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Drug Class Literature Scan: Diabetes, GLP-1 Receptor Agonists

Date of Review: March 2019

Date of Last Review: July 2018
Literature Search: 01/14/19 – 01/30/19

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

Conclusions:
- The majority of previous evidence supports clinically similar hemoglobin A1c (HbA1c) lowering within the glucagon-like peptide-1 (GLP-1) receptor agonists (RA) class.[1] This updated review supports these findings. Cardiovascular (CV) evidence for this class has no new published data, and previous findings are available in **Appendix 6**.
- A Cochrane systematic review in patients with diabetes and chronic kidney disease (CKD) demonstrated more HbA1c lowering for patients treated with GLP-1 RAs compared to placebo by a mean difference (MD) of -0.53% (95% CI, -1.01 to -0.06; P=0.029) in patients with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 (moderate evidence).[7]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on review of the clinical data.
- Modify prior authorization (PA) criteria to allow use of basal insulin in combination with a GLP-1 receptor agonist, and reorganize questions asking about concomitant insulin use.
- After evaluation of cost in executive session, add exenatide vials (Bydureon®) and liraglutide (Victoza® 2 and 3 pak) to the PDL. Allow auto-PA of preferred therapies if patient has a history of metformin use in the previous 40 days.

Summary of Prior Reviews and Current Policy
- Evidence has demonstrated similar HbA1c lowering between the different classes of anti-diabetic treatments.[8] Data on efficacy and harms supports the use of metformin as first-line therapy in patients with type 2 diabetes (T2DM) requiring medication.[9,10] There is no consensus on the most appropriate second-line therapy.
- The Drug Effectiveness Review Project found that there was moderate evidence of more HbA1c lowering with daily lixisenatide compared to daily liraglutide and more HbA1c lowering with once-weekly exenatide compared to exenatide twice daily.[1] The differences were 0.5% to 0.6% suggesting benefit in patients close to goal HbA1c.
- Liraglutide is indicated to reduce the risk of CV events in patients with established CVD based on a small benefit over placebo.[2,3] Liraglutide, compared to placebo, in patients with type 2 diabetes (T2DM) taking standard therapy and with a history of cardiovascular disease (CVD) or at high risk of CVD, over the time period of 3.5 years demonstrated an actual risk reduction [ARR] in composite CV events (death from CV causes, nonfatal myocardial infarction [MI], or

nonfatal stroke) of 1.9% and number needed to treat [NNT] of 53 favoring and reduction in CV death also favored liraglutide (ARR 1.3%/ NNT 77).[2] Cardiovascular studies of exentatide extended release (ER), semaglutide and lixisenatide demonstrated neutral effects on the composite CV endpoint compared to placebo. [4–6] Dulaglutide CV safety studies are ongoing and albiglutide has been discontinued.

- Daily exenatide (Byetta) is the only preferred GLP-1 RA and accounts for 6% of the market share. The majority of the utilization is for liraglutide.
- Current prior authorization criteria require metformin and sulfonylurea trial, or have contraindications to these treatments, for GLP-1 RA approval.

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. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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.

New Systematic Reviews:

Cochrane – Insulin and Glucose-lowering Agents for Treating People with Diabetes and Chronic Kidney Disease

A systematic review and meta-analysis by Cochrane analyzed efficacy and safety of insulin and other antidiabetic treatments in people with diabetes and CKD.[7] Forty-four trials were included in the review, two of these trials evaluated the use of GLP-1 receptor agonists. Both studies included liraglutide compared to placebo in patients with an eGFR of less than 60 mL/min/1.73 m^2. Trials were found to be at low risk of bias for all domains except attrition bias which was high in both studies, and both trials were funded by industry. Fasting blood glucose (FBG) and HbA1c reduction were the primary outcomes, and death was an important secondary outcome.[7] Hypoglycemia and discontinuations due to adverse events were safety outcomes.

Mean HbA1c lowering was greater for GLP-1 RAs compared to placebo, MD -0.53% (95% CI, -1.01 to -0.06; P=0.029) based on moderate evidence.[7] FBG was reduced by 1.08 mmol/L (95% CI, -1.71 to -0.45; P=0.0008) in one trial and not reported by the other trial (very low quality evidence).[7] Liraglutide was not found to have any effect on the risk of death compared to placebo (relative risk [RR] 3.91; 95% CI, 0.44 to 34.58) based on low quality evidence. Liraglutide had no effect on hypoglycemia risk compared to placebo in patient with eGFR 30 to less than 60 mL/min/1.73m^2 (RR 0.79; 95% CI, 0.51 to 1.21; P=0.28).[7] Discontinuation rates were 48% with liraglutide compared to 11% for placebo in the one trial that reported discontinuation rates (ARR 37%/NNH 3).[7]

Conclusions for the use of GLP-1 RAs in patients with diabetes and CKD are limited by only two studies of liraglutide available for analysis. Limited evidence suggests liraglutide is effective in HbA1c reduction in this patient population; however, tolerability may be limited by high discontinuation rates.

