

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-773

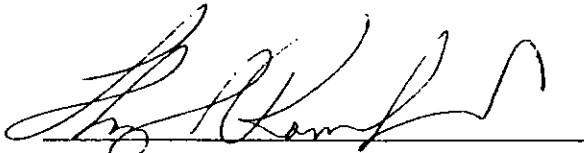
ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG

NDA 21-773 Exenatide Injection

Pursuant to 21 CFR §314.53, Amylin Pharmaceuticals, Inc. hereby submits patent information for Exenatide Injection NDA number 21-773 and claims market exclusivity under 21 CFR §314.50(j) under the provisions of 21 CFR §314.108(b)(2).

The undersigned declares that patent number 5,424,286 covers the formulation, composition and/or method of use of exenatide (exendin-4). This product is the subject of this application for which approval is being sought:



Lloyd A. Rowland
Vice President, Legal, Secretary
and General Counsel

8 JUNE 2004

Date

<u>Owner</u>	<u>Patent No.</u>	<u>Expiration Date</u>	<u>Type</u>
John Eng	5,424,286	13 June 2012	Method of Use

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-773

NAME OF APPLICANT / NDA HOLDER

AMYLIN PHARMACEUTICALS, INC.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)

exendin-4

STRENGTH(S)

0.25 mg/mL

DOSAGE FORM

Injection, Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,424,286

b. Issue Date of Patent
13 June 1995

c. Expiration Date of Patent
13 June 2012

d. Name of Patent Owner
John Eng

Address (of Patent Owner)
5427 Arlington Avenue

City/State
Bronx/New York

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FAX Number (if available)

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E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

☐ Yes

☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

☐ Yes

☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☐ No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☐ No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☐ No
- 2.6 Does the patent claim only an intermediate? ☐ Yes ☐ No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☐ No
- 3.2 Does the patent claim only an intermediate? ☐ Yes ☐ No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 4.2 Patent Claim Number (as listed in the patent) 6 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
Support for the method of Claim 6 can be found in at least the following places in the proposed label:
1. DESCRIPTION – paragraph 1
2. CLINICAL PHARMACOLOGY, Mechanisms of Action – paragraphs 1, 2, 4, 5 and Figure 1
3. Pharmacodynamics, Fasting Glucose - paragraph 1 and Figure 3

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product. ☐ Yes

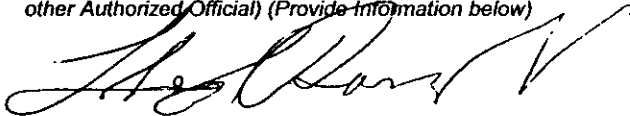
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed
June 15, 2004



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder

☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

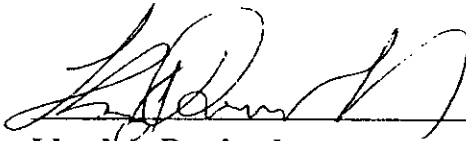
Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT CERTIFICATION WITH RESPECT TO ANY PATENT THAT
CLAIMS THE DRUG (21 U.S.C. §355(b)(2))**

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No certification is necessary because this application is for drug for which investigations described in 21 U.S.C. §355(b)(1)(A) and relied upon by the applicant for approval of this application were conducted by or for the applicant, and this application is not an abbreviated application for a new drug.



Lloyd A. Rowland
Vice President, Legal, Secretary
and General Counsel

8 JUNE 2004

Date

DEBARMENT CERTIFICATION

NDA 21-773 Exenatide Injection

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §335a(k), as amended by the Generic Drug Enforcement Act of 1992, we, Amylin Pharmaceuticals, Inc., state the following with respect to this new drug application:

Amylin Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Lloyd A. Rowland
Vice President, Legal, Secretary
and General Counsel

8 June 2004
Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 25, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-773 (combination therapy)
[REDACTED]
Byetta (exenatide injection)
Amylin Pharmaceuticals, Inc.

SUBJECT: NDA review issues and recommended action

Background

Exenatide is a 39-amino acid peptide originally isolated from the salivary secretions of the Gila monster. It is a homologue of human glucagon-like-peptide-1 (GLP-1), an incretin (gut derived) hormone with physiologic roles in post-prandial nutrient metabolism. Specifically, after an oral glucose load (in contrast to an intravenous glucose load), the normal insulin response is in part mediated by what has been deemed an "incretin effect" of, among other hormones, GLP-1, to stimulate insulin secretion from the beta cell. In DM2, GLP-1 secretion by the gut in response to a meal is impaired for unknown reasons, though the glucose-dependent response to GLP-1 by the beta cell is apparently relatively preserved. The beta cell response to another key physiologic incretin hormone, gastric inhibitory peptide (GIP), is severely impaired in DM2.

Endogenous GLP-1 is extremely short-lived in the circulation, as a result of rapid proteolytic degradation. Therapeutics design targeting the GLP-1 pathway has taken two tacks: development of proteolysis-resistant GLP-1 analogues versus slowing of degradation of endogenous GLP-1 by inhibition of the enzyme dipeptidyl peptidase-IV (DPP-IV). Exenatide is a protease-resistance homologue of human GLP-1 that specifically recognizes and activates the GLP-1 receptor. It is equipotent to human GLP-1 *in vitro*. Its activities include stimulation of glucose-dependent insulin secretion, inhibition of glucagon secretion, and delay of gastric emptying via presumed vagal-dependent mechanisms. Its principal side effects are gastrointestinal in nature, and include nausea and vomiting, which wane in most patients with continued treatment.

Clinical efficacy and safety findings

The sponsor has proposed indications for exenatide in the management of DM2 as both monotherapy and as adjunctive therapy to metformin, SFU, or their combination in patients failing to achieve adequate glycemic control. The division finds the safety and efficacy data adequate to support the combination therapy indication. The division recommends an "approvable" action on the monotherapy proposal pending further study.

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Approximately 1900 subjects received exenatide in clinical trials. This included 840 who received drug for 6 months or more and 272 who were treated for 12 months or more. Approximately 40% were women, 27% were black or Hispanic. The mean age was 53 with 15% aged over 65 years. Mean baseline BMI was 32.5 kg/m². Over half the patients receiving exenatide in clinical trials received the highest recommended dose of 10 mcg BID.

Three pivotal, 7-month, phase 3 trials of exenatide as adjunctive therapy to other oral antidiabetic therapy were conducted. These were placebo-controlled studies in patients whose glycemia was not adequately controlled on metformin (study 112), SFU (study 113), or both (study 115). In these studies, men and women with DM2 with HbA1c from 7.1% to 11.0%, on maximally effective doses of these other OADs, not previously treated long-term with insulin and not currently treated with TZDs were randomized to exenatide or placebo. In study 115, patients on SFU were further randomized to one of two SFU dosing schemes: either to maintain the high dose with dose reduction as needed to address hypoglycemia, or to reduce the dose to a minimum recommended dose of SFU with upward dose adjustment for elevated fasting glucose. A placebo run-in and four-week initiation phase during which exenatide patients were treated with 5 mcg SQ BID before breakfast and dinner was followed after randomization by a 26-week maintenance phase in which patients were treated, fully blinded, either with placebo, exenatide 5 mcg BID or exenatide 10 mcg BID. The primary endpoint was change from baseline in HbA1c.

The major efficacy and safety results of these pivotal trials are summarized in table 1 of Dr. Gabry's review, reproduced below.

Table 1: Key Results of Exenatide in the long term controlled studies

Study	Metformin 112			SFU 113			Metformin +SFU 115		
	placebo	5 µg	10 µg	placebo	5 µg	10 µg	placebo	5 µg	10 µg
n	113	110	113	123	125	129	247	245	241
Baseline Mean HbA1c	8.20	8.26	8.18	8.69	8.49	8.61	8.49	8.46	8.50
LSM Change HbA1c	-0.00	-0.46	-0.86	0.06	-0.51	-0.91	0.12	-0.66	-0.88
Difference vs. Placebo		-0.46	-0.86		-0.57	-0.97		-0.78	-1.00
2-sided p-value		0.0016	<0.0001		0.0002	<0.0001		<0.0001	<0.0001
Baseline Body Weight (BW)(kg)	99.9	100.0	100.9	99.1	94.9	95.2	99.1	96.9	98.4
BW change at wk 30	-0.3	-1.6	-2.8	-0.6	-0.9	-1.6	-0.9	-1.6	-1.6
% HbA1c ≤ 7%	13%	31.6%	46.4%	8.8%	32.6%	41.3%	9.2%	27.4%	33.5%
Hypoglycemia	6 (5%)	5 (5%)	6 (5%)	4 (3%)	18 (14%)	46 (36%)	31 (13%)	47 (19%)	67 (28%)
Nausea	26(23%)	40(36%)	51 (45%)	9 (7%)	49 (39%)	66 (51%)	50 (21%)	96 (39%)	117 (49%)
anti-exenatide antibody	3 (3%)	44(40%)	51(46%)	2 (2%)	46 (38%)	51 (41%)	13 (5%)	120 (49%)	107 (45%)

With regard to efficacy, across all three studies, a statistically significant (relative to placebo), dose-dependent effect of exenatide on glycemic control was observed. The placebo-subtracted effect after 7 months of treatment for the high 10 mcg BID dose was, across the trials, 0.86 to 1.0 HbA1c percentage units. Across the three trials, up to 45% of exenatide 10 mcg BID-treated patients achieved HbA1c of equal to or less than 7%, compared to 10-15% of placebo patients. The therapeutic effect of exenatide was maintained as evidenced by data from extensions of these three studies to 52 weeks, as shown in figure 1 on page 12 of Dr. Gabry's review.

Exenatide treatment was associated with a dose-dependent reduction in body weight from baseline relative to placebo. In the pooled analysis of the three phase 3 trials of adjunctive therapy, the mean weight loss from baseline to 30 weeks with placebo was approximately 0.5 kg, with exenatide 5 mcg BID it was 1.5 kg, and with exenatide 10 mcg BID it was approximately 2 kg. These effects were significantly different from placebo. Among 163 completers of the extension studies, weight loss relative to baseline was progressive from week 30 to week 52, which a mean loss of 3.6 kg in this cohort.

Dr. Gabry has reviewed the efficacy data in support of monotherapy in DM2 with exenatide. Briefly, the single pivotal trial presented by the sponsor was a small phase 2 study of 28 days duration in patients not adequately controlled on diet, exercise, or oral antidiabetic therapy alone. Previous treatment was discontinued for 4-5 weeks and patients meeting entry criteria were randomized to receive either placebo or one of three dose regimens of exenatide (10 mcg BID, 10 mcg QD, 20 mcg QD). This was a small study, comprising only 99 subjects total, with 74 randomized to exenatide.

Safety

As shown in table 1, relative to placebo, an increase in the percentage of patients reporting hypoglycemia in association with exenatide therapy was only evident in conjunction with SFU therapy. Indeed, it is fully expected that SFU-mediated hypoglycemia (the result of glucose-independent insulin secretion, thus not attenuated in the setting of low glucose) will be elicited as overall glycemia is reduced (and glycemic "control" is improved). This phenomenon is still the limiting factor in general in the control of blood glucose in diabetes, obviously more of a problem with insulin and secretagogues than with other classes of antidiabetic agents. The hypoglycemia risk with exenatide was further characterized by examination of the hypoglycemia data from study 115, in which the patients whose dose was adjusted downward prior to treatment with exenatide experienced less hypoglycemia than those who maintained the high dose they brought to the trial. Needless to say, always the rule in the treatment of diabetes, a lower risk of hypoglycemia was paralleled by somewhat inferior glycemic control.

While a risk of SFU-mediated hypoglycemia associated with exenatide was clearly evident in the phase 3 clinical trials, it is important to point out that the vast majority of episodes were deemed mild to moderate in severity according to protocol-defined criteria. Specifically, in the controlled trials dataset, 189 (20%) exenatide-treated patients reported at least one hypoglycemic event compared to 41 (8%) placebo patients. The hypoglycemia reporting rate was higher with the high dose of exenatide compared to the low dose (25% vs. 15% of patients in the pool of the three studies). The rate of hypoglycemia was also dose related, with a rate of 1.31 events per patient year at the 10 mcg BID dose (compared to 0.35 and 0.60 events per patient year in the placebo and 5 mcg BID groups, respectively). Most of the hypoglycemia events occurred during

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the initial 4 weeks of treatment. Fully three-quarters of the events were classified as mild (transient, no treatment needed, not interfering with activities). In the controlled trials, there was only 1 severe hypoglycemic event reported. Indeed, in the entire development program, there were only 3 instances of hypoglycemia deemed severe. All patients recovered without sequelae. None was admitted to hospital.

Gastrointestinal side effects predominated with exenatide, with approximately half the patients experiencing nausea, at least transient, at the high dose. Gastrointestinal events constituted the most frequently cited reason for dropout, though fewer than 10% of patients overall discontinued due to adverse events. Notably, withdrawal due to loss of glucose control occurred more frequently with placebo, and among exenatide-treated patients, there was an inverse relationship between dose and percent of patients discontinuing for this reason, consistent with the efficacy findings. Only 2% of patients treated with the 10 mcg BID dose discontinued due to loss of glycemic control (defined as either a 1.5% HbA1c percentage unit increase from baseline or an absolute value equal to or greater than 11.5% at protocol-specified time points).

Exenatide is immunogenic in humans. In the 7-month controlled trials, 44% of patients developed antibodies to exenatide. In 86% of the anti-exenatide-positive patients, antibody titers were "low" (i.e., 1/5 to 1/125) by week 30 of therapy. There appeared to be no difference in the glycemic response to exenatide in this subgroup relative to those without antibodies. The other 14% of antibody-positive patients had higher titers (i.e., 1/625 to 1/15,625) at week 30. At week 30, the mean change from baseline in HbA1c was slightly increased in the subgroup with high antibody titers. At week 52, the mean HbA1c in this subgroup was unchanged from baseline, while the subgroups of patients without antibodies or with low titers showed an approximate reduction in HbA1c of 1 percentage unit.. There were no adverse events attributed to immunogenicity per se (i.e., systemic allergic reactions, dermal reactions). A sample of antibody-positive sera did not reveal cross-reactivity with human glucagon or human GLP-1.

These data suggest that anti-exenatide antibodies may explain some of the variability in response to the drug across patients and should be considered in patients who respond poorly or apparently not at all (i.e., glycemic control continues to deteriorate) to exenatide. More information on the "natural history" of the antibody response to exenatide is needed to develop guidance for physicians on the management of apparent non-responders (e.g., discontinue permanently, discontinue and re-institute at a later date, treat through for some period of time). Further analyses of the data are needed to explore other factors that might have led to apparent non-response in patients in the trials. For example, presumably regardless of antibody status, patients whose dose of SFU was reduced prior to initiation of therapy with exenatide did show less of a glycemic response to treatment, in part since the protocol for trial 115 did not include time for establishment of a new baseline for HbA1c after SFU dose reduction. It is also not known from the FDA review whether the tendency of the drug to cause nausea or gastrointestinal distress may also be reduced by high titer antibodies. If so, given the very high percentage of patients experiencing nausea, its absence in conjunction with poor response may signal treatment failure due to antibodies.

