DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST #2

NDA 21-773

Amylin Pharmaceuticals, Inc.
Attention: John F. Wood, MBA, RAC
Senior Director, Regulatory Affairs
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121

Dear Mr. Wood:

Please refer to your correspondences dated May 16 and August 3, 2006, requesting changes to FDA's March 29, 2006, Written Request for pediatric studies for Byetta (exenatide) Injection.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated March 29, 2006.

TYPE OF STUDIES:

Study 1: A short-term pharmacokinetics (PK), pharmacodynamics (PD), and tolerability study in children with type 2 diabetes.

Study 2: A clinical safety and efficacy study of exenatide as monotherapy and as add-on to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea in children with type 2 diabetes.

INDICATION TO BE STUDIED (OBJECTIVE/RATIONALE):

Study 1: To evaluate the PK, PD, and tolerability of single subcutaneous doses of 2.5 mcg and 5.0 mcg of exenatide in children with type 2 diabetes mellitus.

Study 2: To evaluate the safety and effectiveness of twice daily subcutaneous administration of exenatide treatment at 5 mcg and 10 mcg twice a day in older children with type 2 diabetes who are treated with diet and exercise alone or diet and exercise plus metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

STUDY DESIGN:

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board shall monitor the safety in Study 2 and impose appropriate, pre-specified rescue criteria.

Study 1: A randomized, patient-blinded, dose-rising, placebo-controlled, crossover PK/PD study. Within 4 weeks following the screening visit, eligible participants will report to the study site on Day -1 and will be randomly assigned to their treatment sequences, in which they will receive one dose of study medication per consecutive day (starting in the morning on Day 1), in a dose-rising fashion. The 3 treatments will be placebo, exenatide 2.5 mcg, and exenatide 5 mcg, each administered as a single subcutaneous injection 15 minutes prior to breakfast, on Day 1, Day 2, and Day 3 according to the subject's assigned treatment sequence. Patients will be domiciled at the study site for the 3-day duration of treatment and will be discharged following completion of all study procedures on Day 3. PK endpoints will be measured prior to and over the 8-hour period following study medication administration. PD endpoints will be measured prior to and over the 6-hour period following study medication administration. For patients with HbA1c between 6% and 6.5%, exenatide will be administered only if their morning fasting glucose level is higher than 100 mg/dL, and the patients will be monitored more closely to avoid hypoglycemia if they have been treated with a sulfonylurea. Patients will be discharged approximately 8 hours following their dose of study medication on Day 3 provided that no additional observation is deemed necessary by the investigator.

Study 2: A 28-week, randomized, double-blind, placebo-controlled, safety and efficacy study of the effect of exenatide on glucose control (HbA1c) in adolescent patients with type 2 diabetes treated with diet and exercise alone or diet and exercise plus metformin, a sulfonylurea or a combination of metformin and a sulfonylurea. Patients will be randomized to exenatide 5 mcg twice a day, exenatide 10 mcg twice a day, or placebo injection twice a day in addition to their baseline treatment. The study drug will be administered by subcutaneous injection before the morning and evening meals for a total of 28 weeks. Randomization will be stratified by the patient's use of antidiabetic drugs at baseline (diet and exercise alone versus previous antidiabetic drugs) and baseline HbA1c ($< 8\%$ versus $\geq 8\%$).

The diet and exercise program should be standardized and documented for all treatment arms in Study 2. Documentation must be adequate to permit review and assessment of adherence to diet and exercise. Lack of implementation of this part of the program will constitute failure to adhere to good scientific principles.

AGE GROUP IN WHICH STUDIES WILL BE PERFORMED (Studies 1 and 2):

Male and female patients with type 2 diabetes mellitus ages 10 to 16 years, inclusive.

NUMBER OF PATIENTS TO BE STUDIED:

Study 1: Twelve patients will be enrolled to obtain approximately nine or more completers.

Study 2: A sufficient number of patients will be randomized to provide data from approximately 150 completers (50 per treatment arm).

ENTRY CRITERIA:

Study 1:

A. Main inclusion criteria

- Males and females with an established diagnosis of type 2 diabetes mellitus and who are treated with diet and exercise alone or with a stable dose of metformin, a sulfonylurea, or a combination of metformin plus a sulfonylurea
- HbA1c 6.0% to 11.0%

B. Main exclusion criteria

- Known hypersensitivity to exenatide or any of the components of study medication
- Patients taking sulfonylurea chlorpropramide
- If female, is sexually active and not actively practicing birth control per protocol; protocol will specify the use of two methods of birth control throughout the study
- A female who is pregnant or lactating

Study 2:

A. Inclusion Criteria

- Males and females with an established diagnosis of type 2 diabetes and who are treated with diet and exercise alone or diet and exercise plus a stable dose of metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea for at least 3 months
- Fasting C-peptide >0.6 ng/mL
- HbA1c 6.5% to 11%, inclusive

