Drug Use Research & Management Program
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New Dosage Formulation

Month/Year of Review: April 2012
Generic Name: Exenatide extended–release injection (EQW)
PDL Class: Incretin Mimetics
Preferred Agents: Metformin, glimepiride, glipizide, glyburide, pioglitazone
Non-preferred Agents: Sitagliptin, saxagliptin, exenatide, liraglutide, pramlintide

End date of literature search: February 2012
Brand Name (Manufacturer): Bydureon (Amylin Pharmaceuticals)
Dossier Received: Pending
Comparator Therapies: Metformin, sulfonylureas, pioglitazone sitagliptin, saxagliptin, exenatide, liraglutide, pramlintide

FDA Approved Indications: Exenatide extended–release, once weekly injection (EQW) is a glucagon-like peptide-1 (GLP-1) agonist approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. EQW is an extended release formulation of the twice daily injectable product exenatide (Byetta) which was FDA approved in 2005. The dose of EQW is a 2mg subcutaneous (SQ) injection once weekly at any time of day without regard to meals.[1]

Background: The GLP-1 analogues, which include EQW, twice daily exenatide and liraglutide, stimulate GLP-1 receptors to increase insulin production in response to glucose, which decreases postprandial glucagon release and slows gastric emptying. Exenatide immediate release was evaluated in the 2011 systematic review on newer drugs for the treatment of diabetes mellitus from the Oregon Drug Effectiveness Review Project (DERP).[2] There were no studies that examined the impact of exenatide therapy on long term health outcomes and four trials found moderate strength evidence that there is no significant difference between exenatide and insulin in reduction in HbA1c (range for exenatide -1.0% to -1.4%; range for insulin -0.9% to -1.4%). As labeling suggests, the GLP-1 analogues are not recommended as first line agents but in the appropriate patients they can be a useful option for optimizing glycemic control while promoting weight loss. The American Diabetes Association (ADA) considers the GLP-1 analogues tier-2 agents; helpful for those patients experiencing hypoglycemia or in which weight loss is important. Additionally, they suggest that GLP-1 analogues be used in conjunction with lifestyle modifications and metformin.[3] The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommends GLP-1 analogues as one of their preferred agents, after metformin, because of effectiveness and low risk of hypoglycemia, used alone or in a multi-drug treatment regimen. The AACE/ACE preference the GLP-1 analogues over the dipeptidyl peptidase-4 (DPP-4) inhibitors due to better postprandial glucose reductions and weight loss.[4] The American

College of Physicians (ACP) guidelines found low or insufficient evidence for efficacy of GLP-1 agonists without specific recommendations for use.[5] Animal studies suggest beta cell preservation and stimulation of beta cell proliferation, however, it is unknown if this can be expected in humans.[6]

Clinical Efficacy: EQW was studied as monotherapy and in combination therapy in two double-blind (DURATION-2 and DURATION-4) and three open-label studies (DURATION-1, DURATION-3, DURATION-5).[7,8,9,10,11] Studies included patients with type 2 diabetes and mean baseline HbA1c values of 8.3- 8.5%. Patients naïve to drug therapy and those on one or more anitdiabetic agents were included. The study durations ranged from 24 to 30 weeks. EQW was compared to twice daily exenatide, metformin, pioglitazone and sitagliptin. The primary outcome was change in HbA1c from baseline. No long-term data is available. No all-cause mortality, microvascular or macrovasular outcomes have been evaluated.

The two double-blind, double-dummy, placebo controlled, RCTs with EQW found similar results, with exception of the pioglitazone comparison arm. In DURATION-4 Patients were randomized to subcutaneous (SQ) EQW once weekly + oral placebo daily, metformin 2000mg/day + SQ placebo once weekly, pioglitazone 45mg/day + SQ placebo once weekly or sitagliptin 100mg/day + SQ placebo once weekly.[9] EQW was found to be noninferior to metformin, inferior to pioglitazone and superior to sitagliptin (Table1). EQW significantly decreased weight more than pioglitazone (-2.0kg for EQW vs. +1.5kg with pioglitazone, p<0.001) and sitagliptin (-2.0kg for EQW vs. -0.8kg for sitagliptin, p<0.001). In DURATION-2 EQW 2mg SQ + oral placebo once daily (n= 160) was compared to 100mg oral sitagliptin + placebo injection weekly (n=166) and 45mg pioglitazone + placebo injection weekly (n=165), with all groups on background metformin therapy.[7] Treatment with EQW resulted in greater HbA1c reductions compared to either sitagliptin or pioglitazone groups. Treatment differences for EQW compared to sitagliptin were -0.6% (95% CI -0.9 to -0.4, p<0.0001) and -0.3% (95% CI -0.6 to -0.1, p=0.0165) for EQW compared to pioglitazone (Table 2). Weight loss was greater with EQW than with sitagliptin or pioglitazone.

