Brand Name: Bydureon

Generic Name: Exenatide extended-release (ER)

Manufacturer: Amylin Pharmaceuticals

Drug Class [1,2,3,4,5]**:** Antidiabetic; glucagon-like peptide-1 (GLP-1) receptor agonist

Uses:

Labeled Uses[1,2,3,4, 5]: Treatment of type 2 diabetes mellitus (noninsulin dependent DM) to improve glycemic control. Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Exenatide extended-release is not recommended as first-line therapy. Concomitant use with insulin is not recommended.

Unlabeled Uses[1]: No current unlabeled use

Mechanism of Action:[1,2,3,4,]:

Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. Exenatide extended-release is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, slows gastric emptying, reduces food intake, and promotes β-cell proliferation. Exenatide acutely improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes. Exenatide leads to a release of insulin only in the presence of elevated glucose concentrations. Insulin secretion subsides as euglycemia occurs. First-phase insulin response (release of insulin within 10 minutes following a glucose load) is lost in patients with type 2 diabetes. Loss of first-phase response is a beta cell defect. Exenatide restores first-phase insulin response to an IV bolus of glucose. Exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. Exenatide does not impair the normal glucagon response to hypoglycemia. Exenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

Exenatide extended release provides a controlled release of exenatide through Medisorb® biodegradable microspheres. In this technology, exenatide is encapsulated in microspheres made of a medical-grade polymer called polylactide co-glycolide (PLG). Each microsphere is roughly the same diameter of a human hair. After injection, the microspheres immediately absorb water, leading to swelling of the microsphere. This process begins a phase where a small amount of exenatide at or near the surface of the microspheres is released. Over time water slowly breaks down the polymer structure allowing exenatide release, resulting in sustained release of medication. The polymer matric is then eliminated from the body as carbon dioxide and water.

Pharmacokinetics:

Absorption:

T_{max}	SubQ: initial peak - 2 weeks; second peak - 6 to 7 weeks [1,2,3,4]
V_d	23.8 L[1,2,3,4]
$t_{½}$	2 weeks[1,2,3,4]
Clearance	10 weeks[1,2,3,4]
Protein binding	No data reported [1,2,3,4]
Bioavailability	65% to 76% (animal data)[1]

Metabolism: Exenatide is metabolized by proteolytic degradation by dipeptidyl peptidase IV. Animal studies have demonstrated much greater resistance of exenatide to degradation by dipeptidyl peptidase IV compared to GLP-1. This difference may be related to the presence of a glycine moiety at position 2 of exenatide; GLP-1 has an alanine in this position, which is recognized by dipeptidyl peptidase IV.

Elimination: Exenatide is predominantly eliminated by the kidney through glomerular filtration.

Efficacy:

Best, J. H., R. R. Rubin, M. Peyrot, Y. Li, P. Yan, J. Malloy, and L. P. Garrison. "Weight-Related Quality of Life, Health Utility, Psychological Well-Being, and Satisfaction With Exenatide Once Weekly Compared With Sitagliptin or Pioglitazone After 26 Weeks of Treatment." ***Diabetes Care*** **34.2 (2011): 314-19. Print.**

Study Design: randomized, double blind, double-dummy, multicenter clinical trial.

Description of Study: *Methods* **-** This study was designed to assess the clinical outcomes, patient reported outcomes, and safety after 26 weeks of treatment with exenatide once weekly compared with maximum approved doses of sitagliptin or pioglitazone in patients with type 2 diabetes currently treated with metformin. Patients were randomized into one of 3 groups: (1) exenatide 2mg injection weekly + placebo capsule. (2) sitagliptin 100mg daily + placebo injection weekly. (3) pioglitazone 45 mg daily + placebo injection weekly. Weight-related quality of life, health utility, psychological well-being, and diabetes treatment satisfaction were assessed at baseline and week 26. Mean group changes from baseline to week 26 were estimated by ANCOVA. *Results* - Weight-related quality of life total scores improved significantly in the exenatide once weekly and sitagliptin arms only; the exenatide once weekly group experienced significantly greater improvement than the pioglitazone group in weight-related quality of life total scores and in several domain scores (See table 2 in study). Health utility scores improved significantly for exenatide once weekly and sitagliptin groups ($P > 0.05$) with no significant difference between the exenatide once weekly

group and the pioglitazone group. All groups experienced significant improvements on the psychological well-being global scale and all six domain scores, with no significant difference between the exenatide once weekly group and either comparator. All groups experienced significant improvements in total diabetes treatment satisfaction scores. The exenatide once weekly group experienced greater improvement than the sitagliptin group in treatment satisfaction total scores.

