7.2% HR 1.00 (95% CI, 0.89 to 1.12) *moderate strength of evidence*	Event rate (2 y FU): 3.2% vs. 2.9% HR 1.03 (0.87 to 1.22) *moderate strength of evidence*
Green, 2015 TECOS Sitagliptin 14,671	Established CV disease HbA1c: 7.2 Duration of diabetes: 12 y	Event rate (3.0 y FU) 10.2% vs. 10.2% HR 0.99 (95% CI, 0.89 to 1.10) *moderate strength of evidence*	Event rate (3.0 yr FU) 5.2% vs. 5.0% HR 1.03 (95% CI, 0.89 to 1.19) *moderate strength of evidence*
GLP-1 Agonists			
Marso, 2016 SUSTAIN-6 Semaglutide 3,297	Established CV disease (age ≥ 50 years) or CV risk factors (age ≥ 60 years) HbA1c: 8.7 Duration of diabetes: 14 y	Event rate (2.1 y FU): 6.6% vs. 8.9% HR 0.74 (95%CI, 0.58 to 0.95) For noninferiority *moderate strength of evidence*	Event rate (2.1 y FU): 2.7% vs.2.8% HR 0.98 (95% CI, 0.65 to 1.48) *insufficient evidence*
Pfeffer, 2015 ELIXA Lixisenatide 6,068	Recent acute coronary syndrome HbA1c: 7.7 Duration of diabetes: 9.3 y	Not reported – used an alternated composite endpoint of unstable angina, CV death, nonfatal MI or stroke. No difference compared to placebo was found.	Event rate (2.1 y FU) 5.1% vs. 5.2% HR 0.98 (95% CI, 0.78 to 1.22) *moderate strength of evidence*
Marso, 2016 LEADER Liraglutide 9,340	Established CV disease (age ≥ 50 years) or CV risk factors (age ≥ 60 years) HbA1c: 8.7 Duration of diabetes: 13 y	Event rate (3.8 y FU): 13.0% vs. 14.9% HR 0.87 (95% CI, 0.78 to 0.97) *moderate strength of evidence*	Event rate (3.8 y FU): 4.7% vs. 6.0% HR 0.78 (95% CI, 0.66 to 0.93) *moderate strength of evidence*

Abbreviations: CI = confidence interval; CV = cardiovascular; FU = follow up; HbA1c = hemoglobin A1c; HR = hazard ratio; NR = not reported; y = years

Semaglutide CV Trial (SUSTAIN-6)

In addition to the results in Table 1, other important outcomes are presented below:

- Semaglutide was found to have a 1.1% decreased risk of nonfatal stroke compared to placebo (HR 0.61; 95% CI, 0.38 to 0.99) based on moderate strength of evidence.[1]
- The risk of nonfatal MI was similar between semaglutide and placebo, 2.9% and 3.9%, respectively (low strength of evidence).
- The risk of hospitalization was 3.6% with semaglutide and 3.3% with placebo, suggesting no difference (low strength of evidence).

- The incidence of retinopathy complications was 3.0% with semaglutide compared to 1.8% with placebo (HR 1.76; 95% CI, 1.11 to 2.78). The composite outcome of retinopathy complications included diabetes-related blindness, vitreous hemorrhage, or need for treatment with photocoagulation or intravitreal agents.
- New or worsening nephropathy was less with semaglutide compared to placebo, 3.8% vs. 6.1% (HR 0.64; 95% CI, 0.46 to 0.88).
- Subgroup analyses found no clinically significant differences between semaglutide and placebo based on history of prior CV disease, chronic HF, prior MI or stroke, or established CV disease versus CV risk factors only.

Within Class Comparisons

Twelve trials evaluated within class comparisons which lasted anywhere from 16-52 weeks and included 66 to 835 patients with ages from 44 to 57 years.[1] Most trials included patients that were inadequately controlled on metformin, sulfonylureas, a TZD or combination of these antidiabetic agents.

- *Sitagliptin vs. saxagliptin*: similar HbA1c lowering at 24 weeks, -1.07% vs. -1.34%, respectively based on low strength of evidence. Adverse events and withdrawals due to adverse events were not statistically significantly different between groups.
- *Dulaglutide once weekly vs. daily liraglutide*: drugs were compared over 26 weeks (both groups on background metformin) and found similar HbA1c reductions, -1.42% vs. -1.36%, respectively. Additionally, both groups achieved a HbA1c of less than 7% in 68% of patients (low strength of evidence).[1] Adverse events were similar. Weight loss was numerically greater with liraglutide compared to dulaglutide but clinical benefit was small, -2.90 kg versus -3.61 kg, respectively.
- *Daily liraglutide vs. weekly albiglutide*: both groups on background metformin, TZDs, sulfonylureas or combination therapy with HbA1c reductions of -0.99% vs. -0.79%, respectively (treatment difference -0.21%; 95% CI, 0.08% to 0.34%; low strength of evidence).[1] Fifty-two percent of patients receiving liraglutide obtained an HbA1c less than 7% compared to 42% for albiglutide (RR 1.23; 95% CI, 1.06 to 1.42). Patient receiving liraglutide experienced 1.55 kg more weight loss compared to albiglutide patients.
- *Daily lixisenatide vs. daily liraglutide*: patients taking metformin in both groups, HbA1c reductions were -1.8% with lixisenatide versus 1.2% with liraglutide (treatment difference -0.6%; 95% CI, -0.8% t0 -0.4%; moderate strength of evidence).[1] More patients receiving lixisenatide obtained an Hba1c less than 7% compared to liraglutide (74.2% vs. 45.5%; P<0.0001). Adverse events and decreases in body weight were similar between the two groups.
- *Twice daily exenatide vs. weekly dulaglutide*: background therapies included metformin and/or pioglitazone which resulted in 78% of patients taking dulaglutide 1.5 mg and 66% of patients taking dulaglutide 0.75 mg obtained a HbA1c of less than 7% compared to 52% taking exenatide (P<0.001 for all comparisons)(low strength of evidence).[1] Dulaglutide 1.5 mg weekly had similar weight loss and adverse events as exenatide.
- *Exenatide XR (once-weekly) vs. exenatide twice daily:* meta-analysis of three trials found -0.46% (95% CI, -0.69 to -0.23) more HbA1c lowering with exenatide XR compared to exenatide twice daily (moderate strength of evidence).[1]
- *Liraglutide once daily vs. exenatide twice daily*: HbA1c lowering was -1.12% with liraglutide compared with -0.79% with exenatide (both groups on background metformin or sulfonylurea or both)(MD -0.33%; 95% CI, -0.47 to -0.18; P<0.0001) based on low strength of evidence.[1]

Between Class Comparisons

Twenty publications were identified for between class comparisons of antidiabetic therapies. All but two trials were considered fair or good quality. Two studies graded as poor quality evidence did not meet inclusion criteria for DURM reviews as outlined in the methods.[1]

DPP-4 inhibitors were compared to GLP-1 analogs in eight studies that were graded as fair quality. Patients ranged from 47 to 63 years old with women comprising 34% to 52% of the population.

- *Sitagliptin vs. exenatide XR*: low strength of evidence found exenatide XR to lower HbA1c more than sitagliptin at 26 weeks in patients also taking metformin (WMD -0.48%; 95% CI, -0.69 to -0.26).[1] Sixty-two patients taking exenatide XR obtained HbA1c less than 7% compared to 39% of patients taking sitagliptin (RR 1.57; 95% CI, 1.34 to 1.83). More weight loss was demonstrated in patients taking exenatide XR compared to sitagliptin with a WMD of -1.32 kg (95% CI, -1.87 to -0.76); however is unlikely to be clinically impactful.
- *Sitagliptin vs. exenatide*: insufficient evidence.
- *Sitagliptin vs. liraglutide*: in patients also taking metformin, liraglutide 1.2 mg once daily was found to lower HbA1c -0.34% (95% CI, -0.51% to -0.16%) more than sitagliptin 100 mg once daily at 26 weeks.[1] Liraglutide 1.8 mg once daily lowered HbA1c by -0.60% (95% CI, -0.77 to -0.43) more than sitagliptin 100 mg once daily. Both findings were based on low strength of evidence. An extension phase lasting 52 weeks confirmed HbA1c findings of the 26-week study. Difference in mean weight loss was 2.3 kg more with liraglutide compared to sitagliptin. There was moderate evidence that withdrawals due to adverse events were higher in patients taking liraglutide compared to sitagliptin (RR 3.28; 95% CI, 1.81 to 5.93). A second study found that similar HbA1c reductions were seen in patients taking liraglutide 1.2 mg and sitagliptin 100 mg at 26-weeks.
- *Sitagliptin vs. albiglutide*: weekly albiglutide 30 mg was more effective in lowering HbA1c compared to sitagliptin 100 mg daily in patients taking metformin after 104 weeks of treatment. HbA1c lowering was -0.63% with albiglutide compared to -0.28% with sitagliptin (P<0.001) based on low strength of evidence. Weight loss was not significantly different between groups.[1]
- *Sitagliptin vs. dulaglutide*: low strength of evidence found a higher number of patients were able to obtain a HbA1c of less than 7% in patients taking dulaglutide 0.75 mg and dulaglutide 1.5 mg compared to sitagliptin 100 mg, 55%, 61% and 38%, respectively (P<0.001 for both dulaglutide versus sitagliptin comparisons).[1] An additional study out to 104 weeks demonstrated more patients obtaining an HbA1c less than 7% taking dulaglutide compared to sitagliptin.

DPP-4 inhibitors were compared to SGLT-2 inhibitors in nine trials of fair to good quality and 2 good quality systematic reviews. Patients were 52-59 years old with T2DM and 43% to 67% were men.

