Drug Use Research & Management Program
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New Drug Evaluation: Dulaglutide

Month/Year of Review: January 2015
Generic Name: Dulaglutide
PDL Class: Oral Hypoglycemics

End date of literature search: November 15, 2014
Brand Name (Manufacturer): Trulicity ™ (Eli Lilly)
Dossier Received: Yes

FDA Approved Indication:[1]

Dulaglutide is a glucagon-like peptide (GLP-1) receptor agonist used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Dulaglutide is not recommended as first-line therapy or in those with type 1 diabetes mellitus, pancreatitis or severe gastrointestinal disease.

Research Questions:

- Is there evidence of superior efficacy of dulaglutide compared to other T2DM therapies when considering important outcomes such as reduced microvascular and macrovascular outcomes or attainment of HbA1c goals?
- Is there evidence dulaglutide has a better safety profile than other treatments for T2DM?
- Are there subpopulations that would benefit more from dulaglutide therapy or are at increased risk of harms?

Conclusions:

- There is insufficient evidence at this time that dulaglutide reduces microvascular or macrovascular outcomes.
- There is moderate strength of evidence that both doses of dulaglutide significantly reduces short term HbA1c from baseline, ranging from -0.78% to -1.51% for dulaglutide 1.5 mg and -0.71% to -1.30% for dulaglutide 0.75 mg. Both the 0.75 mg and 1.5 mg doses respectively reduced HbA1c relative to exenatide by -0.31% and -0.52%, sitagliptin by -0.47% and -0.71%, and metformin by -0.15% and -0.22%.[2-5]
- The most common adverse reactions associated with dulaglutide are gastrointestinal in nature (nausea, vomiting, and diarrhea). Discontinuations due to adverse effects in clinical trials were similar to comparators but higher for gastrointestinal reactions in patients taking dulaglutide. Patients should be monitored for risk of rare but serious adverse reactions of pancreatitis and thyroid cancer.[1]
- There is insufficient evidence to recommend dulaglutide use with basal insulin.[1]

Recommendations:

- A prior authorization is recommended to limit use of dulaglutide to patients that have tried and failed other treatments for T2DM that have proven benefit on microvascular or macrovascular outcomes. No changes to the PDL are recommended.

Reason for Review:
Dulaglutide is the third once-weekly GLP-1 receptor agonists approved for the treatment of T2DM. Comparison of the efficacy and safety data of dulaglutide to other diabetes treatments is necessary for the management of the preferred drug list (PDL) and prior authorization (PA) criteria.

Background:

Type 2 diabetes mellitus is a prevalent disease which affects an estimated 25.6 million people in the United States.[6] Despite a variety of treatments, a significant number of patients fail to meet HbA1C goals and within three years of being diagnosed and 50% of patients require combination therapy to control rising glucose levels. According to the Centers for Disease Control and Prevention (CDC), as many as 1 in every 3 adults will have diabetes by 2050.[7] Treatment guidelines recommend a trial of lifestyle modifications to control hyperglycemia in patients with type 2 diabetes and add pharmacotherapy for persistent elevated glucose levels. Guidelines recommend a goal HbA1C of less than 7% to minimize macrovascular and microvascular complications. Lower or higher HbA1c goals may be appropriate depending on patient specific characteristics. Therapy should be tailored according to patient factors, such as concomitant comorbidities.[10,11] A number of therapeutic options are available for management of glycemic variances associated with diabetes.[10] Classes of anti-hyperglycemic agents (AHA) currently available are: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose co-transporter 2 (SGLT2) inhibitors, insulins, meglitinides, sulfonylureas, thiazolidinediones (TZD), bile acid sequestrants, dopamine-2 agonists and amylin mimetics.

