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THE ROLE OF EXENATIDE IN DIABETES: A FOCUS ON BYDUREON®

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In 2010 26 million people in the United States had diabetes, or roughly 8.3% of the U.S. population.[1] Of the 18.8 million who were diagnosed, only 84% were being treated with oral medications or insulin.[1]

The current standard of treatment for patients diagnosed with Type 2 diabetes mellitus (DM) is diet and exercise plus metformin (MET).[2] If monotherapy is not able to reach or maintain the American Diabetic Association (ADA) hemoglobin A1c (HbA1c) goal of <7% for most non-pregnant adults, then addition of a second or third agent is recommended. Second line therapy can include MET plus a sulfonylurea (SU), or MET plus insulin.[2] If dual therapy plus lifestyle changes are still not reaching the goal HbA1c, additional classes of anti-diabetic agents can be added, such as thiazolidinediones (TZD), meglitinides, glucagon-like peptide-1 (GLP-1) agonists, or dipeptidyl peptidase-4 (DPP-IV) inhibitors.

GLP-1 agonists have been on the market since 2005 when Amylin Pharmaceuticals released exenatide immediate release (ExIR) injection, marketed as Byetta®.[3] Following Byetta®, in January 2010 the FDA approved Novo Nordisk's liraglutide (Victoza®), a GLP-1 agonist that only needs to be injected once daily.[4] Most recently in February 2012, the FDA approved exenatide extended-release (ExER) (Bydureon®), a once weekly injection. Bydureon® is also made by Amylin Pharmaceuticals and is indicated for adjunct treatment in adult patients with Type 2 DM who are not controlled with lifestyle modifications. ExER is a long acting form of ExIR, and therefore the two should not be used in conjunction.[5]

The objective of this article is to review the use of exenatide in the management of Type 2 DM, focusing on the pharmacology, clinical trials, dose, safety and cost of ExER.

Pharmacology and Pharmacokinetics

Pharmacology

Incretins are gastrointestinal hormones that increase the amount of insulin released by the pancreas. Glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) are the two endogenous incretins. Exenatide is classified as a GLP-1 agonist, mimicking the effects of endogenous GLP-1 by binding to the GLP-1 receptor in the pancreas. Binding to this receptor stimulates the adenylyl cyclase pathway, which increases insulin secretion. Exenatide enhances the secretion of insulin in the presence of glucose, suppresses glucagon secretion, slows gastric emptying, and reduces food intake.[2,6] Other advantages that have been attributed to exenatide include promoting B- cell proliferation and weight loss.[2]

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Pharmacokinetics

ExER is injected subcutaneously (SC) once weekly compared to ExIR, which is injected SC twice daily. A difference in formulation gives the two drugs different rates of absorption (**Table 1**). A polymer-based microsphere is used to store and release the exenatide in ExER over the course of 10 weeks.[7] Initially, after injection of ExER, exenatide that is surface-bound to the microsphere is released. Then, over 10 weeks, the exenatide is released from the microsphere, with concentrations peaking twice in the body. The first peak occurs at week two, and the second occurs at weeks 6 to 7 when steady state levels are achieved. [7] In a study assessing the pharmacokinetics and pharmacodynamics of ExER, 2 mg administered once weekly achieved steady state concentrations within the 10th to 90th percentile range maximum plasma concentration (Cmax) that is observed when administering ExIR twice daily.[8] Since ExER is released over the course of 10 weeks, once a patient is stopped on the drug it can take 10 weeks for drug levels to fall below the minimum detectable concentration of 10pg/ml.[6] With ExIR, the maximum concentration of the drug is reached approximately 2.1 hours after SC administration.[9]

Clinical Trials

The safety and efficacy of ExER has been assessed in the DURATION trials (**Table 2**). Two of these trials compared ExER to ExIR while the rest compared ExER to other anti-diabetes therapies.