After review, four systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[11–13]

New Guidelines:
No high-quality guidelines were identified.

Additional Guidelines for Clinical Context:
American Diabetes Association – Standards in Medical Care 2019
GLP-1 RAs are part of the annual update by the American Diabetes Association.[9] 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.

Metformin is recommended as the first line treatment for patients with T2DM.[9] GLP-1 RAs are recommended as a second line treatment for patients with the following characteristics: need to minimize hypoglycemia, compelling need to minimize weight gain or promote weight loss. In patients with established atherosclerotic cardiovascular disease (ASCVD) GLP-1 RAs with proven CV benefit (i.e., liraglutide, semaglutide, and exenatide ER [in this order based on evidence]) are recommended as second line treatment.[9] In patients with heart failure (HF) or chronic kidney disease (CKD) GLP-1 RAs, with CV benefit, are recommended if SGLT-2 inhibitors are not tolerated or contraindicated.

American College of Endocrinology
The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published a T2DM management algorithm in 2019, which included guidance on GLP-1 RAs.[10] 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. GLP-1 RAs are recommended as monotherapy, after metformin. Preference may be given to GLP-1 RAs in patients with CVD and CKD. GLP-1 RAs are also recommended as combination therapy in patients taking one or more anti-diabetic therapies.

New Formulations:
No new formulations identified.

New FDA Safety Alerts:
No new FDA safety alerts identified.

References:

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
exenatide	BYETTA	PEN INJCTR	Y
dulaglutide	TRULICITY	PEN INJCTR	N
exenatide microspheres	BYDUREON BCISE	AUTO INJCT	N
exenatide microspheres	BYDUREON PEN	PEN INJCTR	N
exenatide microspheres	BYDUREON	VIAL	N
liraglutide	VICTOZA 2-PAK	PEN INJCTR	N
liraglutide	VICTOZA 3-PAK	PEN INJCTR	N
lixisenatide	ADLYXIN	PEN INJCTR	N
semaglutide	OZEMPIC	PEN INJCTR	N

Appendix 2: New Comparative Clinical Trials

A total of 28 citations were manually reviewed from the initial literature search. After further review, 23 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 5 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Guja, et al[14] (DURATION 7) MC, DB, Phase 3, PC	Exenatide ER 2 mg weekly + insulin glargine (E) vs. Placebo weekly + insulin glargine ± metformin for both groups	Adult patients with type 2 diabetes that were inadequately controlled on titrated insulin glargine ± metformin (n=464)	Change from baseline HbA1c at week 28	E: -0.96% P: -0.23% LSMD – 0.73% (95% CI, -0.93% to -0.53%) P<0.001
Jabbour, et al[15] (DURATION 8) Phase 3, MC, DB	Exenatide 2 mg weekly + dapagliflozin daily vs. Exenatide 2 mg weekly vs. Dapagliflozin	Adult patients with type 2 diabetes that were inadequately controlled on metformin monotherapy that participated in an open label extension study following original study duration of 28 weeks (n=695)	Safety endpoints such as hypoglycemia, abnormal vital signs and reported adverse events at 52-weeks.	No major safety findings emerged. No episodes of major hypoglycemia (loss of consciousness, seizure, or coma resolving after glucose administration, event requiring third party assistance, or concentration < 3.0 mmol/L) were reported. Efficacy endpoints were exploratory and therefore not reported.