B. Exclusion Criteria

- Presence of anti-glutamic acid decarboxylase (GAD65) antibodies or anti-islet cell antibodies
- Use of insulin, an alpha-glucosidase inhibitor, a meglitinide, pramlintide, or exenatide for more than 1 week during the 3 months prior to screening
- Renal disease or serum creatinine >1.6 mg/dL (males) or >1.4 mg/dL (females)
- Hepatic dysfunction (>3 times upper limit of normal for aspartate aminotransferase and alanine aminotransferase)
- Known hypersensitivity to exenatide or any of the components of study medication
- A female who is sexually active and not willing to use two methods of birth control throughout the study
- A female who is pregnant or lactating
- Participated in another investigational study within the past 2 months

STUDY ENDPOINTS:

Study1:

A. Pharmacokinetic endpoints including:

- Area under concentration curve ($AUC_{0-\infty}$ and AUC_{0-8h})
- Peak plasma concentration (C_{max})
- Time to peak concentration (T_{max})
- Terminal elimination half-life ($t_{1/2}$)
- Apparent elimination rate constant (k)

- Apparent clearance (CL/F)
- Apparent volume of distribution (V/F)

B. Pharmacodynamic endpoints:

- Plasma glucose: absolute and incremental $AUC_{0\text{-}3h}$, absolute and incremental $AUC_{0\text{-}6h}$, $C_{ave(0\text{-}6h),}$ C_{max}, and T_{max}
- Serum insulin: absolute and incremental $AUC_{0\text{-}3h}$, absolute and incremental $AUC_{0\text{-}6h}$, $C_{ave(0\text{-}6h),}$ C_{max}, and T_{max}

C. Safety endpoints:

- Incidence and frequency of adverse events, including hypoglycemia
- Changes in vital signs, ECGs, and laboratory values

Study 2:

A. The primary endpoint will be change in HbA1c from study baseline to Week 28
B. Secondary endpoints will include the incidence and frequency of hypoglycemia, percentage of patients achieving an HbA1c of <7%, change of body weight, fasting plasma glucose and serum insulin concentrations and seven-point self-monitored blood glucose (SMBG) profile
C. Safety evaluation will include reporting of adverse events, anti-exenatide antibodies, vital signs, electrocardiograms, and laboratory measurements

DRUG INFORMATION:

Dosage form: Pre-filled pens are available to deliver exenatide at doses of either 5 mcg or 10 mcg. Each pre-filled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).
Route of administration: Subcutaneous Injection
Formulation: Same as marketed

Byetta (exenatide in sodium acetate buffer) 0.25 mg/mL sterile, preserved solution is administered by subcutaneous injection twice daily. A multiple-use, pen-cartridge device is used to deliver the study medication.

REGIMEN:

Study 1: Following an overnight fast, a single subcutaneous injection of study medication will be administered 15 minutes prior to breakfast, according to the patient's assigned treatment sequence. Each patient will receive a single subcutaneous injection of placebo, exenatide 2.5 mcg, and exenatide 5 mcg on three separate days.

Study 2: There will be three arms corresponding to placebo, exenatide 5 mcg twice a day, and exenatide 10 mcg twice a day before the morning and evening meals. Patients randomized to the 10 mcg twice a day arm will be started on 5 mcg twice a day for the first 4 weeks to minimize nausea, then the drug will be administered at its full dosage of 10 mcg twice a day for the subsequent 24 weeks.

DRUG-SPECIFIC SAFETY CONCERNS:

A. The incidence, frequency, and severity of gastrointestinal adverse events (reported rates in adults: nausea in 44%, vomiting in 13%, diarrhea in 13%, and dyspepsia in 6% of exenatide-treated patients).
B. The titers of anti-exenatide antibodies and their impact on efficacy.
C. The incidence, frequency, and severity of clinically significant hypoglycemia. The addition of exenatide to a sulfonylurea increases the risk of hypoglycemia.
D. The incidence, frequency, and severity of hyperglycemia-diabetic ketoacidosis.

STATISTICAL INFORMATION, INCLUDING POWER OF STUDY AND STATISTICAL ASSESSMENT:

Study 1: A sample size based on 9 completed patients is expected to provide sufficient information to evaluate the PK, PD, and general tolerability of exenatide in adolescent patients with type 2 diabetes mellitus.

Study 2: The analysis of the primary efficacy variable will use an ANCOVA model with HbA1c change from baseline at Week 28 or last prior visit as the dependent variable, treatment and randomization stratification factors as independent variables, and baseline HbA1c as covariate. The primary analysis population will be the intent-to-treat (ITT) population which includes all randomized patients who have a baseline HbA1c and at least one post-randomization HbA1c. The sample size of 50 per treatment group will provide 84% power to detect a 0.6% difference between treatment groups in HbA1c change from baseline with a 5% significant level.

LABELING THAT MAY RESULT FROM THE STUDIES:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the studies*:* Reports of the above studies must be submitted to the Agency on or before December 31, 2010. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request: As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical

Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 796-1168.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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