Table 1. Primary Outcome Results for DURATION-4[9]

Comparator Treatment	Mean reductions in HbA1c	Actual Treatment Difference EQW vs. Comparator	98.3% Confidence Intervals	P-value
EQW	-1.53%	----	-----	----
Metformin	-1.48%	-0.05%	-0.26 to 0.17	0.62
Pioglitazone	-1.63%	0.10%	-0.15 to 0.35	0.33
Sitagliptin	-1.15%	-0.38%	-0.62 to -0.13	<0.001

Table 2. Primary Outcome Results for DURATION-2[7]

Comparator Treatment	Mean reductions in HbA1c	Actual Treatment Difference EQW vs. Comparator	95%Confidence Intervals	P-value
EQW	-1.5%	----	----	----
Pioglitazone	-1.2%	-0.3%	-0.6 to -0.1	0.0165
Sitagliptin	-0.9%	-0.6%	-0.9 to -0.4	<0.0001

Safety: Studies found the most common adverse reactions (≥5%) to be nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection site nodules and dyspepsia. EQW use was associated with a 4.9% (n=45) incidence of withdrawals due to adverse events compared to 4.9% (n=13) with exenatide twice daily and 2.0% (n=23) for comparator therapies.[1] Overall incidence of minor hypoglycemia associated with EQW (monotherapy and combination therapy) ranged from 1.3% to 3.7%, excluding studies with sulfonylureas. In trials with concomitant sulfonylurea therapy minor hypoglycemia rates ranged from 12.5-20%. No major hypoglycemia was reported in any study.[1]

EQW is not recommended for use with insulin. EQW may increase international normalized ratios (INR) in patients taking warfarin. It is recommended to monitor INR frequently if warfarin and EQW are to be administered concomitantly. EQW has a black box warning due to the potential for causing thyroid C-cell tumors in rats and for being contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Postmarketing reports have shown fatal and non-fatal hemorrhagic or necrotizing pancreatitis and renal impairment sometimes requiring hemodialysis and kidney transplant. EQW is not recommended to be used in patients with a history of pancreatitis, renal impairment (CrCl <30 mL/min), severe gastrointestinal disease or hypersensitivity reactions. Caution is advised when using in moderate renal impairment (CrCl 30-50 mL/min). Hypoglycemia risk increases when EQW is used in combination with sulfonylureas and dosage reduction is recommended.[1]

Conclusion: EQW has demonstrated efficacy of as a once weekly formulation of exenatide. Other than the obvious convenience of a once weekly preparation, EQW differs from twice daily exenatide by having a black box warning, due to thyroid C-cell tumor risk, and the ability to administer the weekly dose without regard to meals. Similar side effects are experienced by both formulations with the exception of injection site pruritus and injection site nodules associated with EQW and a higher incidence of nausea associated with twice daily exenatide (30% vs. 14%). Evidence suggests that EQW is similar in efficacy and safety to other currently available GLP-1 agonists, which are recommended as tier 2 agents. EQW is a treatment option for those patients whom hypoglycemia and weight gain are of concern and are unable to tolerate or experience treatment failure with tier 1 agents.

Recommendation: It is recommended to use clinical prior authorization criteria to limit the use of EQW to patients that have tried and failed antidiabetic treatments that have a proven history of safety and efficacy as outlined in the PA criteria for Incretin Mimetics (appendix).

APPENDIX:

Incretin Mimetics

Initiative: To optimize the correct use of insulin mimetics.

Length of Authorization: Up to 1 year

Preferred Alternatives: Listed at: http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Exenatide (Byetta®) and Liraglutide (Victoza®), Exenatide Extended-Release (Bydureon®)

Approval Criteria		
1. Does the patient have a diagnosis of Type 2 diabetes?	Yes: Go to #2	No: Deny based on appropriateness of therapy.
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml.	**Yes:** Inform provider of covered alternatives in class. http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/main.html	**No:** Go to #3.
3. Has the patient tried and failed metformin **and** sulfonylurea therapy or have contraindications to these treatments? Contraindications to metformin: - Known hypersensitivity - Renal disease or renal dysfunction - Acute or chronic metabolic acidosis - Increased risk of lactic acidosis (CHF,	**Yes:** Go to #4.	**No: Deny. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.**

advanced age, impaired hepatic function) Contraindications to sulfonylureas: - Known hypersensitivity		
4. Is the patient currently taking insulin?	**Yes:** Go to #5	**No:** Approve for up to 1 year.
5. Is the patient requesting exentatide (Byetta) and is taking insulin glargine?	**Yes:** Approve for up to 1 year.	**No:** Deny. The safety and efficacy of other insulin formations and GLP-1 Agonists have not been studied.

Initiating Metformin

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

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DUR Board Action: 3/17/11 (KS), 4/26/12 (KS)
Revision(s): 1/31/12 (KS)
Initiated:

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