- *Sitagliptin vs. canagliflozin*: canagliflozin 300 mg was found to decrease HbA1c more than sitagliptin 100 mg based on moderate quality of evidence. Pooled data found a mean difference in HbA1c lowering was -0.16% (95% CI, -0.29 to -0.02) more for canagliflozin compared to sitagliptin (moderate strength of evidence).[1] Canagliflozin therapy resulted in more weight loss compared to sitagliptin with a mean difference of -2.91 kg (95% CI, -3.50 to -2.33) based on moderate evidence. Incidence of mycotic infections were higher with canagliflozin compared to sitagliptin (RR 11.96; 95% CI, 2.84 to 50.41 in men and RR 3.99; 95% CI, 2.15 to 7.40 in women).
- *Sitagliptin vs*. *empagliflozin*: A 12-week study found a similar incidence of patients obtaining a HbA1c less than 7% in patients taking empagliflozin 10 mg or empagliflozin 25 mg compared to sitagliptin, 38%, 37% and 34%, respectively (moderate strength of evidence).[1] Weight loss ranged from -2.26 to -4.30 kg with empagliflozin (10-25 mg) compared to -0.4 kg to 0.18 kg with sitagliptin based on moderate evidence (P<0.05 for both empagliflozin to sitagliptin comparisons). An extension study lasting an additional 78 weeks found a similar incidence in all three groups of patients reaching an HbA1c less than 7%. A second study in patient who were treatment naïve found similar numbers of patients obtaining an HbA1c of less than 7% in patients taking empagliflozin 10 mg, empagliflozin 25 mg and sitagliptin, 35%, 44% and 38% (P>0.05 for empagliflozin versus sitagliptin comparisons).[1] Genital infections were 4 times greater with empagliflozin compared to sitagliptin. Pooled analysis of the two studies found moderate evidence of no difference in HbA1c lowering between empagliflozin and sitagliptin.
- *Sitagliptin vs. dapagliflozin:* low strength of evidence from one small study found HbA1c reductions of -0.8% with dapagliflozin compared to -0.6% with sitagliptin, which were not statistically or clinically different.
- *Linagliptin vs. empagliflozin*: pooled data from two, 24 week studies of either treatment naïve patients or patients on background metformin, found a higher chance of obtaining an HbA1c of less than 7% with empagliflozin compared to linagliptin (OR 3.3: 95% CI, 1.9 to 4.7) (moderate quality

evidence).[1] Genital mycotic infections occurred in 7% of patients taking empagliflozin compared to 3% taking linagliptin (RR 2.50; 95% CI 1.11 to 5.47). Weight loss was 1-2 kg more for both empagliflozin doses compared to linagliptin based on moderate evidence (P<0.05). Risk of hypoglycemia and urinary tract infections were similar between groups.

- *Saxagliptin vs. dapagliflozin*: one study of 355 patients found a similar number of patients obtaining a HbA1c less than 7% with saxagliptin 5 mg and dapagliflozin 10 mg, 17% and 23%, respectively (low strength of evidence).[1] The mean weight change with dapagliflozin treatment was 2.4 kg compared to 0 kg with saxagliptin. The risk of genital infections was 6% with dapagliflozin compared to 0.6% with saxagliptin (RR 9.83; 95% CI, 1.27 to 76).

The GLP-1 agonist, exenatide 5 mg once weekly, plus the SGLT2 inhibitor, dapagliflozin 10 mg daily, was compared to the monotherapy components in a fair-quality trial of 685 patients who were uncontrolled on metformin. HbA1c lowering was similar for all groups with decreases from baseline of -1.4% to 2.0% based on low quality evidence.

Fixed-dose Combination Products (FDCP)

There were fifteen fair to good quality trials identified that studied FDCP (**Table 2**). Most patients had been previously treated with oral antidiabetic therapy with a mean baseline HbA1c of 8%.

Table 2. Fixed-dose Combination Product Trial Results.[1]

Comparison	Study Quality (number of studies)*	Outcome Studied	Results	Strength of Evidence†
GLP-1 Agonists and Long-Acting Insulins				
Lixisenatide + insulin glargine (Soliqua™) **vs.** **lixisenatide** **or** **insulin glargine** (background metformin or long-acting insulin)	Fair to good (2)	Percent of patients with HbA1c of <7%	FDCP: 55-84% lixisenatide: 33% glargine: 30-78% FDCP vs. lixisenatide: MD 40.6% (95% CI, 33.6 to 47.6) FDCP vs. glargine: MD 14.3% (95% CI, 8.4 to 20.3) and MD 25.5% (95% CI, 18.9 to 32.1)	Moderate
Liraglutide + insulin degludec (Xultophy®) **vs.** **degludec** **or** **liraglutide** **or** **insulin glargine**	Fair to good quality (3)	Percent of patients with HbA1c of <7%	FDCP: 60% degludec: 23% OR 5.44 (95% CI, 3.42 to 8.66) P-value not reported FDCP: 72% insulin glargine: 47% (P<0.001); *CI not provided* FDCP: 81% degludec: 65%	Low to moderate

(background metformin, insulin naïve or insulin glargine and metformin)			OR 2.38 (95% CI, 1.78 to 3.18) FDCP: 81% liraglutide: 60% (P<0.0001)	
SGLT2 Inhibitors and DPP-4 Inhibitors				
Empagliflozin + linagliptin (Glyxambi®) **vs.** **empagliflozin** **or** **linagliptin** (background metformin or drug naïve)	Quality not reported (2)	HbA1c reduction from baseline	<u>Study 1</u> FDCP 25/5 mg: -1.08% linagliptin 25 mg: -0.67% empagliflozin 5 mg: - 0.95% FDCP vs. linagliptin: MD -0.41% (95% CI, -0.61% to -0.22%) FDCP vs. empagliflozin: MD -0.14% (95% CI, -0.33% to 0.06%) FDCP 10/5 mg: -1.24% empagliflozin: -0.83% linagliptin 5 mg: -0.67% FDCP vs. empagliflozin: MD -0.41% (95% CI, -0.61% to -0.21%) FDCP vs. linagliptin: MD -0.57% (95% CI, -0.76% to -0.37%) <u>Study 2</u> FDCP 25/5mg: -1.19% empagliflozin 25 mg: -0.62% linagliptin 5 mg: -0.70% FDCP 25/5 mg vs. empagliflozin 25 mg: MD -0.58% (95% CI, -0.75% to -0.41%) FDCP 25/5 mg vs. linagliptin 5 mg: MD -0.50% (95% CI, -0.67% vs. -0.32%) FDCP 10/5mg: -1.08% empagliflozin 25 mg: -0.66% linagliptin 5 mg: -0.70%	Moderate

			FDCP 10/5 mg vs. empagliflozin 10 mg: MD -0.42 (95% CI, -0.59% to -0.25%) FDCP 10/5 mg vs. linagliptin 5 mg: MD -0.39% (95% CI, -0.56% to -0.21%)	
DPP-4 Inhibitors with other Oral Diabetes Medicines				
Alogliptin + pioglitazone (Oseni®) **vs.** **alogliptin 12.5 mg or 25 mg** **or** **pioglitazone 30 mg**	Quality not reported (1)	Percent of patients with HbA1c of <7%	FDCP 12.5/30mg: 53% FDCP 25/30 mg: 63% pioglitazone 30mg: 34% alogliptin: 24% FDCP 12.5/30 mg vs. pioglitazone: RR 1.58 (95% CI, 1.22 to 2.05) ARR 19%/NNT 6 FDCP 25/30 mg vs. pioglitazone: RR 1.86 (95% CI, 1.46 to 2.38) ARR 29%/NNT 4 FDCP 12.5/30 mg vs. alogliptin: Not SS FDCP 25/30 mg vs. alogliptin: RR 2.58 (95% CI, 1.92 to 3.46) ARR 39%/NNT 3	Low
Alogliptin + metformin (Kazano®) **(12.5/500 mg twice daily or 12.5/1000 mg twice daily)** **vs.** **alogliptin 25 mg daily** **or** **alogliptin 12.5 mg twice daily** **or** **metformin 500 mg twice daily** **or**	Quality not reported (1)	HbA1c reduction from baseline	FDCP 12.5/500 mg: -1.22% FDCP 12.5/1000 mg: -1.55% alogliptin 25 mg: -0.52% alogliptin 12.5 mg: -0.56% metformin 500 mg: -0.65% metformin 1000 mg: -1.11% P<0.001 for all FDCP compared to monotherapy	Strength of evidence not provided

metformin 1000 mg twice daily (treatment naïve)				
Linagliptin + metformin twice daily (Jentadueto®) vs. linagliptin vs. metformin	Quality not reported (2)	HbA1c reduction from baseline	*Favors FDCP for all comparisons* - Study 1: FDCP 5/1000mg vs. linagliptin 5mg: MD -0.70% (95%, CI, -0.98 to -0.42) FDCP 5/2000 mg vs. linagliptin 5 mg: MD -1.10 (95% CI, -1.38 to -0.82) FDCP 5/1000mg vs. metformin 1000 mg: MD -0.60% (95%, CI, -0.88 to -0.32) FDCP 5/2000mg vs. metformin 2000 mg: MD -0.50% (95%, CI, -0.78 to -0.22) Study 2: FDCP 5/1500-2000mg vs. linagliptin 5 mg: MD 0.8% (95% CI, -1.1 to -0.5)	Moderate
Sitagliptin + metformin (Janumet®) vs. sitagliptin vs. metformin	Quality not reported (5)	HbA1c reduction from baseline	FDCP 100/2000mg vs. metformin: WMD -0.60 (95% CI, -0.75 to -0.45)	Moderate
SGLT2 Inhibitors with other Oral Diabetes Medications				
Canagliflozin 100 mg or 300 mg + metformin extended release vs. metformin XR	Quality not reported (1)	Percent of patients with HbA1c of <7%	FDCP 300: 56.8% metformin XR: 43.0% canagliflozin 300 mg: 42.8% FDCP 300 mg vs. metformin XR:	Low

or **canagliflozin 100 mg**			RR 1.32 (95% CI, 1.10 to 1.59) ARR 14%/NNT 8 FDCP 300 mg vs. canagliflozin 300mg: RR 1.32 (95% CI, 1.11 to 1.60) ARR 14%/NNT 8 FDCP 100 mg: 49.6% metformin XR: 43.0% canagliflozin 100 mg: 38.8% FDCP 100 vs. metformin XR: NS FDCP 100 vs. canagliflozin 100 mg: RR 1.28 (95% CI, 1.05 to 1.57) ARR 11%/NNT 9	
Abbreviations: ARR – absolute risk reduction; FDCP – fixed-dose combination product; HbA1c – hemoglobin A1c; MD – mean difference; NNT – number needed to treat; NR – not reported; NS – non-significant; SS – statistically significant; WMD – weighted mean difference Key: * study duration 24 weeks, ł strength of evidence was rated by DERP				

Table 3. Dual Antidiabetic Therapy (Not in Fixed Dose Combination Product).[1]

Comparison	Study Quality* (number of studies)	Outcome	Results	Strength of Evidence ł
Exenatide 2 mg weekly + dapagliflozin 10 mg daily **vs.** **exenatide 2 mg weekly** **or** **dapagliflozin 10 mg** (patients on background metformin)	Fair (1)	Percent of patients with HbA1c of <7%	DT: 45% exenatide: 27% dapagliflozin: 19% DT vs. exenatide: ARR 18%/NNT 6 P<0.001; *CI not provided* DT vs. dapagliflozin: ARR 26%/NNT 4 P<0.001; *CI not provided*	Not provided
Linagliptin 5 mg + metformin low dose (ld) metformin (1000 mg/day) **or** **linagliptin 5 mg + high-dose (hd) metformin (2000 mg/day)**	Good (1)	Percent of patients with HbA1c of <7%	linagliptin + ld metformin: 56.7% linagliptin + hd metformin: 56.3% P=NS	Not provided

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; DT – dual therapy; HbA1c – hemoglobin A1c; MD – mean difference; NNT – number needed to treat; NS – non-significant
Key: * study duration 14-28 weeks, ł strength of evidence was rated by DERP

Newer Diabetes Medications compared with Metformin

Comparisons between newer diabetes medications and metformin were identified in 20 studies lasting 12-26 weeks in a majority of studies. Studies were done primarily in patients without significant comorbidities (**Table 4**).

