

National PBM Monograph Dulaglutide (Trulicity)

VHA Pharmacy Benefits Management Services Medical Advisory Panel and VISN Pharmacist Executives

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- Dulaglutide is a glucagon-like peptide-1 (GLP-1) agonist that is dosed once-weekly. Other GLP-1 agonists include once weekly exenatide (Bydureon), twice daily exenatide (Byetta), once daily liraglutide (Victoza), and once weekly albiglutide. Dulaglutide is approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (T2DM). It is not recommended as first-line therapy.
- Dulaglutide is contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC), Multiple Endocrine Neoplasia syndrome type 2 (MEN 2), or history of serious hypersensitivity to dulaglutide or any product components.
- Do not use in patients with type 1 diabetes or severe gastrointestinal disease (e.g., gastroparesis). Dulaglutide has not been studied in patients with a history of pancreatitis; other agents should be considered for these patients. Dulaglutide has not been studied in combination with basal insulin.
- The dose is 0.75mg injected **subcutaneously** once weekly (administer in the abdomen, thigh, or upper arm region) and may be administered any time of day without regards to meals. The dose may be increased to 1.5mg once weekly if glycemic response is inadequate. No dosage adjustment is required in patients with renal impairment including end-stage renal disease. Monitor renal function in patients with renal impairment reporting severe adverse GI reactions. This once-weekly product does not require premixing prior to use.
- The drug development program for dulaglutide includes the AWARD trials. There are 6 trials (26-52 weeks); one monotherapy trial and the others in combination with metformin, metformin + pioglitazone, metformin + sulfonyleurea, and insulin lispro ± metformin. Active comparator arms included liraglutide, exenatide, insulin glargine, metformin, and sitagliptin.
- Mean baseline A1C for the study population ranged from 7.6-8.5%. Mean change in A1C from baseline ranged between -0.7 to -1.6% (26 week data) and -0.6 to -1.5% (52 week data).
- Mean baseline weight ranged from 85-97kg. Mean change in weight from baseline ranged from 0.2 to -2.9kg. The average weight loss was less when dulaglutide was combined with agents known to cause weight gain (e.g., pioglitazone, sulfonyleureas, insulin). There was greater weight loss with liraglutide than dulaglutide (-3.6 vs. -2.9kg respectively).
- The rates of overall hypoglycemia were low when used as monotherapy or in combination with metformin or pioglitazone; however, higher rates were observed when dulaglutide was co-administered with a sulfonyleurea or insulin.
- The most commonly reported adverse events (AEs) were gastrointestinal-related and occurred at a greater frequency with dulaglutide than with placebo or comparator arms containing metformin (except for diarrhea), sitagliptin, lispro, or glargine. The frequency of adverse GI events with dulaglutide 1.5mg was similar to exenatide and liraglutide.
- There have been post-marketing reports of acute pancreatitis including fatal and non-fatal hemorrhagic or necrotizing pancreatitis with the GLP-1 agonists. In Phase 2 and 3 trials, there were 12 cases of pancreatitis

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(3.4 cases per 1000 patient-years) in patients receiving dulaglutide versus 3 in the non-incretin comparators (2.7 cases per 1000 patient-years). An adjudicated analysis of events confirmed 5 cases (1.4 per 1000 patient-years) and 1 case (0.88 per 1000 patient-years) for dulaglutide and non-incretin therapies respectively.

- Injection site reactions were more common with dulaglutide (1.7%) than placebo (0.9). The number of injection site reactions was similar for dulaglutide, exenatide, and liraglutide.
- Pooled trial data show no increased risk for major cardiovascular events with dulaglutide relative to comparator (HR=0.57; 95%CI 0.30, 1.10). The FDA has required a cardiovascular outcome study that will evaluate the addition of dulaglutide or placebo to usual diabetes medications in patients with established cardiovascular disease or cardiovascular risk factors.
- There have been post-marketing reports of altered renal function in patients receiving GLP-1 agonists sometimes requiring hemodialysis. Majority of events occurred in patients experiencing nausea, vomiting, diarrhea, or dehydration.

Introduction

Dulaglutide is a GLP-1 agonist that is dosed once-weekly. Other GLP-1 agonists include once weekly exenatide (Bydureon), twice daily exenatide (Byetta), once daily liraglutide (Victoza), and once weekly albiglutide (Tanzeum). The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating dulaglutide for possible addition to the VA National Formulary.

