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Edoxaban: A New Target Specific Oral Anticoagulant and It's Place in a New and Growing Class

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Oral vitamin K antagonists (VKAs), mainly warfarin in the United States, have been the mainstay for oral anticoagulant therapy since their development in the early 1950s. Vitamin K antagonists are indicated for prevention of stroke and systemic embolization in patients with non-valvular atrial fibrillation (AF) and for treatment, primary prevention, and secondary prevention of venous thromboembolic events (VTEs) in current practice guidelines.[1,2] Atrial fibrillation is the most common cardiac arrhythmia, affecting an estimated 2.2 million people in the United States.[3] Vitamin K antagonist use is associated with a 62% relative risk reduction in stroke, compared to placebo, in patients with AF who account for about 15% to 20% of all stroke sufferers annually.[4,5] Additionally, VTE affect at least 700,000 people in the United States each year and the use of VKAs in this setting is associated with a significant reduction in the risk for recurrent VTEs compared with placebo.[6-8]

Historically, recommendations for the treatment of VTE consisted of initial treatment with low molecular weight heparin for 5 to 10 days and subsequent treatment with a VKA for 3 months. Despite the noted benefits of VKAs, they have many therapeutic limitations, including a relatively long time to onset and offset, a narrow therapeutic range, numerous drug-drug and drug-food interactions, bleeding risk, and variable dose-response according to genetic and non-genetic factors. These limitations warrant frequent monitoring and dose adjustments that may lead to underuse of VKAs. For example, in the vast majority of clinical trials of stroke prevention in patients with AF, fewer than 60% of patients with previous stroke and AF receive indicated VKA treatment.[9] Further, even in patients who are prescribed warfarin and start therapy, 32% are no longer taking warfarin at 30 months.[10]

In response to these limitations, several new oral anticoagulants – so called target-specific oral anticoagulants (TSOACs) – recently were developed and granted FDA-approved indications for the prevention of stroke and VTE. In contrast to warfarin and other VKAs that inhibit the production or function of vitamin K dependent coagulation factors II, VII, IX, and X, these new agents target specific factors in the coagulation cascade.[11] In 2010, the first of the TSOACs, dabigatran (Pradaxa®), a direct thrombin inhibitor, was granted an approved indication to reduce the risk of stroke and systemic embolism in patients with non-valvular AF. Soon to follow were two factor Xa inhibitors, rivaroxaban (Xarelto®), granted an approved indication in 2011 for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement, and apixaban (Eliquis®), granted an approved indication in 2012 for reducing the risk of stroke and systemic embolism in patients with non-valvular AF.

Most recently, edoxaban (Savaysa®), another factor Xa inhibitor, received an FDA-approved indication on January 8, 2015 for reducing the risk of stroke and systemic embolism in patients with non-valvular AF and for the treatment of DVT and PE following 5 to 10 days of initial therapy with a parenteral anticoagulant. The purpose of this article is to review the pharmacology and pharmacokinetics, key clinical evidence, and dosing and administration of edoxaban, as well as to consider its place in a growing class of new treatment options for anticoagulation.

Pharmacology & Pharmacokinetics

Edoxaban, which is supplied as edoxaban tosylate monohydrate, is a selective inhibitor of free factor Xa. This inhibition leads to a reduction in the generation of thrombin (factor II) through the inhibition of clotting cascade progression which ultimately leads to reduced thrombus formation.[12] Factor Xa is a serine protease which binds to factor Va on activated platelets to form the complex which converts prothrombin to thrombin. Factor Xa acts as the primary amplification site in the coagulation cascade and one factor Xa molecule can lead to the activation of ~1000 prothrombin molecules.[13] Edoxaban binds directly to the active site of factor Xa, which prevents factor Xa from binding to its substrate.[14]

Edoxaban is administered orally and reaches its maximum concentration in two hours.[12] The bioavailability and absorption of edoxaban are not affected by administration with food. Edoxaban has a biphasic distribution and is 55% protein-bound to plasma proteins as demonstrated by *in vitro* studies. As edoxaban undergoes minimal metabolism, the parent drug is the most readily found entity in plasma. Edoxaban is excreted in urine, bile, and feces and is a P-glycoprotein (P-gp) substrate. Additional pharmacokinetic parameters can be found in **Table 1.**

Edoxaban exhibited stable and predictable pharmacokinetics in phase 1 trials.[15] Edoxaban exhibited no accumulation with once-daily dosing and steady state was achieved within 3 days. No dif-

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ference in exposure was noted according to sex, age, or race. Mild and moderate hepatic impairment (Child-Pugh A or B) was not associated with altered pharmacokinetics of edoxaban. Potentially clinically significant pharmacokinetic differences among groups were identified with regard to renal function, weight, and P-gp inhibitor co-administration. Relative to those subjects with CrCl ≥80 mL/min, exposure to edoxaban increased by 32% in those with CrCl >50 mL/min to <80 mL/min, 74% in those with CrCl 30 to 50 mL/min, 72% in those with CrCl <30 mL/min, and 93% in those undergoing peritoneal dialysis. In phase 1 studies, edoxaban exposure was increased by 13% in patients with low body weight (median, 55 kg) compared to those patients with a greater body weight (median, 84 kg), although the clinical significance of this finding is unclear (see additional information in the Administration & Monitoring section).[15] Edoxaban exposure also was significantly increased with co-administration of P-gp inhibitors such as verapamil and quinidine.

TABLE 1 | Pharmacokinetics of edoxaban.[12]

Parameter	Edoxaban
T_{max}	1-2 hours
Elimination $t_{1/2}$	10-14 hours
Bioavailability	62%
Metabolism	Minimal (5-10%) hydrolysis, CYP3A4
V_d	107 L
Elimination	50% renal (11 L/hr), ~50% biliary/ intestinal
Protein Binding	55%

$t_{1/2}$ = half-life; T_{max} = time to maximum concentration; V_d = volume of distribution.