Table 4. Newer Diabetes Medications compared with Metformin.[1]

Comparison	Study Quality^ (number of studies)	Outcome	Results	Strength of Evidenceł
DPP-4 Inhibitors compared with Metformin				
Linagliptin 5 mg vs. metformin 500 mg twice daily (M500) or metformin 1000 mg twice daily (M1000)	Fair (2)	HbA1c reduction from baseline	linagliptin: -1.29% M1000: -2.07% linagliptin vs. M1000: MD -0.60% (95% CI, -0.88 to -0.32) linagliptin vs. M500: NS	Low
Sitagliptin 100 mg vs. metformin 2000 mg	Fair (3)	HbA1c reduction from baseline	Meta-analysis of trials 24-26 weeks*: metformin vs sitagliptin: WMD -0.30% (95% CI, -0.52 to -0.09)	Moderate
Saxagliptin 5 mg vs. metformin 2000 mg (uptitrated from 1500 mg)	Fair (2)	HbA1c reduction from baseline	saxagliptin 5 mg vs. metformin: WMD -0.31% (95% CI, -0.74% vs. 0.13) P=NS	Low
GLP-1 agonists compared to metformin				
Exenatide XR 2 mg vs. metformin 2000 mg	Fair (1)	HbA1c reduction from baseline	exenatide XR: -1.53% metformin: -1.48% P=0.62; *CI not provided*	Low
Dulaglutide 0.75 mg or 1.5 mg vs. metformin 1500-2000mg	Fair (1)	Percent of patients with HbA1c of <7%	dulaglutide 0.75 mg: 63% dulaglutide 1.5 mg: 62% metformin: 54% P=0.02 for both comparisons; *CI not provided*	Low
SGLT2 Inhibitors Compared with Metformin				
Dapagliflozin 5 mg and 10 mg vs. metformin XR	Fair (3)	HbA1c reduction from baseline	dapagliflozin 5 mg vs. metformin XR: WMD -0.12% (95% CI, -0.15 to -0.08) dapagliflozin 10 mg vs. metformin XR:	Low

			WMD -0.11% (95% CI, -0.11 to -0.05)	
Empagliflozin 10 mg or 25 mg vs. metformin	Fair (2)	HbA1c reduction from baseline	*Study 1* empagliflozin 10mg: -0.50% empagliflozin 25 mg: -0.60% metformin: -0.70% *P-values and CI not provided* *Study 2* empagliflozin 10mg: -1.36% empagliflozin 25 mg: -1.35% metformin: -1.47% *P-values and CI not provided*	Moderate
Canagliflozin 100 mg or 300 mg vs. metformin ER	Fair (1)	Percent of patients with HbA1c of <7%	canagliflozin 100 mg: 39% canagliflozin 300 mg: 43% metformin ER: 43% *comparisons not SS, p-values not provided*	Low
Abbreviations: CI – confidence interval; HbA1c – hemoglobin A1c; ER – extended release; MD – mean difference; NS – non-significant: SS – statistically significant; WMD – weighted mean difference				
Key: * additional trials support pooled results but were not included due to significant trial heterogeneity, ^18-52 weeks, ł strength of evidence was rated by DERP				

Subgroup Analyses

- Empagliflozin, canagliflozin and dapagliflozin were associated with a higher incidence of genital infections compared to sitagliptin, saxagliptin or linagliptin which was consistent for males and females. The relative risk was 3.91 (95% CI, 1.92 to 7.99) for females and 3.62 (95% CI, 2.20 to 5.97) for males.[1]

New Guidelines:

The American Diabetes Association (ADA) published their annual Standards of Medical Care in Diabetes for 2018 in January.[34] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions.

A second guidance on the cardiovascular management of non-pregnant adults with diabetes was published by the ADA in April of 2018.[20] However, details are not included due to the same limitations cited above for the Standards of Medical Care in Diabetes.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a T2DM management algorithm in 2018.[35] Similar to the ADA recommendations, this management algorithm was authored by a majority of authors with industry affiliations and the methods for guideline development were not disclosed. Due to these limitations, the algorithm will not be presented.

The International Diabetes Federation (IDF) published clinical practice recommendations for managing type 2 diabetes in primary care.[36] Recommendations were based on worldwide diabetes treatment guidelines. Guidelines were graded by the Agree II instrument with scores ranging from 36-97%. The practice recommendations were based a combination of guidance that has met criteria for inclusion into Drug Use Research and Management documents and on guidelines that are not included due to methodological flaws. Therefore, the IDF recommendations will not be included in detail.

New Formulations or Indications:
Exenatide ER once weekly single dose auto-injector formulation (Bydureon BCise™) is a GLP-1 RA approved by FDA in October 2017 for patients with T2DM as an adjunct to diet and exercise.[37] This new formulation joins the currently available once weekly injectable exenatide ER formulation, Bydureon™, and is thought to be easier for patients to administer. A noninferiority trial in T2DM patients comparing Bydureon BCise (BB) to exenatide, as add-on to oral antidiabetic therapy, found similar HbA1c lowering, -1.39% to -1.03%, respectively. In a second comparison of BB to sitagliptin, BB was found to non-significantly lower HbA1c by -0.28% (95% CI, -0.62 to 0.02) more than sitagliptin, in patients taking metformin.[37] Most common adverse reactions with BB were injection-site nodules and nausea. Similar to other GLP-1 RAs BB has a black box warning for risk of thyroid c-cell tumors.

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 183 citations were manually reviewed from the initial literature search. After further review, 182 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Safety Outcome	Trial Methodology	Results	Limitations
Holman, et al[16]	Exenatide ER 2mg weekly vs. Placebo weekly 3.2 years	Adult patients with T2DM (n=14,752), 73% with previous CV disease	Composite outcome of first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke	- Primary outcome on ITT population - non-inferiority margin set at 1.3 for the upper limit of the CI for the HR - Supportive analysis was done on PP population	Exenatide: 11.4% Placebo: 12.2% HR 0.91 (95% CI, 0.83 to 1.00) P<0.001 for noninferiority and P=0.06 for superiority	- Primary outcome done on ITT population which biases results in favor of no difference between treatments in trials with a NI design; however, PP population results supported noninferiority findings. - Higher use of SGLT-2 inhibitors (which may have CV benefit in exenatide group - Higher use of lipid lowering medication, including statins, in the exenatide group - Results applicable to patients with previous CV disease - Industry funded
Abbreviations: CI – confidence interval; CV – cardiovascular; HR – hazard ratio; ITT – intention-to-treat; NI - non-inferiority; PP – per protocol; T2DM – type 2 diabetes mellitus						

NEW DRUG EVALUATION: ertugliflozin (Steglatro™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Once-daily ertugliflozin is a SGLT-2 inhibitor approved by the FDA in 2017 as monotherapy and in fixed dose combination products with metformin (Segluromet™) or sitagliptin (Steglujan™). Approval for ertugliflozin was based off of seven trials in patients with T2DM; five placebo-controlled, two active-treatment comparisons (glimepiride and sitagliptin).[10–15] The CV effects of ertugliflozin are currently being studied with a completion date in 2019. One study specifically evaluated ertugliflozin in patients with moderate renal impairment and changes in HbA1c were not found to be significantly different from placebo.[38] Therefore, ertugliflozin is not recommended in these patients and this trial will not be critically evaluated. All trials had similar inclusion criteria of enrolling adult patients with T2DM that were predominately healthy with normal renal function.[9]

Efficacy Trials

Placebo-controlled comparisons of ertugliflozin were studied for 26 weeks (1 trial had an extension study without formal comparison data) in adult patients with T2DM. Three trials were monotherapy comparisons with or without background therapy and one trial compared ertugliflozin/sitagliptin to placebo.[10–13] All trials were multicenter, double-blind, randomized controlled trials enrolling 291-621 patients. Reductions in the primary endpoint of HbA1c lowering from baseline were -0.7% for ertugliflozin 5 mg and -0.8% to -0.9% for ertugliflozin 15 mg compared to placebo.[10–12] For the combination comparison of ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 15 mg/sitagliptin 100 mg versus placebo, HbA1c decreased at week 26, -1.6%, -1.7% and -0.4%, respectively.[13] Ertugliflozin was found to be superior to placebo in all placebo-controlled study comparisons (P<0.05).

Ertugliflozin was compared to sitagliptin in patients with T2DM inadequately controlled on metformin for 52 weeks in a phase 3, double-blind, multicenter, fair quality, randomized controlled trial. Patients (n=1233) were randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, ertugliflozin 5 mg/sitagliptin 100 mg (E5/S) or ertugliflozin 15 mg/sitagliptin 100 mg (E15/S).[15] Enrolled patients were a mean age of 55 years, and baseline HbA1c of 8.6%. In contrast to other trials, this trial included a shorter duration of diabetes history, 5 years. The distribution of males and females enrolled in each group were similar except for the sitagliptin group which had 62% males compared to 51% in the other four groups. North American sites represented 30% of the patient population and Europe had the highest patient representation with approximately 40% of patients. The study was funded by industry and had a low risk of bias for all other study domains except for an unclear risk of detection bias. The primary endpoint was change from baseline in HbA1c at 26 weeks, patients were followed for a total of 52 weeks (**Table 6**). HbA1c reduction favored the combination of E5/S compared to ertugliflozin (LSMC -0.5%; 95% CI -0.6 to -0.3; P<0.001) and for E15/S compared to ertugliflozin (LSM -0.4%; 95% CI, -0.6 to -0.3; P<0.001).[15] Combination therapy was also more effective at reducing HbA1c compared to sitagliptin monotherapy; E5/S vs. sitagliptin (LSM -0.4%; 95% CI, -0.6 to -0.3; P<0.001) and E15/S vs. sitagliptin (LSM -0.5%; 95% CI, -0.6 to -0.3; P<0.001).[15] The percent of patients obtaining an HbA1c less than 7% and amount of weight loss also favored combination therapy (**Table 6**). The percent of patients with an HbA1c less than 7% decreased in all groups at 52 weeks; however, least square mean differences between groups for HbA1c reductions were similar to week 26 results and reductions were still clinically significant.