Ahmann, et al[16] (SUSTAIN 3) Phase 3a, OL, NI, PG, RCT	Semaglutide 1.0 mg (S) vs. Exenatide ER 2.0 mg (ER)	Adult patients with type 2 diabetes that were taking oral antidiabetic drugs (96% biguanides, sulfonylureas 48%) (n=813)	Change from baseline in HbA1c at week 56	S: -1.5% E: -0.9% ETD -0.62% (95% CI, -0.80 to -0.44) P<0.0001 for noninferiority and superiority
Pratley, et al[17] (SUSTAIN-7) PG, Phase 3b, OL, NI, RCT	Semaglutide 0.5 mg weekly (S 0.5) vs. Dulaglutide 0.75 mg weekly (D 0.75) Semaglutide 1.0 mg weekly (S 1.0) vs. Dulaglutide 1.5 mg weekly (D 1.5)	Adult patients with inadequately controlled type 2 diabetes on metformin	Change from baseline in HbA1c at week 40	S 0.5: -1.5% D 0.75: -1.1% ETD 0.4% (95% CI, -0.55 to -0.25) P<0.0001 for noninferiority and superiority S 1.0: -1.8% D 1.5: -1.4% ETD -0.41% (95% CI, -0.57 to -0.25) P<0.0001 for noninferiority and superiority
Ludvik, et al[18] (AWARD -10) Phase 3b, DB, PC, MC	Dulaglutide 1.5 mg weekly (D1.5) vs. Dulaglutide 0.75 mg weekly (D.75) vs. Placebo weekly (P) + SGLT-2 inhibitor in each group (most commonly dapagliflozin or empagliflozin)	Adult patients with type 2 diabetes inadequately controlled with a SGLT-2 inhibitor ± metformin (n=424)	Change from baseline HbA1c at 24 weeks	D1.5: -1.34% D.75: -1.21% P: -0.54% D1.5 vs. P: LSMD -0.79% (95% CI, -9.2 to -5.4) P<0.0001 D.75 vs. P: LSMD -0.66% (-0.84 to -0.49) P<0.001)

Abbreviations: DB = double-blind; E= extended release; ETD = estimated treatment difference; HbA1c = hemoglobin A1c; LSMD = least-squares mean difference; MC = multi-center; NI = noninferiority; OL = open label; PC = placebo controlled; PG = parallel group; RCT = randomized clinical trial; SGLT-2 = sodium-glucose cotransporter-2

Appendix 3: Abstracts of Comparative Clinical Trials

Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study.

Guja C, Frías JP, Somogyi A, Jabbour S, Wang H, Hardy E, Rosenstock J

AIMS:

To compare the efficacy and safety of adding the glucagon-like peptide-1 receptor agonist exenatide once weekly (QW) 2 mg or placebo among patients with type 2 diabetes who were inadequately controlled despite titrated insulin glargine (IG) ± metformin.

METHODS:

This multicentre, double-blind study (ClinicalTrials.gov identifier: NCT02229383) randomized (1:1) patients with persistent hyperglycaemia after an 8-week titration phase (glycated haemoglobin [HbA1c] 7.0%-10.5% [53-91 mmol/mol]) to exenatide QW or placebo. The primary endpoint was HbA1c change from baseline to week 28. Secondary endpoints included body weight, 2-hour postprandial glucose, and mean daily IG dose.

RESULTS:

Of 464 randomized patients (mean: age, 58 years; HbA1c, 8.5% [69 mmol/mol]; diabetes duration, 11.3 years), 91% completed 28 weeks. Exenatide QW + IG vs placebo + IG significantly reduced HbA1c (least-squares mean difference, -0.73% [-8.0 mmol/mol]; 95% confidence interval, -0.93%, -0.53% [-10.2, -5.8 mmol/mol]; P < .001; final HbA1c, 7.55% [59 mmol/mol] and 8.24% [67 mmol/mol], respectively); body weight (-1.50 kg; -2.17, -0.84; P < .001); and 2-hour postprandial glucose (-1.52 mmol/L [-27.5 mg/dL]; -2.15, -0.90 [-38.7, -16.2]; P < .001). Significantly more exenatide QW + IG-treated patients vs placebo + IG-treated patients reached HbA1c <7.0% (<53 mmol/mol) (32.5% vs 7.4%; P < .001); daily IG dose increased by 2 and 4 units, respectively. Gastrointestinal and injection-site adverse events were more frequent with exenatide QW + IG (15.1% and 7.8%, respectively) than with placebo + IG (10.8% and 3.0%, respectively); hypoglycaemia incidence was similar between the exenatide QW + IG (29.7%) and placebo + IG (29.0%) groups, with no major hypoglycaemic events.

CONCLUSIONS:

Among patients with inadequate glycaemic control, exenatide QW significantly improved glucose control and decreased body weight, without increased hypoglycaemia or unexpected safety findings.

Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Controlled Trial.