CLINICAL TRIALS

Non-Valvular Atrial Fibrillation

The efficacy and safety of edoxaban for reducing the risk of stroke and systemic thromboembolism in patients with non-valvular AF were evaluated in the ENGAGE AF-TIMI 48 trial.[16,17] The ENGAGE AF-TIMI 48 trial was a multinational (46 countries), double-blind, non-inferiority study in which a total of 21,105 patients were randomly assigned in a 1:1:1 fashion to one of three treatment arms: high-dose edoxaban (60 mg once daily), low-dose edoxaban (30 mg once daily), or warfarin once daily titrated to an INR of 2 to 3. Patients in the edoxaban arm had sham INRs drawn and received warfarin placebos and patients in the warfarin arm received edoxaban placebos to maintain blinding. In the two edoxaban arms, the treatment dose was reduced by 50% if patients presented with CrCL ≤50 mL/min, a body weight ≤60 kg, or used P-gp inhibitors including verapamil, quinidine, and dronedarone. This dose-reduction was based upon differences in exposure to edoxaban noted in earlier phase 1 trials, simulation and modeling (see Pharmacology section). Once-daily dosing was used due to the results of a phase 2 dose ranging study showing a decreased incidence of bleeding and similar efficacy, with once-daily dosing versus twice-daily dosing.[18]

Enrolled patients were ≥21 years of age with AF diagnosed by any electrical tracing in the last 12 months, and a $CHADS_2$ score of ≥2. Key exclusion criteria were an estimated creatinine clearance ≤30 mL/min, active liver disease, a high risk of bleeding (**Box**), acute coronary syndrome, coronary revascularization, stroke within 30 days before randomization, chronic cyclosporine therapy, or a known positive test for HIV or hepatitis B or C. The median age of the 21,105 patients was 72 years, 38% were female and 81% were Caucasian. Almost 23% of patients had $CHADS_2$ scores ≥4, indicating a high risk for thromboembolic events. No differences in baseline characteristics were observed comparing the three treatment arms. In each of the edoxaban arms, 25.4% of the patients had a 50% dose reduction. The mean ± SD time in therapeutic range was 64.9% ± 18.7% for warfarin-treated patients, which is generally considered moderately good control and which is comparable to other large-scale outcomes studies using warfarin. Only 0.5% of the randomized population was lost to follow-up.

The primary end point of ENGAGE AF-TIMI 48 was the time to first stroke (ischemic or hemorrhagic) or systemic embolic event (SEE).[16,17] The major safety endpoint was major bleed during treatment. The pertinent results for the efficacy endpoints are summarized in **Table 2.** In analysis of the primary endpoint, both the high-dose and low-dose edoxaban groups were non-inferior to dose-adjusted warfarin therapy. Neither of the edoxaban treatment arms achieved superiority over warfarin with regards to the primary endpoint.

The reduction in primary outcome events between the warfarin and high-dose edoxaban arm was driven primarily by a decrease in hemorrhagic stroke events, with a rate of 0.26% in the high-dose edoxaban group versus 0.47% in warfarin-treated patients (HR 0.54; 95% CI 0.38-0.77; superiority p<0.001). The low-dose edoxaban arm also had a significantly lower risk for hemorrhagic stroke compared with the warfarin arm (HR 0.33; 95% CI 0.22-0.50; superiority p<0.001). No difference was observed in ischemic stroke rates between the warfarin (1.25%) and high-dose edoxaban (1.25%) groups (HR 1.00, 95% CI 0.83-1.19; superiority p=0.97). However, the low-dose edoxaban arm had a higher risk of ischemic strokes compared to the warfarin arm (HR 1.41, 95% CI 1.19-1.67; superiority p<0.001). Both the high- and low-dose edoxaban treatment arms had lower rates of death from cardiovascular causes than did the warfarin arm, but myocardial infarction rates did not differ between both edoxaban treatment arms

BOX | High-risk bleeding conditions for exclusion from the ENGAGE AF-TIMI 48 trial.[16]

- History of intracranial, spinal, retroperitoneal, or intraarticular bleeding
- Overt gastrointestinal bleeding or active ulcer in previous year
- Severe trauma, major surgery, or deep organ biopsy within past 10 days
- Active infective endocarditis
- Uncontrolled hypertension (blood pressure >170/100 mm Hg)
- Hemorrhagic disorder (including hereditary or acquired bleeding or coagulation disorders)

TABLE 2 | ENGAGE AF-TIMI 48 efficacy endpoints.[17]

Endpoint	Edoxaban 60 mg	Edoxaban 30 mg	Warfarin	Edoxaban 60 mg vs Warfarin	Edoxaban 30 mg vs Warfarin
First stroke or SEE[a]	1.18%	1.61%	1.50%	0.79 (0.63-0.99; p<0.001)[b]	1.07 (0.87-1.31; p=0.005)[b]
Stroke	1.49%	1.91%	1.69%	0.88 (0.75-1.03; p=0.11)	1.13 (0.97-1.31; p=0.12)
Ischemic stroke	1.25%	1.77%	1.25%	1.00 (0.83-1.19; p=0.97)	1.41 (1.19-1.67; p<0.001)
Hemorrhagic stroke	0.26%	0.16%	0.47%	0.54 (0.38-0.77; p<0.001)	0.33 (0.22-0.50; p<0.001)
SEE	0.08%	0.15%	0.12%	0.65 (0.34-1.24; p=0.19)	1.24 (0.72-2.15; p=0.43)
Stroke/SEE/CV death	3.85%	4.23%	4.43%	0.87 (0.78-0.96; p=0.005)	0.95 (0.86-1.05; p=0.32)
CV death	2.74%	2.71%	3.17%	0.86 (0.77-0.97; p=0.013)	0.85 (0.76-0.96; p=0.008)

Data represent percent of patients per year or HR (95% Confidence Interval; p-value). **CV =** cardiovascular; **SEE =** systemic embolic event.
[a]Primary outcome.
[b]Data represent non-inferiority p-value and 97.5% CIs.

vs. warfarin.[17] The primary efficacy outcome event rate was lower in the high-dose edoxaban arm than in the low-dose edoxaban arm, which was driven by a 64% relative risk reduction in ischemic stroke in the high-dose edoxaban arm that exceeded the modestly higher rate of hemorrhagic strokes in the high-dose edoxaban arm.

Both edoxaban treatment arms had lower rates of major bleeding and minor bleeding than did the warfarin treatment arm (**Table 3**). One major exception to the lower rate of bleeding outcomes in the edoxaban arms was gastrointestinal (GI) bleeding, primarily upper GI bleeds, which occurred at a higher rate in the high-dose edoxaban arm compared to the warfarin arm. On the other hand, a lower rate of GI bleeding was observed with low-dose edoxaban arm compared to the warfarin arm. The low-dose edoxaban arm had lower rates of bleeding than the high-dose edoxaban arm.

Although the results from the ENGAGE AF-TIMI 48 study were positive for edoxaban, a subgroup analysis of the primary efficacy endpoint and its components showed differences based on renal function (**Table 4**). As discussed previously, approximately 50% of an edoxaban dose is excreted renally and edoxaban blood concentrations are decreased in patients with CrCl ≥80 mL/min when compared to patients with a CrCl of >50 to ≤80 mL/min. In ENGAGE AF-TIMI 48, among patients with CrCl >95 mL/min, those treated with warfarin had lower rates of the primary outcome (stroke or SEE) and ischemic stroke than those treated with edoxaban, suggesting that in patients with CrCl >95 mL/min, edoxaban may be inferior to warfarin.