ExER and ExIR were compared in a 30 week, randomized, open-label, comparator-controlled multicenter study called the DURATION-1 trial.[10] Patients with type 2 DM (n=295) on no therapy or on one or more oral anti-diabetic agents were randomized to receive ExER 2 mg each week or ExIR 10 mcg twice daily. They primary endpoint of the trial was the change in HbA1c at 30 weeks. Patients in the ExER group had a greater mean reduction compared to subjects receiving ExIR at 30 weeks (-1.9% versus -1.5%, respectively, p=0.0023).[10] ExER also had a significantly greater reduction in fasting blood glucose (FBG) compared to ExIR (p<0.0001) at 30 weeks. Subjects in both treatment groups showed similar decreases in bodyweight over the course of the trial (Table 2).[10]

Table 1 | Pharmacokinetics of Exenatide [6,9]

Property	Data
Bioavailability	65-76%
Time to Peak Concentration	**Extended Release:** *Initial peak*= 2 weeks; *second peak*= 6-7 weeks (steady state) **Immediate Release:** 2.1 hours
Half life	2.4 hours
Volume of distribution	Subcutaneous 28.3 L
Excretion	Renal clearance. Primarily glomerular filtration, with proteolytic degradation.

After 30 weeks of treatment, some patients were switched from ExIR 10 mcg BID to ExER 2 mg once weekly for an additional 22 weeks. Patients who were switched to ExER, and those who continued ExER, showed further improvements in their HbA1c and FBG levels.[11]

The DURATION-3 trial was a 26 week, randomized, open label study conducted to compare ExER to insulin glargine.[12] It included 456 patients with type 2 DM who were previously uncontrolled on MET or MET and a SU for at least 3 months prior, and had been on a stable dose of the medication for at least 8 weeks. The subjects were randomized based on their country of origin and previous oral anti-diabetic regimen to receive either 2 mg ExER once weekly or insulin glargine started at 10 units/dose. Over 26 weeks, the insulin glargine was adjusted as needed to achieve a glucose range of 4.0-5.5 mmol/L (72-99 mg/dl). The primary endpoint was reduction of HbA1c from baseline. Secondary endpoints included FBG levels, proportion of patients who achieved HbA1c < 7%, and average change in bodyweight from baseline. At 26 weeks, patients in the ExER group had an average mean reduction in HbA1c of 1.5%. Patients who received insulin glargine had a significantly lower average mean reduction in HbA1c of 1.3% compared to ExER (p=0.017). Patients in the insulin glargine group had significantly greater reductions in mean FBG levels than patients in the ExER group (p=0.001). Results of secondary outcomes are listed in Table 2.[12]

The DURATION-5 trial compared ExER to ExIR in a 24 week, randomized, open-label, comparator-controlled study.[13] The study enrolled 252 type 2 DM patients with uncontrolled blood glucose levels. Patients had to be on diet and exercise alone or any combination of MET, SU, or TZD for at least 2 months prior to the study. Subjects were randomized to receive either ExER 2 mg SC once weekly or ExIR (5 mcg SC twice daily titrated after 4 weeks to 10 mcg SC twice daily for 20 weeks). The primary endpoint of the trial was the change in HbA1c from baseline at week 24. ExER lowered the HbA1c by an average of 1.6% compared to ExIR, which lowered the HbA1c by an average of 0.6% (p<0.0001). Fasting blood glucose levels were analyzed as a secondary endpoint. Patients who received ExER had a significantly greater decrease in FBG than patients who received ExIR (p=0.0008) (Table 2). Change in bodyweight from baseline and proportion of patients achieving HbA1c < 7%were al-

Table 2 | Clinical Trials for Extended Release Exenatide [10-16]