Limitations: The authors of this study are employees and stock holders of Amylin Pharmaceuticals, which is the manufacturer of exenatide extended-release®. All groups in this study received some sort of anti-diabetic therapy. Patients in all study groups reported increased treatment satisfaction despite receiving self-administered injections. Increased patient reported outcome (PRO) scores in the once weekly injection group could be masked by increased glucose control despite having to inject themselves less often than the other groups. In addition, this study cannot be used to determine if exenatide once weekly results in improved glucose control and increased quality of life (QOL) in patients who are not taking metformin. In addition, it was not known whether participants of this study were taking sulfonylureas or insulin, therefore the results of this study cannot be used to determine if exenatide once weekly results in improved glucose control or QOL in patients taking these medications. This study can only be used in patients taking metformin + exenatide extended-release, pioglitazone + exenatide extended-release, or sitagliptin + exenatide extended-release.

Conclusion: The results of this study indicate that it is possible for patients taking metformin to see improved glucose control and QOL with Exenatide extended-release. This study also indicates that Exenatide extended-release can improve patient reported outcomes and quality of life. Other studies comparing Exenatide extended-release with other antidiabeteic medications and diabetic treatment regimens need to be consulted in conjunction with the results of this study before a decision can be made whether to start a patient on Exenatide extended-release therapy.

Bergenstal R.M., Wysham C., MacConell L., Malloy J., Walsh B., Yan P., Wilhelm K., Porter L.E. "Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomized trial." (2010) The Lancet, 376 (9739), pp. 431-439

Study Design: Randomized, double-blind, double-dummy, multi-centered, superiority trial

Description of Study: *Methods* – In this study, 170 patients were assigned to receive once weekly exenatide, 172 to receive sitagliptin, and 172 to receive pioglitazone. 491 patients received at least one dose of study drug and were included in the intention-to-treat analysis (160 on exenatide, 166 on sitagliptin, and 165 on pioglitazone). Primary endpoint was change in HbA1c between baseline and week 26. Eligible patients were at least 18 years old, had type 2 DM but were otherwise healthy, had been treated with stable metformin therapy for at least 2 months before this study, HbA_{1c} of 7.1-11% and BMI of 25-45kg/m^2. Pregnant women were excluded.

Results - Treatment with exenatide reduced HbA1c (least square mean –1·5%, 95% CI –1.7 to –1.4) significantly more than did sitagliptin (–0.9%, –1.1 to –0.7) or pioglitazone (–1·2%, –1·4 to –1·0). Treatment differences were –0·6% (95% CI –0·9 to –0·4, p<0·0001) for exenatide versus sitagliptin, and–0·3% (–0·6 to –0·1, p=0·0165) for exenatide versus pioglitazone. All treatments improved fasting plasma glucose; exenatide once weekly resulted in a significantly greater reduction (–1·8 mmol/L, 95% CI –2·2 to –1·3) than did sitagliptin (–0·9 mmol/L, –1·3 to –0·5), but not pioglitazone (–1·5 mmol/L, –1·9 to –1·1; Weight loss with exenatide (–2·3 kg, 95% CI–2·9 to –1·7) was significantly greater than with sitagliptin (difference –1·5 kg, 95% CI –2·4 to –0·7, p=0·0002) or pioglitazone (difference –5·1 kg, –5·9 to –4·3, p<0·0001). No episodes of major hypoglycemia occurred. The most frequent adverse events with exenatide and sitagliptin were nausea (n=38, 24%, and n=16, 10%, respectively) and diarrhea (n=29, 18%, and n=16, 10%, respectively); upper-respiratory-tract infection (n=17, 10%) and peripheral edema (n=13, 8%) were the most frequent events with pioglitazone.

Limitations: A key limitations to this study is that Amylin Pharmaceuticals and Eli Lilly participated in the study design, study conduct, and data collection, and assisted the authors in data analysis and interpretation of the results and in preparation and review of the report. The drug companies, however, were not involved in the randomizations of subjects into groups. Another limitation is that there were more dropouts in the exenatide once weekly group, which resulted in less patients in this group compared to others. Exenatide once weekly had the most patients lost due to adverse reactions. This study is also limited by the fact that other classes of drugs used as adjuvant treatment in type 2 diabetes were not studied, such as basal insulin and sulfonylureas. This study also did not compare exenatide to liraglutide, which is a GLP-1 analog. Assessment of intermediate outcome markers such as, HbA1c, bodyweight, blood pressure, and fasting lipid profile, rather than long-term outcomes, such as mortality and cardiovascular disease, is also a limitation.