Treatment of DVT and PE

The safety and efficacy of edoxaban for the treatment of DVT and PE was evaluated in the phase 3 Hokusai VTE trial.[19,20] This multinational (involving 37 countries), randomized, parallel group, double blind, non-inferiority trial randomly assigned patients in a 1:1 fashion to treatment with either heparin (enoxaparin or unfractionated heparin) followed by edoxaban or heparin followed by warfarin. Patients received at least 5 days of open-label enoxaparin or unfractionated heparin using dosing according to a standard protocol. Warfarin (in the warfarin arm) and a matching placebo (in the edoxaban arm) were started concurrently with the heparin. Warfarin was dose-adjusted to an INR of 2 to 3 with a target of 2.5. Sham INRs were used in the edoxaban arm to maintain blinding. Heparin could be stopped following ≥5 days of treatment and an INR (or sham INR) ≥2.0 for 2 measurements, at least a day apart. Edoxaban and its matching placebo (in the warfarin arm) were started 12 ± 3 hours after the last dose of twice daily enoxaparin, 24 ± 3 hours after the last dose of the once-daily enoxaparin dose or 4 ± 1 hours after the discontinuation of IV unfractionated heparin. The edoxaban regimen was 60 mg orally once daily taken with or without food. A 50% reduction in dose to 30 mg daily was used for patients with CrCl 30 to 50 mL/min, body weight of ≤60 kg or in those who were using concomitant strong P-gp inhibitors (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole). Treatment with warfarin or edoxaban was continued for a minimum of 3 months to a maximum of 12 months, as determined by the investigator based upon the individual patient and their risk for recurrent VTE, bleeding, and patient preference. Patients 18 years of age or older with an objectively diagnosed acute, symptomatic DVT involving the popliteal, femoral, or iliac veins or an acute, symptomatic PE were eligible to participate in the study. Exclusion criteria for the trial included having contraindications to heparin or warfarin, receiving >48 hours of therapeutic doses of heparin, a diagnosis of cancer, receiving more than

TABLE 3 | ENGAGE AF-TIMI 48 safety and net clinical endpoints.[17]

Endpoint	Edoxaban 60 mg	Edoxaban 30 mg	Warfarin	Edoxaban 60 mg vs Warfarin	Edoxaban 30 mg vs Warfarin
Major Bleeding	2.75%	1.61%	3.43%	0.80 (0.71-0.91; p<0.001)	0.47 (0.41-0.55; p<0.001)
GI Bleeding	1.51%	0.82%	1.23%	1.23 (1.02-1.50; p=0.03)	0.67 (0.53-0.83; p<0.001)
Minor Bleeding	4.12%	3.52%	4.89%	0.84 (0.76-0.94; p=0.002)	0.72 (0.65-0.81; p<0.001)
Primary Net Outcome[a]	7.26%	6.79%	8.11%	0.89 (0.83-0.96; p=0.003)	0.83 (0.77-0.90; p<0.001)

Data represent percent of patients per year or HR (95% Confidence Interval; p-value).
[a]The primary net clinical outcome was a composite of death from any cause, stroke, systemic embolic event, or major bleeding.

TABLE 4 | Effect of renal function on primary efficacy endpoint components in ENGAGE AF-TIMI 48.[12]

Endpoint	Warfarin	Edoxaban 60 mg	Hazard Ratio (95% CI)
Stroke/SEE			
≤95 mL/min	1.8%	1.2%	0.68 (0.55-0.84)
≤50 mL/min	2.0%	1.8%	0.90 (0.60-1.34)
>50 to ≤80 mL/min	2.0%	1.1%	0.53 (0.40-0.70)
>80 to ≤95 mL/min	1.0%	1.1%	1.05 (0.61-1.82)
>95 mL/min	0.6%	1.0%	1.87 (1.10-3.17)
Ischemic Stroke			
≤95 mL/min	1.1%	0.9%	0.80 (0.62-1.04)
≤50 mL/min	1.1%	1.2%	1.11 (0.66-1.84)
>50 to ≤80 mL/min	1.2%	0.8%	0.63 (0.44-0.89)
>80 to ≤95 mL/min	0.7%	0.8%	1.11 (0.58-2.12)
>95 mL/min	0.4%	0.9%	2.16 (1.17-3.97)
Hemorrhagic Stroke			
≤95 mL/min	0.6%	0.3%	0.50 (0.33-0.75)
≤50 mL/min	0.7%	0.5%	0.66 (0.32-1.36)
>50 to ≤80 mL/min	0.7%	0.3%	0.38 (0.22-0.67)
>80 to ≤95 mL/min	0.3%	0.2%	0.76 (0.24-2.38)
>95 mL/min	0.2%	0.2%	0.98 (0.31-3.05)

Data represent percent of patients per year unless otherwise noted. **CI =** confidence interval; **HR =** hazard ratio; **SEE =** systemic embolic event.

one dose of VKA for treatment of the current DVT/PE prior to study enrollment, having other indications for VKA therapy, receiving dual antiplatelet therapy or doses of aspirin >100 mg per day, having creatinine clearance <30 mL/min or treatment with antiretroviral therapy or cyclosporine.

The primary efficacy outcome was the incidence of symptomatic recurrent VTE, defined as DVT or fatal or nonfatal PE.[19,20] The primary efficacy outcome was analyzed as events in the overall study period and, separately, as events while on treatment. Events during the overall study period were defined as any event occurring within the 12 months following initiation of treatment regardless of whether the event occurred while the patient was still receiving either warfarin or edoxaban (per the study protocol, treatment could be stopped anywhere between 3 and 12 months post-initiation). On-treatment events were defined as any event which occurred during treatment with warfarin or edoxaban. The primary safety outcome was a composite of major bleeding or clinically relevant non-major bleeding.

A total of 8,292 patients with a mean age of ~56 years and ~57% were men were enrolled.[20] Patients who received the reduced dose of 30 mg edoxaban at randomization represented 17.8% of the edoxaban arm. No differences were observed in baseline characteristics between the treatment arms. Approximately 60% of patients presented with DVT only. The median duration of heparin following randomization was 7 days and 40% of patients received a full 12 months of the study drugs. The time in therapeutic range for the warfarin treated patients was 63.5%.