Trial	Design	Patients	Intervention	Reduction HbA1c	Other Results
DURATION-1[10]	30-week, R, OL, MC, CC	Type 2 DM treated with diet/exercise and/or MET, SU, and TZDs for at least 2 months	ExER 2 mg QWk vs. ExIR 10 µg BID	Red. HbA1c at 30 wks: ExER:-1.9% ExIR: -1.5% (p=0.0023)	Red. Wt at 30 wks: ExER: -3.6% ExIR: -3.7% (p>0.05) Red. FBG: ExER: -2.3 mmol/L (41.4mg/dl) ExIR: -1.4 mmol/L (25.2 mg/dl) (p<0.0001)
DURATION-2[15]	26-week, DB, R, MC, Superiority	Type 2 DM treated with MET for at least 2 mo.	ExER 2 mg QWk + oral placebo QD; 100 mg po Sit QD+ injected placebo QWk; or 45 mg po Pio QD+ injected pl QW	ExER: -1.5% Sit: -0.9% (p<0.001) Pio: -1.2% (p=0.0165)	Red. Wt: ExER: -2.3 kg Sit: -0.8 kg (p=0.0002) Pio: -2.8 kg (p<0.0001) Red. FBG: ExER: -1.8mmol/L (32.4mg/dl) Sit: -0.9 mmol/L (16.2mg/dl) (p=0.0038) Pio: -1.5 mmol/L (27 mg/dl) (p=0.3729)
DURATION-3[12]	26-week, R, OL	Type 2 DM, MET and/or SU for 3 mo. and on stable dose for 8 weeks prior	ExER 2mg injected QWk vs. InG, initially 10 IU QD	ExER: -1.5%, InG: -1.3%, (p=0.017)	Red. Wt: ExER: -2.6kg InG: +1.4 kg (p<0.0001) Red. FBG: ExER: -2.1 mmol/L (37.8mg/dl) InG : -2.8 mmol/L (50.4mg/dl) (p=0.001) Proportion HbA1c<7%: ExER: 60% InG:48% (p=0.010)
DURATION-4	26-week, DB, R	Type 2 DM not controlled with diet/ exercise. No OAMs.	ExER 2mg QWk vs. Sit 100mg/day + SC pl vs. Pio 45mg QD+ SC pl vs. metformin 2,000mg QD + SC pl	ExER= -1.53% Sit= -1.15% (p<0.001) MET=-1.48% (p=0.620) Pio= -1.63% (p=0.328)	Red. Wt: ExER=-2 kg Sit= -0.8kg (p<0.001) MET= -2kg (p=0.892) Pio= +1.5kg (p<0.001)
DURATION-5	24-week, R, OL, MC, CC	Type 2 DM treated with diet/exercise alone or in any combination with metformin, SU, TZD for at least 2 months.	ExER 2 mg QWk vs. ExIR 5 µg (4wks) and 10 µg (20 wks) BID	ExER: -1.6% ExIR: -0.9% (p<0.0001)	Red. FBG: ExER: -35mg/dl (1.94 mmol/L) ExIR: -12 mg/dl (0.67mmol/L) (p<0.0008) Red. Wt: ExER: -2.3 kg ExIR: -1.4 kg (p<0.05) Proportion HbA1c <7%: ExER: 58.1% ExIR: 30.1% (p<0.0.0001)
DURATION-6	26-week, OL, MC, NI trial	Type 2 DM treated with diet/exercise and OAMs	ExER 2 mg QWk vs. Lira 1.8 mg QD	ExER= -1.28% Lira= -1.48% (95% CI: 0.08-0.34)	GI AEs: ExER: N= 9.3 %, V= 3.7%, D= 6.1% Lira: N=20.4%, V=10.7%, D= 13.1% Hypoglycemia: ExER: 10.8% Lira: 8.9% (p=0.374)

Abbreviations: AEs: adverse effects; BID: twice daily; CC: comparator controlled; D: diarrhea; DM: diabetes mellitus; ExER: exenatide extended-release; ExIR: exenatide immediate-release; InG: Insulin glargine; Lira: Liraglutide; MC: multicenter; N:nausea; NI: non-inferiority; OAMs: oral antihyperglycemic medications; OL: open-label; Pio: pioglitazone; pl: placebo; QD: once daily; QWk: once weekly; R: randomized; Red.: reduction; Sit: sitagliptin; SU: sulfonylurea; TZD: thiazolidinediones; V: vomiting; WL: weight loss

so analyzed as secondary endpoints (Table 2).[13]