Important outcomes in patients with diabetes are: mortality, microvascular complications (chronic kidney disease, retinopathy, peripheral neuropathy) and macrovascular complications (cardiovascular events, stroke/ischemic attacks, coronary heart disease, amputations). Intermediate outcomes of interest are HbA1C and weight. Adverse event outcomes are: severe adverse events, hypoglycemia rates, and withdrawals due to adverse events. Hemoglobin A1C is often used as a surrogate outcome to assess comparative efficacy of different AHA therapies, as hyperglycemia has been shown to correlate with microvascular complications and potentially macrovascular outcomes.[9] Available data is limited to short-term studies, which prevents the assessment of the durability of available AHAs to control glucose levels long-term and to compare the effectiveness of AHAs on outcomes such as microvascular and macrovascular complications. Differing definitions of hypoglycemia also complicate the comparisons of safety between the differing AHA agents. Available evidence suggests that metformin is likely to reduce the incidence of cardiovascular disease based on data from the United Kingdom Prospective Diabetes Study (UKPDS) trial.[9] UKPDS data has also indicated a reduced incidence of microvascular risk with sulfonylurea and insulin therapy. Thiazolidinediones, alpha-glucosidase inhibitors and dopamine-2 agonists have studies that suggest reduced cardiovascular events but additional data is needed.[9] The effect of many of the AHAs on long-term complications of T2DM remains unknown.

Clinical Efficacy:
Dulaglutide was studied in three, phase 3, double-blind, published, randomized controlled studies in patients with T2DM.[2-4] These studies evaluated dulaglutide as monotherapy[3] and against active comparators[2,4,5]: with placebo, metformin, sitagliptin, and exenatide. An open-label study also compared dulaglutide with liraglutide.[5] Patients enrolled in the trials were a mean age of 56 years, mean HbA1 ranging from 7.6% -8.1%, with normal or mildly impaired renal function and obese (mean BMI 33 mg/k^2).[2-5] Most common pre-existing conditions were hypertension followed by hyperlipidemia. The primary endpoint in all the trials was change in HbA1c from baseline to 26 or 52 weeks, with treatment durations extending out to 104 weeks. Key secondary endpoints were number of patients reaching a target HbA1c less than 7% and change in weight from baseline.[2-5] Dulaglutide was compared to insulin glargine in two unpublished trials. These trials

were not included in our assessment as unpublished literature has not been peer reviewed and therefore does not meet the inclusion criteria for new drug reviews done by the Drug Use Research and Management Group.

AWARD-1

In a 52 week study, dulaglutide 1.5 mg subcutaneously (sc) weekly, dulaglutide 0.75 mg sc weekly, exenatide 10 mcg sc twice daily and placebo sc injection weekly were compared in 976 patients with T2DM.[2] In this phase 3, double-blind study the primary endpoint was change in baseline HbA1c at 26 weeks. Patients were a mean age of 56 years with a mean HbA1c of 8.1% and mean BMI of 33 mg/k^2 (considered obese). Patients were on maximum tolerated doses of pioglitazone (30-45 mg orally daily) and metformin (1,500-3,000 mg orally daily). At 26 weeks, HbA1c reductions from baseline were the following: -1.51% for dulaglutide 1.5 mg, -1.30% for dulaglutide 0.75 mg, -0.99% for exenatide and -0.46% for placebo. At 26 weeks, dulaglutide 1.5 mg was superior to placebo (-1.05% [95% CI -1.22 to -0.88%, p<0.001]) and exenatide (-0.52% [95% CI -0.66 to -0.39%, p<0.001)]. Dulaglutide 0.75 mg was also superior to placebo (-0.84% [95% -1.01 to -0.67%, p<0.001)] and exenatide (-0.31% [95% -0.44 to -0.18%, p<0.001)]. At 52 weeks, dulaglutide maintained superiority over exenatide; however, HbA1c lowering was less at 52 weeks than at 26 weeks for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and exenatide (-1.36%, -1.07%, -0.80%, respectively). At 26 weeks, both dulaglutide doses were superior to exenatide for the percentage of patients obtaining an HbA1c goal less than 7%, with a number needed to treat (NNT) of 4 and 7, respectively. Only dulaglutide 1.5 mg was superior to exenatide for the percentage of patients obtaining an HbA1c goal less than 7% at 52 weeks. Compared to placebo, dulaglutide 1.5 mg and exenatide demonstrated statistically significant weight loss of 1.30 kg and 1.07 kg, respectively.