For the primary outcome with analysis of the overall study period, VTE recurrence occurred in 3.2% of the edoxaban arm and in 3.5% of the warfarin arm (HR 0.89; 95% CI 0.70-1.13; non-inferiority p<0.001). The on-treatment analysis of the primary outcome also demonstrated the non-inferiority of edoxaban. **Table 5** summarizes additional pertinent efficacy endpoint data. Among patients with a PE at baseline, the primary outcome occurred less frequently in the edoxaban arm versus the warfarin arm, whereas no difference was observed between treatment arms among patients with a baseline DVT. Results were similar in the subgroup of patients with a reduced (30-mg) dose of edoxaban.

The primary safety outcome of major bleeding or clinically relevant non-major bleeding occurred in 8.5% of edoxaban-treated patients and in 10.3% of warfarin-treated patients (HR 0.81; 95% CI 0.71-0.94; superiority p=0.004). **Table 6** summarizes pertinent safety endpoint results. Similar results were seen in the subgroup of patients who qualified for edoxaban 30-mg dosing.

ADVERSE REACTIONS

The most common adverse reaction observed in the trials of edoxaban was bleeding (**Tables 3** and **6**). In the ENGAGE AF-TIMI 48 trial, the most common non-bleeding adverse reactions were rash, which was observed in 4.2% of high-dose edoxaban-treated patients versus 4.1% of warfarin treated patients, and abnormal liver function tests which were observed in 4.8% of patients and 4.6% of patients, respectively.[12] Interstitial lung disease (ILD) was also seen in 0.2% of edoxaban-treated patients and 0.1% of warfarin-treated patients, however these data may be confounded by amiodarone use (which is also associated with ILD) in many of the identified cases. In the Hokusai-VTE trial, rash was identified in 3.6% of edoxaban-treated patients and 3.7% of warfarin-treated patients. Anemia was also identified in 1.7% of edoxaban-treated patients and 1.3% of warfarin-treated patients.

Edoxaban carries a three-part black box warning.[12] The first part of the warning addresses the reduced efficacy in non-valvular AF for patients with CrCl >95 mL/min. The second part of the warning states that premature discontinuation of edoxaban increases the risk of ischemic events. If edoxaban is to be discontinued for reasons other than bleeding or a completion of course, coverage with another anticoagulant should be considered. The final part of the black box warning discusses the risk for spinal/epidural hematoma occurring when receiving neuraxial anesthesia or spinal puncture while on edoxaban. This hematoma may result

Table 5 | Primary outcome (recurrent VTE or VTE-related death) results in the Hokusai-VTE trial.[20]

Analysis	Edoxaban	Warfarin	Edoxaban vs Warfarin
All Patients: Overall study period	3.2%	3.5%	0.89 (0.70-1.13)[a]
All Patients: On treatment period	1.6%	1.9%	0.82 (0.60-1.14)[a]
Patients with index DVT: Overall study period	3.4%	3.3%	1.02 (0.75-1.38)
Patients with index PE: Overall study period	2.8%	3.9%	0.73 (0.50-1.06)

Data represent percent of patients experiencing event or HR (95% CI). **CI =** confidence interval; **DVT =** deep vein thrombosis; **HR =** hazard ratio; **PE =** pulmonary embolism.
[a]Non-inferiority p<0.0001.

in long-term paralysis.

Administration and Monitoring

Savaysa ® (edoxaban) is available in 60-mg, 30-mg and 15-mg tablets.[12] Edoxaban can be taken with or without food. Missed doses should be taken as soon as possible the same day and the usual schedule resumed on the next day. Doses should never be doubled up. For use in non-valvular AF, CrCl should be estimated utilizing the Cockcroft-Gault equation before initiation of edoxaban. Edoxaban should not be used to treat non-valvular AF for patients with CrCl >95 mL/min (approximately 25% of the population which was studied in ENGAGE AF-TIMI 48 had CrCl >95 mL/min). Edoxaban should be initiated at 60 mg once daily, unless CrCl is 15 to 50 mL/min, in which case edoxaban should be initiated at 30 mg once daily.

For treatment of DVT and PE following 5 to 10 days of parenteral anticoagulation, edoxaban should be initiated at 60 mg once daily in most patients. A 30-mg dose should be initiated in those with a CrCl of 15 to 50 mL/min, weight <60 kg, or current use of specific P-gp inhibitors, including verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole or oral ketoconazole. Scarce data exist on the use of edoxaban in patients with CrCl <15 mL/min. Recommendations regarding transitioning from other anticoagulants to edoxaban and from edoxaban to other anticoagulants can be found in **Table 7**.

Edoxaban is contraindicated in persons with pathological bleeding. Concomitant use of aspirin, antiplatelets, other anticoagulants and NSAIDs with edoxaban should be avoided when possible. The concomitant use of rifampin also should be avoided. Edoxaban has not been studied in the setting of mechanical valves or moderate to severe mitral stenosis.

Edoxaban is categorized as FDA pregnancy class C and has not been studied in breast feeding. In the Hokusai VTE study, 10 pregnancies were exposed to edoxaban for at least six weeks during the first trimester of pregnancy. Six babies were live births with two of the six born premature. One pregnancy spontaneously aborted and there were elective abortions in three of the pregnancies.

Edoxaban prolongs prothrombin time (PT) and activated partial thromboplastin time (aPTT) through the inhibition of factor Xa, however the changes are small and highly variable. Consequently, typical anticoagulation monitoring tests (i.e., aPTT or INR) are not very useful in monitoring edoxaban.

A comparison of the pharmacological properties of the four

Comparison of Oral Anticoagulants

TSOACs and warfarin can be found in **Table 8.** However, no head-to-head trials have compared one TSOAC against another. Thus, comparisons of outcomes across trials are difficult given varying study methodologies, patient populations, and outcomes. Indications, administration, dosing, dose adjustment, and limitations of use for the oral anticoagulants can be found in **Table 9**.

Two limitations that all TSOACs share compared to warfarin are the current lack of specific reversal agents/antidotes (although some are in development) and cost. Edoxaban currently has no antidote agent, however an antidote for edoxaban (PER977) has shown promise in early phase 2 trials.[24] Although price data for edoxaban is currently unavailable, the cost is likely to be comparable to the other TSOACs.