ExER and liraglutide were compared in the DURATION-6 trial. Results were reported in an abstract reported at the 47th annual meeting of the European Association for the Study of Diabetes, published in Diabetologia in 2011.[14] The trial was a head to head, non-inferiority, open-label, 26 week trial comparing the average reduction in HbA1c between ExER and liraglutide. The trial enrolled 912 subjects with type 2 DM who were previously uncontrolled with diet and exercise, MET, a SU, MET plus a SU, or MET plus pioglitazone. Patients were randomized to receive either ExER 2 mg once weekly or liraglutide 1.8 mg daily. The primary endpoint was reduction in HbA1c from baseline between treatment groups. Patients who received ExER had an average HbA1c reduction of 1.28% compared to 1.48% in the liraglutide group (95% CI: 0.08-0.34). Since the upper limit of the confidence interval was >0.25% for the difference in baseline HbA1c between ExER and liraglutide, it could not be concluded that ExER was non-inferior to liraglutide. However, subjects in the ExER group experienced fewer side effects including nausea, vomiting, and diarrhea than subjects in the liraglutide group. Both groups had similar rates of hypoglycemia over the 26 weeks (Table 2).[14]

Adverse Effects

ExER has generally been well tolerated with few hypoglycemic events.[6] Compared to MET, sitagliptin (Sit), and pioglitazone (Pio) in the DURATION-4 study, ExER had a 2.0% incidence of minor hypoglycemia, while the other groups had no hypoglycemic events.[16] In the DURATION-3 trial, in the group that received concomitant SU, the patients in the ExER group had a greater (20%) incidence of minor hypoglycemia compared to those who received insulin glargine (43.9%).[12] In the DURATION-5 trial, patients who received ExER with a SU had a 12.5% incidence, which was similar to the patients receiving ExIR 10 mcg (11.8%).[13]

Compared to ExIR 10 mcg twice daily in the DURATION-1 trial, subjects who received ExER 2 mg weekly experienced less nausea and vomiting at 30 weeks (**Table 3**). However, diarrhea and injection site pruritis were more common in the subjects receiving ExER.[6,10] The most common adverse effects experienced by patients in the DURATION trials were nausea, vomiting, diarrhea and injection site reactions.

ExER has a black box warning for a risk of thyroid c-cell tumors. The drug is contraindicated in patients with a family or a personal history of Medullary Thyroid Carcinoma (MTC) or Multiple Endocrine Neoplasia Syndrome Type 2 (MEN2). An increased incidence of thyroid c-cell tumors was found in rats that received the ExER compared to placebo. The increased risk of thyroid c-cell tumors has not yet been established in humans.[6]

Pancreatitis risk is another concern with ExER. Severe abdominal pain that radiates to the back is the hallmark symptom of pancreatitis. ExER should be discontinued if the patient experiences severe abdominal pain. In the DURATION-1 trial, at 52 weeks, no cases of pancreatitis were reported in patients receiving ExER or ExIR.[11]

Administration

ExIR (Byetta®) is given as twice daily SC injections in either 5 mcg or 10 mcg doses.[9]

ExER has a fixed dose of 2 mg SC once every 7 days. The use of ExER has not yet been studied in pre-diabetics or in patients with renal impairment or hepatic impairment. An advantage of ExER compared to ExIR is that it can be taken without regard to meals. Bydureon® is supplied in a package containing four trays. Each tray contains the supplies needed for a single injection. The supplies in one tray include: 2 mg exenatide powder, syringe filled with diluent, vial connector, and two needles.[6]

Table 3 | DURATION-1 Trial Adverse Effects at 30 weeks [6]

Side Effect	Bydureon 2 mg (%)	Byetta 10 mcg (%)
Nausea	27.0	33.8
Diarrhea	16.2	12.4
Vomiting	10.8	18.6
Injection Site Pruritus	18.2	1.4
Constipation	10.1	6.2
Gastroenteritis viral	8.8	5.5
Gastroesophageal reflux disease	7.4	4.1
Dyspepsia	7.4	2.1
Injection site erythema	7.4	0.0
Fatigue	6.1	3.4
Headache	6.1	4.8
Injection site hematoma	5.4	11.0

Data obtained from Bydureon Package insert. Incidence rates differed from DURATION-1 trial.

Cost

The mean retail price from an informal survey of three different retail pharmacies for a single dose (one week supply) of ExER is $103.84, ranging from $94.52 to $112.00. From this data, the estimated yearly cost of ExER is $4,984.44, assuming that the patient takes one injection every 7 days.