Table 6. Efficacy Outcomes for Ertugliflozin versus Sitagliptin.[15]

Treatment Group	HbA1c Reduction from Baseline	LS Mean Difference in HbA1c	Patients with HbA1c <7.0%	Weight Change
Ertugliflozin 5 mg	-1.0%		26%	-2.7 kg
Ertugliflozin 15 mg	-1.1%		32%	-3.7 kg
Sitagliptin 100 mg	-1.1%		33%	-0.7 kg
Ertugliflozin 5 mg/sitagliptin 100 mg	-1.5%	*E5/S100 vs. ertugliflozin* -0.5 (95% CI, -0.6 to -0.3) P<0.001 *E5/S100 vs. sitagliptin* -0.4 (95% CI, -0.6 to -0.3) P<0.001	52%	-2.5 kg
Ertugliflozin 15 mg/sitagliptin 100 mg	-1.5%	*E15/S100 vs. ertugliflozin* -0.4 (95% CI, -0.6 to -0.3) P<0.001 *E15/S100 vs. sitagliptin* -0.5 (95% CI, -0.6 to -0.3) P<0.001	49%	-2.9 kg

Limitations:

- Unclear risk of detection bias.
- Funded by industry.
- Short term trial with insufficient data on long-term efficacy and safety outcomes.
- Patients had a 5-year history of diabetes which is shorter than other diabetic treatment studies which may bias the results to increased HbA1c lowering due to less time of attenuation to therapy glucose lowering over time.

In a second active comparison trial ertugliflozin 5 mg or 15 mg was compared to glimepiride (mean dose 3 mg) in a noninferiority, phase 3, double-blind, randomized trial in 1326 patients who were inadequately controlled on metformin.[14] Glimepiride doses were initiated at 1 mg and titrated to a max dose of 8 mg based on a maximum tolerated dose. Patients were studied for 52 weeks and in a second phase of 52 weeks, which is published separately. Patients included in the trial were a mean age of 58 years with a 7.5-year history of T2DM. Baseline HbA1c was lower than comparator studies, with a mean value of 7.8%. Seventy-three percent of the participants were Caucasian and a majority were classified as obese based on body mass index (BMI). The study was industry funded and included patients from US sites but the specific number was not provided. The primary efficacy outcome was change in HbA1c from baseline. Noninferiority was determined if the upper bound of the 95% CI for HbA1c did not exceed 0.3%, which is a commonly accepted delta for trials evaluating antidiabetic therapy. Full analysis set was used for the primary outcome analysis. Ertugliflozin 15 mg was found to be noninferior to glimepiride (**Table 7**). The 5 mg dose of ertugliflozin had a value higher than 0.3% for the upper CI, and therefore was inferior to glimepiride. The per protocol analysis found both doses of ertugliflozin to be noninferior to glimepiride, supporting the primary outcome for the 15 mg dose. Weight loss favored ertugliflozin by a mean difference compared to glimepiride of -3.0 to -3.4 kg ($p<0.001$).[15]

Table 7. Efficacy Outcomes for Ertugliflozin versus Glimepiride.[14]

Treatment Group	HbA1c Reduction from baseline	LS Mean Difference	Weight Change
Ertugliflozin 5 mg	-0.6%	0.2% (95% CI, 0.1 to 0.3) *inferior*	-2.7 kg
Ertugliflozin 15 mg	-0.6%	0.1% (95% CI, -0.0 to 0.2) *noninferior*	-3.7 kg
Glimepiride (3 mg mean dose)	-0.7%	NA	-0.7 kg

Abbreviations: CI – confidence interval; NA = not applicable

Limitations:

- Analysis of full analysis set can bias results in favor of no difference (noninferiority) between treatments; however, the per protocol population supported noninferiority findings of the 15 mg ertugliflozin dose.
- Unknown external validity to US Medicaid patients without additional details on study sites.
- Insufficient details on detection blinding.
- High attrition rate (19-24%) could bias results in favor of no difference between treatments.
- Inherent conflict of interest with trial funding by manufacturer.

Clinical Safety:

The most common adverse effects seen in 2% of patients treated with ertugliflozin compared to placebo were female and male genital infections, urinary tract infections, and headache (**Table 8**).[9] Hypoglycemia was rare in placebo-controlled studies with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, 2.6%, 2.6% and 0.7%, respectively.

Table 8. Common Adverse Reactions Occurring in Patients Treated with Ertugliflozin Compared to Placebo.[9]

Adverse Reaction	Ertugliflozin 5 mg (N=519)	Ertugliflozin 15 mg (N=510)	Placebo (N=515)
Female genital mycotic infections	9%	12%	3%
Male genital mycotic infections	4%	4%	0.4%
Urinary tract infections	4%	4%	4%
Headache	4%	3%	2%
Vaginal pruritus	3%	2%	0.4%

As with other SGLT-2 inhibitors, ertugliflozin has warnings for hypotension, ketoacidosis, acute kidney injury and impairment in renal function, urosepsis and pyelonephritis, increased low-density lipoprotein cholesterol (LDL-C) and hypoglycemia when used with insulin or insulin secretagogues. Ertugliflozin was found to have a higher incidence of lower limb amputations in patients who were considered at-risk subjects (e.g., preexisting CV disease, cerebrovascular and/or peripheral arterial disease). Across the phase 3 trials the risk was 1 (0.1%) in non-ertugliflozin treated patients, 3 (0.2%) in the ertugliflozin 5 mg group and 8 (0.5%) in the ertugliflozin 15 mg group.[9]

Table 9. Ertugliflozin Pharmacology and Pharmacokinetic Properties.[9]

Parameter	
Mechanism of Action	Blocks reabsorption of glucose from the glomerular filtrate from entering back into the circulation by blocking the SGLT2 transporter. This results in reduced renal absorption of filtered glucose and lowers the renal threshold for glucose causing an increase in urinary glucose excretion.
Oral Bioavailability	100%
Distribution and Protein Binding	Highly protein bound (93.6%)
Elimination	41% in the feces and 50% urine
Half-Life	16.6 hours
Metabolism	UGT1A9 and UGT2B7-mediated O-glucuronidation. CYP-mediated (oxidative) metabolism is around 12%.

NEW DRUG EVALUATION: semaglutide (Ozempic®)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Semaglutide is a once-weekly GLP-1 RA indicated for use in patients with T2DM, bringing the number of GLP-1 RAs to seven. Approval of semaglutide was based on six multi-national efficacy trials, 2 trials conducted in Japan and a CV safety trial. In the efficacy studies semaglutide was compared to placebo, exenatide, insulin glargine, sitagliptin and dulaglutide in trials lasting 30-56 weeks.[3–8] To minimize GI adverse events, the dose of semaglutide was initiated at 0.25 mg weekly and increased to 0.5 mg after 4 weeks. Patients randomized to receive semaglutide 1.0 mg were titrated after up after an additional 4 weeks. The primary efficacy endpoint of HbA1c change from baseline was the same for all efficacy trials. Two trials comparing semaglutide to placebo (one with background basal insulin and one in treatment naïve patients) were conducted with similar findings to active-comparator trials.[7,8]

Efficacy Trials
Six semaglutide efficacy studies have been published; two placebo-controlled and four noninferiority, active treatment comparison trials. These types of trials are excluded if possible, due to limitations outlined in DURM methods, but are required for inclusion for this NDE due to lack of higher quality evidence. Two additional trials including only Japanese patients from Japan were excluded from the NDE due to low external validity.[39,40] All trials were funded by industry.

Semaglutide 0.5 mg or 1.0 mg was compared to daily sitagliptin 100 mg in patients (n=1231) with T2DM inadequately controlled on metformin, TZDs or both.[5] The trial was a multi-center, parallel group, noninferiority study. Patients were treated for 56 weeks using a double-dummy design to preserve blinding. Obese adult T2DM patients with a mean age of 55 years and baseline HbA1c of 8.1% from non-US sites were enrolled. Semaglutide was considered noninferior to sitagliptin if the upper boundary of the 95% CI of the estimated treatment difference was below the noninferiority margin of 0.3%. Results were analyzed for the ITT population and no analysis of the per protocol population was done. The difference in HbA1c lowering between semaglutide 0.5 mg and sitagliptin was -

0.77% (95% CI, -0.92 to -0.62; P<0.001) and -1.06% (95% CI -1.21 to -0.91) with semaglutide 1.0 mg (p<0.001 for both comparisons for noninferiority and superiority).[5] The proportion of patients who obtained an HbA1c less than 7% was 63% with semaglutide 0.5 mg, 74% with semaglutide 1.0 mg and 27% with sitagliptin. Body weight was decreased by -2.25 kg more with semaglutide 0.5 mg and -4.20 kg more with semaglutide 1.0 mg (p<0.001 for both comparisons).

A second efficacy trial was an open-label comparison between semaglutide 0.5 mg and 1.0 mg and insulin glargine in adult patients with T2DM inadequately controlled on metformin, with or without sulfonylureas, who were insulin naïve.[3] The trial was a noninferiority, parallel group, multicenter, phase 3, randomized study of 1089 participants. Patients receiving semaglutide were titrated up on a fixed-dose escalation regimen and glargine was initiated at 10 IU/daily and titrated weekly based on pre-breakfast self-monitored glucose levels. Patients were a mean age of 56 years, baseline HbA1c of 8.2%, mean BMI of 33.0 kg/m^2 and 77% were Caucasian. The primary outcome was based on a modified intent to treat (mITT) population and semaglutide was considered noninferior to glargine if the noninferiority margin was less than 0.3%. The decrease in HbA1c from baseline was -1.21% with semaglutide 0.5 mg, -1.65% with semaglutide 1.0 mg and -0.83% with glargine. Treatment differences were the following: semaglutide 0.5 mg -0.38% (95% CI, -0.52 to -0.24); semaglutide 1.0 mg -0.81% (95% CI, -0.96 to -0.67) (p<0.001 for both comparisons).[3] Fifty-seven patients receiving semaglutide 0.5 mg obtained a HbA1c less than 7% compared to 73% taking semaglutide 1.0 mg and 38% using glargine (P<0.0001 for both comparisons). Differences in weight loss favoring semaglutide ranged from 4.6 kg to 6.3 kg compared to glargine. Severe hypoglycemia was statistically and clinically significantly more common with glargine (11%) compared with semaglutide 0.5 mg (4%) and semaglutide 1.0 mg (6%). Withdrawals due to adverse events were 6% with semaglutide 0.5 mg, 8% with semaglutide 1.0 mg and 1% with glargine. Adverse GI events accounted for the most common reason for discontinuation.