AWARD-3

Dulaglutide 1.5 mg sc weekly, dulaglutide 0.75 mg sc weekly or metformin (2000 mg daily or 1,500 mg daily depending upon tolerability) were studied in 807 patients with T2DM.[3] This double-blind, double-dummy, phase 3 trial lasted 52 weeks, with the primary outcome measured at 26 weeks. Patients were mildly uncontrolled (mean baseline HbA1c 7.6%) on diet and exercise or one medication for diabetes. Dulaglutide 1.5 mg was associated with a change from baseline HbA1c of -0.78% and dulaglutide 0.75 mg resulted in HbA1c lowering of -0.71%. The mean change in HbA1c in the metformin group was -0.56%. Both doses of dulaglutide were superior to metformin at 26 weeks. At 52 weeks, dulaglutide 1.75 mg was superior to metformin with a difference in HbA1c lowering of -0.19%, p=0.02; however clinical difference is minimal. Hemoglobin A1c lowering in dulaglutide 0.75 mg and metformin groups were similar at 52 weeks. The number of patients obtaining an HbA1c <7% was also higher for both dulaglutide groups, NNT of 11 and 13. All groups demonstrated weight loss with the greatest amount in the dulaglutide 1.5 mg group, followed by metformin and then dulaglutide 0.75 mg.

AWARD-5

Dulaglutide was studied in a 104-week trial of 1,098 patients.[4] Patients moderately uncontrolled on metformin were randomized to dulaglutide 1.5 mg sc weekly, dulaglutide 0.75 mg sc weekly, sitagliptin 100 mg orally daily or placebo. A dose finding portion of the study (about 13 weeks) preceded the efficacy study. Patients were moderately uncontrolled (mean HbA1c of 8.1%), mean age of 56 years and equally divided been male and female sex. The primary endpoint was change from baseline HbA1c at 52 weeks. Patients in the placebo arm, which satisfied the dose finding phase of the study, were switched to sitagliptin after 26 weeks to maintain blinding, but not analyzed after 26 weeks. In the dulaglutide versus sitagliptin comparison arm, dulaglutide was found to be superior to sitagliptin. The difference in HbA1c from baseline at 52 weeks were -1.10% for dulaglutide 1.5 mg, -0.87% for dulaglutide 0.75 mg and -0.39% for sitagliptin. More patients in the dulaglutide 1.5 mg and 0.75 mg arms obtained an HbA1c target of less than 7% compared to sitagliptin at 52 weeks, with a NNT of 4 and 6, respectively. Small decreases in body weight of 2.6 to 3.0 kg significantly favored both dulaglutide groups relative to sitagliptin.

AWARD-6
In an open-label, fair quality trial, dulaglutide 1.5 mg sc weekly (n=299) was compared to liraglutide 1.8 sc mg daily (n=300) in patients on background metformin therapy.[5] Patients were a mean age of 57 years of age with mean HbA1c of 8.1%. The primary endpoint was change in baseline HbA1c at 26 weeks. Dulaglutide was found to be non-inferior to liraglutide with an HbA1c lowering of -1.42% and -1.36%, respectively. Sixty-eight percent of patients in each group achieved HbA1c goal of less than 7%. Weight loss was small for both arms, though there was a statistically significant improvement with liraglutide.

Dulaglutide was studied in two unpublished efficacy trials. The AWARD-2 trial was an open-label trial comparing dulaglutide 0.75 mg weekly and dulaglutide 1.5 mg weekly to insulin glargine daily in 807 patients. Included patients had a history of T2DM and were on maximum tolerated doses of metformin and glimepiride. At 52 weeks dulaglutide 0.75 mg, dulaglutide 1.5 mg and insulin glargine groups had decreases in HbA1c, -0.8%, -1.1% and -0.6%, respectively. The difference in treatment effect between the dulaglutide and insulin glargine excluded the pre-specified non-inferiority margin of 0.4%. In the AWARD-4 study, 884 patients were studied in an open-label trial comparing dulaglutide 0.75 mg weekly and dulaglutide 1.5 mg weekly to daily insulin glargine. Patients were on background insulin lispro three times daily, plus or minus metformin therapy. At 26 weeks, the following HbA1c reductions were demonstrated: -1.6% for dulaglutide 0.75 mg weekly, -1.6% for dulaglutide 1.5 mg weekly and -1.4% for insulin glargine. The difference in treatment effect between the dulaglutide and insulin glargine excluded the pre-specified non-inferiority margin of 0.4%.

Limitations of most of these studies related to study design. There is a potential for performance and detection bias because no details on blinding or assessment were provided. Additionally, many studies did not include information on patient recruitment. Study populations primarily from non-US sites could limit applicability to our treatment population. Results from these trials are most applicable to patients with T2DM who are already close to goal with HbA1cs around 7.5 to 8%.