Pediatric studies

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The sponsor requested a waiver of pediatric studies for children under age 12 years. The sponsor has identified the 12-16 year old age group as that in which exenatide maybe a suitable treatment and could potentially provide a meaningful benefit. The division proposes a deferral of studies in this age group and further propose that the sponsor commit to a study in children with type 2 diabetes who have not achieved adequate glycemic control on metformin, sulfonylurea, or a combination of the two, with final report by December 31, 2007.

Microbiology

Approval is recommended based on product quality microbiology review. There are no deficiencies noted and no phase 4 commitments recommended.

Device review

Review by CDRH concludes that information provided regarding operation, dose accuracy, performance, stability, and labeling for the Pen-injectors (5 mcg/dose, 10 mcg/dose) is acceptable and from the standpoint of the CDRH consultant, the NDA may be approved.

Chemistry

ONDC recommends approval based on review of the CMC package. Additional information requests are recommended by the ONDC reviewer:

1. A list of which control facilities are utilized for perform various release testing and stability testing for the product
2. Clarification whether the [redacted] process [redacted] and a recommendation that if not, a particular [redacted] degradation product be monitored during storage.

3. [redacted]

4

[redacted]

5

[redacted]

Environmental Assessment

A categorical exclusion from the requirement to prepare an environmental assessment report was proposed and deemed acceptable to ONDC.

Establishment Inspections

Inspections of manufacturing facilities for drug substance and drug product, of testing laboratory, and of the packaging and labeling facility were found acceptable by the Office of Compliance.

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Data integrity/DSI audits

Four investigative sites were audited by DSI related to studies 112, 113, and 115. The global assessment was that the data submitted by these four clinical investigators were acceptable for review.

Amylin contracted its own audit of site 087 based on concerns about compliance with Amylin's SOPs and GCP standards. Based on this audit, all subjects were withdrawn from this site and, at the discretion of each patient, transferred to an alternate site. FDA was notified of these findings and of this action. Sixty-eight patients in the phase 3 trials were affected.

Biopharmaceutics

OCPB finds the application acceptable. The following summarizes key findings of the biopharmaceutics review:

The site of injection of the drug did not impact its PK profile. The Cmax and AUC for the drug are dose proportional for the 5 and 10 mcg doses.

Studies of the pharmacodynamic effects of the drug on modulation of post-prandial glucose excursions suggests the optimum effect occurs with administration from 0 to 60 minutes before the meal. When the drug was given 30 minutes after the start of the meal, there was essentially no effect on the post-prandial glucose profile compared to placebo. In a saline-injection-controlled study of the meal-associated insulin response after intravenous exenatide injection, post-drug insulin secretion was markedly increased over saline placebo in patients with DM2 and similar to or greater than the response in saline-treated normals.

Studies in healthy volunteers demonstrated the glucose-dependent insulinotropic action of exenatide when infused intravenously. At a plasma glucose concentration of 90 mg/dL, exenatide induced a 3.5-fold increase in insulin secretion relative to placebo. At a glucose concentration of 80 mg/dL, this effect was markedly reduced, and at a glucose concentration of 72 mg/dL, the effect was negligible compared to placebo. Counter-regulatory responses (glucagon, epinephrine, norepinephrine, cortisol, and growth hormone) were not affected.

Based on an acetaminophen absorption study, showing a delay in Tmax of acetaminophen by 3.6 hours, exenatide markedly delayed gastric emptying.

Exenatide delayed the absorption but did not affect the steady state kinetics of digoxin. Exenatide co-administration reduced the AUC and Cmax of lovastatin by 40% and 28%, respectively.

The drug is primarily renally cleared. In patients with mild to moderate renal impairment, the clearance of exenatide was not affected compared to healthy subjects. No dose adjustment is necessary for mild to moderate renal impairment. Clearance was markedly reduced in patients with ESRD and the labeling recommends against its use in these patients.




OCPB recommends the following additional information be obtained, and I concur.

1. As a phase 4 commitment, a pharmacokinetic drug interaction study with a combination oral contraceptive product to inform labeling regarding appropriate timing of dosing relative to exenatide administration.
2. As further information not in the form of a formal commitment, additional investigations of the mechanism(s) of the lovastatin interaction. Additionally, further studies of the effects of exenatide on the bioavailability of drugs that are labeled to be taken with food (either for purposes of mitigating tolerability issues or to enhance extent of absorption).

Pharmacology

Pharmacology-toxicology recommends approval. The drug was minimally toxic in gram/kg single doses in mice, rats, and monkeys. There was minimal toxicity in mice, rats, and monkeys in chronic repeat dose studies at doses up to 760, 250, and 150 mcg/kg/day, respectively. The drug was neither clastogenic nor mutagenic, nor tumorigenic in mice. In rats, there was an increased incidence of thyroid C-cell adenomas in females receiving doses producing 95 times the human exposure at 10 mcg BID relative to controls. The drug produced no impairment in fertility in male or female mice. The drug was not teratogenic in mice or rabbits at doses in marked excess of human exposures.


ODS/DDMAC

DMETS recommends against use of the proprietary name, Byetta, citing look-alike, sound-alike potential confusion with Diabeta, Zyrtec, Zebeta,  and Viagra. As all but  are oral dosage forms ( is dosed intravaginally) and Byetta is an injection, the division does not believe that medication errors at the patient level are at all likely. That is, patients prescribed the other products will not know what to do with an injection if it were dispensed, and patients prescribed Byetta should have been informed by the prescribing office that they will be dispensed an injection. Indeed, insofar as the drug is not approved for use (nor yet recommended for use) with insulin, most patients prescribed Byetta will need training on self-injection. Therefore, if an oral drug is dispensed, the patient should immediately recognize the error. We therefore find the proposed name Byetta acceptable.

DMETS also had comments about the pen injector, including that manipulation of the pen might be difficult for patients with dexterity or vision problems, common in the diabetic population. They also commented about recapping of needles after injection and manual removal of the needles on the multi-dose pen device. These are issues common to all multi-dose insulin pens which are used commonly by patients with both DM1 and DM2. Indeed, since Byetta pens are not dose adjustable (as are insulin pens), but rather come as either 5 mcg/dose or 10 mcg/dose denominations, they are simpler to use than insulin pens. The division does not believe the pen needs to be simplified with regard to capping and removing/replacing needles.

Risk management

The sponsor proposed a risk management plan with general goals of understanding the risks of exenatide in the commercial environment, understanding how these risks might differ from those identified in the clinical trials program, understanding whether there are immune-related risks, and understanding whether there are risks to pregnant women and fetuses with exenatide exposure. The risk management plan is discussed in detail in Dr. Gabry's review, beginning on page 140. At present, there are no proposals for use of other than routine pharmacovigilance

NDA 21-773, 
 Byetta (exenatide injection)
 Treatment of DM2

tools and analysis of data from ongoing and future clinical trials to address these issues. I concur with these proposals and plans.

In addition to labeling addressing risks and methods of safe and effective use, currently under discussion, the sponsor intends to have a health care practitioner call center that will be identified on all information pieces and promotional materials.

Labeling

Final labeling has been negotiated. The division did not accept statements about _____ associated with exenatide therapy. The label contains sufficient information to describe the mechanism of action of exenatide to promote glucose-dependent insulin secretion by the beta cell. _____

Labeling to address the need to consider the potential impact of concomitant administration of exenatide and certain drugs (e.g., oral contraceptives) whose effect is dependent on C_{max} has been added. In addition, language has been added stating that the impact of exenatide on the absorption and effectiveness of oral contraceptives has not been investigated.

Phase 4 commitments

As above, a drug interaction study with oral contraceptives to assess the effects of exenatide on the PK of the components of the OC.

Recommendation

NDA 21-773, proposing the use of exenatide in patients with DM2 not adequately controlled on metformin, sulfonylurea, or the combination of the two, should be approved, pending final labeling.

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/s/

David Orloff
4/25/05 03:06:07 PM
MEDICAL OFFICER

Robert Meyer
4/26/05 10:59:59 AM
MEDICAL OFFICER

**ADRA Rev #1 of Action Package for NDAs 21-773 — Byetta (exenatide)
Injection**

Reviewer: Lee Ripper, HFD-102

Date received: April 15, 2005

Date of review: April 18, 2005

Date original NDA received: June 30, 2004

UF goal date: April 29, 2005

ACTION DATE: April 27, 2005

Proposed Indication:

NDA 21-733: To improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control on metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

Action type: NDA 21-733: AP

RPM: Lina AlJuburi

Drug Classification: 1SV

505(b)(1) application

Patent Info on form FDA 3542a: Received

Debarment Certification: AC

Safety Update: in MOR.

Clinical Inspection Summary: 4 sites inspected, data AC, 3/22/05.

ODS/DMETS Review of Proprietary Name: DMETS does not recommend use of name Byetta, review #2 dated 3/11/05

DSRCS Review of PPI: 2/1/05

DDMAC Review: Review of PI, 4/7/05. Per DMETS review, DDMAC find name Byetta AC.

EA: CMC #1, page 66: categorical exclusion

EER: AC 12/7/04.

Financial Disclosure: AC.

CMC section to Eric Duffy, 4/19/05

P/T section to Ken Hastings, 4/19/05

1. Letters revised to include my comments.

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/s/

Leah Ripper
4/27/05 05:08:18 PM
CSO

19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Sam S. Miller, M.D.
S.A.M. Clinical Research Center
7711 Louis Pasteur Drive, Suite 300
San Antonio, Texas 78229

MAR 22 2005

Food and Drug Administration
Rockville MD 20857

Dear Dr. Miller:

Between January 10 to February 4, 2005, Mr. James H. Robinson, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of the following clinical investigations of the investigational drugs [REDACTED] (exenatide injection) sponsored by [REDACTED] Amylin Pharmaceuticals, Inc., respectively:

[REDACTED]

Protocol #2995-115, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Twice Daily in Subjects with Type 2 Diabetes Mellitus Treated with Metformin and a Sulfonylurea"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection reports and the documents submitted with the reports, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Robinson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN/FEI: _____

Field Classification: NAI

Headquarters Classification:

☒ 1)NAI

☐ 2)VAI- no response required

☐ 3)VAI- response requested

☐ 4)OAI

cc:

HFA-224

HFD-510 Doc.Rm. NDA#s _____ '21-773

HFD-510 Review Div.Dir./Orloff

HFD-510 MO/Gierhart/Gabry

HFD-510 PM/Hedin/Aljuburi

HFD-46/47c/t/s/ GCP File #9368

HFD-46/47 GCP Reviewer/Slavin

HFR-SW150 DIB/Glasgow

HFR-SW1540 Bimo Monitor/Martinez

HFR-SW1540 Field Investigator/Robinson

HFR-SW140 DCB/Rodriguez—release EIR per FMD-145

GCF-1 Seth Ray

r/d: (AS): 3/10/05
reviewed:NK: 3/21/05
f/t:as: 3/22/05

o:\slavin\untitled letters\Miller letter

Reviewer Note to Rev. Div. M.O.

This was a routine inspection of Dr. Miller conducted in support of NDAs — 21-773.

#2993-115 (exenatide injection)

Dr. Miller screened 56 subjects and enrolled/randomized 30 subjects. Twenty-six subjects completed the study. The inspection encompassed an audit of informed consent forms for all 56 subjects. Fourteen of 30 subjects' records were audited in-depth for data integrity. In general, data in sponsor provided data listings were supported by data in source documents and CRFs at the site. No objectionable conditions were noted. Form FDA 483 was not issued. The inspection was limited due the blinding of the clinical investigator to HbA_{1c} values; therefore, the data could not be audited at the site. Data will be audited at the central lab —
— Data from this site are acceptable.

The inspection is classified as NAI.

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/s/

Ni Aye Khin
4/4/05 02:50:20 PM

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 16, 2005

TO: David Orloff, MD, Director
Division of Metabolic and Endocrine Drug Products (DMEDP),
HFD -510

FROM: Claudia B. Karwoski, Pharm.D.,
Scientific Coordinator for Risk Management Programs (detail)
Office of Drug Safety, HFD-400

DRUG: [REDACTED] (exenatide injection)

NDA#: 21-773

APPLICANT: Amylin Pharmaceuticals, Inc.

SUBJECT: Review of Proposed Risk Management Program (RMP) submitted
June 24, 2004

PID #: D040527

INTRODUCTION/BACKGROUND

The Office of Drug Safety (ODS) has reviewed the proposed Risk Management Program (RMP) for [REDACTED], as submitted on June 24, 2004, and concludes that it does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance. The other measures proposed by the sponsor including the studies to evaluate the effect of anti-exenatide antibodies and the plan for an observational study to determine if there is any risk to the pregnant woman or developing fetus seem reasonable but would appear to be routine given the potential or theoretical risk.

Exenatide is an injectable hypoglycemic agent belonging to a new class known as incretin mimetics. The proposed indication is to improve glycemic control in patients with type 2 diabetes mellitus either alone or as an adjunctive therapy to metformin, a sulfonylurea, or a

combination of metformin and a sulfonylurea. Exenatide will be given subcutaneously twice daily before meals at a dose of 5 mcg or 10 mcg via a prefilled pen.

In the long-term, controlled studies, treatment-emergent adverse events with an incidence of at least 5% and a greater incidence with exenatide- than placebo-treated patients were nausea, hypoglycemia, vomiting, diarrhea, feeling jittery, dizziness, headache, and dyspepsia. The incidence of hypoglycemia was 20% for exenatide versus 8% in placebo-treated patients. This imbalance was observed only in patients receiving exenatide in combination with a sulfonylurea drug.¹

Eddie Gabry, M.D., the medical officer assigned to the clinical review of this NDA, indicated in a meeting with the Office of Drug Safety on September 30, 2004 and again on March 8, 2005 that risk management measures beyond professional and patient labeling to address the risk of hypoglycemia were not warranted. He verified that the sponsor's assessment of the risk of hypoglycemia was accurate, that the hypoglycemia observed in the clinical trials, was mostly mild or moderate in nature. There was only one subject who developed hypoglycemia rated as severe.

The sponsor has also identified potential risks that are not yet adequately characterized. These include:

- 1) unknown risks posed by an increase in anti-exenatide antibodies
- 2) unknown risk to the fetus exposure to exenatide

REVIEW OF PROPOSED RMP

The proposed risk management goals are to:

- Understand the known risks of exenatide treatment in the commercial environment.
- Understand whether there are risks in patient populations different from those identified in the clinical program or occurring at a frequency too low to have been previously detected.
- Understand whether there are immune-related risks associated with exenatide treatment.
- Understand whether there are risks to pregnant women and fetuses who are exposed to exenatide.