An additional open-label trial comparing semaglutide 1.0 mg to once-weekly exenatide ER 2.0 mg was studied in patients (n=813) taking 1-2 oral antidiabetic drugs (OADs) and followed for 56 weeks.[4] Patients were a mean age of 57 years, baseline HbA1c of 8.3%, mean BMI of 34 kg/m^2, 97% were taking metformin and 48% were taking sulfonylureas. Similar to other trials, the noninferiority margin was set at 0.3%. The mean change in HbA1c from baseline was -1.5% for semaglutide and -0.9% for exenatide ER (ETD -0.62%; 95% CI, -0.80 to -0.44; P<0.001 for noninferiority and superiority).[4] An upper bound of 0.44% of the confidence interval suggests a clinically relevant change in HbA1c. Other studies of exenatide ER have demonstrated a HbA1c lowering of 1-2%, suggesting noninferiority to semaglutide but not superiority.[41,42] Body weight was decreased more with semaglutide compared to exenatide ER (ETD -3.78 kg; 95% CI, -4.58 to -2.98; P<0.0001). Adverse GI effects were common and occurred in 42% of semaglutide treated patients and 33% of exenatide ER treated patients. The incidence of injection site reactions was more common with exenatide ER compared to semaglutide, 22.0% versus 1.2%, respectively.[4]

An open-label, multicenter, phase 3, noninferiority trial compared once weekly semaglutide to once weekly dulaglutide in 1201 adult patients with T2DM and on metformin monotherapy.[6] Patients were an average age of 56 years with a baseline HbA1c of 8.2% and predominately Caucasian. Patients were randomized to semaglutide 0.5 mg, semaglutide 1.0 mg, dulaglutide 0.75 mg or dulaglutide 1.5 mg. Comparisons were between the lower doses of semaglutide and dulaglutide and the higher doses of semaglutide and dulaglutide. The analysis was done on the ITT population with an HbA1c noninferiority margin of 0.4%. The primary endpoint was change in HbA1c from baseline at 40 weeks with a secondary outcome analysis of bodyweight. Results for HbA1c lowering and weight are presented in **Table 10**. The number of patients obtaining an HbA1c of less than 7% ranged from 68%-79% for semaglutide and 52%-67% for dulaglutide, which statistically favored semaglutide for low (ARR 16%/NNT 7) and high dose comparisons (ARR 12%/NNT 9). An analysis of HbA1c lowering in the per protocol population found similar results as the ITT findings; ETD -0.42 (95% CI, -0.58 to -0.26; P<0.001) for the low dose comparison and ETD -0.38 (95% CI, -0.54 to -0.22; P<0.001) for the high dose comparison.

Table 10. Efficacy Outcomes for Once-weekly Semaglutide versus Once-Weekly Dulaglutide.[6]

Treatment Group	HbA1c Reduction from baseline	Estimated Treatment Difference in HbA1c	Weight Change
Semaglutide 0.5 mg (S.5)	-1.5%	*S.5 vs. D.75:* -0.40% (95% CI, -0.55 to -0.25) P <0.0001	-4.6 kg
Dulaglutide 0.75 mg (D.75)	-1.1%	*noninferior and superior*	-2.3 kg
Semaglutide 1.0 mg (S1)	-1.8%	*S1 vs. D1.5* -0.41% (95% CI, -0.57 to -0.25) P<0.0001 *noninferior and superior*	-6.5 kg
Dulaglutide 1.5 mg (D1.5)	-1.4%		-3.0 kg

Abbreviations: CI – confidence interval; HbA1c – hemoglobin A1c

An oral formulation of semaglutide is being studied and phase 2 studies have shown efficacy in HbA1c lowering when compared to placebo and subcutaneous semaglutide.[43] Submission for regulatory approval of the oral formulation is expected in 2019.

CV Safety Trial

Semaglutide 0.5 mg and 1.0 mg were compared to placebo in patients 50 years and older with T2DM and a history of CV disease or chronic kidney disease or 60 years and older with risk factors for CV disease in a phase 3, double-blind, double-dummy, multi-center, noninferiority, randomized controlled trial (**Table 13**).[2] Patients were a mean age of 65 years, had a 14-year history of T2DM, a baseline HbA1c of 8.7% and 34% were from US treatment sites. Comorbidities of included patients were: hypertension (90%), cholesterol abnormalities (31%), coronary artery disease (23%), obesity (24%), myocardial ischemia (23%) and osteoarthritis (20%).[2,44] Eighty-three percent of patients had CV disease, kidney disease or both. A majority of patients were also taking angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and other antidiabetic therapies, which was similar between groups. The noninferiority margin was set at 1.8 for the upper boundary of the 95% CI of the hazard ratio. This was chosen based on data from other studies which showed a 1.8% event rate of the primary outcome to be considered conservative but not low. The primary outcome was measured in the ITT population for the composite endpoint of CV death, nonfatal MI or nonfatal stroke.

The composite primary outcome occurred in 6.6% of patients taking semaglutide doses compared to 8.9% in the placebo group (HR 0.74; 95% CI, 0.58 to 0.95; P<0.001 for noninferiority).[2] The upper bound of the CI was less than 1.8 in the semaglutide group, supporting noninferiority. Additionally, the upper bound of the HR was 0.95 which is an acceptable finding indicating no increased risk of CV risk with semaglutide, which is more important than the point estimate in noninferiority trials. The study was not powered for superiority so superiority testing was not pre-specified. The decrease seen with semaglutide was driven by the reduction in stroke risk compared to placebo, 1.6% vs. 2.7% (HR 0.61; 95% CI, 0.38 to 0.99; P=0.04).[2] The incidence of nonfatal MI was lower with semaglutide compared to placebo (MD -1.0%; P=0.12) but unlikely to be clinically impactful. Death due to CV causes was 2.7% with semaglutide compared to 2.8% with placebo (HR 0.98; 95% CI, 0.65 to 1.48; P=0.92). The estimated number of patients that would need to be treated over 24 months to prevent one event was 45, as estimated by Kaplan-Meier analysis. A subgroup analysis of patients with only CV risk factors demonstrated no benefit of semaglutide therapy compared to placebo based on a HR of 1.0 (95% CI, 0.41 to 2.46) and there was no benefit demonstrated in a subgroup analysis in patients from US treatment sites (HR 0.87; 95% CI, 0.57 to 1.34).

Limitations:

- All studies were funded by industry.
- Use of ITT analysis for the primary outcome can bias the results in favor of no difference between groups when using a noninferiority design. A per protocol analysis would be a more appropriate and well-designed non-inferiority studies will provide both analyses.
- Study methods suggest optimization of approved antidiabetic therapies to obtain effective glycemic control in both groups in the CV study; however, HbA1c values were 0.7% to 1.0% lower in patients treated with semaglutide compared to placebo (P<0.001) which could bias results in favor semaglutide due of evidence of benefit with improved glucose levels.

Clinical Safety:

As with all GLP-1 RAs there is a boxed warning due to the risk of thyroid c-cell tumors. The most common adverse reactions for semaglutide seen in clinical trials were: nausea, vomiting, diarrhea, constipation and abdominal pain (**Table 11**).[24] The risk of hypoglycemia was 2-4% in clinical trials with semaglutide compared to 0% for placebo. No episodes of severe hypoglycemia were observed in either group. Semaglutide was associated with a higher incidence of withdrawals due to adverse events primarily due to GI disorders. Discontinuation rates due to adverse events ranged from 6-10% for semaglutide compared to 1-3% for placebo. Mild increases in lipase and amylase concentrations seen with semaglutide and other GLP-1 RAs warrant continual monitoring to ensure long-term use does not increase the risk of pancreatitis.

Unlike other GLP-1 RAs there was an increased risk for diabetic retinopathy complications in 3% of semaglutide-treated patients compared to 1.8% of placebo-treated patients (HR 1.76; 95% CI, 1.11 to 2.78).[44] A rapid decrease in glucose levels may be the causative reason for the increased risk; however, improved glucose control has previously been shown in other studies to decrease the risk of microvascular complications. Further studies are needed to provide clarity on the long-term risk benefit of semaglutide on microvascular outcomes.

Table 11. Adverse Reactions for Semaglutide compared to Placebo Reported in ≥5 % of Patients.[24]

Adverse Reaction	Semaglutide 0.5 mg (N=260)	Semaglutide 1.0 mg (N=261)	Placebo (N=262)
Nausea	16%	20%	6%
Vomiting	5%	9%	2%
Diarrhea	9%	9%	2%
Abdominal Pain	7%	6%	5%
Constipation	5%	3%	2%

Table 12. Semaglutide Pharmacology and Pharmacokinetic Properties.[24]

Parameter	
Mechanism of Action	GLP-1 analogue that lowers glucose by insulin secretion and reduces glucagon secretion.
Oral Bioavailability	NA
Distribution and Protein Binding	Highly (>99%) protein bound.

Elimination	Renal and hepatic
Half-Life	1 week
Metabolism	Proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

Abbreviations: NA – not applicable

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Number of patients obtaining an A1c <7%
2) Mortality
3) Macrovascular outcomes
4) Microvascular outcomes
5) Serious adverse events
6) Study withdrawals due to an adverse event

Primary Study Endpoint:

1) Composite of CV death, nonfatal MI, or nonfatal stroke

Table 13. Comparative Evidence Table for Semaglutide.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Marso, et al[2] PC, PG, DB, RCT	1. Semaglutide 0.5 mg or 1.0 mg weekly 2. Placebo 0.5 mg or 1.0 mg Dose was initiated at 0.25 mg weekly and titrated after 4 weeks until maintenance dose was reached 104-week treatment phase and 109-week observation	Demographics: - Mean age: 65 years - Male: 61% - Duration of T2DM: 14 years - Baseline HbA1c: 8.7% - Established CV disease or kidney disease or both: 83% Key Inclusion Criteria: - T2DM - ≥ 50 years old with established CV disease or chronic kidney disease stage 3 or higher or ≥ 60 years with ≥ 1 CV risk factor	ITT: 1. 1648 2. 1649 PP: 1. 1623 2. 1609 Attrition: 1. 1.5% 2. 2.4%	Primary Endpoint: Composite of CV death, nonfatal MI, or nonfatal stroke: Semaglutide: 108 (6.6%) Placebo: 146 (8.9%) HR 0.74 (95% CI, 0.58 to 0.95) P<0.001 for non-inferiority Secondary Endpoints: CV Death: Semaglutide: 44 (2.7%) Placebo: 46 (2.8%) HR 0.98 (0.65 to 1.48) P=0.92 Nonfatal MI: Semaglutide: 47 (2.9%) Placebo: 64 (3.9%) HR 0.74 (95% CI, 0.51 to 1.08) P=0.12	NA for all	Withdrawals due to Adverse Events: Semaglutide: 107 (13%) Placebo: 55 (7%) Gastrointestinal Disorders: Semaglutide: 425 (52%) Placebo: 292 (36%) Severe or Symptomatic Hypoglycemia: Semaglutide: 185 (23%) Placebo: 175 (21%) Serious Adverse Events: Semaglutide: 283 (34%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1:1:1 by an interactive voice web response system. Performance Bias: (low) Placebo was volume-matched to maintain blinding. Detection Bias: (low) Data analysis done by manufacturer. Outcomes were adjudicated by an independent committee that was blinded to treatment assignment. Attrition Bias: (low) Attrition was low in both groups. Analysis was done on ITT population. Reporting Bias: The study was funded by the manufacturer. **Applicability**: Patient: Eighty-three percent of patients had established CV disease, kidney disease of both and 17% had CV risk factors. Patients were allowed to be on other OADs. Eighty-four percent of patients were also taking ARBs or ACE inhibitors. Seventy-seven percent were taking lipid lowering medications.