Pharmacology

Glucagon-like peptide-1 is released from the L-cells located in the distal ileum and colon, in response to food containing carbohydrates and fats. Incretins enhance glucose-dependent insulin secretion from the pancreas, suppress inappropriately elevated glucagon secretion, and delay gastric emptying. Native GLP-1 is rapidly metabolized by dipeptidyl peptidase-4 (DPP-4). Dulaglutide is a fusion protein that consists of 2 identical, disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to the Fc portion of a modified human immunoglobulin G4 (IgG4) heavy chain by a small peptide linker and is produced using mammalian cell culture. The GLP-1 analog portion of dulaglutide is 90% homologous to native human GLP-1 (7-37). Structural modifications were introduced in the GLP-1 part of the molecule responsible for interaction with the enzyme DPP-4

FDA-Approved Indications

As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes.

Limitations of Use

- Dulaglutide is not recommended as first-line therapy.
- Has not been studied in combination with **basal** insulin
- Use in patients with a history of pancreatitis has not been studied; consider other agents in these patients
- Do not use in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
- Not for use in patients with pre-existing severe gastrointestinal (GI) disease

Current VA Formulary Alternatives

None in this class; other agents on the formulary used to treat diabetes include metformin, glipizide, saxagliptin, acarbose, NPH insulin, long-acting insulin analogs, regular insulin, insulin aspart, premixed insulins.

Dosage and Administration

Please refer to the product package insert for detailed instructions on how to prepare the pen for injection.

- 0.75mg injected **subcutaneously** once weekly (administer in the abdomen, thigh, or upper arm region)
- May increase dose to 1.5mg once weekly if glycemic response is inadequate
- May be administered any time of day without regards to meals
- No dosage adjustment is required in patients with renal impairment including end-stage renal disease. Monitor renal function in patients with renal impairment reporting severe adverse GI reactions
- See Instructions for Use for detailed information on administration. Dulaglutide is the first once-weekly GLP-1 agonist that does not require pre-mixing.
- Rotate the site of injection each week
- Risk of hypoglycemia is increased when co-administered with insulin or insulin secretagogues. Consider reducing the dose of insulin or insulin secretagogue when initiating dulaglutide.
- If a dose is missed, patients should administer as soon as possible if there are at least 3 days until the next scheduled dose. If less than 3 days remain before the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day. Thereafter, the patients can resume dosing on their usual day of administration. If it is more than 3 days after the missed dose, the patient should wait until their next regularly scheduled weekly dose.
- A medication guide is required to be dispensed with each prescription.

Dosage Form/Strength/Storage

Dulaglutide 0.75mg and 1.5mg are available in cartons of 4 single-dose pens AND in cartons of 4 single-dose prefilled syringes.

Dulaglutide should be stored in the refrigerator at 36-46°F (2-8°C). Do not freeze dulaglutide. Do not use dulaglutide if it has been frozen. Patients may store dulaglutide at room temperature not to exceed 86°F (30°C) for a total of 14 days.

Efficacy

The drug development program for dulaglutide includes the AWARD trials. There are 6 trials (26-52 weeks); one monotherapy trial and the others in combination with metformin, metformin + pioglitazone, metformin + sulfonylurea, and insulin lispro ± metformin. Active comparator arms include liraglutide, exenatide, insulin glargine, metformin, and sitagliptin. Rescue therapy with another anti-glycemic agent was allowed according to predefined criteria was allowed in all trials except AWARD 4 and AWARD 5.

Key inclusion criteria were type 2 diabetes, age ≥18years, A1C 6.5-11% (range varied by trial), BMI > 23 kg/m² and ≤ 45 kg/m². Please see **Appendix 1** for key exclusion criteria.

Pooled demographic and mean baseline information for pooled placebo- and active-controlled trials were age 56 years (2% ≥75yrs), 51% male, 71% White, duration of diabetes 8.2 years, A1C 7.6-8.5%, and 95.7% with eGFR ≥60mL/min /1.73m² (for AWARD 6: age 56.5 years, 48% male, 86% White, duration of diabetes 8.2 years, A1C 8.1%).

Glycemic Efficacy

The treatment arms and dosing for the AWARD trials are shown in **Table 1**. The trials were designed to show superiority versus placebo and non-inferiority versus active comparators. If non-inferiority criteria were met, testing for superiority was conducted.

Hemoglobin A1C

Across studies, the mean change in A1C from baseline ranged with dulaglutide ranged between -0.7 to -1.6% (26 week data) and -0.6 to -1.5% (52 week data). **Table 1**

Dulaglutide vs. DPP-4 inhibitor: both doses of dulaglutide significantly reduced A1C more than sitagliptin at weeks 26 and 52.

Dulaglutide vs. metformin: both doses of dulaglutide significantly reduced A1C more than metformin at week 26; at week 52 only dulaglutide 1.5mg significantly reduced A1C more than metformin.