To address the known gastrointestinal risks the risk of hypoglycemia as well as the unknown risks referred to above, Amylin proposes to utilize standard informational tools (professional and patient labeling and medical education) as well as pharmacovigilance/surveillance activities.

Professional and Patient Labeling

The sponsor proposes to address the risk of hypoglycemia in the *Precautions* section of the professional label.

¹ Exenatide (AC2993, LY2148568) Risk Management Plan (NDA 21-773, June 22, 2004); Section .2.2: pg 6-8.

Hypoglycemia

hypoglycemia was recorded if the patient reported symptoms subjectively associated with hypoglycemia with an accompanying blood glucose <60 mg/dL or if symptoms were reported without an accompanying blood glucose measurement. When [REDACTED] was used in combination with metformin, no increase in the incidence of hypoglycemia was observed over that of placebo in combination with metformin. In contrast, when [REDACTED] was used in combination with a sulfonylurea, the incidence of hypoglycemia was increased over that of placebo in combination with a sulfonylurea. Therefore, patients receiving [REDACTED] in combination with a sulfonylurea may have an increased risk of hypoglycemia (see ADVERSE REACTIONS, Table [REDACTED]). To reduce the risk of hypoglycemia associated with the use of a sulfonylurea, reduction in the dose of sulfonylurea may be considered (see DOSAGE AND ADMINISTRATION).

[REDACTED] did not alter the counter-regulatory hormone responses to insulin-induced hypoglycemia in a randomized, double-blind, controlled study in healthy subjects.

The professional label will also be utilized to convey information about the gastrointestinal adverse effects, the lack of association of adverse events with the presence of anti-exenatide antibodies, and precautionary language regarding use of exenatide during pregnancy.

A separate Patient Package Insert (PPI) consult was performed by the ODS Division of Surveillance, Research and Communication Support (DSRCS)².

Pharmacovigilance/Surveillance Activities

- The sponsor proposes standard pharmacovigilance and safety surveillance to identify potential signals in accordance with CFR 314.80.
- There are several active studies in place to evaluate the characteristics of the anti-exenatide antibody response and the safety profile over an extended timeframe.
- The sponsor plans to address the unknown effects of exenatide use during pregnancy through an observational study to determine if there is any risk to the pregnant woman or developing fetus.

Evaluation

The Sponsor proposes to assess process metrics and outcome metrics. However it is not clear what processes or outcomes they plan to measure. The quality of their evaluation plan thus cannot be assessed.

CONCLUSION

The sponsor's proposed Risk Management Plan for exenatide, NDA 21-773, with regard to the risk of hypoglycemia does not appear to differ substantially from a typical new product labeling and routine passive post-marketing safety surveillance. The other measures proposed by the sponsor including the studies to evaluate the effect of anti-exenatide antibodies and the

² Jeanine Best, M.S.N., R.N., P.N.P., DSRCS Review of Patient Labeling for [REDACTED] February 1, 2005.

plan for an observational study to determine if there is any risk to the pregnant woman or developing fetus seem reasonable but would appear to be routine given the potential or theoretical risk.

The Division of Surveillance, Research and Communication Support (DSRCS) completed a separate Patient Package Insert (PPI) consult² and the Division of Medication Error and Technical Support (DMETS) conducted a separate review of the proprietary name, container labels, carton and insert labeling, and pen device³. If the sponsor or the review division identifies a safety concern and determines that a Risk Minimization Action Plan (RiskMAP) is warranted or should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

/s/

Claudia B. Karwoski, Pharm.D., Scientific Coordinator (detail)
Office of Drug Safety, HFD-400

³ Felicia Duffy, R.N., DMETS Proprietary Name Review of [REDACTED], February 14, 2005.

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/s/

Mary Dempsey
3/18/05 10:00:47 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
3/18/05 04:15:57 PM
DRUG SAFETY OFFICE REVIEWER

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

For Consulting Center Use Only:

Date Received: 8/26/04
Assigned to: PRS
Date Assigned: 8/26/04
Assigned by: Tony Watson
Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF Z-480
Consulting Reviewer Name: Pandu Soprey
Building/Room #: CORP, Rm 340-L
Phone #: 301-594-1287 x178
Fax #: 301-480-3002
Email Address: prs@cdhrh.fda.gov
RPM/CSO Name and Mail Code: _____

From (Originating Center):

Center: CDER
Division: Division of Metabolic and Endocrine Drug Products
Mail Code: HFD-510
Requesting Reviewer Name: Lina AlJuburi
Building/Room #: PKLN, Rm 14B-45
Phone #: 301-827-6414
Fax #: 301-443-9282
Email Address: aljuburi@cdcr.fda.gov
RPM/CSO Name and Mail Code: Lina AlJuburi, HFD-510
Requesting Reviewer's Concurring
Supervisor's Name: Kati Johnson, R.Ph.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: August 20, 2004

Requested Completion Date: March 4, 2005

Submission/Application Number: NDA 21-773
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☒ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination
☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: June 30, 2004

Official Submission Due Date: April 30, 2005

Name of Product: (exenatide injection)

Name of Firm: Amylin Pharmaceuticals, Inc.

Intended Use: to improve glycemic control in patients with type 2 diabetes mellitus as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

NDA 21-773 was submitted electronically as an eCTD submission and can be found in the cdr through EVS. A paper copy of the labeling and working models of the pen-injectors to be used for drug administration (both the 5 and 10 mcg doses) are being provided for your review. Please let me know if there is anything else you need.

Documents to be returned to Requesting Reviewer? ☐ Yes ☒ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☒ Consultative Review ☐ Collaborative Review

(exenatide injection) is a new molecular entity for the treatment of type 2 diabetes. The route of administration is an injection with a prefilled pen. DMEDP is consulting you in regard to the approvability of this prefilled pen for patient use.

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/s/

Lina Aljuburi

8/20/04 01:12:39 PM

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

NDA 21-773 Exenatide Injection

NDA number: 21-773

Sponsor: Amylin Pharmaceuticals, Inc.

Proposed Indication: To improve glycemic control in patients with type 2 diabetes mellitus as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

1. **What age ranges are included in your waiver request?**

Amylin Pharmaceuticals, Inc. is not planning to conduct pediatric studies in the following age groups:

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)

2. **Reasons for waiving pediatric studies:**

- (a) No meaningful therapeutic benefit over existing treatments **and** is unlikely to be used in a substantial number of pediatric patients
- (b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed
- ~~(c) The product would be ineffective or unsafe in all pediatric age groups~~
- ~~(d) Attempts to develop a pediatric formulation for a specific age group have failed~~
- (e) Disease-specific waiver indicated for the treatment of the condition in adults (please check)

<input type="checkbox"/> Alzheimer's disease	<input type="checkbox"/> Age-related macular degeneration
<input type="checkbox"/> Prostate Cancer	<input type="checkbox"/> Breast cancer
<input type="checkbox"/> Renal cell cancer	<input type="checkbox"/> Non-germ cell ovarian cancer
<input type="checkbox"/> Hairy cell cancer	<input type="checkbox"/> Pancreatic cancer, colorectal cancer
<input type="checkbox"/> Osteoarthritis	<input type="checkbox"/> Squamous cell cancers of the oropharynx
<input type="checkbox"/> Uterine cancer	<input type="checkbox"/> Basal cell and squamous cell cancer
<input type="checkbox"/> Endometrial cancer	<input type="checkbox"/> Small cell and non-small cell lung cancer
<input type="checkbox"/> Parkinson's disease	<input type="checkbox"/> Amyotrophic lateral sclerosis
<input type="checkbox"/> Arteriosclerosis	<input type="checkbox"/> Symptoms of menopause
<input type="checkbox"/> Infertility	<input checked="" type="checkbox"/> Other (please state and justify)

Justification for not conducting studies in all pediatric age groups for type 2 diabetes mellitus: While the majority of patients with type 2 diabetes are adults over the age of 18 years, there is an increasing incidence of adolescent-onset type 2 diabetes in patients age 12 to 16 years old. Amylin has identified 12 to 16 year old patients with type 2 diabetes as the age group in which BYETTA™ may be used and could therefore provide a meaningful benefit. Thus, this would be a partial waiver of the pediatric ruling limiting development of BYETTA™ to adolescent patients ages 12 to 16 years.

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On Original**

REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

NDA 21-773 Exenatide Injection

On 02 February 2004, a Pre-NDA meeting was held with Amylin Pharmaceuticals, Inc. (Amylin) and the Division of Metabolic and Endocrine Drug Products, whereby Amylin requested and was granted a pediatric deferral. Please refer to Question 21 of FDA minutes dated 27 February 2004.

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On Original*

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✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling



FEB 28 2005

Food and Drug Administration
Rockville MD 20857

Waldo Harvey Jr., M.D.
Gold Coast Internal Medicine
1009 N. Clark Street
Chicago, Illinois 60610

Dear Dr. Harvey:

Between December 6 and 28, 2004, Mr. Kujtim Sadiku, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #2993-115 entitled: "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Twice Daily in Subjects with Type 2 Diabetes Mellitus Treated with Metformin and a Sulfonylurea") of the investigational drug [REDACTED] (exenatide injection), performed for Amylin Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Sadiku presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your responses, dated January 20 and February 3, 2005, and wish to emphasize the following:

1. You did not adhere to the investigational plan [21 CFR 312.60].
 - a. The protocol required a serum FSH measurement for postmenopausal women taking no hormonal replacement therapy; or a serum pregnancy test for surgically sterile women to eliminate the possibility of a tubal or ectopic pregnancy, and for those who are of child-bearing potential who practice appropriate contraceptive methods, at screening (visit 1).

Subject 08827 did not have a serum pregnancy test performed at visit 1 on [REDACTED]
The subject was randomized into the study on [REDACTED]

- b. The protocol required a body mass index (BMI) of 27 kg/m² to 45 kg/m² to be enrolled in the study. Subject 08806 had an exclusionary BMI of 24 kg/m² and was enrolled in the study.
 - c. The protocol required subjects in the Minimum Recommended Dose (MinRD) Sulfonylurea (SFU) Management Group to have their SFU dose reduced to the minimum recommended dose at visit 3. The dose of glyburide for subject 08832 was not reduced to 1.25 mg/day at visit 3.

2. You did not promptly report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66].

Subject 08846 experienced a serious adverse event (SAE) of cellulitis requiring hospitalization on [REDACTED]. You were aware of this SAE on [REDACTED] however, the IRB was not informed of this SAE until [REDACTED].

3. You did not adequately obtain informed consent [21 CFR 50.20].
 - a. Subject 08339 was initially consented on [REDACTED] with a consent form for study 2993-112. The subject did not sign a consent form for study 2993-115 until visit 8 on [REDACTED].
 - b. Subject 08841 signed an out-dated version of the consent form and was not re-consented with the [REDACTED] version of the consent form.

We acknowledge your commitment as stated in your January 20 and February 3, 2005 written responses, to make appropriate changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Sadiku during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,



Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN/FEI: .

Field Classification: OAI

Headquarters Classification:

- ☐ 1)NAI
- ☐ 2)VAI- no response required
- ☐ 3)VAI- response requested
- ☒ 4)VAI-RR-response received and accepted
- ☐ 5)OAI

If Headquarters classification is a different classification, explain why: Dr. Harvey has provided an acceptable response to the observations noted on Form FDA 483.

Deficiencies noted:

- ☒ failure to obtain subject consent (02)
- ☒ failure to adhere to protocol (05)
- ☒ failure to notify IRB of changes, failure to submit progress reports (15)

Deficiency Codes: 2, 5, 15

cc:

HFA-224
HFD-510 Doc.Rm. NDA#21-773
HFD-510 Review Div.Dir./Orloff
HFD-510 MO/Gabry
HFD-510 PM/Aljuburi
HFD-46/47c/r/s/ GCP File #11387
HFD-46/47 GCP Reviewer/Slavin
HFR-CE650 DIB/Berg
HFR-CE6520 Bimo Monitor/Yuscus
HFR-CE650 Field Investigator/Sadiku
HFR-CE640 DCB/Harrison—release EIR per FMD-145
GCF-1 Seth Ray

r/d: (AS): 2/14/05, 2/18/05, 2/25/05
reviewed:NK: 2/24/05
f/t:as: 2/25/05

o:\slavin\untitled letters\Harvey letter

Reviewer Note to Rev. Div. M.O.

This was a routine, pre-approval, PDUFA inspection of Dr. Harvey conducted in support of NDA 21-773. This was his initial inspection. Dr. Harvey conducted the study in collaboration with a site management organization (SMO). Dr. Harvey screened 67 subjects; enrolled 35 subjects and randomized 32 subjects. Twenty-six subjects completed the study. All subjects' records were audited for the presence of a signed and dated consent form. Twelve subjects' records were audited in-depth for data integrity. At the completion of the inspection, a 6-page Form FDA 483 was issued to Dr. Harvey. The following observations were listed on Form FDA 483: 4 subjects received restricted concomitant medications, 25 protocol deviations were reported post study, 2 subjects were enrolled with clinically significant abnormal lab results, 1 subject enrolled who had less than 5 years remission from a clinically significant malignancy, 1 subject who increased metformin and 1 subject who did not decrease glyburide as required by the protocol, 2 SAEs that were not reported to the sponsor per protocol, 4 subjects who missed doses of study medication, 4 subjects who did not have FSH/pregnancy test performed at visit 1, 1 subject with an exclusionary BMI, 1 subject who did not inject herself with the study medication at 2 visits, 2 subjects with one out-of-window visit, 2 reports submitted late to the IRB, 2 SAEs that were reported late to the IRB, informed consent issues, drug accountability issues and 1 discrepancy between the source document and the CRF for 1 subject.

Dr. Harvey submitted a written response to Form FDA 483 in which he refuted some, but not all, of the observations. The following deviations were noted during the inspection, but are not listed on the data listing provided by the sponsor:

#08824—prescribed Vicodin after an appendectomy

#08832—violated inclusion criterion #11 (abnormal LFTs)

#08853—prescribed Valium while hospitalized

#08845—prescribed Reglan, Darvon, Fentanyl, Xanax and Valium while hospitalized, and increased metformin dose during the study

The major deviations and the observations that were not refuted in his written response have been cited in the letter. Data are acceptable in support of NDA 21-773. The inspection is classified as VAI-RR, response received and accepted.