		- HbA1c >7% - ≤ 2 antihyperglycemic drugs +/- insulin <u>Key Exclusion Criteria</u>: - Treatment with a DPP-4 inhibitor within 30 days of screening - Treatment with a GLP-1 RA or insulin (other than basal or premixed) within 90 days of screening - Acute coronary or cerebral vascular event - Dialysis		Nonfatal Stroke: Semaglutide: 27 (1.6%) Placebo: 44 (2.7%) HR 0.61 (95% CI, 0.38 to 0.99) P=0.04 <u>Retinopathy Complications</u>: Semaglutide: 50 (3%) Placebo: 29 (1.8%) HR 1.76 (95% CI, 1.11 to 2.78) P=0.02 <u>New or Worsening Nephropathy</u>: Semaglutide: 62 (3.8%) Placebo: 100 (6.1%) HR 0.64 (95% CI, 0.46 to 0.88) P=0.005		Placebo: 314 (38%) 95% CI and p-values not reported		<u>Intervention</u>: FDA approved dose of semaglutide. <u>Comparator</u>: Placebo comparison adequate to determine no excess CV risk of semaglutide. <u>Outcomes</u>: Composite outcome of CV death, nonfatal MI or nonfatal stroke required by FDA. <u>Setting</u>: Twenty countries and 230 sites. 34% from US sites.
<u>Abbreviations</u> [alphabetical order]: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = double blind; HbA1c = hemoglobin A1c; HR = hazard ratio; ITT = intention to treat; mitt = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OAD = oral antidiabetic therapy; PC = placebo-controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; T2DM = type 2 diabetes mellitus								

References:

1. McDonagh M, Blazina I, Holmes R, Lazur BH. Newer diabetes medications and combinations. Final update 3 report prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Heatlh & Science University, Portland, Oregon, October 2017.

2. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141

3. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(5):355-366. doi:10.1016/S2213-8587(17)30085-2

4. Ahmann AJ, Capehorn M, Charpentier G, et al. efficacy and safety of once-weekly semaglutide versus exenatide er in subjects with type 2 diabetes (sustain 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care*. 2018;41(2):258-266. doi:10.2337/dc17-0417

5. Ahren B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *The Lancet Diabetes & Endocrinology*. 2017;5(5):341-354. doi:10.1016/S2213-8587(17)30092-X

6. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol*. 2018;6(4):275-286. doi:10.1016/S2213-8587(18)30024-X

7. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomised, controlled trial. *J Clin Endocrinol Metab*. April 2018. doi:10.1210/jc.2018-00070

8. Sorli C, Harashima S-I, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(4):251-260. doi:10.1016/S2213-8587(17)30013-X

9. Steglatro Prescribing Information. Merck and Col, INC. Whitehouse Station, NJ; 2017.

10. Aronson R, Frias J, Goldman A, et al. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. *Diabetes Obes Metab*. February 2018. doi:10.1111/dom.13251

11. Dagogo-Jack S, Liu J, Eldor R, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: The VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab*. 2018;20(3):530-540. doi:10.1111/dom.13116

12. Rosenstock J, Frias J, Páll D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). *Diabetes Obes Metab*. 2018;20(3):520-529. doi:10.1111/dom.13103

13. Miller S, Krumins T, Zhou H, et al. Ertugliflozin and sitagliptin co-initiation in patients with type 2 diabetes: the vertis sita randomized study. *Diabetes Ther*. 2018;9(1):253-268. doi:10.1007/s13300-017-0358-0

14. Hollander P, Liu J, Hill J, et al. ertugliflozin compared with glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin: the vertis su randomized study. *Diabetes Ther*. 2018;9(1):193-207. doi:10.1007/s13300-017-0354-4

15. Pratley RE, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab*. 2018;20(5):1111-1120. doi:10.1111/dom.13194

16. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917

17. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. Clinical Guideline Update. December 2015. Available at https://www.nice.org.uk/guidance/ng28. Accessed June 6, 2017.

18. Canadian Agency for Drugs and Technology in Health. New drugs for type 2 diabetes: second-line therapy – recommendations report .Available at: https://www.cadth.ca/sites/default/files/pdf/TR0012_T2DM_Final_Recommendations.pdf. Accessed June 21, 2017.

19. Maruthur NM, Tseng E, Hutfless S, et al. diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. [Review]. *Annals of Internal Medicine*. 2016;164(11):740-751. doi:10.7326/M15-2650.

20. Chamberlain JJ, Johnson EL, Leal S, et al. Cardiovascular disease and risk management: Review of the American Diabetes Association Standards of Medical Care in Diabetes 2018. *Ann Intern Med*. 2018;168(9):640-650. doi:10.7326/M18-0222.

21. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720.

22. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. June 2017. doi:10.1056/NEJMoa1611925.

23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *Journal of Medicine*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.

24. Ozempic Prescribing Information. Novo Nordisk, Plainsboro, NJ; 2017.

25. Oregon Health Authority. Oreogn Diabetes Report - A report on the burden of diabetes in Oregon and progress on the 2009 strategic plan to slow the rate of diabetes. January 2015. http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Diabetes/Documents/OregonDiabetesReport.pdf.

26. Centers for Disease Control and Prevention Press Release. Number of Americans with diabetes projected to double or triple by 2050. 2010. http://www.cdc.gov/media/pressrel/2010/r101022.html. Accessed July 23, 2013.

27. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149. doi:10.2337/dc14-2441

28. Redmon B, Caccamo D, Flavin P. Diagnosis and management of type 2 diabetes mellitus in adults. *Institute for Clincal Systems Improvement*. July 2014. https://www.icis.org/_asset/3rrm36/Diabetes.pdf.

29. Johansen MY, MacDonald CS, Hansen KB, et al. Effect of an Intensive Lifestyle intervention on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318(7):637-646. doi:10.1001/jama.2017.10169.

30. American Diabetes Association. Diabetes Advocacy: Standards of Medical Care in Diabetes-2018. *Diabetes Care*. 2018;41(Suppl 1):S152-S153. doi:10.2337/dc18-S015.

31. Qaseem A, Wilt TJ, Kansagara D, et al. Hemoglobin a1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. *Ann Intern Med*. 2018;168(8):569-576. doi:10.7326/M17-0939.

32. Canadian Agency for Drugs and Technology in Health. Drugs for Type 2 Diabetes: Second- and Third-Line Therapy Review Update. Available at: https://www.cadth.ca/drugs-type-2-diabetes-second-and-third-line-therapy-review-update. Accessed June 21, 2017.

33. Garber AJ, Abrahamson MJ, Barzilay JI, et al. consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2018 executive summary. *Endocr Pract*. 2018;24(1):91-120. doi:10.4158/CS-2017-0153

34. American Diabetes Association. Standards of Medical Care in Diabetes -2018. Diabetes Care 2018;41(Suppl. 1):S1–S2.

35. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. *Endocr Pract*. 2017;23(2):207-238. doi:10.4158/EP161682.CS

36. International Diabetes Federation. Recommendations For Managing Type 2 Diabetes In Primary Care, 2017. www.idf.org/managing-type2-diabetes.

37. BCise Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE; 2017.

38. Grunberger G, Camp S, Johnson J, et al. Ertugliflozin in patients with stage 3 chronic kidney disease and type 2 diabetes mellitus: The VERTIS RENAL randomized study. *Diabetes Ther*. 2018;9(1):49-66. doi:10.1007/s13300-017-0337-5.

39. Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. *Diabetes Obes Metab*. 2018;20(2):378-388. doi:10.1111/dom.13082

40. Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: A randomized trial. *Diabetes Obes Metab*. 2018;20(5):1202-1212. doi:10.1111/dom.13218.

41. Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. *Lancet Diabetes Endocrinol*. 2014;2(6):464-473. doi:10.1016/S2213-8587(14)70029-4.

42. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. *Diabetes Care*. 2012;35(2):252-258. doi:10.2337/dc11-1107.

43. Davies M, Pieber TR, Hartoft-Nielsen M-L, et al. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. 2017;318(15):1460-1470. doi:10.1001/jama.2017.14752.

44. Food and Drug Administration. Semaglutide medical summary. Center for drug evaluation and research . Application number: 209637Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209637Orig1s000MedR.pdf. Accessed: May 15, 20018.

45. Kernan WN, Viscoli CM, Furie KL, et al. pioglitazone after ischemic stroke or transient ischemic attack. *Journal of Medicine*. 2016;374(14):1321-1331. doi:10.1056/NEJMoa1506930

46. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373(9681):2125-2135. doi:10.1016/S0140-6736(09)60953-3

47. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366(9493):1279-1289. doi:10.1016/S0140-6736(05)67528-9

48. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm.

49. Scirica BM. Saxaglitin and cardovscular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.

50. White W, Cannon C, Heller S, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369:1327-1335.

51. Food and Drug Administration. Drug Safety Podcasts - FDA announced that a safety review has found type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure. https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm497914.htm. Accessed May 15, 2017.

52. Food and Drug Administration. Drug Safety and Availability - FDA Drug Safety Communication: 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. https://www.fda.gov/drugs/drugsafety/ucm500965.htm. Accessed May 16, 2017.

53. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagiptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(3):232-42. doi: 10.1056/NEJMoa1501352.

