DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Rexner Vargas, Senior Manager, Regulatory Affairs
Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121-3030

RE: NDA 21-773, 21-919
Byetta® (exenatide) injection
MACMIS #18144

Dear Mr. Vargas:

This letter notifies Amylin Pharmaceuticals, Incorporated (Amylin), and, by copy, Eli Lilly (Lilly), which also markets Byetta® (exenatide) injection, that, as part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by Lilly and Amylin representatives on June 10 and June 11, 2009, regarding Amylin's drug Byetta at the 91st Endocrine Society's Annual Meeting (ENDO) held in Washington DC. Several of these oral statements promote an unapproved use (as of the date the statements were made), broaden the drug's indication, and overstate the efficacy of Byetta. Other statements made by the representatives exaggerate potential weight loss benefits associated with Byetta. Thus, these promotional activities misbrand the drug in violation of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 352(f)(1) & (n), and FDA implementing regulations. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(i) & (e)(6)(i).

Background

According to the Indications and Usage section of the FDA-approved product labeling (PI)[1]:

> BYETTA is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.

The Clinical Studies section of the PI includes the following table:

[1] At the time of this violative action, the approved PI (and the version referred to within this letter) for Byetta was the version dated January 11, 2008. The most recent PI is dated October 30, 2009. The current PI reflects the approval of monotherapy indication including the addition of an Important Limitations of Use section. The current PI also includes additional changes to the Warnings and Precautions regarding pancreatitis, renal impairment, and macrovascular outcomes.

Table 1: Results of Thirty-Week Placebo-Controlled Trials of BYETTA in Patients With Inadequate Glucose Control Despite the Use of Metformin, a Sulfonylurea, or Both

	Placebo BID	BYETTA 5 mcg BID	BYETTA 10 mcg* BID
	In Combination With Metformin		
Intent-to-Treat Population (N)	113	110	113
HbA_{1c} (%), Mean			
Baseline	8.2	8.3	8.2
Change at Week 30	+0.1	−0.4†	−0.8‡
Proportion Achieving HbA_{1c} ≤7%§	13.0%	31.6%†	46.4%†
Body Weight (kg), Mean			
Baseline	99.9	100.0	100.9
Change at Week 30	−0.3	−1.6†	−2.8‡
	In Combination With a Sulfonylurea		
Intent-to-Treat Population (N)	123	125	129
HbA_{1c} (%), Mean			
Baseline	8.7	8.5	8.6
Change at Week 30	+0.1	−0.5†	−0.9‡
Proportion Achieving HbA_{1c} ≤7%§	8.8%	32.6%†	41.3%‡
Body Weight (kg), Mean			
Baseline	99.1	94.9	95.2
Change at Week 30	−0.6	−0.9	−1.6†
	In Combination With Metformin and a Sulfonylurea		
Intent-to-Treat Population (N)	247	245	241
HbA_{1c} (%), Mean			
Baseline	8.5	8.5	8.5
Change at Week 30	+0.2	−0.6‡	−0.8‡
Proportion Achieving HbA_{1c} ≤7%§	9.2%	27.4%‡	33.5%‡
Body Weight (kg), Mean			
Baseline	99.1	96.9	98.4
Change at Week 30	−0.9	−1.6†	−1.6†

* BYETTA 5 mcg twice daily (BID) for 1 month followed by 10 mcg BID for 6 months before the morning and evening meals.
† $p \leq 0.05$, treatment vs. placebo
‡ $p \leq 0.0001$, treatment vs. placebo
§ Patients eligible for the analysis with baseline HbA_{1c} >7%.

Broadening of Indication/Promotion of Unapproved Use

On June 10, 2009, at approximately 2:00 p.m., during the ENDO Meeting, a Lilly representative made the following claims in word or substance to a DDMAC representative:

- Although Byetta is not indicated for use by itself because it was not FDA approved this way and the FDA requires additional studies, Byetta can be used by itself.

- There might be managed care, like Medicare or Medicaid issues when prescribing Byetta alone, but there are ways to deal with that.