Summary

Edoxaban (Savaysa®) is a newly available oral anticoagulant which directly inhibits factor Xa. At a dose of 60 mg once daily and a reduced dose of 30 mg once daily in specific populations, edoxaban has been studied for use in non-valvular AF (in the ENGAGE AF-TIMI 48 trial) and to treat DVT and PE (in the Hokusai-VTE trial). Both studies demonstrated non-inferiority of edoxaban to warfarin for their primary efficacy endpoints and superiority for bleeding outcomes when compared to warfarin. However, reduced efficacy was observed in patients with normal renal function (CrCl >95 mL/min) in the ENGAGE AF-TIMI 48 trial. Other than bleeding adverse events, edoxaban is generally well-tolerated. Meaningful comparisons of efficacy and safety

Table 6 | Hokusai-VTE safety endpoints.[20]

Endpoint	Edoxaban	Warfarin	Edoxaban vs Warfarin
Major bleeding or clinically relevant non-major bleeding[a]	8.5%	10.3%	0.81 (0.71-0.94; p=0.004)
Major Bleeding	1.4%	1.6%	0.84 (0.59-1.21; p=0.35)
Clinically relevant non-major bleeding	7.2%	8.9%	0.80 (0.68-0.93; p=0.004)
Any bleeding	21.7%	25.6%	0.82 (0.75-0.90; p<0.001)

Data represent percent of patients experiencing event or HR (95% CI; p-value). **CI =** confidence interval; **HR =** hazard ratio.
[a]Primary safety endpoint.

Table 7 | Prescribing recommendations for transitioning to and from edoxaban.[12]

Transitioning to Edoxaban	
From	**Recommendation**
Warfarin or other VKA	Discontinue warfarin (other VKA) and start edoxaban when INR is ≤2.5.
Other TSOACs	Discontinue current TSOAC and start edoxaban at the time of the next scheduled dose of the previous TSOAC.
LMWH	Discontinue LMWH and start edoxaban at the time of the next scheduled dose of LMWH.
UFH	Discontinue UFH infusion and start edoxaban 4 hours later.
Transitioning from Edoxaban	
To	**Recommendation**
Warfarin or other VKA	**Oral option:** For patients taking 60 mg edoxaban, reduce dose to 30 mg and begin warfarin. For patients taking 30 mg edoxaban, reduce dose to 15 mg and begin warfarin. INR must be measured at least weekly and just prior to edoxaban daily dose to minimize edoxaban's influence on INR readings. Once INR is stable at ≥2, discontinue edoxaban and continue warfarin. **Parenteral option:** Discontinue edoxaban and start parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once INR is stable at ≥2, then discontinue parenteral anticoagulant and continue warfarin.
Other TSOAC	Discontinue edoxaban and start other TSOAC at the time of the next dose of edoxaban.
Parenteral Anticoagulant	Discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban.

LMWH = Low molecular weight heparin; **TSOAC =** Target Specific Oral Anticoagulant (i.e., dabigatran, rivaroxaban, apixaban); **VKA =** Vitamin K antagonist; **UFH =** unfractionated heparin.

between the other TSOACs and edoxaban are limited by a lack of head-to-head studies. Thus, edoxaban's place in the clinical management of patients with AF and VTE remains to be seen.

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Table 8 | Comparison of oral anticoagulant pharmacologic properties.[21-23]

Property	Edoxaban	Apixaban	Rivaroxaban	Dabigatran	Warfarin
Mechanism of Action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor	Vitamin K antagonist
T_{max}, hours	1-2	3	2.5-4	1	72-96
Half-life, hours	9-11	8-13	5-9 (9-13 elderly)	14-17	4-5
Bioavailability	50%	66%	80%	6.5%	100%
Interactions	P-gp inhibitors	Potent CYP3A4 inhibitors	Potent CYP3A4 inhibitors; P-gp inhibitors	P-gp inhibitors; Proton pump inhibitors	CYP2C9, 1A2, & 3A4 inhibitors; Dietary vitamin K
Renal excretion	45%	50%	66%	80%	1%
Antidote	No	No	No	No	Vitamin K

TABLE 9 | Comparison of oral anticoagulant administration and dosing.[21-23]

	Edoxaban	Apixaban	Rivaroxaban	Dabigatran	Warfarin
FDA-approved Indications	• DVT/PE treatment following 5-10 days of parenteral anticoagulation • NVAF	• NVAF • DVT/PE treatment • DVT/PE prophylaxis • DVT prophylaxis following hip or knee surgery	• NVAF • DVT/PE treatment • DVT/PE prophylaxis • DVT prophylaxis following hip and knee surgery	• NVAF • DVT/PE treatment following 5-10 days of parenteral anticoagulation • DVT/PE prophylaxis	• DVT/PE treatment • DVT/PE prophylaxis • Valvular AF & NVAF • Post-MI
Administration	Once Daily	Twice Daily	Once or Twice Daily	Twice Daily	Once Daily
Dosing	60 mg daily	5 mg BID (2.5 mg BID for DVT prophylaxis)	20 mg daily (15 mg BID for treatment DVT/PE, 10 mg daily DVT prophylaxis hip/knee surgery)	150 mg BID	Individualized
Dose adjustment	• For DVT/PE: 30 mg for <60 kg, concomitant P-gp inhibitor, or CrCl -50 mL/min • NVAF: 30 mg for CrCl 15-50 mL/min	• 2.5 mg BID for patients with 2 of: age ≥80 years, body weight ≤60 kg, or SCr ≥1.5 mg/dL	• 15 mg daily if CrCl is 15-50 mL/min	• 75 mg BID if CrCl 15-30 mL/min • Consider 75 mg BID if CrCl 30-50 mL/min or on dronedarone or ketoconazole	• Adjusted based upon INR
Clinical Pearls			Take with food for ≥15 mg/day	Must keep in original container and use within 4 months of opening	Requires INR monitoring
Use Limitations	• Avoid if CrCl <15 mL/min • NVAF: **do not use** if CrCl >95 mL/min	• Avoid if CrCl <25 mL/min or severe liver impairment	• Avoid in moderate or severe hepatic impairment	• Avoid if CrCl ≤30 mL/min • Caution in ages >80 years	
Cost[a]	N/A	$377.99	$377.64	$377.64	$20.04
Major Phase 3 Clinical Trials	ENGAGE-AF TIMI 48, Hokusai-VTE	ARISTOTLE, ADVANCE 2 and 3	ROCKET AF, RECORD 1-4, EINSTEIN	RE-LY, RECOVER, RENOVATE I and II, REMODEL	AFASAK, SPAF, BAATAF, CAFA, SPINAF, WARIS I -II

AF = atrial fibrillation; **BID =** twice daily; **CrCl =** creatinine clearance; **DVT =** deep vein thrombosis; **INR =** international normalized ratio; **MI =** myocardial infarction; **PE =** pulmonary embolism; **NVAF =** non-valvular atrial fibrillation.
[a]Average cash price for usual month supply.