Note: The inspection was limited due to the blinding of clinical investigators to the primary efficacy variable. An inspection assignment has been issued to audit the primary efficacy variable data—HbA_{1c} values—at [REDACTED]

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 1/13/05	DESIRED COMPLETION DATE: 3/4/05 PDUFA DATE: 4/30/05	ODS CONSULT #: 05-0014
TO: David Orloff, MD Director, Division of Metabolic and Endocrine Drug Products HFD-510		
THROUGH: Lina AlJuburi Project Manager HFD-510		
PRODUCT NAME: Byetta™ (Exenatide Injection) 0.25 mg/mL NDA#: 21-773		NDA SPONSOR: Amylin Pharmaceuticals
SAFETY EVALUATOR: Felicia Duffy, RN		
RECOMMENDATIONS: 1. DMETS does not recommend the use of the proprietary name, Byetta. 2. DMETS recommends implementation of the label and labeling revisions outlined in section III of ODS consult #03-0287-1 in order to minimize potential errors with the use of this product. 3. DDMAC finds the proprietary name Byetta acceptable from a promotional perspective.		
Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664		Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 18, 2005

NDA# 21-733

NAME OF DRUG: Byetta™
(Exenatide Injection)
0.25 mg/mL

NDA HOLDER: Amylin Pharmaceuticals

***** NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary name, "Byetta", regarding potential name confusion with other proprietary or established drug names. The sponsor initially submitted [REDACTED] as the proprietary name (ODS consults #03-0287 and 03-0287-1). DMETS had no objections to the use of the name [REDACTED]. However, the sponsor prefers to use Byetta as the primary proprietary name in lieu of [REDACTED] per the Division Project Manager's correspondence. DMETS reviewed the container labels, carton and insert labeling with the previous [REDACTED] submission. Revised labels and labeling were not submitted. Therefore, refer to ODS consult # 03-0287-1 section III for label and labeling comments.

PRODUCT INFORMATION

Byetta (Exenatide Injection) is an anti-hypoglycemic agent. It is indicated to improve glycemic control in patients with type 2 diabetes mellitus alone or as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. Byetta will be given subcutaneously twice daily before meals at a dose of 5 mcg or 10 mcg via a prefilled pen. Each prefilled pen will deliver 60 doses. Byetta will be supplied as a 0.25 mg/mL solution. The product should be stored in the refrigerator and protected from light.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2}, as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Byetta to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Byetta. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Byetta acceptable from a promotional perspective.
2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Byetta. Additionally, through independent analysis, the drug name **—**^{***} was identified as having the potential for confusion with Byetta. These products are listed in table 1 (see pages 3 and 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Byetta	Exenatide Injectable: 0.25 mg/mL	5 mcg to 10 mcg subcutaneously twice daily.	
Diabeta	Glyburide Tablets: 1.25 mg, 2.5 mg, 5 mg	<u>Initial dose:</u> 2.5 mg to 5 mg by mouth daily with first main meal. <u>Maintenance dose:</u> 1.25 mg to 20 mg by mouth daily (given as a single dose or in divided doses).	SA

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

***** NOTE:** This review contains confidential and proprietary information that should not be released to the public.***

Product Name	Established Name, Dosage form(s)	Usual adult dose	Other
Byetta	Lixenatide Injectable: 0.25 mg/mL	5 mcg to 10 mcg subcutaneously twice daily	
Zyrtec	Cetirizine HCl Tablets: 5 mg, 10 mg Syrup: 5 mg/5 mL	5 mg to 10 mg by mouth once daily.	LA
Zebeta	Bisoprolol Fumarate Tablets: 5 mg, 10 mg	5 mg to 20 mg by mouth once daily.	LA/SA
<hr/>			
Viagra	Sildenafil Citrate Tablets: 25 mg, 50 mg, 100 mg	50 mg by mouth approximately 1 hour before sexual activity. Maximum dosing frequency is once per day.	SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike) ***Name pending approval. Not FOI releasable.			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Byetta were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:


Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Byetta with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Byetta (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> <i>Byetta</i> <i>Sig: 5mcg BID SC</i> <i>Before meals #1</i>	<p>Byetta Sig: 5 mcg twice a day subcutaneously Before meals Dispense 1</p>
<u>Inpatient RX:</u> <i>Byetta 5mcg bid SC before meals #1</i>	


2. Results:

One respondent from the verbal study interpreted the proposed name as "Viada". Two additional respondents from the same study interpreted the name as "Viata" which sounds similar to the currently marketed product, Viagra. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Byetta, the primary concerns related to look-alike and sound-alike confusion with Diabeta, Zebeta, Zyrtec, and Viagra. Similarly, through independent review, one additional drug name,  ^{***}, was also determined to have potential for confusion with Byetta.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Byetta.

Upon further review of the names gathered from EPD and independent analysis, the names Viagra and  ^{***} were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Byetta in addition to numerous differentiating product characteristics such as product strength, indication for use, frequency of administration, route of administration and dosage form.

1. Zyrtec may look similar to Byetta when scripted. Zyrtec is indicated for the treatment of chronic urticaria, and perennial and seasonal allergic rhinitis. Zyrtec and Byetta contain six letters and share the letter "y" in the second position. In addition, the letter "B" in Byetta and the letter "Z" in Zyrtec may look similar when scripted. Furthermore, the ending of each name may appear similar when they are not prominently scripted ("tta" vs. "tec"). Differentiating product characteristics include indication for use (allergies vs. diabetes), frequency of administration (once daily vs. twice daily), route of administration (oral vs. subcutaneous), dosage form (tablet, syrup vs. injection), and storage conditions (room

^{***} NOTE: This review contains confidential and proprietary information that should not be released to the public.^{***}

temperature vs. refrigerator). However, Zyrtec and Byetta share overlapping numerals in the usual dose and similar dosing units (5 mg, 10 mg vs. 5 mcg, 10 mcg). The Zyrtec dose and the Byetta dose may easily be confused since 5 mg and 10 mg looks almost identical to 5 mcg and 10 mcg. Additionally, both products may be written with the directions: "Use as directed. Dispense 1 month supply". Despite the difference in frequencies of administration, (QD vs. BID), this may not serve as a sufficient differentiating characteristic, as shown in post marketing medication error reports (e.g. Amaryl and Reminyl). For example, a written outpatient prescription for "Zyrtec 5 mg QD UD" may be misinterpreted as "Byetta 5 mcg QD UD". Although the patient is likely to recognize the medication error prior to administering the wrong drug, the confusion and error has nonetheless already occurred. Furthermore, if Zyrtec and Byetta are used concomitantly in an inpatient setting, it is possible to receive a D/C, or discontinue order, for either drug. If the order received reads as "D/C Zyrtec" and it is misinterpreted as "D/C Byetta", the incorrect drug will be discontinued which could potentially lead to an episode of hyperglycemia. Contrarily, if the order received reads as "D/C Byetta" and is misinterpreted as "D/C Zyrtec", the patient will miss a dose of their allergy medication, but more importantly, the patient may experience hypoglycemia, especially if a new diabetic agent is added to the patient's order set with the expectation that Byetta would be discontinued. Due to the strong orthographic similarities and overlapping product characteristics, there is an increased risk of medication errors between Zyrtec and Byetta.

Byetta / Zyrtec

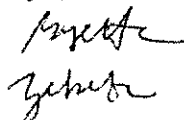
Byetta

Zyrtec

2. Diabeta may sound similar to Byetta when pronounced. Diabeta is indicated for the treatment of type 2 diabetes. Diabeta and Byetta may sound similar because the ending of each name is phonetically similar ("eta" vs. "etta"). Although Diabeta contains four syllables, it may be pronounced as only three syllables if the letter "a" is not enunciated, and the name is pronounced as "Di-beta". Under these circumstances, Diabeta and Byetta may have increased phonetic similarities. In addition, the beginning of the names have phonetic similarity due to their rhyming quality ("Di" vs. "By"). However, the letter "b" in the middle of Diabeta and the "yet" sound in the middle of Byetta help to distinguish between the two names. Diabeta and Byetta share overlapping numerals in the usual dose and similar dosing units (5 mg, 10 mg vs. 5 mcg, 10 mcg), indication for use (type 2 diabetes), frequency of administration (twice daily), and patient and prescriber population. Despite the overlapping characteristics, Diabeta and Byetta differ in route of administration (oral vs. subcutaneous), dosage form (tablet vs. injection), and storage conditions (room temperature vs. refrigerator). Although Diabeta and Byetta share several overlapping product characteristics, the lack of prominent phonetic similarities minimize the potential for medication errors between the two drug products.
3. Zebeta may look similar to Byetta when scripted. Zebeta is indicated for the treatment of hypertension. The letter "B" in Byetta and the letter "Z" in Zebeta may look similar when scripted. Additionally, the endings may appear orthographically similar ("eta" vs. "etta"). However, the letter "y" in Byetta is orthographically distinct from the letters "eb" in Zebeta due to the downstroke of the letter "y" and the upstroke of the letter "b". Zebeta and Byetta share overlapping numerals in the usual dose and similar dosing units (5 mg vs. 5 mcg). Both drugs may also overlap in patient population. Differentiating product characteristics between Zebeta

and Byetta include indication for use (hypertension vs. diabetes), frequency of administration (once daily vs. twice daily), route of administration (oral vs. subcutaneous), dosage form (tablet vs. injection), and storage conditions (room temperature vs. refrigerator). Overall, the lack of convincing orthographic similarity between Zebeta and Byetta will help to minimize the risk of confusion and error between the drug products.

Byetta / Zebeta

Handwritten signatures of the drug names Byetta and Zebeta, showing their orthographic similarity.


III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Byetta. In reviewing the proprietary name, the primary concerns related to look-alike confusion with Zyrtec.

Zyrtec may look similar to Byetta when scripted. Zyrtec is indicated for the treatment of chronic urticaria, and perennial and seasonal allergic rhinitis. Zyrtec and Byetta contain six letters and share the letter "y" in the second position. In addition, the letter "B" in Byetta and the letter "Z" in Zyrtec may look similar when scripted. Furthermore, the ending of each name may appear similar when they are not prominently scripted ("tta" vs. "tec"). Differentiating product characteristics include indication for use (allergies vs. diabetes), frequency of administration (once daily vs. twice daily), route of administration (oral vs. subcutaneous), dosage form (tablet, syrup vs. injection), and storage conditions (room temperature vs. refrigerator). However, Zyrtec and Byetta share overlapping numerals in the usual dose and similar dosing units (5 mg, 10 mg vs. 5 mcg, 10 mcg). The Zyrtec dose and the Byetta dose may easily be confused since 5 mg and 10 mg looks almost identical to 5 mcg and 10 mcg. Additionally, both products may be written with the directions: "Use as directed. Dispense 1 month supply". Despite the difference in frequencies of administration, (QD vs. BID), this may not serve as a sufficient differentiating characteristic, as shown in post marketing medication error reports (e.g. Amaryl and Reminyl). For example, a written outpatient prescription for "Zyrtec 5 mg QD UD" may be misinterpreted as "Byetta 5 mcg QD UD". Although the patient is likely to recognize the medication error prior to administering the wrong drug, the confusion and error has nonetheless already occurred. Furthermore, if Zyrtec and Byetta are used concomitantly in an inpatient setting, it is possible to receive a D/C, or discontinue order, for either drug. If the order received reads as "D/C Zyrtec" and it is misinterpreted as "D/C Byetta", the incorrect drug will be discontinued which could potentially lead to an episode of hyperglycemia. Contrarily, if the order received reads as "D/C Byetta" and is misinterpreted as "D/C Zyrtec", the patient will miss a dose of their allergy medication, but more importantly, the patient may experience hypoglycemia, especially if a new diabetic agent is added to the patient's order set with the expectation that Byetta would be discontinued. Due to the strong orthographic similarities and overlapping product characteristics, there is an increased risk of medication errors between Zyrtec and Byetta.

Byetta / Zyrtec

Handwritten signatures of the drug names Byetta and Zyrtec, showing their orthographic similarity.

The container labels, carton and insert labeling of Byetta were previously reviewed with the  consult. Please refer to ODS consult # 03-0287-1 for DMETS' recommendations.

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name Byetta.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of ODS consult #03-0287-1 in order to minimize potential errors with the use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Byetta acceptable from a promotional perspective

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. Byetta Prescription Study Results

Written Inpatient	Written Outpatient	Verbal
Bayetta	Bijetta	Bieta
Bizetta	Bijette	Byetta
ByeHA	Byetta	Ietta
Byetta	Byetta	Ietta
Byetta	Byetta	Viada
Byetta	Byetta	Viata
Byetta	Byetta	Viata
Byetta	Byetta	Viatda
Byetta	Byetta	Vieta
Byetta	Byetta	Vietta
Byetta	Byetta	Vietta
Byetta	Byette	
Byetta	Byette	
ByrHA	Byette	
	Byetten	

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/s/

Felicia Duffy
3/11/05 03:56:01 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/11/05 04:00:52 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/11/05 04:06:23 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 1, 2005

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Lina Aljuburi, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for [REDACTED] (exanatide injection), NDA 21-773

Summary

The attached patient labeling represents the revised risk communication materials for [REDACTED] (exanatide injection), NDA 21-773. We have simplified the wording, made it consistent with the PI, removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

The revisions are based on draft labeling submitted by the sponsor on June 29, 2004. Patient information should always be consistent with the prescribing information (PI). All future relevant changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please call us if you have any questions.

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
2/1/05 03:38:10 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/1/05 03:50:29 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



JAN 28 2005

Food and Drug Administration
Rockville MD 20857

Eric J. Klein, M.D.
Capital Clinical Research Center
406 Yaeger Way SW, Suite A
Olympia, Washington 98502-8151

Dear Dr. Klein:

Between November 8 and 22, 2004, Ms. Astrida B. Mattson, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #2993-112 entitled: "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with Metformin Alone") of the investigational drug (exenatide injection), performed for Amylin Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

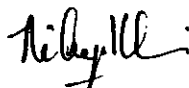
From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Mattson presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your response, dated December 14, 2004, and wish to emphasize the following:

1. You did not adhere to the investigational plan [21 CFR 312.60].
 - a. The protocol specified "the subject has an HbA_{1c} value of 7.5% to 11.0% inclusive, at screening." Subject 10810 had a screening HbA_{1c} value of 7.3%. This subject was enrolled in the study before you submitted a protocol deviation form for sponsor concurrence.
 - b. The protocol specified prior insulin therapy as one of the exclusionary criteria. Subject 10812, who met this exclusion criterion, was enrolled in the study.
2. You did not prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)]. For subject 10810, concomitant medications acetaminophen/codeine and trazodone HCl were recorded in a source document, but were not recorded in the case report form.

We acknowledge your commitment as stated in your December 14, 2004 written response, to make appropriate changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Mattson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

A handwritten signature in black ink, appearing to read "Ni A. Khin".