Dulaglutide vs. other GLP-1 agonists:

- Both doses of dulaglutide significantly reduced A1C more than exenatide BID at weeks 26 and 52.
- Dulaglutide 1.5mg was non-inferior to liraglutide 1.6mg at week 26

Dulaglutide vs. insulin glargine:

- AWARD-2: Dulaglutide 1.5mg significantly reduced A1C more than glargine at weeks 52 and 78; dulaglutide 0.75mg was non-inferior to glargine at decreasing A1C at both time points. The mean dose of glargine was not reported; additionally, the FDA reviewer stated that the dose of glargine was not optimized (24% titrated to the intended goal of FPG<100mg/dL).
- AWARD-4: Both doses of dulaglutide significantly reduced A1C more than glargine (mean dose 62U) at weeks 26 and 52. However, a higher dose of insulin lispro was needed for both dulaglutide groups compared to glargine (96.7U, 93.2U, 67.8U respectively)

Fasting glucose (FPG)

Mean reduction in fasting glucose was greater with dulaglutide than exenatide BID and sitagliptin and similar to liraglutide and metformin. Both insulin studies showed insulin glargine reduced FPG more than dulaglutide.

(Table 1)

Post-prandial glucose (PPG)

- Both doses of dulaglutide significantly reduced PPG more than exenatide BID and weeks 26; at week 52, only dulaglutide 1.5mg showed significantly greater improvement than exenatide (data shown graphically in publication).
- Dulaglutide 1.5mg was non-inferior to liraglutide 1.6mg (-46.1mg/dL and -43.7mg/dL respectively)
- There was no significant difference between both dulaglutide doses and metformin at all time points

Weight

Mean baseline weight ranged from 85-97kg. Mean change in weight from baseline ranged from 0.2 to -2.9kg. The average weight loss was less when dulaglutide was combined with agents known to cause weight gain (e.g., pioglitazone, sulfonylureas, insulin). There was less weight loss with dulaglutide than liraglutide (-2.9kg vs. -3.6kg respectively). **Table 1**

Table 1: Glycemic Efficacy and Weight

Study	Design	Duration	n	Treatment arms	Dosing	Baseline A1C (%)	A1C (%)	A1C <7% (%pts)	Baseline FPG (mg/dL)	FPG (mg/dL)	Rescue (%)	Baseline Weight (kg)	Weight (kg)	
AWARD-1 Wysham 2014	R, DB, PC	Weeks 26/52	280	DUL 0.75+MET+PIO	86% receiving MET≥2550mg and PIO45mg EXEN 10 BID (started with 5BID x 4 weeks) PBO+MET+PIO	8.1	-1.30* [^] / ⁻ 1.07 [^]	66* [^] /48 [^]	159	-34* [^] / [§]	5.0/9.6	96	0.2* [^] / [§]	
			279	DUL 1.5+MET+PIO		8.1	-1.51* [^] / ⁻ 1.36 [^]	78* [^] /57 [^]	162	-43* [^] / [§]	1.4/3.9	96	-1.3* [^] / [§]	
			276	EXEN+MET+PIO		8.1	-0.99* [^] / ⁻ 0.8	52/35	164	-24* [^] / [§]	4.7/11.2	97	-1.1* [^] / [§]	
			141	PBO+MET+PIO		8.1	-0.46/NA	43/NA	166	-5/NA	15.6/NA	94	1.2/NA	
AWARD-2	R, OL	Weeks 52/78	272	DUL 0.75+MET+SU	MET ≥1500mg and GLM ≥4mg	8.1	-0.8/ ⁻ 0.6	37/34	161	-16	7.4	86.4	-1.3 [^] / ⁻ 1.5 [^]	
			273	DUL 1.5+MET+SU	Mean doses for MET, GLM, GLA not reported	8.2	-1.1 [^] / ⁻ 0.9 [^]	53 [^] /49 [^]	165	-27	4.0	85.2	-1.9 [^] / ⁻ 2.0 [^]	
			262	GLA+MET+SU		8.1	-0.6/ ⁻ 0.6	31/31	163	-32	3.1	87.6	1.4/1.3	
AWARD-3 Umpierrez 2014	R, DB	Weeks 26/52	270	DUL 0.75	MET (~85% receiving 2000mg/d)	7.6	-0.7 [^] / ⁻ 0.55	63 [^]	161	-26/ ⁻ 18	2.2/3.0	92.7	-1.4	
			269	DUL 1.5		7.6	-0.8 [^] / ⁻ 0.7 [^]	62 [^]	164	-29/ ⁻ 28 [^]	2.2/4.5	92.7	-2.3	
			268	MET		7.6	-0.6/ ⁻ 0.51	54	161	-24/ ⁻ 21	2.6/3.0	92.4	-2.2	
AWARD-4	R, OL	Weeks 26/52	293	DUL 0.75+LISP±MET	Mean LISP dose 96.7U, 93.2U, 67.8U for DUL 0.75, DUL 1.5, GLA respectively Mean GLA dose 62U	8.4	-1.6 [^] / ⁻ 1.4 [^]	33 [^] /20 [^]	150	4		91.7	0.2/0.9	
			295	DUL 1.5+LISP±MET		8.5	-1.6 [^] / ⁻ 1.5 [^]	25 [^] /19 [^]	157	-5	NA	91.0	-0.9/ ⁻ 0.4	
			296	GLA+LISP±MET		8.5	-1.4/ ⁻ 1.2	6/5	154	-28		90.8	2.3/2.9	
AWARD-5 Nauck 2014	R, DB, PC	Weeks 26/52	302	DUL 0.75+MET		8.2	-1.0* [^] / ⁻ 0.87 [^]	55* [^] /49 [^]	174	¶ [^] / ⁻ 30 [^]			86	¶ [^] / ⁻ 2.6 [^]
			304	DUL 1.5+MET		8.1	-1.2* [^] / ⁻ 1.1 [^]	61* [^] /58 [^]	173	¶ [^] / ⁻ 41 [^]	NA	87	¶ [^] / ⁻ 3.0 [^]	
			315	SIT100+MET		8.1	-0.6* [^] / ⁻ 0.39	38* [^] /33	171	¶ [^] / ⁻ 14		86	¶ [^] / ⁻ 1.5	
			177	PBO + MET		8.1	0.03/NA	21/NA	-	¶/NA		87	¶/NA	
AWARD-6 Dungan 2014	R, OL	Week 26	299	DUL 1.5+MET	Mean MET ~2040mg LIRA uptitrated to 1.6mg/day	8.1	-1.42	68	167	-34.7	N=1	93.8	-2.9	
			300	LIRA +MET		8.1	-1.36	68	166	-34.2	N=3	94.4	-3.6	