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Dulaglutide: A New GLP-1 Receptor Agonist for the Treatment of Diabetes

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Type 2 diabetes is characterized by hyperglycemia as a result of insulin resistance, decreased insulin secretion, or a combination of both. Type 2 diabetes can lead to macrovascular complications, like heart disease and stroke, and microvascular complications, like nephropathy, neuropathy, and retinopathy.[1] As of 2012, an estimated 29.1 million Americans have diabetes, with 90% to 95% of cases being type 2.[1]

Several classes of medication are available for the treatment of type 2 diabetes. The American Diabetes Association recommends metformin as initial pharmacological therapy for type 2 diabetes, followed by a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin if combination therapy is necessary.[2] The GLP-1 receptor agonists are beneficial as add-on therapy to metformin because they lower HbA1c, promote weight loss, and have a low risk of hypoglycemia.[3] Older GLP-1 receptor agonists, including exenatide, liraglutide, and albiglutide, vary in efficacy, tolerability, administration, and cost. In September 2014, a fourth GLP-1 receptor agonist, dulaglutide (Trulicity®; Eli Lilly and Company, Indianapolis, IN), was granted an FDA-approved indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The purpose of this article is to review the pharmacology, clinical trials, adverse events and precautions, and dosing and administration of dulaglutide. The article will also include a comparison of dulaglutide to other GLP-1 receptor agonists.

Pharmacology

Dulaglutide is a human GLP-1 receptor agonist that promotes glucose-dependent insulin release, glucagon secretion, and delayed gastric emptying.[4] Glucagon-like peptide-1 is an incretin, a gastrointestinal hormone that increases insulin release. Dulaglutide binds to GLP-1 receptors that are expressed by β cells in the pancreas, mimicking the actions of endogenous GLP-1. In patients with type 2 diabetes, dulaglutide reduces both fasting glucose and postprandial glucose concentrations. The reduction in glucose concentrations is seen as early as after the first dose. The delay in gastric emptying is greatest after the first dose and decreases after subsequent doses.

Dulaglutide reaches a maximum concentration in 24 to 72 hours.[4] Steady-state concentrations are reached between 2 and 4 weeks after regular weekly administration. Metabolism of dulaglutide is thought to occur through degradation into amino acids by protein catabolism. **Table 1** summarizes the pharmacokinetic properties of dulaglutide.[4]

Clinical Trials

The efficacy and safety of dulaglutide were evaluated in six phase 3 studies, known as the AWARD trials, comparing dulaglutide to active treatment (**Table 2**). In the AWARD-1 trial, once-weekly dulaglutide was compared to twice-daily exenatide in a 52-week randomized, placebo-controlled study.[5] The primary endpoint was change in HbA1c from baseline at 26 weeks. Prior to randomization, patients underwent a 12-week lead-in period in which they were treated with metformin and pioglitazone titrated to maximally tolerated doses. Following this lead-in period, a total of 976 patients were randomly assigned to one of four arms: dulaglutide 1.5 mg once weekly, dulaglutide 0.75 mg once weekly, exenatide 10 mcg twice daily, or placebo once weekly. Enrolled patients were ≥18 years of age with a BMI between 23 and 45 kg/m^2 and an HbA1c between 7% and 11%. At 26 weeks post-randomization, HbA1c was reduced significantly more in patients treated with dulaglutide 0.75 mg once weekly (-1.3%) or 1.5 mg once weekly (-1.5%) compared to those treated with placebo (-0.5%) or exenatide (-1.0%; $p<0.001$ for each dulaglutide dose compared with placebo or exenatide). Patients treated with dulaglutide 1.5 mg once weekly had a similar decrease in body weight (-1.3 kg) when compared to exenatide (-1.1 kg; $p=0.47$); treatment with dulaglutide 0.75 mg once weekly was associated with no decrease in body weight (+0.2 kg; $p<0.001$ for the comparison to exenatide). The incidence of adverse effects, which are discussed later, was similar with dulaglutide and exenatide, and the discontinuation rate due to adverse effects was similar across treatment arms.[5]

The AWARD-2 trial was a 78-week, open-label, noninferiority study that compared dulaglutide to insulin glargine in patients treated with background metformin and glimepiride.[6] As of this writing, the AWARD-2 trial had been published only in abstract form. Enrolled patients had an HbA1c between 7% and 11% despite treatment with 1 to 3 oral anti-hyperglycemic medications. After a 10-week lead-in period, 807 patients were randomly assigned to dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or insulin glargine at an initial dose of 10 units once daily. The primary outcome was change in HbA1c from baseline at 52 weeks: dulaglutide 1.5 mg once weekly was superior to insulin glargine at 52 weeks (-1.08% vs. -0.63%, respectively; $p<0.001$) and 78 weeks (-0.90% vs. -0.59%, respectively; $p<0.001$); dulaglutide 0.75 mg once weekly was noninferior to insulin glargine at 52 weeks (-0.76% vs. -0.63%, respectively; non-inferiority $p<0.001$) and 78 weeks (-0.62% vs. -0.59%, respectively; non-inferiority $p<0.001$). The available published abstract states that insulin was titrated to a fasting glucose of <100 mg/dL, but does not provide additional information as to how the patients were monitored. Thus, the superiority of dulaglutide over insulin glargine may be due, in part, to inadequate dosing in the insulin glargine group. Mean body weight decreased in patients taking dulaglutide 1.5 mg once weekly (-1.87 kg) and dulaglutide 0.75 mg once weekly (-1.33 kg), whereas mean body weight increased in patients assigned to insulin glargine (+1.44 kg). Both dulaglutide groups reportedly had a significantly higher incidence of nausea compared with the insulin glargine group, though the published abstract does not report the actual incidence. The incidence of

hypoglycemia was significantly higher for insulin glargine (7.9 events/patient/year) compared to dulaglutide 1.5 mg weekly (5.2 events/patient/year; p<0.05) and dulaglutide 0.75 mg weekly (4.8 events/patient/year; p<0.001).[6]

The AWARD-3 trial was a 52-week double-blind study comparing dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, and metformin 1500 to 2000 mg daily.[7] The study enrolled 807 patients that were previously inadequately treated with diet, exercise, and a suboptimal dose of one anti-diabetic agent. The primary endpoint was change in HbA1c from baseline at 26 weeks. The study included patients aged ≥18 years that had type 2 diabetes for a duration of 3 months to 5 years with an HbA1c between 6.5% and 9.5%. A greater reduction in HbA1c was observed in patients treated with dulaglutide 1.5 mg once weekly (-0.78%) and dulaglutide 0.75 mg once weekly (-0.71%) compared to patients treated with metformin (-0.56%; p<0.025). A decrease in body weight was observed in all three treatment arms: -2.29 kg for patients treated with dulaglutide 1.5 mg once weekly, -1.36 kg for dulaglutide 0.75 mg once weekly, and -2.22 kg for metformin.