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN/FEI: _____

Field Classification: VAI

Headquarters Classification: VAI-RR

- ☐ 1)NAI
- ☐ 2)VAI- no response required
- ☐ 3)VAI- response requested
- ☒ 4)VAI-RR (response received and accepted)
- ☐ 5)OAI

Deficiencies noted:

- ☒ failure to adhere to protocol (05)
- ☒ inadequate and inaccurate records (06)

Deficiency Codes: 5, 6

cc:

HFA-224
HFD-510 Doc.Rm. NDA#21-773
HFD-510 Review Div.Dir./Orloff
HFD-510 MO/Gabry
HFD-510 PM/Aljuburi
HFD-46/47c/r/s/ GCP File #11366
HFD-46/47 GCP Reviewer/Slavin
HFR-PA350 DIB/Corcoran
HFR-PA350 Bimo Monitor/Gripp
HFR-PA3540 Field Investigator/Mattson
HFR-PA340 DCB/Gripp—release EIR per FMD-145
GCF-1 Seth Ray

r/d: (AS): 1/24/05
reviewed:NK: 1/26/05
f/t:as: 1/27/05

o:\Slavin\untitled letters\Klein letter

Reviewer Note to Rev. Div. M.O.

This was a routine, pre-approval inspection of Dr. Klein conducted in support of NDA 21-773. Dr. Klein screened 21 subjects and enrolled 17 subjects. Fifteen subjects completed the study. The inspection encompassed an audit of all subjects' records for the presence of a signed and dated consent form. Eight subjects' records were audited in-depth for data integrity. In general, data in source documents and CRFs at the site, matched data in sponsor provided data listings. At the completion of the inspection, a 4-item Form FDA 483 was issued to Dr. Klein. The observations pertained to enrollment of subjects who did not meet inclusion criteria due to exclusionary screening hemoglobin A1c values, and prior insulin therapy; an adverse event of a darkened mole that was not reported to the sponsor, and concomitant medications for one subject that were not reported to the sponsor. Dr. Klein received protocol waivers on the day of enrollment for 2 of the subjects cited on Form FDA 483 (subjects 10820 and 10821); therefore, these subjects were not cited in the letter. The subject with the darkened mole (10802) had a biopsy and the mole was a benign nevus. In his written response, Dr. Klein disputed that this was an AE, and we accepted his response. Data from this site appear acceptable in support of NDA 21-773. The inspection is classified as VAI-RR, response received and accepted.

The inspection was limited by the fact that clinical investigators were blinded to the primary efficacy variable; therefore, an inspection assignment has been issued to conduct an audit of week 30 hemoglobin A1c values at the central laboratory, _____



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 14 2005

Ms. Ginger L. Graham
President and Chief Executive Officer
Amylin Pharmaceuticals, Inc.
9360 Town Center Drive, Suite 100
San Diego, California 92121

Dear Ms. Graham:

Between November 10 and 19, 2004, Mr. James P. Stumpff, representing the Food and Drug Administration (FDA), conducted an inspection of Amylin's management procedures for the following clinical studies of the investigational drug [REDACTED] (exenatide injection):

Protocol #2993-112, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with Metformin Alone"

Protocol #2993-113, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with a Sulfonylurea Alone"

Protocol #2993-115, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with Metformin and a Sulfonylurea"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that Amylin Pharmaceuticals, Inc. adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

Page 2 – Ginger L. Graham—Amylin Pharmaceuticals, Inc.

We appreciate the cooperation shown Investigator Stumpff during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Ni A. Khin'.

Ni A. Khin, M.D.

Branch Chief

Good Clinical Practice Branch I, HFD-46

Division of Scientific Investigations

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place, Room 125

Rockville, MD 20855

Page 3 -- Ginger L. Graham--Amylin Pharmaceuticals, Inc.

cc:

HFA-224

HFD-510 / Document Room: NDA 21-773, [REDACTED] (exenatide injection)

HFD-510 / Review Division Director: David Orloff, M.D.

HFD-510 / Review Division Medical Officer: K. Eddie Gabry, M.D.

HFD-510 / PM: Lina Aljuburi

HFD-45 / Division File/ Reading File

HFD-47 / Chron File

HFD-46 / Khin / Slavin

HFD-47 / GCPB I File #11362

HFR-PA252 DIB (Maxwell)

HFR-PA2565 BIMO MONITOR (Koller)

HFR-PA2535 FIELD INVESTIGATOR (Stumpff)

GCF-1 Seth Ray

FEI#: [REDACTED]

CIB (GCP I): 11156

FACTS#: 577701

Field Classification: NAI

Headquarters Classification:

<input checked="" type="checkbox"/> 1)NAI	
<input type="checkbox"/> 2)VAI	no response required
<input type="checkbox"/> 3)VAI-R	response requested
<input type="checkbox"/> 4)VAI-RR	adequate response received prior to issuance of VAI-R letter
<input type="checkbox"/> 5)OAI-WL	warning letter

O: \\(slavin\untitled letters\Amylin letter)

drafted: AS (12/30/04)

reviewed: NK (1/11/05)

finalized: AS: (1/12/05)

Reviewer's Note to MO: Inspection of Amylin Pharmaceuticals (Ref: NDA 21-773)

This was a routine inspection of this firm conducted in support of NDA 21-773. The inspection encompassed a review of the sponsor's contracts, financial disclosures, SOPs, monitoring reports, adverse event reporting, and data collection and handling. Ten investigators' files from each study were randomly selected and audited for the presence of Form FDA 1572. In general, no major violations of FDA regulations were noted. Form FDA 483 was not issued, however; the following issues were discussed with the firm: Regarding the termination of Dr. Nath, it was felt this decision could have been made in a timelier fashion, and the letter to FDA regarding the termination could have been clearer. The firm's SOP for handling scientific misconduct does not address a mechanism for notifying the FDA, the clinical investigator, and the IRB when a clinical site is terminated. The firm created their SOP for handling scientific misconduct after Dr. Nath's site was terminated. The performance of the CRO in following up on issues noted during monitoring visits could have been improved. The sponsor needs to improve timeliness of receiving information from Eli Lilly regarding adverse events in order to fulfill regulatory reporting obligations. Amylin and Eli Lilly have an agreement to jointly develop exenatide. Eli Lilly is conducting exenatide clinical trials in Europe.

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this page is the manifestation of the electronic signature.**

/s/

Ni Aye Khin

1/19/05 02:05:38 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DEC 28 2004

Food and Drug Administration
Rockville MD 20857

Walter N. Gaman, M.D.
Healthcare Associates of Irving
1110 Cottonwood Lane, Suite #200
Irving, Texas 75038

Dear Dr. Gaman:

Between November 8 and 17, 2004, Mr. Christopher D. Rush, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #2993-113 entitled: "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of AC2993 Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with a Sulfonylurea Alone") of the investigational drug, (exenatide injection), performed for Amylin Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

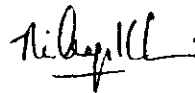
From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Rush presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter, dated November 18, 2004, and wish to emphasize the following:

1. You did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)].
 - a. Subjects 05514 and 05521 had histories of an appendectomy and a hernia repair, respectively, that were not recorded in the case report form (CRF).
 - b. Subject 05522 had a history of herpes and erectile dysfunction that were not recorded in the CRF. In addition, this subject was prescribed Mobic®, Famvir®, Anaprox DS®, Phenergan® and Viagra® during the study. None of these medications were recorded in the CRF.
 - c. Subject 05534 reported a pinched nerve at visit 2 that was recorded on a source document, but was not recorded in the CRF.

We note that as of January 2, 2004, you are no longer conducting clinical research; however, if you should resume clinical research, please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Rush during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

A handwritten signature in black ink, appearing to read "Ni A. Khin".

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

CFN/FEI: _____

Field Classification: VAI

Headquarters Classification:

- ____ 1)NAI
- ____ 2)VAI- no response required
- ____ 3)VAI- response requested
- X ____ 4)VAI-RR (response received and accepted)
- ____ 5)OAI

Deficiencies noted:

X ____ inadequate and inaccurate records (06)

Deficiency Codes: 6

cc:

HFA-224
HFD-510 Doc.Rm. NDA#21-773
HFD-510 Review Div.Dir./Orloff
HFD-510 MO/Gabry
HFD-510 PM/Aljuburi
HFD-46/47c/r/s/ GCP File #9627
HFD-46/47 GCP Reviewer/Slavin
HFD-46/47 CS
HFR-SW150 DIB/Thornburg
HFR-SW1540 Bimo Monitor/Martinez
HFR-SW150 Field Investigator/Rush
HFR-SW140 DCB/Rodriguez—release EIR per FMD-145
GCF-1 Seth Ray

f/t:as: 12/27/04

Reviewer Note to Rev. Div. M.O.

The current inspection for study 2993-113, revealed that Dr. Gaman screened 68 subjects and randomized 26 subjects. He had 18 subjects complete the study. The inspection encompassed a review of 13 subjects' records. Overall, data in sponsor-provided data listings were supported by data in source documents/CRFs at the site. At the completion of the inspection, a Form FDA 483 was issued to Dr. Gaman for observations pertaining to documentation of adverse events, concomitant medications and subject medical histories. There was also an observation pertaining to 2 screen failures who did not sign the most recent version of the consent form. Dr. Gaman's IRB approval for all Amylin studies was terminated on June 2, 2003 due to the NIDPOE letter. The IRB gave him 60 days to transfer subjects to another site. At the time of IRB termination, Dr. Gaman transferred the following subjects to Dr. Rafael Canadas: 112E—3 subjects, 1 subject in 113 completed his/her final visit at Gaman's site and was then transferred to begin the extension study, 113E—7 subjects were transferred. Because the 1998 inspection revealed that the site had fictitious subjects, the FDA investigator was asked to contact study subjects to verify their existence and participation in the study. The FDA investigator contacted 8-9 subjects; some subjects did not return his call. He spoke to 4-5 subjects and verified their existence and their participation in study 2993-113. Data from this site are acceptable. The inspection is classified as VAI-RR, response received and accepted.

Note: we are unable to audit data pertaining to the primary efficacy variable at the sites because the clinical investigators were blinded to this data. An inspection assignment has been issued to audit the primary efficacy variable data—HbA_{1c} values, at _____

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/s/

Ni Aye Khin
1/10/05 02:26:45 PM



DEC 20 2004

Food and Drug Administration
Rockville MD 20857

nc.

Dear Mr. Zaro:

Between November 29 and 30, 2004, Dr. Timothy C. Grome, representing the Food and Drug Administration (FDA), conducted an investigation of [redacted] monitoring procedures for the following clinical studies of the investigational drug [redacted] (exenatide injection), performed for Amylin Pharmaceuticals, Inc.:

Protocol #2993-112, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with Metformin Alone"

Protocol #2993-113, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with a Sulfonylurea Alone"

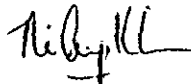
Protocol #2993-115, "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Long-Term, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control (HbA_{1c}) of Exenatide Given Two Times a Day in Subjects with Type 2 Diabetes Mellitus Treated with Metformin and a Sulfonylurea"

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected by appropriate monitoring procedures.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the monitoring of clinical studies of investigational new drugs and the protection of human subjects.

We appreciate the cooperation shown Investigator Grome during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



Ni A. Khin, M.D.

Branch Chief

Good Clinical Practice Branch I, HFD-46

Division of Scientific Investigations

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place, Room 125

Rockville, MD 20855

HFA-224

HFD-510 / Document Room: NDA 21-773, (exenatide injection)

HFD-510 / Review Division Director: David Orloff, M.D.

HFD-510 / Review Division Medical Officer: K. Eddie Gabry, M.D.

HFD-510 / PM: Lina Aljuburi

HFD-45 / Division File/ Reading File

HFD-47 / Chron File

HFD-46 / Khin / Slavin

HFD-47 / GCPB I File #11353

HFR-PA150 DIB (Moss)

HFR-PA150 BIMO MONITOR (Almogela)

HFR-PA1530 FIELD INVESTIGATOR (Grome)

HFR-PA140 DCB (Lee)—release EIR per FMD 145

GCF-1 Seth Ray

FEI#:

CIB (GCP.I): 11353

FACTS#: 577701

Field Classification: NAI

Headquarters Classification:

- | | | | |
|---------------|----|--------|--|
| <u> X </u> | 1) | NAI | |
| <u> </u> | 2) | VAI | no response required |
| <u> </u> | 3) | VAI-R | response requested |
| <u> </u> | 4) | VAI-RR | adequate response received prior to issuance of VAI-R letter |
| <u> </u> | 5) | OAI-WL | warning letter |

O: \\(slavin\untitled letters\ letter)

drafted : AS (12/13/04)

reviewed: NK (12/15/04)

finalized: AS: (12/16/04)

Reviewer's Note to Review Division M.O. Inspection of (Ref: NDA 21-773).

This was a routine pre-approval CRO inspection conducted in support of NDA 21-773. The sponsor transferred monitoring responsibilities to This was the initial inspection of this firm. The inspection encompassed a review of monitoring procedures. used a SOP created by Amylin to monitor clinical sites. A total of 31 monitoring reports were reviewed encompassing the following sites: Dr. Eric Klein (study 112), Dr. Walter Gaman (study 113), Dr. Waldo Harvey (study 115) and Dr. Sam Miller (study 115). was aware that Dr. Gamans's IRB approval was terminated on June 20, 2003 due to the issuance of a NIDPOE letter to Dr. Gaman. Dr. Gaman was instructed by the IRB to transfer all subjects to another qualified site by August 4, 2003. At the time of the IRB action, Dr. Gaman had randomized 26 subjects; he had one active subject in study 113 and had enrolled 17 subjects into the extension study. No objectionable conditions were noted. The inspection is classified as NAI.

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/s/

Ni Aye Khin

12/22/04 09:44:47 AM


45 Day Filing Memo

NDA # 21,773

Application Type NDA
Submission Number 21,773

Letter Date 06/29/2004
Stamp Date 06/30/2004
PDUFA Goal Date 04/30/2005

Reviewer Name K. Eddie Gabry, M.D.

Established Name Exenatide Injection
(Proposed) Trade Name 
Therapeutic Class GLP-1 Analogs (Incretin-mimetics)
Applicant Amylin Pharmaceuticals Inc.