Abbreviations: DB=double-blind; DUL=dulaglutide; EXEN=exenatide; FPG=fasting plasma glucose; GLA=glargine; GLM=glimepiride; LIRA=liarglutide; LISP-lispro; MET=metformin; NA=not applicable; PBO=placebo; OL=open-label; PIO=pioglitazone; PC=placebo-controlled; R=randomized; SIT=sitagliptin; SU=sulfonylurea

*Significant versus placebo

[^]Dulaglutide significant versus active comparator

¶26 week data shown graphically in published article

§52 week data shown graphically in published article

Adverse Events (Safety Data)

In the Phase 2 and 3 trials, 3045 patients received dulaglutide for at least 24 weeks. Among these patients, 2279 received dulaglutide for at least 50 weeks and 369 patients received dulaglutide for approximately 2 years. The treatment exposure rate for up to 26 weeks was 390, 380, and 251 patient-years for dulaglutide 0.75mg, dulaglutide 1.5mg and placebo respectively. In the full treatment data set, the exposure was 1655 and 1688 patient-years for dulaglutide 0.75mg and 1.5mg respectively. Exposure rates for the active control arms were not shown in the FDA transcripts.

Deaths

The number of deaths in the Phase 2 and Phase 3 studies were dulaglutide 7 (0.18%), active comparators 8 (0.4%), and placebo 0. The breakdown according to drug was dulaglutide 0.75mg (n=3; 0.17%), dulaglutide 1.5mg (n= 4; 0.23%), sitagliptin (n=3; 0.68%), and insulin glargine (n=5; 0.90%). The majority of deaths were cardiac or respiratory-related. There were no imbalances between treatment groups.

Other Serious Adverse Events (SAE)

Pooled data were not available; therefore, individual data from the published trials are shown ([Table 2](#)). The incidence of SAEs ranged from 2-9% with dulaglutide and 3-10% with comparators/placebo.

Tolerability

Pooled data were not available; therefore, individual data from the published trials are shown ([Table 2](#)). There were more discontinuations due to adverse events with the higher dulaglutide dose than the lower dose. The incidence of discontinuations ranged from 1-8% with dulaglutide 0.75mg, 3-11% with dulaglutide 1.5mg, and 2-14% with comparators/placebo.