These statements suggested that Byetta is intended for use as monotherapy. However, the version of the PI approved for Byetta at the time of ENDO clearly stated that Byetta is indicated as **adjunctive** therapy to improve glycemic control. The caveat given by the representative that Byetta is not indicated for use by itself does not mitigate the overall impression created by the presentation that Byetta is effective for, and should be used as, monotherapy.

We acknowledge that FDA approved Byetta for the monotherapy use on October 30, 2009; however, the promotional statements referred to above were made five months before this approval and thus constitute a violation of the applicable law and regulations. We are particularly concerned by your representative's promotion of the then-unapproved monotherapy use (b) (4)

Overstatement of Efficacy

During the June 10, 2009, discussion at ENDO, the Lilly representative also misleadingly overstated the efficacy of Byetta. Specifically, the representative stated that Byetta had a positive effect on cholesterol and triglyceride levels and because of this effect, "cardiovascular benefits" are associated with the use of Byetta. FDA is not aware of any substantial evidence or substantial clinical experience that support the claim that Byetta offers any cardiovascular benefit. If you have any evidence to support this claim, please submit them to FDA for review.

False or Misleading Statement

On June 10, 2009, the Lilly representative claimed that 94% of patients in a study lost 7 to 8 pounds without diet or exercise in 30 days. On June 11, 2009, an Amylin representative claimed that 80% of patients in a study lost about 7 to 8 pounds over 30 weeks.

These statements misleadingly exaggerate the weight loss demonstrated in clinical trials with Byetta. According to the PI, the mean change from baseline body weight at week 30 in thirty-week placebo-controlled trials in patients with inadequate glucose control despite the use of metformin, sulfonylurea, or both, with the twice daily use of Byetta 5 mcg or 10 mcg,

(b) (4)

respectively, was -1.6 kg (-3.52 lbs) and -2.8 kg (-6.16 lbs) in combination with metformin; -0.9 kg (-1.98 lbs) and -1.6 kg (-3.52 lbs) in combination with a sulfonylurea; and -1.6 kg (-3.52 lbs) and -1.6 kg (-3.52 lbs) in combination with metformin and a sulfonylurea. Given these mean changes, these statements regarding 80% or 94% of patients experiencing 7 to 8 pounds of weight loss in 30 days or 30 weeks could not have been based on data from the clinical trials cited in the PI. Additionally, when the DDMAC representative queried the Amylin representative about the data to support the claim of 80% of patients losing 7 to 8 pounds over 30 weeks, the DDMAC representative was escorted by the representative to Amylin's Medical Information booth, where the DDMAC representative was given two reprints.[3-4] Neither of these reprints provide substantial evidence to support the weight loss claims made by the representatives; rather, they contain some data from the clinical trials in Byetta's PI summarized above, which do not reflect a weight loss of 7 to 8 pounds in 80% or 94% of patients in 30 days or 30 weeks. The Agency is not aware of any substantial evidence or substantial clinical experience to support these statements. If you have data to support the claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the oral statements made by Amylin and Lilly representatives misbrand Byetta in violation of the Act, 21 U.S.C. 352(f)(1) & (n), and FDA implementing regulations. 21 CFR 201.100(c)(1); 201.128; 202.1(e)(5)(i) & (e)(6)(i).

DDMAC requests that Amylin and Lilly immediately cease violative promotional activities for Byetta such as those described above. Please submit a written response to this letter on or before January 11, 2010 stating whether you intend to comply with this request, listing all promotional materials and/or promotional activities (with the 2253 submission date or date of activity) for Byetta that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials and/or activities and your plans for instructing Amylin and Lilly representatives on compliance with their legal obligations to avoid violative claims. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18144 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Byetta comply with each applicable requirement of the Act and FDA implementing regulations.

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[3] Defronzo R, Ratner R, Han J, Lo D, Fineman M, Baron A: Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes. *Diabetes Care.* 2005;28(5): 1092-1100.

[4] Kendall, DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, Baron AD: Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea. *Diabetes Care*. 2005;28(5): 1083-1091.

Sincerely,

{See appended electronic signature page}

Kendra Y. Jones
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc: Michele Sharp, Pharm.D.
Director, U.S. Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21773	ORIG-1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21919	ORIG-1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION

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/s/

KENDRA Y JONES
12/24/2009