54. Pfeffer MA, Claggett B, Diaz R**,** et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015; 373(23):2247-57.

Appendix 1: Current Preferred Drug List

GLP-1 Receptor Agonists

Generic	Brand	FormDesc	PDL
EXENATIDE	BYETTA	PEN INJCTR	Y
ALBIGLUTIDE	TANZEUM	PEN INJCTR	N
DULAGLUTIDE	TRULICITY	PEN INJCTR	N
EXENATIDE MICROSPHERES	BYDUREON	VIAL	N
EXENATIDE MICROSPHERES	BYDUREON BCISE	AUTO INJCT	N
EXENATIDE MICROSPHERES	BYDUREON PEN	PEN INJCTR	N
LIRAGLUTIDE	VICTOZA 2-PAK	PEN INJCTR	N
LIRAGLUTIDE	VICTOZA 3-PAK	PEN INJCTR	N
LIXISENATIDE	ADLYXIN	PEN INJCTR	N

SGLT-2 Inhibitors

Generic	Brand	FormDesc	PDL
CANAGLIFLOZIN	INVOKANA	TABLET	N
CANAGLIFLOZIN/METFORMIN HCL EXTENDED RELEASE	INVOKAMET XR	TAB BP 24H	N
CANAGLIFLOZIN/METFORMIN HCL	INVOKAMET	TABLET	N
DAPAGLIFLOZIN PROPANEDIOL	FARXIGA	TABLET	N
DAPAGLIFLOZIN/METFORMIN HCL	XIGDUO XR	TAB BP 24H	N
DAPAGLIFLOZIN/SAXAGLIPTIN HCL	QTERN	TABLET	N
EMPAGLIFLOZIN	JARDIANCE	TABLET	N
EMPAGLIFLOZIN/LINAGLIPTIN	GLYXAMBI	TABLET	N
EMPAGLIFLOZIN/METFORMIN HCL	SYNJARDY XR	TAB BP 24H	N
EMPAGLIFLOZIN/METFORMIN HCL	SYNJARDY	TABLET	N

DPP-4 Inhibitors

Generic	Brand	FormDesc	PDL
SITAGLIPTIN PHOS/METFORMIN HCL	JANUMET	TABLET	Y
SITAGLIPTIN PHOSPHATE	JANUVIA	TABLET	Y
ALOGLIPTIN BENZ/METFORMIN HCL	ALOGLIPTIN-METFORMIN	TABLET	N
ALOGLIPTIN BENZ/METFORMIN HCL	KAZANO	TABLET	N
ALOGLIPTIN BENZ/PIOGLITAZONE	ALOGLIPTIN-PIOGLITAZONE	TABLET	N
ALOGLIPTIN BENZ/PIOGLITAZONE	OSENI	TABLET	N
ALOGLIPTIN BENZOATE	ALOGLIPTIN	TABLET	N
ALOGLIPTIN BENZOATE	NESINA	TABLET	N
DAPAGLIFLOZIN/SAXAGLIPTIN HCL	QTERN	TABLET	N
EMPAGLIFLOZIN/LINAGLIPTIN	GLYXAMBI	TABLET	N
LINAGLIPTIN	TRADJENTA	TABLET	N
LINAGLIPTIN/METFORMIN HCL	JENTADUETO XR	TAB BP 24H	N
LINAGLIPTIN/METFORMIN HCL	JENTADUETO	TABLET	N
SAXAGLIPTIN HCL	ONGLYZA	TABLET	N
SAXAGLIPTIN HCL/METFORMIN HCL	KOMBIGLYZE XR	TBMP 24HR	N
SITAGLIPTIN PHOS/METFORMIN HCL	JANUMET XR	TBMP 24HR	N

Miscellaneous Antidiabetic Agents

Generic	Brand	FormDesc	PDL
METFORMIN HCL	GLUCOPHAGE XR	TAB ER 24H	Y
METFORMIN HCL	METFORMIN HCL ER	TAB ER 24H	Y
METFORMIN HCL	GLUCOPHAGE	TABLET	Y
METFORMIN HCL	METFORMIN HCL	TABLET	Y
ACARBOSE	ACARBOSE	TABLET	N
ACARBOSE	PRECOSE	TABLET	N
GLIPIZIDE/METFORMIN HCL	GLIPIZIDE-METFORMIN	TABLET	N
GLYBURIDE/METFORMIN HCL	GLUCOVANCE	TABLET	N
GLYBURIDE/METFORMIN HCL	GLYBURIDE-METFORMIN HCL	TABLET	N
METFORMIN HCL	RIOMET	SOLUTION	N
METFORMIN HCL	FORTAMET	TAB ER 24	N
METFORMIN HCL	METFORMIN HCL ER	TAB ER 24	N
METFORMIN HCL	GLUMETZA	TABERGR24H	N
METFORMIN HCL	METFORMIN HCL ER	TABERGR24H	N
MIGLITOL	GLYSET	TABLET	N
MIGLITOL	MIGLITOL	TABLET	N
NATEGLINIDE	NATEGLINIDE	TABLET	N
NATEGLINIDE	STARLIX	TABLET	N

PRAMLINTIDE ACETATE	SYMLINPEN 120	PEN INJCTR	N
PRAMLINTIDE ACETATE	SYMLINPEN 60	PEN INJCTR	N
REPAGLINIDE	PRANDIN	TABLET	N
REPAGLINIDE	REPAGLINIDE	TABLET	N
REPAGLINIDE/METFORMIN HCL	REPAGLINIDE-METFORMIN HCL	TABLET	N

Sulfonylureas

Generic	Brand	FormDesc	PDL
GLIMEPIRIDE	AMARYL	TABLET	Y
GLIMEPIRIDE	GLIMEPIRIDE	TABLET	Y
GLIPIZIDE	GLIPIZIDE	TABLET	Y
GLIPIZIDE	GLUCOTROL	TABLET	Y
GLYBURIDE	GLYBURIDE	TABLET	Y
CHLORPROPAMIDE	CHLORPROPAMIDE	TABLET	N
GLIPIZIDE	GLIPIZIDE ER	TAB ER 24	N
GLIPIZIDE	GLIPIZIDE XL	TAB ER 24	N
GLIPIZIDE	GLUCOTROL XL	TAB ER 24	N
GLYBURIDE,MICRONIZED	GLYBURIDE MICRONIZED	TABLET	N
GLYBURIDE,MICRONIZED	GLYNASE	TABLET	N
TOLAZAMIDE	TOLAZAMIDE	TABLET	N
TOLBUTAMIDE	TOLBUTAMIDE	TABLET	N

Thiazolidinediones

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

Appendix 2: Abstracts of Comparative Clinical Trials

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes.

Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group.

BACKGROUND: The cardiovascular effects of adding once-weekly treatment with exenatide to usual care in patients with type 2 diabetes are unknown.

METHODS: We randomly assigned patients with type 2 diabetes, with or without previous cardiovascular disease, to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The coprimary hypotheses were that exenatide, administered once weekly, would be noninferior to placebo with respect to safety and superior to placebo with respect to efficacy.

RESULTS: In all, 14,752 patients (of whom 10,782 [73.1%] had previous cardiovascular disease) were followed for a median of 3.2 years (interquartile range, 2.2 to 4.4). A primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.83 to 1.00), with the intention-to-treat analysis indicating that exenatide, administered once weekly, was noninferior to placebo with respect to safety ($P<0.001$ for noninferiority) but was not superior to placebo with respect to efficacy ($P=0.06$ for superiority). The rates of death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

CONCLUSIONS: Among patients with type 2 diabetes with or without previous cardiovascular disease, the incidence of major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo. (Funded by Amylin Pharmaceuticals; EXSCEL ClinicalTrials.gov number, NCT01144338 .).

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to April Week 4 2018

Search Strategy:

#	Searches	Results
1	exenatide.mp.	2428
2	albiglutide.mp.	98
3	dulaglutide.mp.	120
4	exenatide microspheres.mp.	3
5	liraglutide.mp. or LIRAGLUTIDE/	1544
6	lixisenatide.mp.	202
7	canagliflozin.mp. or CANAGLIFLOZIN/	422
8	dapagliflozin.mp.	414

Author: Sentena

Date: July 2018

9	empagliflozin.mp.	485
10	sitagliptin.mp. or Sitagliptin Phosphate/	1523
11	alogliptin.mp.	320
12	saxagliptin.mp.	464
13	linagliptin.mp. or LINAGLIPTIN/	419
14	metformin.mp. or METFORMIN/	14563
15	acarbose.mp. or ACARBOSE/	2075
16	glipizide.mp. or GLIPIZIDE/	1042
17	glyburide.mp. or GLYBURIDE/	6444
18	miglitol.mp.	274
19	nateglinide.mp.	495
20	pramlintide.mp.	328
21	repaglinide.mp.	679
22	glimepiride.mp.	1061
23	chlorpropamide.mp. or CHLORPROPAMIDE/	2047
24	tolazamide.mp. or TOLAZAMIDE/	208
25	tolbutamide.mp. or TOLBUTAMIDE/	6502
26	pioglitazone.mp.	4513
27	rosiglitazone.mp.	5509
28	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	43940
29	limit 28 to (english language and humans and yr="2017 -Current")	1558
30	limit 29 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	183

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OZEMPIC® safely and effectively. See full prescribing information for OZEMPIC.

OZEMPIC (semaglutide) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether OZEMPIC causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **OZEMPIC is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

----------INDICATIONS AND USAGE----------
OZEMPIC is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use:
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy (1, 5.2).
- Not indicated for use in type 1 diabetes mellitus or treatment of diabetic ketoacidosis (1).

----------DOSAGE AND ADMINISTRATION----------
- Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly (2.1).
- Administer once weekly at any time of day, with or without meals (2.1).
- If a dose is missed administer within 5 days of missed dose (2.1).
- Inject subcutaneously in the abdomen, thigh, or upper arm (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:
- Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection (3).
- Single-patient-use pen that delivers 1 mg per injection (3).

----------CONTRAINDICATIONS----------
- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Known hypersensitivity to OZEMPIC or any of the product components (4).

----------WARNINGS AND PRECAUTIONS----------
- Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Diabetic Retinopathy Complications: Has been reported in a clinical trial. Patients with a history of diabetic retinopathy should be monitored (5.3).
- Never share an OZEMPIC pen between patients, even if the needle is changed (5.4).
- Hypoglycemia: When OZEMPIC is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.5).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.6).
- Hypersensitivity Reactions: Discontinue OZEMPIC if suspected and promptly seek medical advice (5.7).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with semaglutide (5.8).

----------ADVERSE REACTIONS----------
The most common adverse reactions, reported in ≥5% of patients treated with OZEMPIC are: nausea, vomiting, diarrhea, abdominal pain and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-888-693-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Oral Medications: OZEMPIC delays gastric emptying. May impact absorption of concomitantly administered oral medications (7.2).

----------USE IN SPECIFIC POPULATIONS----------
Females and Males of Reproductive Potential: Discontinue OZEMPIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STEGLATRO safely and effectively. See full prescribing information for STEGLATRO.

STEGLATRO™ (ertugliflozin) tablets, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

STEGLATRO is a sodium glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 5 mg once daily, taken in the morning, with or without food. (2.1)
- Increase dose to 15 mg once daily in those tolerating STEGLATRO and needing additional glycemic control. (2.1)
- Assess renal function before initiating STEGLATRO and periodically thereafter (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg and 15 mg (3)

CONTRAINDICATIONS

- Severe renal impairment, end-stage renal disease, or dialysis. (4, 5.3)
- History of serious hypersensitivity reaction to STEGLATRO. (4)

WARNINGS AND PRECAUTIONS

- *Hypotension:* May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating, assess and correct volume status. Monitor for signs and symptoms during therapy. (5.1)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function. (5.3)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.5)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.6)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.7)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.8)

ADVERSE REACTIONS

- The most common adverse reactions associated with STEGLATRO (incidence ≥ 5%) were female genital mycotic infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.1, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SEGLUROMET safely and effectively. See full prescribing information for SEGLUROMET.