Table 2: Serious Adverse Events and Discontinuations

Study	n	Treatment arms	Serious AE		D/C due to AE	
			26-wk	52-wk	26-wk	52-wk
AWARD-1 Wysham 2014	280	DUL 0.75+MET+PIO	15(5)	22(8)	4(1)	4(1)
	279	DUL 1.5+MET+PIO	12(4)	18(7)	8(3)	9(3)
	276	EXEN+MET+PIO	15(5)	27(10)	9(3)	10(4)
	141	PBO+MET+PIO	12(9)	NA	3(2)	NA
AWARD-3 Umpierrez 2014	270	DUL 0.75		20(7.4)	6(2.2)	8(3.0)
	269	DUL 1.5	NA	15(5.6)	13(4.8)	14(5.2)
	268	MET		16(6.0)	10(3.7)	12(4.5)
AWARD-5 Nauck 2014	302	DUL 0.75+MET	10(3)	16(5)	12(4)	23(8)
	304	DUL 1.5+MET	17(6)	26(9)	21(7)	33(11)
	315	SIT100+MET	11(4)	17(5)	14(4)	30(10)
	177	PBO + MET	6(3)	NA	24(14)	NA
AWARD-6 Dungan 2014	299	DUL 1.5+MET	5(2)	NA	18(6)	NA
	300	LIRA +MET	11(4)		18(6)	

Abbreviations: AE=adverse event; D/C=discontinued; DUL=dulaglutide; EXEN=exenatide; LIRA=liraglutide; MET=metformin; NA=not applicable; PBO=placebo; PIO=pioglitazone; SIT=sitagliptin

Common Adverse Events

Adverse reactions from **placebo-controlled trials** reported in $\geq 5\%$ of patients treated with dulaglutide are shown in [Table 3](#). Hypoglycemia is discussed separately.

Table 3: Adverse Reactions Reported in $\geq 5\%$ of Patients Treated with Dulaglutide (Placebo-controlled trials)

	Nausea	Diarrhea	Vomiting	Abdominal pain	Decreased appetite	Dyspepsia	Fatigue
DUL 0.75mg (n=923)	12.4	8.9	6.0	6.5	4.9	4.1	4.2
DUL 1.5mg (n=834)	21.1	12.6	12.7	9.4	8.6	5.8	5.6
PBO (n=568)	5.3	6.7	2.3	4.9	1.6	2.3	2.6

Data obtained from product package insert

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Other Adverse Events

Gastrointestinal (GI)

In general, adverse GI effects were more common with dulaglutide than with placebo or active comparators. Frequency of adverse GI events was similar between dulaglutide and liraglutide. In AWARD 1, there were more adverse GI events with dulaglutide 1.5mg, followed by exenatide 10mcg BID, then dulaglutide 0.75mg (**Table 4**).

Severity of reactions reported for the pooled results for dulaglutide 0.75mg and 1.5mg, were mild (58% and 48% of cases respectively), moderate (35% and 43% respectively), and severe (7% and 11% respectively). For those studies with 26 and 52week data, the rates of adverse effects were similar at both time points.

Hypoglycemia

When used as monotherapy or in combination with metformin or pioglitazone, the risk of hypoglycemia with dulaglutide is low; however, the risk increases when combined with insulin or sulfonylureas.

AWARD-4 is the first trial to evaluate the combination of a GLP-agonist with prandial insulin. The greatest number of hypoglycemic events occurred in this trial. When added to insulin lispro, the rate of symptomatic hypoglycemia was similar between dulaglutide and insulin glargine; however, the rate of severe hypoglycemia was higher in the latter group.

When added to metformin+SU, the rate of documented symptomatic hypoglycemia was lower with dulaglutide than insulin glargine. Indirect comparison with studies of GLP-1 agonist + basal insulin, seem to indicate that the risk for hypoglycemia is greater when combined with prandial insulin than basal insulin.

The risk for hypoglycemia was higher with exenatide BID than dulaglutide and similar between dulaglutide 1.5mg and liraglutide. In the overall trials, there were very few cases of severe hypoglycemia (**Table 4**).

Table 4: Commonly Reported Adverse GI Events (%) and Hypoglycemia (%)