Clinical Safety:
The most common adverse reactions associated with dulaglutide are gastrointestinal, including nausea, vomiting, diarrhea, abdominal pain and decreased appetite.[1] Nausea associated with dulaglutide peaked after one to two weeks after starting the drug but decreased to a rate of 1-6% thereafter.[4,5] Discontinuations due to adverse effects were low for both groups and similar to the comparators. Discontinuations due to gastrointestinal events were higher in both dulaglutide groups compared to placebo, with most cases being mild or moderate in severity.[1] Discontinuation rates were twice as high in US treatment sites when compared to non-US sites. Risk of gastrointestinal effects increases in patients with declining renal function. Renal function should be monitored in patients reporting severe gastrointestinal side effects. Incidence of hypoglycemia ranged from 5.3%-12.3% as monotherapy and combination therapy. Hypoglycemia was more common in dulaglutide patients taking a sulfonylurea or insulin. Severe hypoglycemia was rare.[1]

Rare adverse reactions included sinus tachycardia, development of anti-drug antibodies, hypersensitivity, injection site reactions, and increases in lipase or pancreatic amylase levels.[1] Dulaglutide has a Risk Evaluation Mediation Strategy (REMS) program for the risk of medullary thyroid carcinoma due to increased risk observed in rats. Additionally, a REMS program advises against the use of dulaglutide in patients with a history of pancreatitis and recommends that therapy be discontinued if pancreatitis is suspected, as dulaglutide use has been associated with pancreatitis in clinical trials.[1] A study of cardiovascular risk (REWIND) is ongoing.

Conclusion:

In studies ranging from 24-104 weeks, there is moderate strength of evidence that dulaglutide 1.5 mg and 0.75 mg reduce HbA1c in patients with T2DM as monotherapy and adjunctive therapy. Studies of longer duration suggest a decrease in dulaglutide efficacy over time, causing concerns over long-term durability. Small decreases in weight and low incidences of hypoglycemia are potential benefits of treating with dulaglutide. Common adverse reactions include gastrointestinal issues, primarily nausea. Ongoing monitoring of risk of pancreatitis and thyroid cancers will be important as dulaglutide is used long-term.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Microvascular outcomes
2) Macrovascular outcomes
3) Goal HbA1c
4) Hypoglycemia
5) Quality of life
6) Serious adverse reactions

Primary Study Endpoint:

1) Change in HbA1c from baseline

Ref./ Study Design	Drug Regimens/Duration	Patient Population	N mITT (per - protocol)	Outcomes/ Efficacy Results	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Wysham, et al 2014 (AWARD 1)[2] DB, PC, Phase 3, RCT	1. Dulaglutide 1.5 mg sc weekly (D1.5) 2. Dulaglutide 0.75 mg sc weekly (D.75) 3. Exenatide 10 mcg sc twice daily (E)* 4. Placebo injections once weekly (P)** - Patients entered a lead-in period up to 12 weeks. - Patients on maximum tolerated doses of metformin (1,500-3,000mg/day or max allowed dose) and pioglitazone (30-45mg/day). - 52 weeks treatment *Exenatide was initiated at 5 mcg twice daily and increased to 10 mcg twice daily after the first 4 weeks	**Demographics (for randomized patients):** Age (mean): 56 years Male: 59% Baseline HbA1c (mean): 8.1% BMI (mean): 33 kg/m^2 **Inclusion Criteria:** Patients ≥18 years old, body mass index between 23 and 45 kg/m^2, non-pregnant and non-lactating, HbA1c of 7-11% on oral antihyperglycemic medicine monotherapy between 7-10% on combination antihyperglycemic therapy. **Exclusion Criteria:** Use GLP-1 receptor agonists during previous 3 months or on long-term insulin therapy.	1. 279 (245) Attrition 13% 2. 280 (254) Attrition 10% 3. 276 (237) Attrition 16% 4. 141 (121) Attrition 5%	**<u>Primary Endpoint</u>** **Change in HbA1c at 26 weeks:** D1.5: -1.51% D.75: -1.30% E: -0.99% P: -0.46% D1.5 vs P: -1.05% (95% CI -1.22 to -0.88%, p<0.001 for superiority) D.75 vs. P: -0.84% (95% -1.01 to -0.67%, p<0.001, for superiority) D1.5 vs E: -0.52% (95% CI -0.66 to -0.39%, p<0.001 for superiority) D.75 vs. E: -0.31% (95% -0.44 to -0.18%, p<0.001 for superiority) **<u>Secondary Endpoints</u>** **Percentage of patients obtaining an HbA1c goal of**	N/A	**Discontinuations due to Adverse Events at 52 weeks:** D1.5: 9 (3%) D.75: 4 (1%) E: 10 (4%) p-value = NS **Hypoglycemia at 26 weeks:** D1.5: 10.4% D.75: 10.7% E: 15.9% P: 3.5% p-value = NS **Gastrointestinal Events at 52 weeks:** D1.5: 142 (51%) D.75: 94 (34%) E: 128 (46%) D1.5 vs E: P<0.05	D.75 vs E ARR: 12 NNT: 8	**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Randomized via a computer generated random sequence using an interactive voice response system. <u>Performance:</u> Patients and caregivers blinded. No details provided. <u>Detection:</u> Assessors blinded. No details were provided. <u>Attrition:</u> Overall attrition 6-12% at 26 week; mITT analysis with LOCF. **External Validity:** <u>Recruitment:</u> Mexico, Argentina and U.S. <u>Patient Characteristics:</u> A majority (86%) of patients were receiving >2,500mg/day metformin and 45 mg/day pioglitazone. Patients were primarily white and Hispanic. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

