



NDA 021773

**REVISED WRITTEN REQUEST  
AMENDMENT #5**

AstraZeneca AB  
Attention: Cindy Cao, Ph.D.  
Bristol-Myers Squibb Company  
Associate Director, Global Regulatory & Safety Sciences - US  
PO Box 4000  
Princeton, NJ 08543

Dear Dr. Cao:

Please refer to your correspondence dated July 30, 2014, requesting changes to FDA's March 29, 2006, Written Request for pediatric studies for exenatide.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 29, 2006, and as amended on September 8, 2006, April 18, 2007, March 18, 2008, and October 27, 2010, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Reports of the studies that meet the terms of the Written Request dated March 29, 2006, as amended by this letter and by previous amendments dated September 8, 2006, April 18, 2007, March 18, 2008, and October 27, 2010, must be submitted to the Agency on or before **December 31, 2014 2018**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 29, 2006, as amended by this letter and by previous amendments dated September 8, 2006, April 18, 2007, March 18, 2008, and October 27, 2010, must be submitted to the Agency on or before **December 31, 2018**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an 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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request “**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:
  - 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  - 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  - 3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.
- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that exenatide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).
- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:
  - the type of response to the Written Request (i.e., complete or partial response);
  - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
  - the action taken (i.e., approval, complete response); or
  - the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Curtis Rosebraugh, M.D., M.P.H.  
Director  
Office of Drug Evaluation II  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURE:  
Complete Copy of Written Request as Amended

## **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 be randomly assigned to their treatment sequences, in which they will receive a single dose of study medication per study day in a dose-rising fashion on 3 separate days within a 5-week period. The three treatments will be placebo, exenatide 2.5 mcg, and exenatide 5 mcg, each administered as a single subcutaneous injection 15 minutes prior to breakfast, according to the assigned treatment sequence. Patients are admitted to the study site in the morning on Day 1, Day 2, and Day 3 to receive Dose 1, Dose 2, and Dose 3 of the study drug, respectively. 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 remain on the unit until each day's study procedures are completed and will be discharged approximately 8 hours following their dose of study medication on each day, 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. Population PK approach should be used to characterize the plasma exposure; a sparse sampling strategy is acceptable.

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

Male and female patients with type 2 diabetes mellitus ages 10 to 17 years, inclusive. The number of subjects between 16 and 17 years must be limited to 10% of patients in each treatment arm.

#### **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 the 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 (a) diet and exercise alone or (b) diet and exercise plus a stable dose of metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea for at

least 3 months; or (c) a stable dose of metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea for at least 3 months without diet and exercise

- Fasting C-peptide >0.6 ng/mL
- HbA1c 6.5% to 10.5%, inclusive

#### B. Exclusion Criteria

- Presence of anti-glutamic acid decarboxylase (GAD65) antibodies or anti-islet cell antibodies
- Use of an alpha-glucosidase inhibitor, a meglitinide, or pramlintide for more than 1 week during the 3 months prior to screening
- Use of insulin for more than 10 weeks during the 3 months prior to screening
- Prior use of exenatide
- 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:

#### Study 1:

##### 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  $AUC_{0-3h}$ , 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 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
- D. PK endpoints for example, CL/F, V/F, Cmax and AUC derived from the population PK model using the combined data from Study 1 and Study 2 should be reported. The effect of demographic covariates (e.g., age, gender, body weight) on exenatide PK should be analyzed.

#### **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.

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/s/  
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CURTIS J ROSEBRAUGH  
09/16/2014