Conclusion: This study showed that Exenatide extended-release is superior to sitagliptin at decreasing HbA_{1c} and improving fasting glucose in patients with type 2 diabetes. This study also showed that exenatide extended release is superior to pioglitazone at decreasing HbA_{1c} in patients who have HbA_{1c} above 9%. Exenatide once weekly did not result in improved fasting plasma glucose compared to pioglitazone. Based on this study, Exenatide extended-release might be beneficial adjuvant therapy to metformin in patients with type 2 diabetes who are not achieving glucose and HbA_{1c} targets. Other studies should be consulted to determine if Exenatide extended-release is superior to basal insulin, sulfonylureas, or liraglutide.

Diamant, Michaela, Luc Van Gaal, Stephen Stranks, Justin Northrup, Dachuang Cao, Kristin Taylor, and Michael Trautmann. "Once Weekly Exenatide Compared with Insulin Glargine Titrated to Target in Patients with Type 2 Diabetes (DURATION-3): An Open-label Randomised Trial." The Lancet 375.9733 (2010): 2234-243. Print

Study Design: open-label, randomized, parallel study

Description of Study: *Methods* - This 26-week study compared exenatide with insulin glargine in adults with type 2 diabetes who were not achieving glycemic control with maximum doses of blood-glucose lowering drugs for 3 months or longer. 456 patients were randomly assigned to add exenatide 2 mg once-a-week injection or insulin glargine once-daily injection to their blood glucose-lowering regimens. Randomization was done with a one-to-one allocation and block size four, stratified according to country and concomitant treatment (70% metformin only; 30% metformin plus sulphonylurea). The primary endpoint was change in HbA1c from baseline. Secondary endpoints were achieving HbA1c targets, fasting glucose levels, target body weight, and results from five health outcomes questionnaires. Eligible patients with type 2 diabetes were 18 years or older, not achieving glycemic control with maximum doses of metformin or combinated metformin and sulphonylurea treatment, HbA1c concentration between 7.1% and 11.0%, and BMI between 25 - 45 kg/m2. Participants must have been treated with a stable dose of metformin 1500 mg or more per day for 8 or more weeks before screening. Exclusion criteria included: glucocorticoids use within past 4 weeks, treatment for longer than 2 weeks with insulin, thiazolidinediones, α-glucosidase inhibitors, meglitinides, exenatide twice-a-day formulation, DPP-4 inhibitors, or pramlintide. *Results* – Change in HbA1c at 26 weeks was greater in patients taking exenatide (n=228; –1.5%, SE 0.05) than in those taking insulin glargine (n=220; –1.3%, 0.06; treatment difference –0.16%, 0.07, 95% CI –0.29 to –0.03). 12 (5%) of 233 patients allocated to exenatide and two (1%) of 223 taking insulin glargine discontinued participation because of adverse events (p=0·012).

Limitations: Amylin Pharmaceuticals and Eli Lilly were involved in the study design and interpretation of data. Random assignment was achieved with a computer-generated sequence by the drug manufacturer. Patients and investigators were asked to adhere to titration targets; however, there was no supervision to enforce titration. In addition, this study was conducted in a predominantly white population, which means that the results of this study cannot be extrapolated to other ethnic groups. There were also more dropouts in the exenatide extended-release group compared to insulin glargine group, due to injection site reactions. A key limitation in this study was its open label study design, which has potential bias. Information regarding adherence was also not addressed in this study. This study included a "continuing extension period," so the full results of this study will not be seen for another 2-5 years.

Conclusion: Based on the results of this study, it is unclear whether Exenatide extended-release is superior to insulin glargine for improving glycemic control in patients with type 2 diabetes. Exenatide extended-release resulted in a greater HbA1c reduction at week 26 than insulin glargine, however, this might not be clinically significant. Exenatide extended-release decreased HbA1c by only 1.5% compared to insulin glargine, which reduced HbA1c by 1.3%. A difference of 0.2% is not clinically significance to recommend exenatide extended-release over insulin glargine. Exenatide extended-release could be more useful than insulin glargine in overweight Caucasian patients, because it reduced body weight. More studies need to be conducted before exenatide extended release can be recommended over insulin glargine for treating type 2 diabetes.