Summary

ExER (Bydureon®) is a new GLP-1 agonist that is approved by the FDA for the management of Type 2 DM not controlled with diet and exercise. ExER is available by prescription only in a single 2 mg dose that is injected SC once every seven days. ExER is non-inferior to ExIR (Byetta®), oral regimens, and insulin glargine for glycemic control based on the DURATION trials[10-13,15,16]; it appears to be less effective than liraglutide.[14] Compared to ExIR, ExER is associated with less nausea and vomiting and little to no hypoglycemic events.[6,10] Future trials mandated by the FDA will assess the potential risk of thyroid c-cell tumors, pancreatitis, and cardiovascular events in diabetic patients.

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Clinical Trial Update

Diagnosis and Treatment of Acute and Chronic Heart Failure—2012 European Society of Cardiology (ESC) Guidelines[1] — May 2012: New heart failure guidelines were published online in European Heart Journal updating the 2008 version. Notable differences exist in the 2012 update, many of which can have a significant impact on outpatient clinical practice. However, as the guidelines are produced with European patients in mind, the recommendations may not be generalizable to all patient populations in the United States, and caution should be used when in-

terpreting and implementing the recommendations provided by the ESC Guidelines.

Diagnosis and Classification

The recommendations surrounding the diagnosis of heart failure (HF) remain largely unchanged from previous versions: careful physical exam and a thorough patient history is indicated to evaluate and identify common HF signs and symptoms. Laboratory work-up includes obtaining and interpreting an electrocardiogram and echocardiogram, both of which are considered essential investigations in patients with suspected HF as the results will be used to guide future therapy. Laboratory tests such as natriuretic peptides (i.e. BNP, NT-proBNP) can be used in cases where echocardiography is not available to diagnose HF as a normal natriuretic peptide level has a high specificity for ruling out HF. Other laboratory tests such as blood chemistry, thyroid function tests, and chest x-rays should likely be considered in all patients. Exercise testing, cardiac magnetic resonance imaging, coronary angiography, and right and/or left heart catheterization can be utilized in select patients.

The New York Heart Association functional class system (NYHA) is still recommended to quantify symptom severity in patients with HF. Notably the American College of Cardiology/American Heart Association (ACC/AHA) Staging System is not endorsed by the ESC Guidelines.

Chronic Treatment Recommendations

Chronic therapy of HF is heavily based on the results of the echocardiography exam as patients with a reduced EF (EF < 40%) have more evidence supporting treatment recommendations compared to those with a preserved EF (EF > 50%).

For those with reduced EF a beta-blocker plus an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) is still recommended for all patients (Class I, Level A) due to substantial evidence supporting a reduction in morbidity and mortality. However, in patients with preserved EF these therapies have not been shown to consistently reduce morbidity and mortality; treatment of these patients focuses on control of risk factors or comorbidities which may worsen HF, such as hypertension and coronary artery disease among many others.

Perhaps the most notable difference in the 2012 update surrounds the use of mineralocorticoid receptor antagonists (MRAs) such as spironolactone (Aldactone®) and eplerenone (Inspra®). Previous guidelines recommended their use in very select patient populations but based on the results of recent trials the ESC Guidelines now recommend using an MRA in all patients with an EF ≤ 35% who have persistent HF symptoms (NHYA class II-IV symptoms) despite optimal therapy with a beta-blocker and ACEi or ARB (if an ACEi is not tolerated) to reduce the risk of HF hospitalization and risk of premature death (Class I, Level A). MRAs can increase the risk for hyperkalemia, especially when combined with ACEi/ARBs, so caution and frequent laboratory monitoring is indicated.

Ivabradine, a novel agent to reduce heart rate, is also recommended in the ESC Guidelines for patients with an EF ≤ 35%, a heart rate remaining > 70 bpm, and NYHA Class II-IV symptoms despite optimal treatment with a beta-blocker, ACEi/ARB, and MRA. Ivabradine is not currently available in the US but may become available in the near future.

Overall the treatment recommendations are consistent with previous versions with the exception of the expanded role of MRAs in the treatment of HF with reduced HF. Ivabradine is a novel agent that may become part of the HF armamentarium in the near future for patients on optimal background therapy who remain symptomatic.

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