SEGLUROMET™ (ertugliflozin and metformin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue SEGLUROMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

INDICATIONS AND USAGE

SEGLUROMET is a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin. (1)

Limitations of Use:
- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose based on the patient's current regimen. (2.1)
- Maximum recommended dose is 7.5 mg ertugliflozin/1,000 mg metformin twice daily. (2.1)
- Take twice daily with meals, with gradual dose escalation. (2.1)
- Assess renal function before initiating SEGLUROMET (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.
- SEGLUROMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets:
- Ertugliflozin 2.5 mg and metformin hydrochloride 500 mg (3)
- Ertugliflozin 2.5 mg and metformin hydrochloride 1,000 mg (3)
- Ertugliflozin 7.5 mg and metformin hydrochloride 500 mg (3)
- Ertugliflozin 7.5 mg and metformin hydrochloride 1,000 mg (3)

CONTRAINDICATIONS

- Severe renal impairment, end stage renal disease, or dialysis. (4, 5.1, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of serious hypersensitivity reaction to ertugliflozin or metformin. (4)

WARNINGS AND PRECAUTIONS

- *Lactic Acidosis:* See boxed warning. (5.1)
- *Hypotension*: May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating, assess and correct volume status. Monitor for signs and symptoms during therapy. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.6)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.7)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.8)
- *Vitamin B_{12}* Deficiency: Metformin may lower vitamin B12 levels. Measure hematological parameters annually. (5.9)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.10)

ADVERSE REACTIONS

- The most common adverse reactions associated with ertugliflozin (incidence ≥5%) were female genital mycotic infections. (6.1)
- Most common adverse reactions associated with metformin (incidence ≥5%): diarrhea, nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.2)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Advise females of the potential risk to a fetus, especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Females and Males of Reproductive Potential:* Advise premenopausal females of the potential for an unintended pregnancy. (8.3)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.2, 8.5)
- *Renal impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.1, 5.4, 8.6)
- *Hepatic* impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

Date: July 2018

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STEGLUJAN safely and effectively. See full prescribing information for STEGLUJAN.

STEGLUJAN™ (ertugliflozin and sitagliptin) tablets, for oral use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

STEGLUJAN is a combination of ertugliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. (1)

Limitations of Use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)
- Has not been studied in patients with a history of pancreatitis. (1, 5.1)

DOSAGE AND ADMINISTRATION

- Recommended starting dose is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. (2.1)
- Increase dose to 15 mg ertugliflozin/100 mg sitagliptin once daily in those tolerating STEGLUJAN and needing additional glycemic control. (2.1)
- Assess renal function before initiating STEGLUJAN and periodically thereafter (2.2):
  - Do not use in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
  - Initiation is not recommended in patients with an eGFR of 30 to less than 60 mL/minute/1.73 m^2.
  - Continued use is not recommended in patients with an eGFR persistently between 30 and less than 60 mL/min/1.73 m^2.

DOSAGE FORMS AND STRENGTHS

Tablets:

- Ertugliflozin 5 mg and sitagliptin 100 mg (3)
- Ertugliflozin 15 mg and sitagliptin 100 mg (3)

CONTRAINDICATIONS

- Severe renal impairment, end stage renal disease, or dialysis. (4, 5.4)
- History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema. (4, 5.10, 6.2)
- History of serious hypersensitivity reaction to ertugliflozin. (4)

WARNINGS AND PRECAUTIONS

- *Pancreatitis:* There have been postmarketing reports of acute pancreatitis in patients taking sitagliptin, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue. (5.1)
- *Hypotension:* May occur particularly in patients with renal impairment, the elderly, or patients on diuretics. Before initiating assess and correct volume status. Monitor for signs and symptoms during therapy. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue, evaluate and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- *Acute Kidney Injury and Impairment in Renal Function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. There have been postmarketing reports of acute renal failure in patients taking sitagliptin, sometimes requiring dialysis. Monitor renal function. (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.5)
- *Lower Limb Amputation:* Before initiating, consider factors that may increase risk of amputation. Monitor patients for infections or ulcers of lower limbs, and discontinue if these occur. (5.6)
- *Heart Failure:* Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.7)
- *Hypoglycemia:* Consider a lower dose of insulin or insulin secretagogue to reduce risk of hypoglycemia when used in combination. (5.8)
- *Genital Mycotic Infections:* Monitor and treat if indicated. (5.9)
- *Hypersensitivity:* There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly discontinue, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.10)
- *Increased LDL-C:* Monitor and treat as appropriate. (5.11)
- *Severe and Disabling Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate. (5.12)
- *Pemphigoid:* There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue. (5.13)

ADVERSE REACTIONS

- Most common adverse reactions associated with ertugliflozin (incidence ≥5%): female genital mycotic infections. (6.1)
- Most common adverse reactions associated with sitagliptin (incidence ≥5%): upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* Breastfeeding not recommended. (8.2)
- *Geriatrics:* Higher incidence of adverse reactions related to reduced intravascular volume. (5.2, 8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.2, 5.4, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

Appendix 5. Efficacy and Harms Comparison of Non-insulin Antidiabetic Therapies -

Table 14. Non-Insulin Glucose Lowering Drugs Effectiveness and Harms Comparisons

Drug Class	Relative A1C lowering[27]	Cardiovascular Data	Safety Warnings	Effect on Weight[19,20]
Biguanides • Metformin	1% to 1.5%	• UKPDS found that metformin may reduce the risk of CV mortality	• Very small risk of lactic acidosis in patients with poor renal function	• Neutral/ loss
Sulfonylureas (2nd generation) • Glyburide • Glipizide • Glimepiride	1.0% to 1.5%	• No evidence of CV risk reduction	• Risk of hypoglycemia is higher than other oral antidiabetic treatments[19]	• Gain
Thiazolidinediones • Pioglitazone • Rosiglitazone	1.0% to 1.5%	• Use in patients with pre-diabetes and history of stroke or TIA was found to decrease subsequent stroke or MI (ARR 2.8%/NNT 36) compared to placebo over 4.8 years[45] • No CV morbidity or mortality benefit when rosiglitazone was added to metformin and SU[46] • No benefit or harm on CV endpoints with the use pioglitazone compared to placebo (HR 0.90; 95% CI, 0.80 to 1.02; p=0.095)[47]	• Pioglitazone may increase the risk of bladder cancer compared to placebo[48] • TZDs increase the risk of HF exacerbations • TZDs increase the risk of bone fractures	• Gain
DPP-4 Inhibitors • Sitagliptin • Saxagliptin • Alogliptin • Linagliptin	0.5% to 1.0%	• Saxagliptin and alogliptin have demonstrated increased risk in HF related hospitalizations. No difference in CV mortality was demonstrated.[49,50] • Sitagliptin was found to provide no benefit or harm to CV endpoints[53] • Linagliptin is still being evaluated	• Saxagliptin and alogliptin have been linked to increased risk of heart failure [51] • DPP-4 inhibitors may increase risk of pancreatitis • DPP-4 inhibitors may increase risk of severe joint pain	• Neutral/ loss
SGLT2 Inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin • Ertugliflozin	0.5% to 1.0%	• Empagliflozin demonstrated a reduction in the composite endpoint of death from CV causes, nonfatal MI and nonfatal stroke when compared to placebo (ARR 1.6%/NNT 63) over 3.1	• Canagliflozin increases risk for amputations in patients with T2DM who have established CV disease or with 2 or more risk factors for CV disease[52]	• Loss

		years in patients with underlying CV disease.[21] • Canagliflozin reduced CV endpoints (CV mortality, nonfatal MI or nonfatal stroke) more than placebo, 26.9 vs. 31.5/1000 patient-years, in patients with CV disease or at high risk for CV disease (CANVAS – ARR 1.4%/NNT 71 over 5.7 years and CANVAS-R – ARR 1.1%/NNT 91 over 2.1 years).[22]	• Canagliflozin and dapagliflozin are associated with acute kidney injury • SGLT2 inhibitors are associated with ketoacidosis and serious urinary tract infections • Canagliflozin may increase the risk of reduced bone mineral density and fracture • Ertugliflozin may be associated with increased risk of lower-limb amputations	
GLP-1 Receptor Agonists • Exenatide • Exenatide Once-weekly (ER) • Liraglutide • Albiglutide • Lixisenatide • Dulaglutide • Semaglutide	1.0% to 1.5%	• Liraglutide was found to decrease the composite outcome of death from CV causes, nonfatal MI, nonfatal stroke compared to placebo (ARR 1.9%/ NNT 53) over 3.5 years in patients on standard therapy with a history of CV disease or at high risk of CV disease[23] • Semaglutide was found to be noninferior to the composite CV outcome, as defined above, compared to placebo, 6.6% vs. 8.9%, respectively (HR 0.74; 95%CI, 0.58 to 0.95; P<0.001 for noninferiority).[2] • Exenatide ER was found to be noninferior to placebo for the composite CV endpoint, 11.4% vs. 12.2%, respectively (HR 0.91; 95% CI, 0.83 to 1.00; P<0.001 for noninferiority).[22] • Lixisenatide demonstrated no benefit or harm when compared to placebo for the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (HR 1.02; 95% CI, 0.89 to 1.17)[54]	• GLP-1 RA class may increase the risk of pancreatitis • An increased risk of thyroid cell cancers was demonstrated in rodent models • An increased risk of diabetic retinopathy complications was found with semaglutide compared to placebo	• Loss

Meglitinides • Repaglinide • Nateglinide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Gain
Alpha-glucosidase Inhibitors • Acarbose • Miglitol	0.5% to 1.0%	• ACE Trial is ongoing	• No major safety warnings	• Neutral
Amylin Mimetics • Pramlintide	0.5% to 1.0%	• No evidence of CV risk reduction	• No major safety warnings	• Loss

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; SU = sulfonylurea; TIA = transient ischemic attack; UKPDS = United Kingdom Prospective Diabetes Study

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 OAR410-121-0030 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? Message: • Preferred products are evidence-based 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

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*. 2008; 31;1-11.

P&T/DUR Review: *7/18 (KS), 7/17 (KS), 9/15 (KS); 9/14; 9/13; 4/12; 3/11*
Implementation: *1/15; 9/14; 1/14; 2/13*

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 evidence-based 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
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
5. Is the request for semaglutide or dulaglutide?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Is the request for the Bydureon BCISE™ formulation of exenatide extended-release?	**Yes:** Go to #7	**No:** Go to #8
7. Is the patient using prandial or basal insulin?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months
8. Is the patient currently taking insulin?	**Yes:** Go to #9	**No:** Approve for up to 12 months

Approval Criteria		
9. Is the patient requesting exenatide (Byetta or Bydureon®), liraglutide, albiglutide, or lixisenatide (including combination products) and using basal insulin?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. The safety and efficacy of other insulin formations with 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 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 Review: *7/18 (KS), 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *8/15/18; 4/1/17; 2/15; 1/14*

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

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, or • Ertugliflozin 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	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, and GLP-1 agonist.

Renewal Criteria		
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 , or • Ertugliflozin 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

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 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: *7/18 (KS), 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *8/15/18; 10/13/16; 2/3/15; 1/1/14*