Contraindications[1,2,3,4]: Severe hypersensitivity to exenatide or any product component. Personal or family history of medullary thyroid carcinoma, Multiple Endocrine Neoplasia syndrome type 2, patients with type 1 diabetes for the treatment of diabetic ketoacidosis

Black Box warning: Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether EXENATIDE EXTENDED-RELEASE causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. EXENATIDE EXTENDED-RELEASE is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Precautions[1,2,3,4]:

Body mass index: Population pharmacokinetic analysis of patients with body mass indices (BMIs) of at least 30 kg/m^2 and less than 30 kg/m^2 suggest that BMI has no significant effect on the pharmacokinetics of exenatide.[1,3]

Thyroid C-cell tumors: Studies conducted in rats showed that exenatide ER caused a dose-related and duration–dependent increase in thyroid C-cell tumors (adenomas and/or carcinomas). It is unknown whether exenatide ER will cause thyroid C-cell tumors in humans. Patients with thyroid nodules noted on physical examination or neck imaging, or, if serum calcitonin is measured and found to be elevated, patients should be referred to an endocrinologist for further evaluation.

Acute pancreatitis: Exenatide has been associated with acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. After initiation of dose and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent, severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, promptly discontinue therapy and initiate appropriate management. If pancreatitis is confirmed, do not restart therapy. Consider antidiabetic therapies other than exenatide in patients with a history of pancreatitis.

Renal effects: There have been postmarketing reports of altered renal function, including increased SCr, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving 1 or more pharmacologic agents known to affect renal function or hydration status, such as ACE inhibitors, NSAIDs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including exenatide. Exenatide was not directly nephrotoxic in preclinical or clinical studies.

***GI disease*:** Exenatide has not been studied in patients with severe GI disease, including gastroparesis. Its use is commonly associated with GI adverse reactions, including

nausea, vomiting, and diarrhea. Therefore, use is not recommended in patients with severe GI disease.

Hypersensitivity reactions: If a hypersensitivity (eg, anaphylaxis, angioedema) reaction occurs, instruct the patient to discontinue therapy and other suspect medications and promptly seek medical advice.

***Renal Function Impairment*:** Do not use in patients with severe renal impairment (CrCl less than 30 mL/min) or ESRD, and use with caution in patients with renal transplantation.

Hepatic Function Impairment*:* No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidneys, hepatic impairment is not expected to affect blood concentrations of exenatide.

Elderly: Population pharmacokinetic analysis of patients (age range, 22 to 73 years) suggests that age does not influence the pharmacokinetic properties of exenatide.

Children: Exenatide ER has not been studied in pediatric patients.

Adverse Effects[1,2,3,4]:

Occurring in >10% of patients:

Endocrine & metabolic:

Hypoglycemia (2% to 5%; combination therapy with sulfonylurea 14% to 36%, with metformin ≤4%, with thiazolidinedione 11%)

Gastrointestinal:

Nausea – dose dependent (8% to 11%; combination therapy 13% to 44%)
Vomiting (4%; combination therapy 11% to 13%)
Diarrhea (<2% to 11%; combination therapy 6% to 20%)
Constipation (9%; combination therapy 6% to 10%)

Local Injection Site Reactions:

Injection site nodule (6% to 77%),
Erythema, hematoma, pruritus (2% to 18%)

Miscellaneous:

Anti-exenatide antibodies (low titers 38% to 49%, high titers 6% to 12%)

Occurring in 1% to 10% of patients:

Central nervous system:

Nervousness (9%)
dizziness (<2%; combination therapy 9%)
Headache (5% to 9%)
Fatigue (3% to 6%)

Dermatologic:

Hyperhidrosis (3%)

Gastrointestinal:

Viral gastroenteritis (6% to 9%)

Dyspepsia (3% to 7%; combination therapy 5% to 7%)

GERD (3% to 7%)

Decreased appetite (1% to 5%)

Neuromuscular & skeletal:

Weakness (4%)

Drug Interactions[1,2,3,4]

Oral antibiotics, oral contraceptives

Decreased absorption of drugs requiring rapid GI absorption

Other Hypoglycemic agents (eg, insulin, meglitinides [eg, repaglinide], sulfonylureas [eg, glimepiride])

Increased risk of hypoglycemia

Warfarin

Increased INR and possibly increased bleeding with coadministration.