Jabbour SA, Frías JP, Hardy E, Ahmed A, Wang H, Öhman P, Guja C

Abstract

OBJECTIVE:

Among patients with type 2 diabetes uncontrolled with metformin, exenatide once weekly (QW) plus dapagliflozin combination produced greater reductions in glycemia, weight, and systolic blood pressure (SBP) at 28 weeks than exenatide QW or dapagliflozin alone (DURATION-8). Here, we investigated the safety and maintenance of efficacy at 52 weeks, after a 24-week extension.

RESEARCH DESIGN AND METHODS:

This phase 3, multicenter, double-blind study randomized adults with type 2 diabetes (with glycated hemoglobin [HbA_{1c}] 8.0-12.0% [64-108 mmol/mol] and on metformin ≥1,500 mg/day) to exenatide QW (2-mg subcutaneous injection) plus once-daily dapagliflozin (10-mg oral tablet), exenatide QW plus oral placebo, or dapagliflozin plus injected placebo. Extension-period *P*values were nominal.

RESULTS:
Of 1,375 patients screened, 695 were randomized (mean baseline HbA_{1c} 9.3% [78 mmol/mol]); 81.2% completed the study, and 75.3% completed treatment. At 52 weeks, HbA_{1c} reductions were greater with exenatide QW plus dapagliflozin (least squares mean change -1.75% [-19.1 mmol/mol]) versus exenatide QW (-1.38% [-15.1 mmol/mol]; $P = 0.006$) or dapagliflozin (-1.23% [-13.4 mmol/mol]; $P < 0.001$); mean HbA_{1c} values were 6.9% (52 mmol/mol), 7.2% (55 mmol/mol), and 7.4% (57 mmol/mol), respectively. Weight and SBP reductions were greater with exenatide QW plus dapagliflozin (-3.31 kg and -4.5 mmHg) versus exenatide QW (-1.51 kg and -0.7 mmHg; both $P < 0.001$) but similar to those with dapagliflozin (-2.28 kg and -2.7 mmHg; $P = 0.057$ and $P = 0.100$, respectively). The exenatide QW plus dapagliflozin regimen was well tolerated with no unexpected safety findings; more patients treated with exenatide QW experienced gastrointestinal and injection site-related adverse events. No major hypoglycemia occurred.
CONCLUSIONS:
Among patients with type 2 diabetes uncontrolled with metformin, exenatide QW plus dapagliflozin provided sustained improvements in glycemia, weight, and SBP over 52 weeks, with no unexpected safety findings.

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.
Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, Annett MP, Aroda VR
Abstract
OBJECTIVE:
To compare the efficacy and safety of once-weekly semaglutide 1.0 mg s.c. with exenatide extended release (ER) 2.0 mg s.c. in subjects with type 2 diabetes.
RESEARCH DESIGN AND METHODS:
In this phase 3a, open-label, parallel-group, randomized controlled trial, 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomized (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. The primary end point was change from baseline in HbA_{1c} at week 56.
RESULTS:
Mean HbA_{1c} (8.3% [67.7 mmol/mol] at baseline) was reduced by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER (estimated treatment difference vs. exenatide ER [ETD] -0.62% [95% CI -0.80, -0.44] [-6.78 mmol/mol (95% CI -8.70, -4.86)]; $P < 0.0001$ for noninferiority and superiority). Mean body weight (95.8 kg at baseline) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD -3.78 kg [95% CI -4.58, -2.98]; $P < 0.0001$). Significantly more subjects treated with semaglutide (67%) achieved HbA_{1c} <7.0% (<53 mmol/mol) versus those taking exenatide ER (40%). Both treatments had similar safety profiles, but gastrointestinal adverse events were more common in semaglutide-treated subjects (41.8%) than in exenatide ER-treated subjects (33.3%); injection-site reactions were more frequent with exenatide ER (22.0%) than with semaglutide (1.2%).
CONCLUSIONS:
Semaglutide 1.0 mg was superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight after 56 weeks of treatment; the drugs had comparable safety profiles. These results indicate that semaglutide treatment is highly effective for subjects with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs.

Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial.

Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators

Abstract

BACKGROUND:

Despite common mechanisms of actions, glucagon-like peptide-1 receptor agonists differ in structure, pharmacokinetic profile, and clinical effects. This head-to-head trial compared semaglutide with dulaglutide in patients with inadequately controlled type 2 diabetes.