	**Placebo treated patients were switched to dulaglutide 0.75 mg or dulaglutide 1.5 mg weekly, after 26 weeks to maintain blinding. Results only reported out to 26 weeks for placebo group in this study.			**<7% at 26 weeks:** D1.5: 78% D.75: 66% E: 52% D1.5 vs E: P<0.001 D.75 vs E: P<0.001 **Change in bodyweight at 26 weeks:** D1.5: -1.30 kg D.75: 0.20 kg E: -1.07 kg P: 1.24 kg D1.5 vs.p: P<0.001 D.75 vs P: P=0.010 E vs P: P<0.001	D1.5 vs E: 26% / 4 D.75 vs.E: 14% / 7 NA			
Umpierrez G, et al 2013 (AWARD-3)[3] DB, PG, RCT	1. Dulaglutide 1.5 mg sc weekly (D1.5) 2. Dulaglutide 0.75 mg sc weekly 3. Metformin PO daily (≥1500mg) (M) • Study duration was 52 weeks • 2 weeks lead-in period • Metformin was titrated over 4 weeks to 2,000 mg a day or at least 1,500 mg daily dependent upon tolerability.	**Demographics:** Age (mean): 56 years Male: 44% Baseline HbA1c (mean): 7.6% BMI (mean): 33 kg/m^2 **Inclusion Criteria:** Patients with type 2 diabetes ≥18 years old with diabetes ≥3 months and ≤5 years, (body mass index of ≤45 kg/m^2, HbA1c of ≥6.5% and ≤9.5%, on diet and exercise or one oral diabetic medication for ≥3 months prior to screening. If on oral	1. 269 (220) Attrition 18% 2.270 (218) Attrition 19% 3.268 (213) Attrition 21%	**<u>Primary Endpoint</u>** **Change in HbA1c from baseline at 26 weeks:** D1.5: -0.78% D.75: -0.71% M: -0.56% LS mean difference for D1.5 vs. M: -0.22% (95% CI -0.36 to -0.08, p=0.002) LS mean difference for D.75 vs. M: -0.15%, p=0.020) **<u>Secondary Endpoints</u>** **Change in HbA1c**	N/A	**Discontinuations due to Adverse Events at 52 weeks:** D1.5: 14 (5.2%) D.75: 8 (3.0%) M: 12 (4.5%) P-value not reported **Hypoglycemia:** D1.5: 33 (12.3%) D.75: 30 (11.1%) M: 34 (12.7%) P-value not reported **Nausea:** D1.5: 53 (19.7%)		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Patients were randomized via a computer-generated randomization sequence with a voice response system. <u>Performance:</u> No details were provided. <u>Detection:</u> No details were provided. <u>Attrition:</u> Attrition ranged from 10-16% at 26 weeks and 18-21% at 52 weeks, mITT analysis with LOCF. **External Validity:** <u>Recruitment:</u> Not described. <u>Patient Characteristics:</u> Patients were only mildly uncontrolled at baseline with ~75% taking one oral diabetes treatment. Approximately 85% of patients were taking 2,000 mg metformin