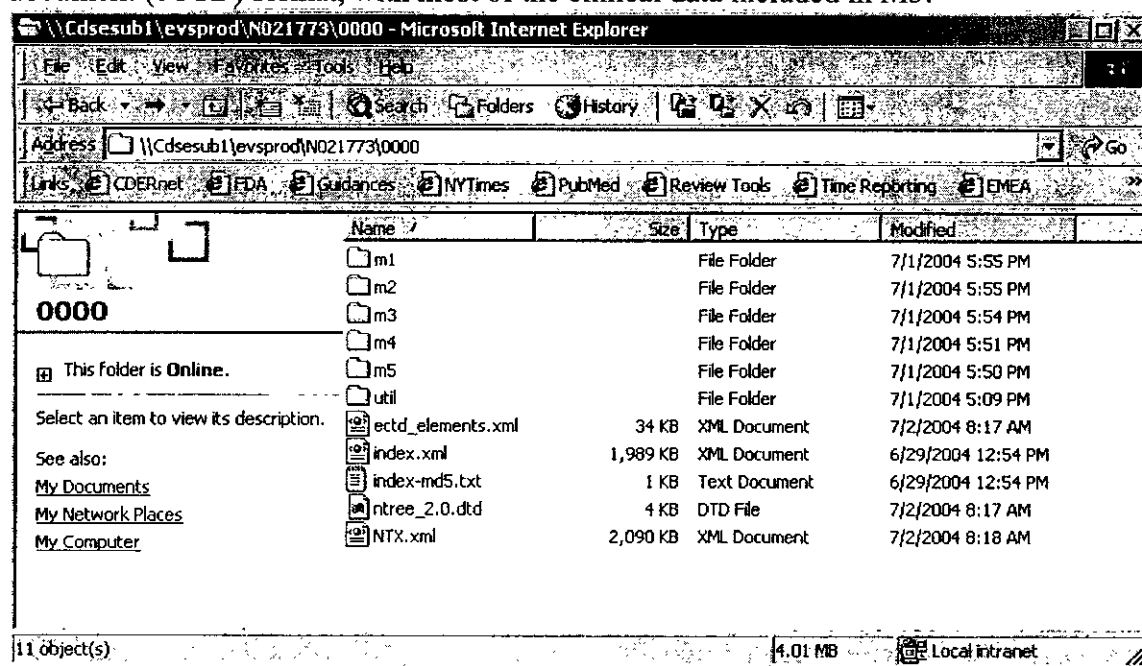
Priority Designation Standard

Formulation 0.25 mg/ml solution
Dosing Regimen BID Injection SQ
Indication To improve glycemic control
Intended Population Patients with Type 2 Diabetes

Conclusion:

The submission seems to include the necessary information to make a clinical recommendation. Therefore, NDA 21,773 is fileable. From the clinical perspective, an Advisory Committee Meeting to discuss the NDA is not warranted. A routine DSI Audit is requested.

The Sponsor submitted NDA #21,773 for the new molecular entity (NME), exenatide on April 30, 2004. The NDA is submitted as an electronic common technical document (eCTD) format, with most of the clinical data included in M5.



As stated in the Filing Meeting on August 24, 2004, the clinical program appears comprehensive. Three pivotal, long term, clinical trials in patients with type 2 diabetes seem to substantiate the Sponsor's claim. The submission is organized and hyperlinked in a way to allow this Reviewer to make an informed clinical recommendation. Therefore, this Reviewer did not have additional requests to be conveyed to the Sponsor in the Filing Notification Letter.

While there seem to be a few review issues, such issues are best handled by the senior reviewers of the Agency. Therefore, a request for an Advisory Committee is not warranted.

As discussed during the Meeting, this Reviewer requests a **routine audit** of the following four clinical study sites in the U.S. The Sites were chosen because they enrolled the highest number of subjects for the pivotal studies supporting the claims of the Sponsor. The DSI consult states that DMEDP (HFD-510) needs the Inspection Summary Results by December 15, 2004.

Site	Investigator	Address	Protocol	Study Title	N (% of total)
Site 088	Waldo Harvey	Illinois Center for Clinical Trials 737 N. La Salle, 3rd Floor Chicago, IL 60610	2993-115	A phase 3, randomized, triple-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin	32 (4.4%)

and a sulfonylurea					
Site 009	Sam Miller	S.A.M. Clinical Research Center 7711 Louis Pasteur Drive, # 300 San Antonio, TX 78229	2993- 115	A phase 3, randomized, triple-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin and a sulfonylurea	30 (4.1%)
and a sulfonylurea					
Site 055	Walter Gaman	North Texas Clinical Research 1110 Cottonwood Lane, # 200 Irving, TX 75038	2993- 113	A phase 3, randomized, triple-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with sulfonylurea alone	26 (6.9%)
alone					
Site 108	Eric Klein	West Olympia Internal Medicine 406 Yauger Way SW, Suite A Olympia, WA 98502	2993- 112	A phase 3, randomized, triple-blind, parallel-group, long-term, placebo-controlled, multicenter study to examine the effect on glucose control (HbA1c) of exenatide given twice daily in subjects with type 2 diabetes mellitus treated with metformin alone	17 (5.1%)

45 DAY MEETING CHECKLIST

Fileability based on initial overview of the NDA application: YES

(1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? Yes

(2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes

(3) On its face, is the clinical section of the NDA legible so that substantive review can begin? Yes

(4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (appropriately designed dose—ranging studies)?

Yes

(5) On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Yes

(6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? Yes

(6) Are all data sets for pivotal efficacy studies complete for all indications requested?

Yes

(7) Do all pivotal efficacy studies appear to be adequate and well controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?

Yes

(8) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?

Yes

(9) Has the application submitted a rationale for assuming the applicability of foreign data in the submission to the US population?

Yes

(10) Has the applicant submitted all additional required case record forms (beyond deaths and dropouts) previously requested by the Division?

Yes

(11) Has the applicant presented the safety data in a manner consistent with center guidelines and/or in a manner previously agreed to by the Division?

Yes

(12) Has the applicant presented a safety assessment based on all current world—wide knowledge regarding this product?

Yes

(13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?

Yes

(14) Has the applicant submitted all special studies/data requested by the Division during pre submission discussions with the sponsor?

Yes

(15) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not.

Yes

Reviewing Medical Officer

K. Eddie Gabry, M.D., M.S., F.A.C.E.

Division of Metabolic and Endocrine Drug Products, HFD-510

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/s/

Kamal Gabry
9/7/04 07:03:18 PM
MEDICAL OFFICER

David Orloff
9/15/04 05:50:20 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/4/04

NDA 21-773

INFORMATION REQUEST LETTER

Amylin Pharmaceuticals, Inc.
Attention: John Wood, M.B.A., R.A.C.
Senior Director, Regulatory Affairs
9360 Towne Centre Drive
San Diego, CA 92121

Dear Mr. Wood:

Please refer to your June 29, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (exenatide) Injection 0.25 mg/mL.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

State whether you have information about any delivery device malfunctions or any overdoses in the clinical trials related to the delivery device. In the *Overdosage* section of the package insert, three patients experienced a 10-fold overdose. Clarify whether these incidents of overdose were related to delivery device error. If there were any device malfunctions, describe what they were (pen device jammed, dial would not turn, etc). This information is needed for a complete safety evaluation.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
10/4/04 02:11:43 PM

12 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857


FILING COMMUNICATION

NDA 21-773

9/9/04

Amylin Pharmaceuticals, Inc.
Attention: David Furlano, Ph.D.
Executive Director, Regulatory Affairs
9360 Town Center Drive, Suite 110
San Diego, CA 92121-3030

Dear Dr. Furlano:

Please refer to your June 29, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for  (exenatide) Injection, 0.25 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 29, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have noticed that you have incorrectly put links to files that are not present in the submission but reside in your server for the folder M2: 24-nonclin-over.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, expanded upon, or modified as we review the application.

We do not expect a response to this letter.

If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lina Aljuburi
9/9/04 01:21:03 PM
Lina AlJuburi for Kati Johnson

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-773

Supplement # N/A

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name:

Generic Name: exenatide injection

Strengths: 0.25 mg/mL

Applicant: Amylin Pharmaceuticals, Inc.

Date of Application: June 29, 2004

Date of Receipt: June 30, 2004

Date clock started after UN: N/A

Date of Filing Meeting: August 23, 2004

Filing Date: August 29, 2004

Action Goal Date (optional): TBD

User Fee Goal Date: April 30, 2005

Indication(s) requested: To improve glycemic control in patients with type 2 diabetes mellitus as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea

Type of Original NDA: (b)(1) X (b)(2)
OR

Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

(2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

 NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S X

P

Resubmission after withdrawal? No

Resubmission after refuse to file? No

Chemical Classification: (1,2,3 etc.) 1

Other (orphan, OTC, etc.) No

Form 3397 (User Fee Cover Sheet) submitted:

YES

NO

User Fee Status:

Paid X

Exempt (orphan, government)

Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the*

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO

If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES
- List referenced IND numbers: 57,725
- End-of-Phase 2 Meeting(s)? Date(s) October 10, 2001
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) February 2, 2004
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES (via ODS and email Aug 6, 2004)
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES (Aug 5, 2004)
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? YES (Aug 5, 2004)

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

N/A YES NO

If Rx-to-OTC Switch application: N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?

N/A YES NO

- Has DOTCDP been notified of the OTC switch application?

YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?

N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment?
If no, did applicant submit a complete environmental assessment?
If EA submitted, consulted to Florian Zielinski (HFD-357)?

YES NO
YES NO
YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ?

YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)?

YES (July 2, 2004)

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 23, 2004

BACKGROUND:

On June 29, 2004, Amylin Pharmaceuticals submitted an original new drug application for (exenatide) Injection (AC-2993). This is a new molecular entity being studied for the management of type 2 diabetes. It mimics the effects of glucagon-like peptide-1 (GLP-1). According to the sponsor, preclinical data indicate that exenatide has several antidiabetic effects which include: enhancement of glucose-dependent insulin secretion with improvement of beta cell function, suppression of inappropriately elevated glucagon secretions, slowing the rate of gastric emptying, and reduction in food intake.

Exenatide Injection is a multiple-use, pre-filled, pen-injector intended for self-injection by the patient. The proposed commercial product is to be supplied in 5µg and 10µg dosing.

ATTENDEES:

Discipline

Medical:
Statistical:
Statistical Team Leader:
Pharmacology:
Pharmacology Team Leader:
Chemistry:
Chemistry Team Leader:
Biopharmaceutical:
Biopharmaceutical Team Leader:
DSI:
Regulatory Project Management:

Reviewer

K. Eddie Gabry
Lee-Ping Pian
J. Todd Sahlroot
John Colerangle
Karen Davis-Bruno
Chien-Hua Niu
Stephen Moore
Jim Wei
Hae-Young Ahn
Andrea Slavin
Lina AlJuburi

ASSIGNED REVIEWERS:

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
Regulatory Project Management:
Other Consults:

Reviewer

K. Eddie Gabry
none
Lee-Ping Pian
John Colerangle
Cynthia Liu
Chien-Hua Niu
N/A
Jim Wei
Vinayak Pawar
N/A
Andrea Slavin
Lina AlJuburi
Pandu Soprey (CBER, medical devices)

Per reviewers, are all parts in English or English translation?
If no, explain:

YES NO

CLINICAL

FILE X

REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY

NA X

FILE _____

REFUSE TO FILE _____

STATISTICS

FILE X

REFUSE TO FILE _____

BIOPHARMACEUTICS

FILE X

REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY

NA _____

FILE X

REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY

FILE X

REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments: submitted as eCTD

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X_____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. **Document no filing issues conveyed to applicant by Day 74.**
Note: Letter was issued September 9, 2004.

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager, HFD-510

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES NO
ORP?

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO

8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- _____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- _____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
- _____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
- _____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
- IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*
- _____ 21 CFR 314.50(i)(1)(ii): No relevant patents.
- _____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
- _____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?

N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO
- EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR
A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Lina Aljuburi
9/9/04 01:43:21 PM
CSO

NDA Filing Meeting Checklist

NDA #: 21-773

DRUG:

Sponsor: Amylin Pharmaceutical, Inc.

Date: August 23, 2004

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? (Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA - e.g., safety pharm, genotox, reprotox, chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? Yes.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

John Colerangle, DVM, Ph.D.
Reviewing Pharmacologist

Karen Davis-Bruno, Ph.D.
Supervisory Pharmacologist

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

/s/

John Colerangle
8/24/04 10:36:28 AM
PHARMACOLOGIST
NDA-21-773: FILING MEETING CHECKLIST

Karen Davis-Bruno
8/24/04 10:43:37 AM
PHARMACOLOGIST
P/T filable, no outstanding issues for 75 data letter



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-773

DFS
July 16, 2004

Amylin Pharmaceuticals, Inc.
Attention: David Furlano, Ph.D.
Executive Director, Regulatory Affairs
9360 Town Center Drive, Suite 110
San Diego, CA 92121-3030

Dear Dr. Furlano:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: (exenatide) Injection, 0.25 mg/mL
Review Priority Classification: Standard (S)
Date of Application: June 29, 2004
Date of Receipt: June 30, 2004
Our Reference Number: NDA 21-773

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2004, in accordance with 21 CFR 314.010(a). If the application is filed, the user fee goal date will be April 30, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on February 2, 2004 for the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-6414.

Sincerely,

{See appended electronic signature page}

Lina AlJuburi, Pharm.D., M.S.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
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/

Lina Aljuburi

7/16/04 01:20:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

9/15/04

Revisions to Pre-NDA mtg minutes

IND 57,725

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

Dear Mr. Wood:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Exenatide Injection.

We also refer to your amendment dated April 6, 2004 (serial # 193), containing comments regarding the Pre-NDA meeting minutes issued on February 27, 2004.

We have completed the review of your submission. You proposed revisions to FDA responses to questions 4a, 6b, 11, and 13. These proposed revisions are acceptable and are repeated below for your reference.

Question 4a:

Does the Agency agree to review additional stability data submitted during the NDA review period (submitted no later than 3 months before the PDUFA date and thus should not trigger an extension of the PDUFA date)?

FDA Response: The Division agrees to this request. The sponsor is asked to submit this information within 3 months after the initial NDA submission.


Revision: The Division agrees to this request. The sponsor agrees to submit this information approximately 3 to 4 months after the initial NDA submission.

Question 6b:

Does the Agency agree to review additional stability data from the additional drug product supplier during the NDA review cycle (submitted no later than 3 months before the PDUFA date and thus should not trigger an extension of the PDUFA date)?

FDA Response: The sponsor agrees to submit 3 month stability data at the time of the initial NDA submission. Six month stability data will be submitted to the Division when available. The sponsor is also to submit a comparison for drug substance and drug product.

In addition, a complete sterility package needs to be included in the initial NDA submission.

Revision: The sponsor agrees to submit 3-month stability data for one lot of each size of the drug product cartridge from the new site, with the stability update to be provided approximately 3 to 4 months after initial NDA submission. Six-month stability data will be submitted to the Division when available. Each stability update should be accompanied by a statistical analysis and a comparison of stability data obtained from product manufactured at  and the new site; therefore, it is not necessary to address the issue of drug substance comparability with drug product stability data from the new site. In addition, a complete sterility assurance package needs to be included in the initial NDA submission. The sponsor may wish to consider including a manufacturing site comparability protocol in the initial NDA submission to allow independent review of the new site if sufficient data cannot be submitted to the NDA in time.

Question 11:




Does the Agency agree that the clinical pharmacology program as described in this document is adequate for submission and filing of the exenatide injection NDA?

FDA Response: The contents in Clinical Pharmacology/Biopharmaceutics section appear to be acceptable. However, bioavailability study reports on obese patients should be submitted to the Agency. Since many type 2 diabetic patients are obese and obesity may affect the absorption of drugs via subcutaneous administration, it is suggested that the sponsor conduct a new clinical study or meta-analysis of obese patients from existing clinical studies to provide the bioavailability information relative to subjects in the normal weight range.