Study	Duration	Treatment arms	Adverse GI Events (%)				Hypoglycemia (%)		
			Any GI	Nausea	Vomiting	Diarrhea	Total hypoglycemia	Documented symptomatic	Severe
AWARD-1	Week 26/52	DUL 0.75+MET+PIO	30/34	16/17	6/6	8/9	10.7	4.6	0
		DUL 1.5+MET+PIO	47/51	28/29	17/17	11/13	10.4	5.0	0
		EXEN+MET+PIO	42/46	26/28	11/12	6/8	15.9	NR	n=2
		PBO+MET+PIO	18/NA	6/NA	1/NA	6/NA	3.5	1.4	0
AWARD-2	52-week	DUL 0.75+MET+SU		7.7		9.2		39*	0
		DUL 1.5+MET+SU	NR	15.4	NR	10.6	NR	40*	0.7
		GLA+MET+SU		1.5		5.7		51*	NR
AWARD-3	26-week	DUL 0.75		10.7	5.9	5.2	11.1		0
		DUL 1.5	NR	19	8.6	10	12.3	NR	0
		MET		14	4.1	13.8	12.7		0
AWARD-4	26-week	DUL 0.75+LISP±MET		17.7		15.7		85^	2.4
		DUL 1.5+LISP±MET	NR	25.8	NR	16.6	NR	80^	3.4
		GLA+LISP±MET		3.4		6.1		83.4^	5.1
AWARD-5	Week 26/52	DUL 0.75+MET	32/37	13/14	7/8	9/10	5.3	2.6	0
		DUL 1.5+MET	38/41	17/17	12/13	13/15	10.2	5.6	0
		SIT+MET	18/23	4/5	2/2	3/3	4.8	NR	0
		PBO+MET	23/NA	4/NA	1/NA	6/NA	1.1	1.1	0
AWARD-6	26-week	DUL 1.5+MET	36	20	7	12	9	2.7	0
		LIRA +MET	36	18	8	12	6	2.7	0

Abbreviations: EXEN=exenatide; GLA=glargine; LIRA=liraglutide; LISP=lispro; MET=metformin; NR=not reported; PBO=placebo; PIO=pioglitazone; SIT=sitagliptin; SU=sulfonylurea

*At 78 weeks, documented symptomatic hypoglycemia was 1.7, 1.7 and 3.0 events/pt-yr for dulaglutide 0.75, dulaglutide 1.5, and insulin glargine respectively

^At 52 weeks, documented symptomatic hypoglycemia was 35, 31, and 39.9 events/pt-yr for dulaglutide 0.75, dulaglutide 1.5, and insulin glargine respectively

Pancreatitis

In Phase 2 and 3 trials, there were 12 cases of pancreatitis (3.4 cases per 1000 patient-years) in patients receiving dulaglutide versus 3 in the non-incretin comparators (2.7 cases per 1000 patient-years). An adjudicated analysis of events confirmed 5 cases (1.4 per 1000 patient-years) and 1 case (0.88 per 1000 patient-years) for dulaglutide and non-incretin therapies respectively.

The number of adjudicated cases of pancreatitis in the trials that had another incretin as a comparator is reviewed. In AWARD-1, there was 1 diagnosis of chronic pancreatitis in a patient receiving dulaglutide 1.5mg approximately 7 months after initiation of study drug. In AWARD-5, there were 2 cases with sitagliptin, 1 with placebo, and none in the dulaglutide group. In AWARD-6, there were no cases with either GLP-1 agonist.

Amylase and lipase

Patients receiving dulaglutide had mean increases from baseline in lipase and/or pancreatic lipase of 14-20% compared to 3% of those receiving placebo. In general the changes were similar between dulaglutide 0.75mg and exenatide or sitagliptin and higher in the dulaglutide 1.5mg arms. The percentage of patients with an abnormal lipase value and median change in amylase was greater with liraglutide than dulaglutide.

Table 5: Amylase and Lipase

	AWARD-1		AWARD-5		AWARD-6
	DULO.75/DUL1.5/EXEN/PBO		DULO.75/DUL1.5/SIT/PBO		DUL1.5/LIRA
	Week 26	Week 52	Week 26	Week 52	Week 26
Abnormal value (%pts)					
Lipase	13/17/11/7	37/32/37/-	37/43/36/25	45/49/41/-	25/33
Amylase	6/9/6/6	18/20/16/-	20/19/14/11	25/24/19/-	6/7
≥3x ULN (%pts)					
Lipase	2.2/3.0/2.7/1.5	2.3/4.0/2.1/-	7.0/6.3/6.3/6.3	8.7/7.3/8.6/-	4/3
Amylase	0.4/0.8/0/0	0.8/0.4/0/-	0.3/0.7/0.3/0.6	1.3/0.7/0.3/-	<1/0
Median change (U/L)					
Lipase	8/19/8/-6	5/16/9/-	5/6/4/-1	5/6/4/-	7/6
Amylase	3/4/2/0	2/4/2/-	3/4/2/0	6/6/4/-	7/11

Pancreatic amylase is shown for AWARD-1 and AWARD-5; total amylase shown for AWARD-6

Thyroid C-cell tumors

The GLP-1 agonists cause thyroid C-cell tumors at clinically relevant exposures in rats. C-cells comprise a very small fraction of the thyroid in humans, but are abundant in rodents. The function of the C-cell is to synthesize and release calcitonin. Spontaneous development of C-cell tumors is common in rats. GLP-1 receptors are found in rodent C-cells, but have not been definitively identified in human C-cells. GLP-1 agonists have been shown to induce thyroid C-cell tumors in rodents at clinically relevant doses. It is unknown if dulaglutide will cause thyroid C-cell tumors including medullary thyroid cancer (MTC).