Acetaminophen

Reduced acetaminophen bioavailability

Digoxin

Decreased digoxin concentrations

Danazol

Increased blood glucose levels

Thyroid hormones (Levothyroxine, Liothyronine, Liothyronine, Thyroglobulin)

Decreased effectiveness of the exenatide

Lovastatin

Decreased lovastatin bioavailability

Trandolapril

Increased blood glucose lowering effect and risk of hypoglycemia

Dosing/Administration[1,2,3,4,5]

Adult Dosing:

2 mg SubQ once weekly

Geriatric Dosing:

Refer to adult dosing

Pediatric Dosing:

Use not recommended. Safety and efficacy have not been established

Dosing: Renal Impairment

Cl_{cr} ≥50 mL/minute: No dosage adjustment necessary

Cl_{cr} 30-50 mL/minute: use caution. (No dosage adjustment provided in manufacturer's labeling)

Cl_{cr} <30 mL/minute: Use not recommended.

Dosing: Hepatic Impairment

No dosage adjustment provided in manufacturer’s labeling (has not been studied); however, hepatic dysfunction is not expected to affect exenatide pharmacokinetics.

Administration:

Subcutaneous injection in the upper arm, thigh, or abdomen; rotate injection sites weekly. Do not administer intravenously (IV) or intramuscularly (IM). Administer immediately after reconstitution. May administer without regard to meals or time of day.

Conversion from immediate release to extended release:

Initiate weekly administration of exenatide extended release the day after discontinuing exenatide immediate. Upon switching from immediate-release exenatide to extended-release exenatide, patients may experience a transient increase in blood glucose concentrations that may last approximately 2 weeks

Note: May administer a missed dose as soon as noticed if the next regularly scheduled dose is due in ≥3 days; resume normal schedule thereafter. To establish a new day of the week administration schedule, wait ≥3 days after last dose given, then administer next dose on new desired day of the week.

Use in special circumstances [1,2,3,4]:

*Pregnancy: C*ategory C

Lactation: Excretion in breast milk unknown/use caution

Conclusion:

Exenatide extended-release is a useful agent for achieving glycemic control in patients with type 2 diabetes who have not achieved HbA1c and plasma glucose target levels with diet and exercise alone or with other antidiabetic therapies. Exenatide extended-release can improve patient reported outcomes and quality of life, due to its once weekly administration. Exenatide extended-release is effective at achieving glycemic targets when used in combination with sulfonylureas, metformin, sulfonylureas plus metformin, thiazolinediones with or without metformin. Exenatide extended-release should not be used as monotherapy or in patients with type 1 diabetes. Is should also not be used along with insulin. More studies need to be conducted to evaluate whether Exenatide extended-release is superior to insulin for lowering HbA1c and plasma glucose. Exenatide extended-release could be recommended in overweight patients because exenatide extended-release has been shown to decrease body weight. It could also be useful in patients who have frequent hypoglycemia episodes, because exenatide extended-release has shown to have minimal hypoglycemic events. Exenatide extended-release is contraindicated in patients with a history or family history of thyroid cancer and should not be used in these patients. Patients and health care professionals should be aware of the possibility of injection site reactions and acute pancreatitis. A cost-benefit analysis should also be conducted before recommending exenatide extended release over other antidiabetic medications. Other antidiabetic medications may cost less and achieve the same results as exenatide extended release. Prescribers should consider a patients willingness to pay for prescription medications and patients' individual insurance plans and co-pays. See table 1 below for prices of antidiabetic medications. Overall, Exenatide extended-release is a safe and effective therapeutic option in patients with type 2 diabetes who desire less frequent injections.

Table 1: Prices of Selected Antidiabetic Medications[11] (not an all-inclusive list)

Drug	Strength	Quantity	Price without ins ($)*
Byetta® (exenatide)	5mcg/0.02 ml	1.2 ml Pen	337.00
Bydureon® (exenatide ER)	2mg/vial	4 vials	375.99
Pioglitazone	15 mg	30	196.48
	30 mg	30	289.98
	45 mg	30	310.00
Sitagliptan	25 mg	90	645.98
	50 mg	30	228.98
	100 mg	30	235.00
Insulin glargine	100 units/ml	10 ml	118.99

*Prices are from www.drugstore.com. Prices may differ depending on pharmacy and patient insurance plan.

Recommended References:

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