		diabetic medication, then dose could not exceed 50% of recommended dose for that country. **Exclusion Criteria:** Use of thiazolidinediones or GLP-1 receptor agonists during previous 3 months.		**from baseline at 52 weeks:** D1.5: -0.7% D.75: -0.55% M: -0.51% P: 0.03% P<0.001 for all comparators vs placebo. D1.5 vs M: -0.19, p=0.02 **Percentage of patients obtaining an HbA1c goal of <7% at 26 weeks:** D1.5: 62% D.75: 63% M: 54% P=0.02 for both dulaglutide doses vs. metformin **Percentage of patients obtaining an HbA1c goal of <7% at 52 weeks:** D1.5: 62% D.75: 54% M: 50% P<0.05 for D1.5 vs M **Change from baseline in body weight at week 26:** D1.5: -2.29 kg D.75: -1.36 kg M: -2.22 kg	N/A D1.5 vs M 8% / 13 D.75 vs. M: 9% / 11 D1.5 vs M 12% / 8 N/A	D.75: 31 (11.5%) M: 43 (16%) P-value = NS **Injection site reactions:** D1.5: 10 (4%) D.75: 6 (2%) M: 4 (1%)	NA	at week 26 and 52. Outcomes: Accepted surrogate end-point used. Data on long-term health outcomes are lacking.
Nauck, et al 2014 (AWARD-5)[4] DB, PC, PG,	1. Dulaglutide 1.5 mg sc weekly (D1.5) 2. Dulaglutide 0.75 mg sc weekly (D.75)	**Demographics:** Age (mean): 54 years Male: 48% Baseline HbA1c (mean): 8.1%	1. 304 (238) Attrition 22% 2. 302(243) Attrition 20%	**Primary Endpoint** **Change in HbA1c from baseline at 52 weeks:** D1.5: -1.10%	N/A	**Discontinuations due to Adverse Events at 52 weeks:** D1.5: 33 (11%)		**Quality rating:** Poor-Fair **Internal Validity:** Selection: Randomized, no details given. Performance: No details on blinding were

Phase 3, RCT	3. Sitagliptin 100 mg PO daily (S) 4. Placebo (P)* • Patients were on background metformin dose (≥1500 mg) • Eligible patients had an 11 week lead-in period. • Treatment duration was 104 weeks. • Dose finding study preceded efficacy study. *Placebo treated patients were switched to sitagliptin at 26 weeks to maintain blinding. Results only reported out to 26 weeks for placebo group.	BMI (mean): 31 kg/m^2 Inclusion Criteria: Patients were 18-75 years with type 2 diabetes, HbA1c ≥8% to ≤ 9.5% on diet and exercise alone or ≥7% to ≤ 9.5% on oral antihyperglycemic medication(s) and BMI ≥25 to ≤40kg/m^2. Exclusion Criteria: Patients taking other GLP-1 receptor agonists in the previous 6 months.	3. 315(238) Attrition 24% 4. 177(112) Attrition 37%	D.75: -0.87% S: -0.39% LS mean difference for D1.5 vs. S: -0.71% (95% CI -0.87 to -0.55, p<0.001 for superiority) LS mean difference for D.75 vs. S: -0.47% (95% CI -0.63 to -0.31, p<0.001 for superiority) **<u>Secondary Endpoints</u>** **Change in HbA1c from baseline at 26 weeks:** D1.5: -1.22% D.75: -1.01 S: -0.61% P: 0.03% P<0.001 for all comparators vs placebo. **Percentage of patients obtaining an HbA1c goal of <7% at 52 weeks:** D1.5: 58% D.75: 49% S: 33% P<0.001 for both dulaglutide doses vs. sitagliptin **Change from baseline in body weight at week 52:** D1.5: -3.03 kg D.75: -2.60 kg	 N/A D1.5 vs S: 25% / 4 D.75 vs S: 16% / 6 N/A	D.75: 23 (8%) S: 30 (10%) p-value = NS **Hypoglycemia at 52 weeks:** D1.5: 31 (10.2%) D.75: 16 (5.3%) S: 15 (4.8%) P-value not reported **Gastrointestinal Events at 52 weeks:** D1.5: 126 (41%) D.75: 111 (37%) S: 73 (23%) P<0.001 for both dulaglutide groups vs. placebo	 ARR D1.5: 18 NNH: 6 ARR D.75: 14 NNH: 7	provided. <u>Detection:</u> No details were provided. <u>Attrition:</u> Overall attrition was high (20-37%); ITT analysis done, with LOCF for missing data. **External Validity:** <u>Recruitment:</u> No details on patient recruitment were provided. <u>Patient Characteristics:</u> Patients uncontrolled on metformin with moderately elevated HbA1c. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking.