The incidence of adverse effects was similar for the three treatment arms. The most common adverse effect was nausea, occurring in 19.7% of patients treated with dulaglutide 1.5 mg once weekly, 11.5% of patients treated with dulaglutide 0.75 mg once weekly, and 16.0% of metformin-treated patients. [7]

The AWARD-4 trial was a 52-week study also comparing dulaglutide to insulin glargine in patients treated with insulin lispro with or without metformin.[8] The primary outcome was reduction in HbA1c after 26 weeks. After a 9-week lead-in period where metformin was titrated to maximally tolerated doses, 884 patients were randomly assigned to dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or insulin glargine once daily. After 26 weeks, a greater reduction in HbA1c was observed in patients treated with dulaglutide 1.5 mg once weekly (-1.64%) and 0.75 mg once weekly (-1.59%), compared to patients treated with insulin glargine (-1.41%; p<0.025 for both comparisons).

The published AWARD-4 abstract states that insulin glargine was titrated according to a treat-to-target algorithm; however it does not include information regarding how patients were monitored or how closely this algorithm was adhered to. Thus, whether insulin dosing had any effect on the superiority of dulaglutide compared with insulin glargine in this study remains unknown. Change in weight was also significantly greater in patients taking insulin glargine (+2.89 kg), compared to those taking dulaglutide 1.5 mg once weekly (-0.35 kg) or dulaglutide 0.75 mg once weekly (+0.86 kg).[8] The incidence of nausea, diarrhea, and vomiting was greater in both dulaglutide groups compared to insulin glargine. Nausea occurred in 25.8% of patients treated with dulaglutide 1.5 mg once weekly, 17.7% of those treated with dulaglutide 0.75 mg once weekly, and 3.4% of those treated with insulin glargine. Diarrhea occurred in 16.6% of those treated with dulaglutide 1.5 mg once weekly, 15.7% of those treated with dulaglutide 0.75 mg once weekly, and 6.1% of those treated with insulin glargine. Vomiting occurred in 12.2% of patients treated with dulaglutide 1.5 mg once weekly, 10.6% of those treated with dulaglutide 0.75 mg once weekly, and 1.7% of those treated with insulin glargine. Hypoglycemia was more common with insulin glargine (39.9 events/patient/year) compared to dulaglutide 1.5 mg once weekly (31.0 events/patient/year) and dulaglutide 0.75 mg once weekly (35.0 events/patient/year).[8]

The safety and efficacy of dulaglutide was compared to sitagliptin in the 104-week placebo-controlled, double-blind AWARD-5 trial.[9] Enrolled patients were aged 18-75 years with type 2 diabetes for ≥6 months, an HbA1c of 8% to 9.5% if treated with diet and exercise alone or an HbA1c of 7% to 9.5% if on oral antidiabetic therapy, and had a BMI between 25 and 40 kg/m^2. A total of 972 patients were randomly assigned, in a 1:1:1 fashion to placebo, dulaglutide 0.75 mg once weekly, dulaglutide 1.5 mg once weekly, or sitagliptin 100 mg once daily. The study included an 11-week lead-in period in which patients were titrated to the maximum tolerated dose of metformin (minimum dose, 1500 mg per day). At 52 weeks post-randomization, HbA1c was reduced significantly more in patients treated with dulaglutide 0.75 mg once weekly (-0.87%) or 1.5 mg once weekly (-1.10%) compared to those treated with sitagliptin (-0.39%; p<0.001 for all comparisons). Weight reduction at 52 weeks was greater with dulaglutide 0.75 mg (-3.03 kg; p<0.001 for the comparison to sitagliptin) and dulaglutide 1.5 mg (-2.60 kg; p<0.001 for the comparison to sitagliptin) than with sitaglitpin (-1.53 kg). The incidence of any gastrointestinal adverse event was significantly greater in the dulaglutide 1.5 mg group (38%; p<0.001 for the comparison to sitagliptin) and the dulaglutide 0.75 mg group (32%; p<0.05 for the comparison to sitagliptin) compared to the sitagliptin group (18%).[9]

The AWARD-6 trial compared the safety and efficacy of dulaglutide 1.5 mg once weekly to liraglutide 1.8 mg once daily in a randomized, open-label, noninferiority study.[10] The study enrolled patients who were ≥18 years of age with type 2 diabetes, an HbA1c ≥7% and ≤10%, and a BMI <45 kg/m^2. All patients were also required to be on a stable dose of metformin (≥1500 mg per day) for at least 3 months. The primary outcome was change in HbA1c from baseline at 26 weeks. Both dulaglutide and liraglutide significantly reduced HbA1c (-1.42% and -1.36%, respectively), and dulaglutide 1.5 mg once weekly was shown to be noninferior to liraglutide 1.8 mg once daily (noninferiority p<0.0001). Though both treatment arms experienced weight loss, patients in the liraglutide lost significantly more weight (-3.61 kg for liraglutide vs -2.90 kg for dulaglutide; p=0.011). Adverse events were predominantly gastrointestinal in nature, with no difference in the incidence between groups.[10]

TABLE 1 | Pharmacokinetics of dulaglutide.[4]

Parameter	Dulaglutide 1.5 mg QW
Absolute Bioavailability	47%
C_{max}	114 ng/mL
AUC	14,000 ng*h/mL
Volume of Distribution	17.4 L
Metabolism	Protein catabolism to amino acid components
Clearance	0.107 L/h
Half-life	5 days

C_{max} = maximum concentration; **QW** = once weekly.

ADVERSE EVENTS & PRECAUTIONS

Adverse Effects

The most common adverse effects associated with dulaglutide are nausea, diarrhea, vomiting, abdominal pain, and decreased appetite. **Table 3** shows the frequency of these adverse effects when compared with placebo. Constipation, flatulence, abdominal distension, and gastroesophageal reflux disease have also been reported, though they occurred in <5% of dulaglutide-

Table 2 | Summary of clinical trials for dulaglutide.[5-10]