Revision: The contents in Clinical Pharmacology/Biopharmaceutics section appear to be acceptable. However, since many type 2 diabetic patients are obese and obesity may affect the absorption of drugs via subcutaneous administration, it is suggested that the sponsor conduct a new clinical study or meta-analysis of obese patients from existing clinical studies to provide the bioavailability information relative to subjects in the normal weight range. The sponsor indicated that a meta-analysis will be included in the NDA.

Question 13:

Do the exenatide data from the development program described in this document support the proposed indication and dosing regimen?





If you have any questions, call Lina AlJuburi, Regulatory Project Manager, at 301-827-6414.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.

Director

Division of Metabolic and Endocrine Drug Products

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/

David Orloff
9/15/04 05:07:48 PM

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 21-773 ^{New NDA} SUPP TYPE & # NOOD Division 510 UFID # 4755
 Applicant Name: Amylin Pharmaceuticals, Inc. Drug Name: (exenatide injectio

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?

☒ Yes ☐ No

2. Firm in Arrears?

☐ Yes ☒ No

3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"

<http://www.fda.gov/cder/guidance>

☒ Yes ☐ No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)

NDA #/Doc Type Div. Fee? (Y/N)

N/A N/A

5. Type 6?

☐ Yes ☒ No

Type 6 to which other application?

NDA # _____ Supp Type & # _____

6. Clinical Data Required for Approval? (Check one)

☒ Yes*

☐ Yes, by reference to another application

NDA # _____ Supp Type & # _____

☐ No

* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" <http://www.fda.gov/cder/guidance>

☐ Yes ☒ No ☐ To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?

☐ Yes ☒ No ☐ To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)

List of exclusions:

- 2 - No fee - administrative split
- 4 - No fee - 505b2
- 7 - Supplement fee - administrative split
- 9 - No fee Subpart H supplement- confirmatory study
- 11 - No fee Orphan Exception
- 13 - No fee State/Federal exemption from fees

N/A

10. Waiver Granted?

☐ Yes (letter enclosed) ☒ No

Select Waiver Type below: Letter Date: _____

- ☐ Small Business ☐ Barrier-to-Innovation
- ☐ Public Health ☐ Other (explain)

11. If required, was the appropriate fee paid?

☒ Yes ☐ No

12. Application Review Priority

☐ Priority ☒ Standard ☐ To be determined

13. Fast Track/Rolling Review Presubmission?

☐ Yes ☒ No

Comments

PM Signature/Date

Aug 5, 2004

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

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HFD-007

Processor Name & Date

DN 7-02-04

QC Name & Date

BA 7-02-04

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Regulatory Contact: David Furlano, PhD Financial Contact: Mark Foletta Amylin Pharmaceuticals, Inc. 9360 Towne Centre Drive, Suite 110 San Diego, California 92121-3030		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N021773
2. TELEPHONE NUMBER (Include Area Code) (858) 642-7248		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME (trade name) Exenatide (generic name)		6. USER FEE I.D. NUMBER 4755

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- | | |
|--|---|
| <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) | <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) |

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

VP of Finance & Chief Financial Officer

6/4/04

WATERMARK IS VISIBLE IN THIS PAPER. HOLD UP TO A LIGHT SOURCE TO VIEW. THIS DOCUMENT HAS A COLORED BACKGROUND ON WHITE SECURITY PAPER.

 **AMYLIN**
PHARMACEUTICALS
9360 Towne Centre Drive, Suite 110
San Diego, California 92121
(858) 552-2200

FIVE HUNDRED SEVENTY THREE THOUSAND FIVE HUNDRED AND 00/100
DOLLARS

DATE	AMOUNT
06/04/2004	*****573,500.00

Void after 180 days

US FOOD & DRUG ADMINISTRATION
FOOD & DRUG ADMIN (350909)
MELLON CLIENT SERVICE CENTER
500 ROSS STREET - ROOM 670
PITTSBURGH, PA 152620001

Two signatures required for \$10,000 or more

⑈028008⑈ ⑈122000661⑈14502⑈02389⑈

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 2, 2004
TIME: 11:00 am to 12:30 pm
LOCATION: Parklawn Building, Potomac Conference Room
APPLICATION: IND 57,725 Exenatide Injection
TYPE OF MEETING: Type B: Pre-NDA
MEETING CHAIR: David Orloff, M.D.
MEETING RECORDER: Lina AlJuburi, Pharm.D.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Division of Metabolic & Endocrine Drug Products

David Orloff, M.D. – Division Director and Clinical Team Leader
K. Eddie Gabry, M.D. – Clinical Reviewer
Dragos Roman, M.D. – Clinical Reviewer
Karen Davis-Bruno, Ph.D. – Pharmacology Team Leader
John Colerangle, Ph.D. – Pharmacology/Toxicology Reviewer
Xiao-Xiong Wei, Ph.D. – Biopharmaceutics Reviewer
J. Todd Sahlroot, Ph.D. – Statistics Team Leader
Randy Hedin, R.Ph. – Regulatory Project Manager
Lina AlJuburi, Pharm.D. – Regulatory Project Manager

CM&C

Eric Duffy, Ph.D. – Director, Division of New Drug Chemistry II
Stephen Moore, Ph.D. – Chemistry, Manufacturing, and Controls Team Leader
Chien Hua Niu, Ph.D. – Chemistry, Manufacturing, and Controls Reviewer

Office of Information Management

Gary Gensinger, MBA – Review Technology Staff

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Amylin

CM&C

Paul Chen, Ph.D. – Principal Regulatory Scientist, Regulatory Affairs
David Lokensgard, Ph.D. – Senior Director, Analytical Research & Development
Christine Smith, Ph.D. – Director, Product Development
Ann Maloney – Regulatory Research Scientist (Lilly)

Nonclinical and Clinical

Mark Fineman – Senior Director, Clinical Development
Richard Hiles, Ph.D. – Executive Director, Preclinical Development
Dennis Kim, M.D. – Director, Clinical Affairs
Orville Kolterman, M.D. – Senior Vice President, Clinical Affairs
Brian Miyazaki – Manager, Regulatory Affairs
Kristin Taylor, Ph.D. – Manager, Clinical Science
Prajakti Kothare, Ph.D. – Senior Pharmacokineticist (Lilly)
Mark Lakshmanan, M.D. – Medical Director, Endocrine Pharmaceutical Products
Karen Lutz, Ph.D. – Senior Manager, Medical Writing
Terri Poon – Clinical Scientist, Clinical Science

Statistics

Jenny Han – Senior Statistician, Biometrics
Larry Shen, Ph.D. – Senior Director, Biometrics

IT/eCTD

Eric Glasnapp – Electronic Submissions Manager
John Wood – Director, Regulatory Affairs
Jay Zhou – Associate Director, Biometrics

Regulatory

Joann Data, MD, PhD – Senior Vice President, Regulatory Affairs & Quality Assurance
David Furlano, Ph.D. – Executive Director, Regulatory Affairs
Paul Gesellchen, Ph.D. – Regulatory Advisor (Lilly)

BACKGROUND:

Exenatide Injection is a new molecular entity being studied for the management of type 1 and 2 diabetes. It mimics the effects of glucagon-like peptide-1 (GLP-1). According to the sponsor, preclinical data indicate that exenatide has several antidiabetic effects which include: enhancement of glucose-dependent insulin secretion with _____, suppression of inappropriately elevated glucagon secretions, slowing the rate of gastric emptying, and reduction in food intake.

Exenatide Injection is a multiple-use, pre-filled, pen-injector intended for self-injection by the patient. The proposed commercial product will be supplied in 5µg and 10µg dosing.

There were three long-term (7-month), Phase 3, placebo controlled trials referred to as the AMIGO (AC2993: Management for Improving Glucose Outcomes) studies that account for the majority of the subjects in the database. The three trial designs are similar with the major difference being the populations under study, as follows:

1. Protocol 2993-112: Type 2 diabetes inadequately controlled using a maximally effective dose of metformin,
2. Protocol 2993-113: Type 2 diabetes inadequately controlled using a maximally effective dose of a sulfonylurea,
3. Protocol 2993-115: Type 2 diabetes inadequately controlled using a maximally effective doses of both metformin and a sulfonylurea (50% of subjects had sulfonylurea dose reduced to minimally effective dose at randomization).

Exenatide Injection for the management of type 2 diabetes mellitus is currently in the pre-NDA stage. The sponsor expects to submit the NDA for review in June 2004.

The firm requested this Type B Pre-NDA meeting on December 8, 2003 and the background package was submitted on December 30, 2003.

MEETING OBJECTIVES:

To discuss the information required in the NDA submission that will lead to a NDA accepted for filing. The sponsor requests concurrence specifically on the following items:

1. The proposed CM&C package, including the electronic organization of data from multiple suppliers, is sufficient for submission.
2. The nonclinical program is sufficient for submission and in principle supports the safety of the product and the labeling objectives.
3. The clinical program is sufficient for submission and in principle supports the proposed indication and the safety of the product for its intended use.
4. The proposed organization, format, and presentation of a fully electronic CTD meet the reviewers' needs and are acceptable for submission.

DISCUSSION POINTS (Sponsor questions followed by Agency response, in bold):

1. Does the Agency agree that the studies summarized above are sufficient to demonstrate the

comparability between the drug substances from the two manufacturers and that no new study is necessary?

The Division agrees that the studies summarized are sufficient. The sponsor is asked to submit structure studies and HPLC chromatograms of release samples from

2. Does the Agency find the design, performance, and planned introduction of Amylin's functional bioassay acceptable.

Yes, this is acceptable. However, the bioassay data for assay validation needs to be submitted with the initial NDA submission.

3. Are the proposed specifications for drug substance and drug product acceptable?

All specifications appear acceptable. The sponsor is asked to use peptide language in the NDA submission. Be certain to submit total and individual related impurity.

4.

- a. Does the Agency agree to review additional stability data submitted during the NDA review period (submitted no later than 3 months before the PDUFA date and thus should not trigger an extension of the PDUFA date)

The Division agrees to this request. The sponsor is asked to submit this information within 3 months after the initial NDA submission.

- b. Does the Agency agree that there will be sufficient stability data to facilitate review of a uniform expiration period for the drug product regardless of drug substance manufacturer?

Yes, the Division agrees.

5. Does the Agency agree that submission of one executed batch record representing the drug product in a 1.2-mL cartridge and one executed batch record representing the drug product in a 2.4-mL cartridge is sufficient?

Yes, the Division agrees.

6.

- a. Does the Agency agree that the information regarding the additional supplier described above is sufficient for filing.

The Division understands that _____ is to be the additional supplier. The Division agrees that the information regarding the additional supplier is sufficient for filing.

- b. Does the Agency agree to review additional stability data from the additional drug product supplier during the NDA review cycle (submitted no later than 3 months before the PDUFA date and thus should not trigger an extension of the PDUFA date)?

The sponsor agrees to submit 3 month stability data at the time of the initial NDA submission. Six month stability data will be submitted to the Division when available. The sponsor is also to submit a comparison for drug substance and drug product. In addition, a complete sterility package needs to be included in the initial NDA submission.

- c. Does the Agency agree that the expiration period for drug product from both _____ and the additional drug product supplier can be based primarily on _____ drug product stability data?

The Division agrees that this is acceptable.

7. Does the Agency agree that results from the patient-use simulation study support a label claim for an in-use period of 30 days under refrigerated storage conditions?

Yes, the Division agrees.

8.

- a. Is it acceptable to the Agency to provide the pen-injector information in a format similar to 510(k)?

The Division agrees that this is acceptable.

- b. Does the Agency agree that post-approval changes to the pen-injector can follow the 510(k) decision tree?

The Division agrees that this is acceptable.

9. Does the Agency agree that the CM&C data package described is sufficient for submission and filing of the exenatide injection NDA?

The Division agrees that this is acceptable.

10. Does the Agency agree that the nonclinical data package described is sufficient for submission and filing of the exenatide injection NDA?

The nonclinical studies reviewed to date appear adequate for submission and filing of the exenatide injection NDA. Since the sponsor plans on including a new manufacturer for AC2993, and in order to qualify any impurities present in the new manufactured lots, a 28-day bridging toxicology study, an Ames test, and chromosome

aberration study with the lots from the new manufacturer should be submitted for review with the NDA.

11. Does the Agency agree that the clinical pharmacology program as described in this document is adequate for submission and filing of the exenatide injection NDA?

The contents in Clinical Pharmacology/Biopharmaceutics section appear to be acceptable. However, bioavailability study reports on obese patients should be submitted to the Agency. Since many type 2 diabetic patients are obese and obesity may affect the absorption of drugs via subcutaneous administration, it is suggested that the sponsor conduct a new clinical study or meta-analysis of obese patients from existing clinical studies to provide the bioavailability information relative to subjects in the normal weight range.

12. Does the Agency agree that summary safety data from the — development program and the type 1 diabetes mellitus development program are appropriate for inclusion in the CTD only as safety summaries?

Yes, the Division agrees.

13. Do the exenatide data from the development program described in this document support the proposed indication and dosing regimen?

The Division's preliminary judgment is that the program was planned to assess the safety and efficacy of the proposed dosage of exenatide as an adjunctive therapy for the treatment of type 2 diabetes. T

14. Does the Agency agree with the proposed approach for the presentation of the Integrated Summary of Safety and Integrated Summary of Efficacy in the exenatide injection NDA?

The proposed presentation of the Integrated Summary of Safety and Integrated Summary of Efficacy appears appropriate. In addition to the proposed summaries of subgroup results for the combined trials, the sponsor should conduct treatment-by-subgroup tests of interaction using the combined data from the three pivotal controlled trials. Subgroups to be tested would include age, race, sex and additional important subgroups as appropriate.

15. Is the proposed approach to organizing and submitting the electronic exenatide injection NDA in eCTD format acceptable to the Agency?

Yes, the proposed approach appears acceptable. Please continue to work with Ken Edmunds regarding eCTD format.

16. At the time of the NDA submission, Study 2993-120, a monotherapy study in patients treated with diet and exercise, will be ongoing. It is our intention to provide the full study report for this study at the 4-month Safety Update as it may provide useful information for understanding the utility of exenatide. Does the Agency agree with our planned approach?

The sponsor is welcome to submit as much data as is available at the 4-month Safety Update. This information may be useful for understanding the utility of exenatide. However, the Division does not guarantee that the proposed study report would suffice to support a monotherapy indication. Please refer to Division's response to question #13.

17. Development of exenatide will continue with additional studies designed to provide additional guidance to physicians and to expand the product indication. It is Amylin and Lilly's intention to follow the current Guidance entitled, "Clinical Evidence of Effectiveness for Human Drug and Biological Products" for direction on whether one adequate and well-controlled study would be sufficient to provide "substantial evidence." Specifically, it is our interpretation that a single study for each indication will be sufficient to provide substantial evidence regarding comparator studies in similar populations, and for additional add-on trials post-approval. Does the Agency agree?