				S: -1.53 P<0.001 for both dulaglutide doses vs. sitagliptin				
Dungan, et al 2014 (AWARD-6)[5] OL, Phase 3, RCT 62 Centers in 9 countries	1. Dulaglutide 1.5 mg sc weekly (D) 2. Liraglutide 1.8 mg sc daily (L) • Both groups on background metformin (>1500 mg/day) • Treatment duration was 26 weeks.	**Demographics:** Age (mean): 57 years Male: 48% Baseline HbA1c (mean): 8.1% BMI (mean): 34 kg/m^2 Inclusion Criteria: Patients ≥18 years with type 2 diabetes inadequately controlled on metformin and for 3 months or longer; HbA1c ≥7.0% to ≤ 10% and BMI ≤45kg/m^2. Exclusion Criteria: Patients on other anti-diabetic therapy, elevated serum calcitonin levels, elevated serum creatinine or reduced creatinine clearance, history of pancreatitis or recent cardiovascular event.	1. 299(269) Attrition 10% 2. 300(269) Attrition 10%	**<u>Primary Endpoint</u>** **Change in HbA1c from baseline at 26 weeks:** D: -1.42% L: -1.36% Mean difference: -0.06% (95% CI -0.19 to 0.07, p<0.001 for non-inferiority) **<u>Secondary Endpoints</u>** **Change from baseline in body weight:** D: -2.90 kg L: -3.61 kg Mean difference: 0.71 (95% CI 0.17 to 1.26, p=0.011)	N/A N/A	**Discontinuations due to Adverse Events:** D: 8 (6%) L: 8 (6%) P=0.99 **Hypoglycemia:** D: 26 (9%) L: 17 (6%) p-value not reported **Nausea:** D: 61 (20%) L: 54 (18%) P=0.46 **Gastrointestinal Disorders:** D: 107 (36%) L: 54 (18%) P=0.98		**Quality rating:** Fair **Internal Validity:** <u>Selection:</u> Computer generated random sequence with interactive voice response system. <u>Performance:</u> Open-label design. <u>Detection:</u> Statistician and medical personnel from sponsor masked to treatment allocation. <u>Attrition:</u> Low overall attrition (10% discontinued); mITT analysis done; LOCF fo missing data. **External Validity:** <u>Recruitment:</u> Patients were recruited from 62 centers in 9 countries. <u>Patient Characteristics:</u> Over 80% of patients were under the age o 65. One patient in the dulaglutide group and three in the liraglutide group required rescue therapy for hyperglycemia. Compliance was 97% or greater for both groups. <u>Outcomes:</u> Accepted surrogate end-point used. Data on long-term health outcomes are lacking. Non-inferiority margin of 0.4% was higher than commonly used 0.3%.

Key: AEs: adverse events, BMI: body mass index, CI: confidence interval, DB: double-blind, DBP: diastolic blood pressure, D/C: discontinuation, eGFR: estimated glomerular filtration rate, GI: gastrointestinal, HbA1c: hemoglobin A1c, kg: kilogram, LOCF: last observation carried forward, MC: multicenter, mITT: modified intent to treat, NA: not applicable, PC: placebo-controlled, PG: parallel group, RCT: randomized controlled trial, SBP: systolic blood pressure, T2DM: type 2 diabetes mellitus

<u>References</u>:

1. Trulicity package information. *Eli Lilly and Company*, Indianapolis, IN; 2014.
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Appendix 1: Current/Proposed PA Criteria

Incretin Mimetics (GLP-1 Analogs)

Initiative: To optimize the correct use of insulin mimetics.

