DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-773 **WRIITEN REQUEST**

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:

Reference is made to your Proposed Pediatric Study Request, dated July 28, 2005, submitted to your new drug application (NDA) for Byetta (exenatide) Injection.

To obtain needed pediatric information on exenatide, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

TYPE OF STUDIES:

Study 1: A short-term pharmacokinetic, pharmacodynamic, and tolerability study in adolescent patients with type 2 diabetes.

Study 2: A clinical safety and efficacy study for the assessment of exenatide as add-on therapy in adolescent patients with type 2 diabetes.

Study 3: A clinical safety and efficacy study for the assessment of exenatide as monotherapy in adolescent patients with type 2 diabetes.

INDICATION TO BE STUDIED (OBJECTIVE/RATIONALE):

Study 1: To evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of single doses of 2.5 mcg, 5.0 mcg, and 10.0 mcg of exenatide in adolescent patients with type 2 diabetes mellitus.

Study 2: To evaluate the safety and effectiveness of twice daily subcutaneous administration of exenatide treatment in adolescent patients with type 2 diabetes being treated with diet and exercise plus metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. The dosage will be determined based on the results of Study 1 in the same age group.

Study 3: To evaluate the safety and effectiveness of diet and exercise plus placebo or diet and exercise plus twice daily subcutaneous administration of exenatide treatment in adolescent patients.

STUDY DESIGN:

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with pre-specified study rescue criteria shall be included in Studies 2 and 3.

Study 1: A randomized, patient-blinded, dose-rising, placebo-controlled, crossover pharmacokinetic study. The study will consist of a screening visit and 4 treatment visits, corresponding to placebo, and exenatide doses of 2.5 mcg, 5.0 mcg, and 10.0 mcg. The total study duration will not exceed 8 weeks. Patients will be blinded to the identity of the study medication. Pharmacokinetic endpoints will be measured prior to and over the 8-hour period following study medication administration. Pharmacodynamic endpoints will be measured prior to and over the 6-hour period following study medication administration. At all treatment visits, patients will be discharged approximately 8 hours following their dose of study medication.

Study 1 is to be performed prior to conducting Studies 2 and 3, in order assess the appropriate pediatric dose. This information must be submitted to and discussed with the Division of Metabolism and Endocrinology Products prior to initiation of Studies 2 and 3.

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/exercise and oral antidiabetic medications. Patients will be randomized to exenatide or placebo as an add-on therapy to their current regimen of diet and exercise plus metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. Treatment will consist of subcutaneous exenatide administered twice daily or the equivalent volume of placebo for 28 weeks. Randomization will be stratified on patients' use of medication at baseline and baseline HbA1c (<8% vs. ≥8%).

Study 3: A 28-week, randomized, double-blind, placebo-controlled, safety and efficacy study of the effect of Byetta (exenatide) compared to placebo on glucose control (HbA1c) in adolescent patients with type 2 diabetes treated with diet and exercise. Patients will be randomized to exenatide or placebo in addition to diet and exercise. Treatment will consist of subcutaneous exenatide administered twice daily or the equivalent volume of placebo for 28 weeks. Randomization will be stratified on baseline HbA1c (<8% vs. ≥8%).

The diet and exercise program should be standardized and documented for all treatment arms in Studies 2 and 3. 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, 2, and 3):

Male and female adolescent 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 9 or more completers.

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

Study 3: A sufficient number of patients will be randomized to provide data from approximately 50 completers per treatment arm.

ENTRY CRITERIA:

Study 1:

A. Main inclusion criteria

- Males and females
- Age 10 to 16 years, inclusive
- Treatment with a stable dose of metformin, a sulfonylurea, or a combination of metformin plus a sulfonylurea for at least 3 months
- HbA1c 6.5% to 10.0%

B. Main exclusion criteria

- Patients taking the sulfonylurea chlorpropamide.
- 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
- If female, pregnant or lactating

Study 2:

A. Inclusion Criteria

- Males and females
- Age 10 to 16 years, inclusive, at screening
- Type 2 diabetes treated with diet and exercise or stable doses 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 10%, inclusive
- Compliance with diet and oral medication regimen

B. Exclusion Criteria

- Presence of anti-glutamic acid decarboxylase (GAD65) antibodies or anti-islet cell antibodies
- Treated with an alpha-glucosidase inhibitor, a meglitinide, pramlintide, or exenatide within 3 months of screening
- Renal disease or has 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
- Participated in another investigational study within the past 2 months
- 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
- If female, is pregnant or lactating

Study 3:

A. Inclusion Criteria

- Males and females
- Age 10 to 16 years, inclusive, at screening
- Type 2 diabetes treated with diet and exercise
- Fasting C-peptide >0.6 ng/mL
- HbA1c 6.5% to 10%, inclusive
- Compliance with diet

B. Exclusion Criteria

- Presence of anti-glutamic acid decarboxylase (GAD65) antibodies or anti-islet cell antibodies
- Treated with an alpha-glucosidase inhibitor, a meglitinide, pramlintide, or exenatide within 3 months of screening
- Renal disease or has 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
- Participated in another investigational study within the past 2 months
- 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 study
- If female, is pregnant or lactating

STUDY ENDPOINTS:

Study1:

A. Pharmacokinetic endpoints such as:

- 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_{0-3h}, absolute and incremental AUC_{0-6h}, $C_{ave(0-6h),}$ C_{max}, and T_{max}.
- Serum insulin: absolute and incremental AUC_{0-3h}, absolute and incremental AUC_{0-6h}, $C_{ave(0-6h),}$ 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 clinically significant added hypoglycemia (percentage of patients achieving an HbA1c of <7%), change of body weight, and fasting plasma glucose and serum insulin concentrations.
C. Safety evaluation will include reporting of adverse events, anti-exenatide antibodies, vital signs, electrocardiograms, and laboratory measurements.

Study 3:
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 clinically significant hypoglycemia, percentage of patients achieving an HbA1c of <7%, change of body weight, and fasting plasma glucose and serum insulin concentrations.
C. Safety evaluation will include reporting of adverse events, anti-exenatide antibodies, vital signs, electrocardiograms, and laboratory measurements

DRUG INFORMATION:

Dosage form: Injection
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.

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

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, exenatide
5 mcg, and exenatide 10 mcg on four separate days.

Study 2: Dosing will be determined based on the results of the adolescent PK/PD study (Study 1). The drug will be administered at one-half of the selected dosage for the first 4 weeks to minimize nausea. The drug will be administered at its full dosage for the subsequent 24 weeks.

Study 3: Dosing will be determined based on the results of the adolescent PK/PD study (Study 1). The drug will be administered at one-half of the selected dosage for the first 4 weeks to minimize nausea. The drug will be administered at its full dosage 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.
D. The incidence, frequency, and severity of hyperglycemia-diabetic ketoacidosis.

STATISTICAL INFORMATION, INCLUDING POWER OF STUDY AND STATISTICAL ASSESSMENT:

Study 1: The sample size of 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.

Studies 2 and 3: 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 studies 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, 2008. 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.

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.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please 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. Please also 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:

- the type of response to the Written Request (complete or partial);
- the status of the supplement (withdrawn after the supplement has been filed or pending);
- the action taken (i.e. approval, approvable, not approvable); or
- 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, please 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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