One case of MTC was reported in a patient treated with dulaglutide. This patient had elevated pretreatment calcitonin levels approximately 8x the upper limit of normal.

The FDA has required the manufacturer to create a medullary thyroid carcinoma case series registry of at least 15 years duration to determine if dulaglutide is associated with increase in MTC.

Dulaglutide antibodies

Antibodies to dulaglutide may develop. In the pooled data which includes four phase 2 and 5 phase 3 trials, 64 (1.6%) patients exposed to dulaglutide developed anti-dulaglutide antibodies.

Among the patients who were positive for dulaglutide antibodies, approximately 34 (0.9%) had dulaglutide-neutralizing antibodies and 36 (0.9%) developed antibodies against native GLP-1.

Injection site reactions

Injection site reactions occurred in 1.7% and 0.9% of dulaglutide and placebo-treated patients. The rate of reactions was not dose dependent. The incidence was higher in those who had developed anti-dulaglutide antibodies versus those who had not (3.1% and 0.5% respectively). In the AWARD 1, one patient each receiving dulaglutide 1.5mg and exenatide had an injection site reaction. In AWARD 6, one patient receiving dulaglutide and 2 receiving liraglutide developed an injection site reaction.

Cardiovascular Safety

The major adverse cardiovascular events (MACE) evaluation was based on a total of 3885 patients were randomized to dulaglutide and 2125 to comparator. The primary endpoint (MACE+) was a composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. Events were adjudicated by a committee who was unaware of treatments. There were 0.7% and 1.2% of patients receiving dulaglutide and comparator respectively experienced an event (HR=0.57; 95% CI 0.30 to 1.10). For the individual MACE+ components, the point estimates of the hazard ratio were less than one except for non-fatal stroke (data not shown in FDA review).

The REWIND study is an ongoing long-term (average duration of follow up 6.5 years) cardiovascular outcome study that will evaluate the addition of dulaglutide or placebo to usual diabetes medications in patients with established cardiovascular disease, subclinical disease, or ≥ 2 cardiovascular risk factors. The primary outcome is the time from randomization to first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The estimated enrolment is 9622 patients and estimated completion date is April 2019.

Renal

There have been post-marketing reports of altered renal function in patients receiving GLP-1 agonists (increased serum creatinine, renal impairment, worsening chronic renal failure, acute renal failure) sometimes requiring hemodialysis. Majority of events occurred in patients experiencing nausea, vomiting, diarrhea, or dehydration.

There was no decline in renal function compared to baseline with both dulaglutide doses as measured by eGFR or urine albumin creatinine ratio. Two patients treated with dulaglutide 0.75mg had shifted from normal renal function (eGFR >90 ml/min/m²) to CKD stage 3b (eGFR ≤ 45 ml/min/m²) and stage 4 (eGFR ≤ 30 ml/min/m²). The incidence of acute renal failure with dulaglutide was comparable to all the comparators.

The FDA has required that a 26-week study (plus 26 week extension) compare dulaglutide 0.75mg, dulaglutide 1.5mg and insulin glargine in patients with moderate or severe renal impairment.

Contraindications

- Patients with personal or family history of medullary thyroid carcinoma (MTC)
- Patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- History of serious hypersensitivity to dulaglutide or any product components

Warnings and Precautions

Please refer to the product package insert or elsewhere in this review for detailed information

- Risk of thyroid C-cell tumors
- Pancreatitis
- Hypoglycemia with concomitant use of insulin secretagogues or insulin
- Systemic hypersensitivity reactions
- Renal impairment
- Severe gastrointestinal disease

Sentinel Events

None

Look-alike/Sound-alike (LASA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 6: Results of LASA Search

NME Drug Name	Lexi-Comp	First Databank	ISMP	Clinical Judgment
Dulaglutide	None	None	None	Albiglutide Liraglutide Teduglutide
Trulicity	None	None	None	

Drug Interactions

- In the drug interaction trials, there were no interactions requiring adjustment of dulaglutide or co-administered drug.
- Dulaglutide slows gastric emptying and may reduce the rate of absorption of orally administered drugs. Use caution when oral medications are concomitantly administered with dulaglutide.

Special Populations

Please refer to the product package insert or elsewhere in this review for detailed information

Pregnancy Category C: In rats and rabbits, dulaglutide administered during major period of organogenesis produced fetal growth reductions and/or skeletal anomalies and ossification deficits in association with decreased maternal weight and food consumption attributed to the pharmacology of dulaglutide. Dulaglutide should not be used during pregnancy unless potential benefits outweigh potential risks.