The Division agrees that adequate evidence supporting a new indication for an approved product within the context of treatment of essentially the same disease can generally be obtained from one well-designed, well-controlled clinical trial. The sponsor inquired whether or not this applies to add-on trials to TZDs or comparing insulin to exenatide. The Division indicated that protocols will have to be individually reviewed and discussed to determine whether they are adequate to support a new proposed use. This is particularly true in the case of insulin trials because of the complexities related to dosing and titration.

18. Does the Agency feel that an Advisory Committee will be warranted?

The Division has not judged, based on the information submitted to date, that an Advisory Committee will be warranted. Upon review, the decision may be made to go to an Advisory Committee. An Advisory Committee may be requested for the simple reason of introducing this new molecular entity. Decision will be made at the time of filing.

19. A risk management plan will be included in the CTD. Amylin and Lilly would welcome suggestions and guidance from the Metabolic and Endocrine Division regarding this important issue.

The Division will need to review the submission and identify risks prior to providing comments and recommendations in regard to the risk management plan.

20. What is the status of the ongoing review of the trade name _____ (03 October 2003, Serial 175)?

Division letter issued 12/23/04: The trade name review of your submission has been completed, and there are no objections to the use of the proprietary name, _____. This is considered a tentative decision. This name, with its associated labels and labeling, must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names.

21. Development of drugs for pediatric indications have recently changed due to legislative actions. What is the Division's interpretation of the current pediatric drug development status relevant to exenatide?

At this pre-NDA meeting, the sponsor requested deferral of pediatric studies and the Division granted the deferral.

22. Does the Agency have any outstanding issues or questions concerning the exenatide program in support of the exenatide injection NDA?

The Division does not have any outstanding questions at this time.

Minutes Preparer: Lina AlJuburi, Pharm.D.

Regulatory Project Manager

Chair Concurrence: David Orloff, M.D.

Division Director

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

/s/

Lina Aljuburi
2/27/04 01:59:50 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 10, 2001

TIME: 12:00pm

LOCATION: Parklawn Building, 3rd Floor, "Chesapeake" Room

APPLICATION: IND 57,725; AC2993 (exendin-4) for Injection

TYPE OF MEETING: End-of-Phase 2 (Type "B" Meeting)

MEETING CHAIR: David G. Orloff, M.D., Division Director

MEETING RECORDER: James T. Cross, Regulatory Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Affiliation</u>
David G. Orloff, M.D.	Director and Acting Medical Team Leader for Diabetes	<u>Division of Metabolic and Endocrine Drug Products, HFD-510</u>
Karen Davis-Bruno, Ph.D.	Pharmacology Team Leader	
Kati Johnson	Chief, Project Management Staff	
Dragos Roman, M.D.	Medical Reviewer	
John Colerangle, D.V.M., Ph.D.	Pharmacology Reviewer	
James Cross	Regulatory Project Manager	
Hae-Young Ahn, Ph.D.	Biopharmaceutics Team Leader	<u>Division of Pharmaceutical Evaluation II, HFD-870</u>
Jim Wei, M.D. Ph.D.	Biopharmaceutics Reviewer	
Lee-Ping Pian, Ph.D.	Biometrics Reviewer	<u>Division of Biometrics II, HFD-715</u>
Eric Duffy, Ph.D.	Deputy Director	<u>Office of New Drug Chemistry, HFD-820</u>

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Affiliation</u>
Orville G. Kolterman, M.D.	Senior V.P., Clinical Affairs	Amylin Pharmaceuticals
Joann Data, M.D., Ph.D.	Sr. VP Regulatory Affairs and Quality Assurance	
Alain Baron, MD	Vice President, Clinical Research	
Richard Hiles, Ph.D.	Senior Director, Preclinical Development	
John F. Wood	Director, Regulatory Affairs	
Mark Fineman	Director, Clinical Science	
Larry Shen, Ph.D.	Director, Biostatistics	
Christine Smith, M.D.	Associate Director, Product Development	
Terrie Burrell	Clinical Investigator	
William O. Butler	Project Manager, Operations	
Brian Miyazaki	Senior Regulatory Associate	

BACKGROUND:

Amylin Pharmaceuticals, Inc. submitted an IND on January 13, 1999, for the investigation of AC2993 (synthetic exendin-4) for Injection in the treatment of type 2 diabetes mellitus. AC2993 is a synthetically manufactured exendin-4, a 39-amino acid peptide, administered by subcutaneous injection. According to the firm, AC2993 has potentially beneficial antidiabetic (glucose-lowering) actions, including glucose-dependent amplification of insulin secretion, suppression of postprandial glucagon secretion, reduction in food intake, and modulation of nutrient delivery. The firm attributes some of the antidiabetic actions of the drug to its binding affinity for the glucagon-like peptide-1 receptor (GLP-1-R). Amylin submitted a Type "B" meeting request, dated July 27, 2001, and a meeting background package, dated September 11, 2001.

The firm has conducted a one Phase 1 (Study 2993-101) and five Phase 2 studies (Study 2993-102, -103, -104, -105, and -107). One Phase 1 (Study 2993-106) and three Phase 2 studies (Study 2993-108, -109, and -110) are ongoing. The firm proposes to conduct two Phase 3 studies: (1) *Study 2993-112* entitled "A Phase 3, Randomized, Triple-Blind, Parallel-Group, Placebo-Controlled, Multicenter Study to Examine the Effect on Glucose Control [HbA1c] of AC2993 Given Two Times a Day for 30 Weeks in Subjects with Type 2 Diabetes Mellitus Treated with Metformin Alone or with Metformin Plus a Sulfonylurea" and, (2) *Study 2993-113* entitled "A Phase 3, Randomized, Triple-Blind, Placebo-Controlled, Multicenter Study to

Examine the Effect on Glucose Control [HbA1c] of AC2993 [10 µg] Given Two Times a Day for 30 Weeks in Subjects with Type 2 Diabetes Mellitus Treated with Oral Agents.”

MEETING OBJECTIVES:

To discuss Amylin's proposed Phase 3 clinical development plan, as outlined in the meeting background package.

DISCUSSION POINTS (*Firm's questions in italics*):

1. *Does the Agency concur that the results from the nonclinical and clinical studies completed to date support initiation of Phase 3 studies as outlined in the briefing document?*

FDA Response: Since the Phase III protocol proposes dosing beyond 6 months data from completed chronic toxicity studies (6-month rodent, 9-month non-rodent) and a male fertility assessment should be submitted prior to initiation of Phase 3 clinical trials to support safety.

2. *Does the Agency agree that the proposed dosing scheme for Studies 2993-112 and 2993-113 (long-term, well-controlled Phase 3 studies) including a 4-week dosing period using a 5µg BID dose to minimize nausea, followed by BID fixed unit doses of 5µg or 10 µg for 26 weeks, is adequate for regulatory decision making?*

FDA Response: The proposed dosing schemes for Studies 2993-112 and 2993-113 appear reasonable. Although the 26-week duration for the fixed dose is adequate, it is recommended that the firm adds a 26-week open-label extension to this study to prove durability of drug effect. The proposed fixed dose seems an acceptable dosing scheme based on the data submitted to date. In principle, it would be preferable to have an additional dose tested in Phase 3 trials in order to assure that a minimum of two doses will show clinical benefit, thus, providing a range of possible dosing regimens for labeling. According to the firm, however, computer modeling data do not suggest an intermediate dose between 5µg BID and 10µg BID and the sponsor trusts this predictive pharmacokinetic model will be sufficient to guide dosage during Phase 3 trials. Additionally, the firm stated that 5µg BID is the lowest dose with which AC 2993 demonstrates meaningful clinical effectiveness.

3. *Does the agency agree that the proposed inclusion/exclusion criteria for the two long-term, well-controlled Phase 3 studies are appropriate to support the proposed indication?*

FDA Response: The proposed general inclusion and exclusion criteria are adequate. For an adjunctive therapy in type 2 diabetes indication, Phase 3 protocols should be designed to emphasize the extent potential benefit of Exendin-4 over various regimens of existing therapy: metformin, sulfonylureas, etc. (also see response to Question 4).

4. *Does the Agency agree with the proposed Phase 3 study designs, randomization procedure, and statistical analysis strategies?*

FDA Response: According to the firm, the Phase 3 trials (in particular Study 2993-113) propose to enroll individuals on multiple combinations of anti-diabetic medications. The Division recommends add-on, placebo controlled, randomized, trial designs during which Exendin-4 is compared side by side to commonly used glucose-lowering drugs such as metformin and sulfonylureas (SU). It is the view of the Division that such studies (using the maximum effective dose for the first line drug) will constitute pivotal studies that will allow labeling of Exendin-4 as a secondary line of therapy in type 2 diabetes. Such study designs are: (1) Patients receiving metformin monotherapy at maximum effective dose, randomized to same dose metformin plus placebo or same dose metformin plus Exendin-4, (2) Patients receiving SU monotherapy at maximum effective dose, randomized to same dose SU plus Exendin-4 or same dose SU plus placebo. In addition, the Division recommends that the firm add an additional arm at 26 weeks in which Exendin-4 monotherapy replaces SU monotherapy.

In response to the wording of the firm's proposed indication, the Division stated that "metabolic control" is a poorly defined term and as such, would not appear in the *Indications* section of the package insert.

The Division also advises the firm to submit, under special protocol assessment, a more specific Phase 3 statistical analysis plan.

5. *Does the Agency agree with the proposed human drug-drug interaction plan?*

FDA Response: The highest recommended dose for Exendin-4 should be used in the proposed drug-drug interaction studies, although there is no such requirement for the co-administered drugs. A drug interaction study with digoxin is also recommended.

6. *Does the Agency agree that this level of patient exposure is adequate?*

FDA Response: For a chronically treated condition, the firm is advised to exceed ICH guidelines for patient exposure (a minimum enrollment of 1500 patients total). A one-year duration of exposure would likely be sufficient for filing an NDA if patients completing the 6 month studies are enrolled in open-label extensions. It is advisable to administer 10 µg AC2993 to provide better data on durability of response (I do not understand this last sentence).

7. *Does the Agency agree with this approach (regarding pens)?*

FDA Response: While no clinical study data on reusable versus disposable pens would be required, an *in vitro* assay showing comparable drug delivery profiles will be sufficient.

8. *Does the Agency agree that the proposed approach will be suitable to assess the safety and effectiveness of AC2993 in the defined group of pediatric patients most likely to use this drug?*

FDA Response: If the proposed Phase 3 clinical studies include patients down to 12 years of age, then a pediatric waiver would be a reasonable. A three or four month efficacy/safety/tolerability study is recommended along with pharmacokinetic bridging data in this pediatric age group.

9. *Based on the overall plan provided is there any additional guidance the Agency would like to provide regarding the development of AC2993?*

FDA Response: The firm is advised to define relevant patient subgroups by existing drug regimens to characterize the safety and efficacy of AC2993 with various anti-diabetic therapies.

ADDITIONAL DISCUSSION:

The firm did not propose a specific site for injection, but it is suggested that the firm conduct a future study to examine the effect of injection site on the pharmacokinetics of the drug.

It is noted by the Agency that all Phase 1 and Phase 2 studies have been conducted with doses based on body weight, but phase 3 studies will be conducted with fixed doses (5 µg and 10 µg), that are based on clinical trial simulation data.

DECISIONS (AGREEMENTS) REACHED:

The firm intends to submit full Phase 3 clinical protocols under special protocol assessment, including a detailed statistical analysis plan.

{See appended electronic signature page}
Minutes Preparer: _____
James T. Cross
Regulatory Project Manager

{See appended electronic signature page}
Chair Concurrence: _____
David G. Orloff, M.D.
Director, HFD-510

Drafted by: J.CROSS/10-19-01

**Revised by: K.JOHNSON/10-23-01; K. DAVIS-BRUNO/10-25-01; H.AHN/10-30-01;
D.ROMAN/10-31-01; D.ORLOFF/11-6-01**

No Comment: L.Pian/10-31-01; J.Colerangle/10-31-01; J.Wei/10-31-01

Final: J.CROSS/11-7-01

MEETING MINUTES

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

/s/

James Cross

11/7/01 02:16:14 PM

David Orloff

11/9/01 12:33:05 PM

DRAFT

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-773	Efficacy Supplement Type SE-N/A	Supplement Number N/A
Drug: Byetta (exenatide injection)	Applicant: Amylin Pharmaceuticals Inc	
RPM: Lina AlJuburi, Pharm.D., M.S.	HFD-510	Phone # 301-827-6414
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):		
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		1
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		April 30, 2005
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

• This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	<input checked="" type="checkbox"/> Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.	
Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?	<input type="checkbox"/> Yes <input type="checkbox"/> No
(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).	
<i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i>	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	<input type="checkbox"/> Yes <input type="checkbox"/> No
<i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i>	
<i>If "No," continue with question (3).</i>	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	<input type="checkbox"/> Yes <input type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

() Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	No
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (x) No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	September 9, 2004 (Project Manager)

Actions	
• Proposed action	(x) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(x) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Ongoing discussions
• Most recent applicant-proposed labeling	Ongoing discussions
• Original applicant-proposed labeling	June 29, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	February 1, 2005 (DSRCS) February 14, 2005 (DMETS) April 7, 2005 (DDMAC)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Ongoing discussions
• Applicant proposed	Ongoing discussions
• Reviews	Ongoing discussions
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	1) CMC: Study for the possibility of modifying the USAN name to include 'acetate' (exenatide acetate) 2) Biopharmaceutics: Study regarding the drug-drug interaction between exenatide and oral contraceptives
• Documentation of discussions and/or agreements relating to post-marketing commitments	Ongoing discussions
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	x
❖ Memoranda and Telecons	x
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	October 10, 2001
• Pre-NDA meeting (indicate date)	February 2, 2004
• Pre-Approval Safety Conference (indicate date; approvals only)	April 5, 2005
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Pending
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	Pending
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See section 7 of clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	March 18, 2005
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Pending submission of request for Pediatric Waiver for ages 0 to 11 (a deferral has been granted for ages 12 to 18 years old until December 31, 2007)
❖ Demographic Worksheet (NME approvals only)	
❖ Statistical review(s) (indicate date for each review)	March 18, 2005
❖ Biopharmaceutical review(s) (indicate date for each review)	Pending
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
Clinical Inspection Review Summary (DSI)	
• Clinical studies	March 22, 2005
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	April 12, 2005
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	CMC review date 4.12.05, page 66
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	March 22, 2005
❖ Facilities inspection (provide EER report)	Date completed: December 7, 2004 (x) Acceptable () Withhold recommendation
❖ Methods validation	(x) Completed, CMC review date 4.12.05, page 64 () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Pending
Nonclinical inspection review summary	N/A
Statistical review(s) of carcinogenicity studies (indicate date for each review)	December 8, 2004
❖ CAC/ECAC report	February 11, 2005

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).