METHODS:

This was an open-label, parallel-group, phase 3b trial done at 194 hospitals, clinical institutions or private practices in 16 countries. Eligible patients were aged 18 years or older and had type 2 diabetes with HbA_{1c} 7·0-10·5% (53·0-91·0 mmol/mol) on metformin monotherapy. Patients were randomly assigned (1:1:1:1) by use of an interactive web-response system to once a week treatment with either semaglutide 0·5 mg, dulaglutide 0·75 mg, semaglutide 1·0 mg, or dulaglutide 1·5 mg subcutaneously. The primary endpoint was change from baseline in percentage HbA_{1c}; the confirmatory secondary endpoint was change in bodyweight, both at week 40. The primary analysis population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment and before the onset of rescue medication. The safety population included all randomly assigned patients exposed to at least one dose of trial product obtained while on treatment. The trial was powered for HbA_{1c} non-inferiority (margin 0·4%) and bodyweight superiority. This trial is registered with ClinicalTrials.gov, number NCT02648204.

FINDINGS:

Between Jan 6, 2016, and June 22, 2016, 1201 patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0·5 mg, 299 to dulaglutide 0·75 mg, 300 to semaglutide 1·0 mg, and 299 to dulaglutide 1·5 mg. 72 (6%) patients withdrew from the trial (22 receiving semaglutide 0·5 mg, 13 receiving dulaglutide 0·75 mg, 21 receiving semaglutide 1·0 mg, and 16 receiving dulaglutide 1·5 mg). From overall baseline mean, mean percentage HbA_{1c} was reduced by 1·5 (SE 0·06) percentage points with semaglutide 0·5 mg versus 1·1 (0·05) percentage points with dulaglutide 0·75 mg (estimated treatment difference [ETD] -0·40 percentage points [95% CI -0·55 to -0·25]; p<0·0001) and by 1·8 (0·06) percentage points with semaglutide 1·0 mg versus 1·4 (0·06) percentage points with dulaglutide 1·5 mg (ETD -0·41 percentage points [-0·57 to -0·25]; p<0·0001). From overall baseline mean, mean bodyweight was reduced by 4·6 kg (SE 0·28) with semaglutide 0·5 mg compared with 2·3 kg (0·27) with dulaglutide 0·75 mg (ETD -2·26 kg [-3·02 to -1·51]; p<0·0001) and by 6·5 kg (0·28) with semaglutide 1·0 mg compared with 3·0 kg (0·27) with dulaglutide 1·5 mg (ETD -3·55 kg [-4·32 to -2·78]; p<0·0001). Gastrointestinal disorders were the most frequently reported adverse event, occurring in 129 (43%) of 301 patients receiving semaglutide 0·5 mg, 133 (44%) of 300 patients receiving semaglutide 1·0 mg, 100 (33%) of 299 patients receiving dulaglutide 0·75 mg, and in 143 (48%) of 299 patients receiving dulaglutide 1·5 mg. Gastrointestinal disorders were also the most common reason for discontinuing treatment with semaglutide and dulaglutide. There were six fatalities: one in each semaglutide group and two in each dulaglutide group.

Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial.

Ludvik B, Frías JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, García-Pérez LE, Woodward DB, Milicevic Z

Abstract

BACKGROUND:

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors improve glycaemic control and reduce bodyweight in patients with type 2 diabetes through different mechanisms. We assessed the safety and efficacy of the addition of the once-weekly GLP-1 receptor agonist dulaglutide to the ongoing treatment regimen in patients whose diabetes is inadequately controlled with SGLT2 inhibitors, with or without metformin.

METHODS:

AWARD-10 was a phase 3b, double-blind, parallel-arm, placebo-controlled, 24-week study done at 40 clinical sites in Austria, Czech Republic, Germany, Hungary, Israel, Mexico, Spain, and the USA. Eligible adult patients (≥18 years) with inadequately controlled type 2 diabetes (HbA_{1c} concentration ≥7·0% [53 mmol/mol] and ≤9·5% [80 mmol/mol]), a BMI of 45 kg/m^2 or less, and taking stable doses (>3 months) of an SGLT2 inhibitor (with or without metformin) were randomly assigned (1:1:1) via an interactive web-response system to subcutaneous injections of either dulaglutide 1·5 mg, dulaglutide 0·75 mg, or placebo once per week for 24 weeks. Patients and investigators were masked to dulaglutide and placebo assignment, and those assessing outcomes were masked to study drug assignment. The primary objective was to test for the superiority of dulaglutide (1·5 mg or 0·75 mg) versus placebo for change in HbA_{1c} concentration from baseline at 24 weeks. All analyses were done in the intention-to-treat population, defined as all randomly assigned patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02597049.