Length of Authorization: Up to 1 year

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	**No:** Pass to RPH; Deny for medical appropriateness.
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class. www.orpdl.org	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin:	**Yes:** Go to **#4.**	**No:** Pass to RPH; Deny for medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for

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- Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF, advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity - Increased risk of hypoglycemia		metformin titration schedule.
4. Is the patient currently taking insulin?	**Yes:** Go to #5	**No:** Approve for up to 12 months.
5. Is the patient requesting exenatide (Byetta), liraglutide (Victoza) or albiglutide (Tanzeum) and is using basal insulin?	**Yes:** Approve for up to 12 months.	**No:** Go to #6.
6. Is the patient requesting dulaglutide (Trulicity) and is using prandial insulin?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPH; Deny for medical appropriateness. The safety and efficacy of other insulin formations and GLP-1 agonists have not been studied.

Initiating Metformin

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

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

DUR Board Action: *1/15 (KS), 9/14 (KS), 9/13(KS), 4/12 (KS), 3/11 (KS)*
Revision(s): *1/15, 1/14*
Initiated: *1/12*

Appendix 2: Specific Drug Information

CLINICAL PHARMACOLOGY [1]

Dulaglutide activates the GLP-1 receptor in pancreatic beta cells, which leads to glucose-dependent insulin release. Decreases in glucagon secretion and delayed gastric emptying are also caused by dulaglutide.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	n/a
Protein Binding	Not described
Elimination	Not described
Half-Life	5 days
Metabolism	Protein catabolism

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Single-dose dulaglutide pens: 0.75 mg/ 0.5 mL and 1.5 mg/0.5 mL Single-dose prefilled dulaglutide syringe: 0.75 mg/ 0.5 mL and 1.5 mg/0.5 mL	Subcutaneous in abdomen, thigh or upper arm.	Once weekly	Initiate at 0.75 mg weekly. Increase to 1.5 mg if needed for glucose control.	Use with caution in patients with severe renal impairment or ESRD and if gastrointestinal adverse events are seen, monitor renal function.	None given – limited clinical experience however no changes in pharmacokinetics were seen in studies of patients with hepatic impairment.	Not studied	No dose adjustments needed based on age. Monitor renal function.	- Administration can be done irrespective of time of day. - If dose is missed administer within 3 days of missed dose.

DRUG SAFETY [1]

Serious (REMS, Black Box Warnings, Contraindications):

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- Risk Evaluation and Mitigation Strategy Program: There is a potential risk of medullary thyroid carcinoma (MTC) based on rodent studies with GLP-1 receptor agonists. It is unknown if dulaglutide carries this same risk. There is a risk of pancreatitis with dulaglutide. Pancreatitis has been reported with the use of GLP-1 receptor agonists. Cases of pancreatitis have been associated wit dulaglutide in studies.
- Black box warning: Do not use dulaglutide in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2.
- Contraindications: Do not use in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2. Do not use patients with serious hypersensitivity to dulaglutide or components.

Warnings and Precautions:

- Dulaglutide was shown to cause thyroid C-cell tumors in animals. Patients should be counseled on risk of thyroid carcinomas and thyroid tumors.
- Pancreatitis has been shown in studies with dulaglutide, discontinue if suspected.
- Hypoglycemia seen with dulaglutide may occur more often in patients on insulin secretagogues or insulin consider reducing the dose of sulfonylurea or insulin to reduce the risk.
- Discontinue dulaglutide hypersensitivity is suspected.
- Monitor renal function in patients with impaired renal function and report severe gastrointestinal reactions.

Monitoring: Monitor renal function in patients with renal impairment.

Drug-Drug interactions: No specific interactions have been identified. Slowed gastric emptying and impaired absorption of orally administered drugs may occur with dulaglutide.

Food-Drug Interactions: No food-drug interactions have been identified.

Pregnancy/lactation rating: Category C. Dulaglutide has not been adequately studied in pregnant women. Data is insufficient to recommend dulaglutide in women who are lactating.

ADVERSE REACTIONS[1]

Adverse reactions occurring in ≥5% of patients treated with dulaglutide were: nausea, diarrhea, vomiting, abdominal pain and decreased appetite.

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