Study	Treatment Arms	Primary Endpoint	Results	Conclusions
AWARD-1[5]	Dulaglutide 1.5 mg (N=279) Dulaglutide 0.75 mg (N=280) Exenatide 10 mcg (N=276) Placebo (N=141)	Change in HbA1c from baseline at 26 weeks	Dulaglutide 1.5 mg: -1.51% Dulaglutide 0.75 mg: -1.30% Exenatide: -0.99% Placebo: -0.46%	Both doses of dulaglutide were superior to placebo and non-inferior to twice-daily exenatide
AWARD-2[6]	Dulaglutide 1.5 mg (N=273) Dulaglutide 0.75 mg (N=272) Insulin glargine (N=262)	Change in HbA1c from baseline at 52 weeks	Dulaglutide 1.5 mg: -1.08% Dulaglutide 0.75 mg: -0.76% Insulin glargine: -0.63%	Dulaglutide 1.5 mg superior to insulin glargine; dulaglutide 0.75 mg non-inferior to insulin glargine
AWARD-3[7]	Dulaglutide 1.5 mg (N=269) Dulaglutide 0.75 mg (N=270) Metformin (N=268)	Change in HbA1c from baseline at 26 weeks	Dulaglutide 1.5 mg: -0.78% Dulaglutide 0.75 mg: -0.71% Metformin: -0.56%	Dulaglutide 1.5 mg was superior to metformin; dulaglutide 0.75 mg was noninferior to metformin
AWARD-4[8]	Dulaglutide 1.5 mg (N=295) Dulaglutide 0.75 mg (N=293) Insulin glargine (N=296)	Change in HbA1c from baseline at 26 weeks	Dulaglutide 1.5 mg: -1.64% Dulaglutide 0.75 mg: -1.59% Insulin glargine: -1.41%	Both doses of dulaglutide were superior to insulin glargine
AWARD-5[9]	Dulaglutide 1.5 mg (N=304) Dulaglutide 0.75 mg (N=302) Sitagliptin (N=315)	Change in HbA1c from baseline at 52 weeks	Dulaglutide 1.5 mg: -1.10% Dulaglutide 0.75 mg: -0.87% Sitagliptin: -0.39%	Both doses of dulaglutide were superior to sitagliptin
AWARD-6[10]	Dulaglutide 1.5 mg (N=299) Liraglutide 1.8 mg (N=300)	Change in HbA1c from baseline at 26 weeks	Dulaglutide 1.5 mg: -1.42% Liraglutide 1.8 mg: -1.36%	Dulaglutide 1.5 mg once weekly was noninferior to liraglutide 1.8 mg once daily

treated patients in placebo-controlled trials. Dulaglutide may increase the risk of hypoglycemia, especially when used in combination with insulin or a sulfonylurea. Dulaglutide may also cause injection site reactions, including rash and erythema.[4]

Precautions

Dulaglutide is classified as Pregnancy Category C and should only be used during pregnancy if the potential benefits outweigh the potential risks. When studied in rats, clinically relevant doses of dulaglutide resulted in an increase in the incidence of thyroid C-cell tumors. However, whether the same effect occurs in humans is not known. Dulaglutide should not be used in patients with a history of pancreatitis, and patients should be monitored for signs and symptoms of pancreatitis. Severe gastrointestinal adverse effects have been associated with dulaglutide, therefore its use is not recommended in patients with a history of severe gastrointestinal disease, such as severe gastroparesis.[4]

Dosing & Administration

Dulaglutide is administered as a once weekly subcutaneous injection and is available in 0.75-mg and 1.5-mg doses. The initial dose for dulaglutide in treatment-naïve patients is 0.75 mg once weekly, which may be increased to 1.5 mg once weekly if the glycemic response is inadequate. Dulaglutide should be injected subcutaneously in the abdomen, thigh, or upper arm, and it can be administered at any time of day without regard to meals. If a dose is missed, patients should administer the medication as soon as possible, unless there are fewer than 3 days before the next scheduled dose. If fewer than 3 days remain before the next scheduled dose, the missed dose should be skipped and the normal weekly dosing schedule should be resumed. No dose adjustment recommendations are available for patients with renal impairment or end-stage renal disease. Due to an increased risk for hypoglyce-

Table 3 | Adverse effects reported in ≥5% of dulaglutide-treated patients in placebo-controlled trials.[4]

Adverse Effect	Dulaglutide 0.75 mg QW (N=836)	Dulaglutide 1.5 mg QW (N=834)	Placebo (N=568)
Nausea	12.4%	21.1%	5.3%
Diarrhea	8.9%	12.6%	6.7%
Vomiting	6.0%	12.7%	2.3%
Abdominal Pain	6.5%	9.4%	4.9%
Decreased Appetite	4.9%	8.6%	1.6%

QW = once weekly.

Table 4 | Comparison of available GLP-1 receptor agonists.

Drug	Half-life	Dosing Frequency	Cost[a]
Dulaglutide (Trulicity®)	5 days	Weekly	$586.00
Albiglutide (Tanzeum®)	3-5 days	Weekly	$391.16
Exenatide (Byetta®)	2.4 hours	Twice daily	$574.01
Exenatide (Bydureon®)	2 weeks	Weekly	$570.32
Liraglutide(Victoza®)	13 hours	Once daily	$470.88

[a]Cost represents monthly average wholesale price; data are from Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: http://online.lexi.com. Accessed January 30, 2015.

mia, the dulaglutide dose may need to be reduced when administered concomitantly with sulfonylureas or insulin.[4]

Comparison of GLP-1 Agonists

Four GLP-1 receptor agonists are now available following the introduction of dulagtlutide. Although they all share the same mechanism of action, they differ in half-life, dosing frequency, efficacy, tolerability, and cost. Table 4 provides a comparison of the available GLP-1 receptor agonists. As a class, GLP-1 receptor agonists have proven to lower HbA1c and reduce weight, with a limited risk of hypoglycemia. While no trial has compared all four of the GLP-1 receptor agonists in head-to-head fashion, the AWARD trials have shown that dulaglutide is as effective or better at lowering HbA1c than exenatide twice daily and liraglutide once daily. Data also suggest that once-weekly formulations have fewer gastrointestinal adverse effects than those that are dosed daily or twice daily.[3]

Summary

Dulaglutide is the newest GLP-1 receptor agonist approved for the treatment of type 2 diabetes. Evidence suggests that dulaglutide is more effective than twice-daily exenatide and as effective as once-weekly liraglutide. Dulaglutide use resulted in a greater reduction in HbA1c when compared with sitagliptin and insulin glargine. However, specifics as to how insulin glargine was administered in AWARD-2 and AWARD-4 are yet to be published in peer-review journal format. Data also suggest that dulaglutide is at least as effective as metformin at lowering HbA1c. Dulaglutide is administered once weekly at a dose of 0.75 mg or 1.5 mg. Like other approved GLP-1 agonists, gastrointestinal adverse effects are common with dulaglutide. Dulaglutide should not be used in pregnancy, those with a history of thyroid cancer, or those with a history of pancreatitis. Additional research is needed to determine the exact role of dulaglutide versus other available GLP-1 receptor agonists in the first-line treatment of type 2 diabetes.

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