Nursing mothers: It is not known if dulaglutide is excreted into human milk. A decision should be made to discontinue dulaglutide or nursing taking into account the importance of the drug to the mother versus potential risk to the infant.

Geriatric patients: 18.6% of patients in the clinical trials were ≥ 65 years of age and 1.9% were ≥ 75 years of age. There was no difference in efficacy and safety between older and younger patients; however, greater sensitivity in some older patients cannot be ruled out.

Hepatic impairment: Clinical experience is limited in patients with mild, moderate, or severe hepatic impairment; therefore, use with caution in these patients. In a clinical pharmacology study with patients with varying degrees of hepatic impairment, there was no clinically relevant change in dulaglutide pharmacokinetics.

Renal impairment: In four Phase 2 and five phase 3 trials, 1.2% and 4.3% of patients had mild and moderate renal impairment respectively. There were no patients with severe renal impairment. There was no difference in efficacy and safety between those with and without renal impairment; however, conclusions are limited due to the small numbers. In a clinical pharmacology study with patients with varying degrees of renal impairment, including ESRD, there was no clinically relevant change in dulaglutide pharmacokinetics. Use with caution in patients with renal impairment.

Conclusions

Dulaglutide is the fourth GLP-1 agonist in the class and the third that offers once weekly dosing. Dulaglutide offers another option for add-on therapy when oral agents (i.e. metformin, sulfonylureas, TZDs) no longer provide adequate glycemic control. They may also be considered for patients unable to use insulin or who cannot advance to more complex insulin regimens.

At this time, the once weekly agents have been directly compared to exenatide BID and liraglutide. Some differences in efficacy and adverse events between dulaglutide and exenatide BID were shown, whereas dulaglutide

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(1.5mg dose studied) and liraglutide appear to have a similar profile. Trials directly comparing the once weekly agents to each other are needed to determine if there are differences in safety and efficacy. Compared to the other once-weekly GLP-1 agonists, dulaglutide does not require pre-mixing prior to injection.

References

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FDA review documents for dulaglutide

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000MedR.pdf

Product Package Insert for Dulaglutide (TRULICITY) 9/2014

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Contact Person: Deb Khachikian, PharmD

Appendix 1: Key Exclusion Criteria for AWARD trials

Type 1 diabetes, treated with another GLP-1 analog in past 6 months, chronic insulin therapy (except AWARD 4), DKA or hyperosmolar state/coma requiring hospitalization in past 6 months, known clinically significant gastric emptying abnormality (e.g. severe diabetic gastroparesis, gastric outlet obstruction), undergone gastric bypass surgery, chronic use of drugs that directly reduce gastrointestinal motility, current use of drugs to promote weight loss, clinical signs or symptoms of liver disease, acute or chronic hepatitis, a history of chronic pancreatitis or idiopathic acute pancreatitis, or alanine transaminase (ALT) levels ≥ 3.0 times the upper limit of the reference range, serum creatinine ≥ 1.5 mg/dL, or a creatinine clearance ≤ 60 ml/minute (for AWARD-4 eGFR ≤ 30 mL/min/1.73 m²), significant active, uncontrolled endocrine or autoimmune abnormality, history of a transplanted organ (corneal transplants allowed), receiving chronic (≥ 2 weeks) systemic glucocorticoid therapy, active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years, any other condition (such as, known drug or alcohol abuse or psychiatric disorder) that may preclude the patient from following and completing the protocol, taking CNS stimulants, personal or family history of medullary C-cell hyperplasia, focal hyperplasia, carcinoma (including sporadic, familial or part of MEN 2A or 2B syndrome) or serum calcitonin ≥ 20 pg/mL at screening, systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg, change in antihypertensive medications between screening and randomization, evidence of renal artery stenosis, or evidence of labile blood pressure including symptomatic postural hypotension, screening ECG reading considered outside the normal limits by the investigator and relevant for interpretation or indicating cardiac disease (including QTc [Bazett] interval ≥ 450 ms for males or ≥ 470 ms for females); aberrant, blocked, or impaired propagation (PR interval ≥ 220 ms); and clinically significant signs of ischemic heart disease

Any of the following cardiovascular events within six months: unstable angina requiring hospitalization, CABG, AMI (within 2 months for AWARD 2, 3, 4, 6) PCI, atrial or ventricular arrhythmia, pacemaker or defibrillator implantation, TIA, CVA (within 2 months for AWARD 2, 3, 4, 6) NYHA Class III or IV HF (within 2 months for AWARD 2, 3, 4, 6; for AWARD 1, NYHA Class II also excluded), past history of edema or fluid retention in past 2 months (AWARD 1 only)