FINDINGS:

Between Dec 7, 2015, and Feb 3, 2017, 424 patients were randomly assigned to dulaglutide 1·5 mg (n=142), dulaglutide 0·75 mg (n=142), and placebo (n=140). One patient in the dulaglutide 0·75 mg group was excluded from the analysis because they did not receive any dose of the study drug. The reduction in HbA_{1c} concentration at 24 weeks was larger in patients receiving dulaglutide (least squares mean [LSM] for dulaglutide 1·5 mg -1·34% [SE 0·06] or -14·7 mmol/mol [0·6]; dulaglutide 0·75 mg -1·21% [0·06] or -13·2 mmol/mol [0·6]) than in patients receiving placebo (-0·54% [0·06] or -5·9 mmol/mol [0·6]; p<0·0001 for both groups vs placebo). The LSM differences were -0·79% (95% CI -0·97 to -0·61) or -8·6 mmol/mol (-10·6 to -6·7) for dulaglutide 1·5 mg and -0·66% (-0·84 to -0·49) or -7·2 mmol/mol (-9·2 to -5·4) for dulaglutide 0·75 mg (p<0·0001 for both). Serious adverse events were reported for five (4%) patients in the dulaglutide 1·5 mg group, three (2%) patients in the dulaglutide 0·75 mg group, and five (4%) patients in the placebo group. Treatment-emergent adverse events were more common in patients treated with dulaglutide than in patients who received placebo, mainly because of an increased incidence of gastrointestinal adverse events. Nausea (21 [15%] patients in the dulaglutide 1·5 mg group vs seven [5%] in the dulaglutide 0·75 mg group vs five [4%] in the placebo group), diarrhoea (eight [6%] vs 14 [10%] vs four [3%]), and vomiting (five [4%] vs four [3%] vs one [1%]) were more common with dulaglutide than with placebo. One episode of severe hypoglycaemia was reported in the dulaglutide 0·75 mg group. Two (1%) patients receiving dulaglutide 1·5 mg died, but these deaths were not considered to be related to study drug; no deaths occurred in the other groups.

Appendix 4: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to January Week 3 2019

Search Strategy:

#	Searches	Results
1	exenatide.mp.	2582
2	dulaglutide.mp.	158
3	exenatide microspheres.mp.	4
4	liraglutide.mp. or LIRAGLUTIDE/	1774
5	lixisenatide.mp.	256
6	1 or 2 or 3 or 4 or 5	4019
7	limit 6 to (english language and humans)	2702
8	limit 7 to yr="2018 -Current"	183
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	35

Appendix 5: Key Inclusion Criteria

Population	Adult patients with type 2 diabetes
Intervention	GLP-1 receptor agonist
Comparator	Placebo or active treatment
Outcomes	HbA1c lowering or cardiovascular composite endpoint or cardiovascular death
Timing	NA
Setting	Outpatient

Appendix 6: Cardiovascular Trials of GLP-1 Receptor Agonists Compared to Placebo

Study	Population	CV Death, Nonfatal MI, or Nonfatal Stroke	CV Death
Marso, 2016 SUSTAIN-6 Semaglutide N=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 N=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 N=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*
Holman, 2018 EXSCEL Exenatide ER N=14,752	Adult patients (mean age of 62 years) with T2DM (73.1% with established CV disease) HbA1c: 8.0% Duration of diabetes: 12.0 y	Event rate (3.2 y FU): 11.4% vs. 12.2% HR 0.91 (95% CI, 0.83 to 1.00) For noninferiority *moderate strength of evidence*	Event rate (3.2 y FU): 4.6% vs. 5.2% HR 0.88 (95% CI, 0.76 to 1.02) *moderate strength of evidence*

Abbreviations: CI = confidence interval; CV = cardiovascular; ER = extended release; FU = follow-up; HR = hazard ratio; HbA1c = hemoglobin A1c; T2DM = type 2 diabetes mellitus

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:
- GLP-1 receptor agonists that are preferred products do not require PA when prescribed as second-line therapy in conjunction with metformin.
- All non-preferred GLP-1 receptor agonists require a PA

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

Approval Criteria		
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 patient currently taking prandial insulin?	**Yes:** Pass to RPh. Deny; medical appropriateness The safety and efficacy of other insulin formations with GLP-1 agonists have not been studied.	**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 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: *3/19 (KS), 7/18, 9/17; 1/17; 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *5/1/19; 8/15/18; 4/1/17; 2/15; 1/14*