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APPLICATION NUMBER:

21-919

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 18 th , 2009
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	21919 Complete Response to original submission
Applicant	Amylin
Date of Submission	March 19 th , 2008
PDUFA Goal Date	
Proprietary Name / Established (USAN) names	Byetta / exenatide
Dosage forms / Strength	5 or 10 µg SC bid
Proposed Indication(s)	1. Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	Approval

1. Introduction

This application is a resubmission in response to an Approvable Letter issued on April 28th, 2005, for exenatide use as monotherapy for glycemic improvement in subjects with Type 2 Diabetes Mellitus (T2DM). On that same day, an Approval Letter was issued for exenatide use when added on to other antidiabetic medications, under the new drug application (NDA) 21773.

2. Background

Exenatide is a first in class agonist of the glucagon-like peptide 1 (GLP-1) receptor approved in 2005 to improve glycemic control in diabetic patients already treated with other antidiabetic agents. An approvable letter was issued to the applicant regarding the indication for exenatide use in monotherapy (NDA 21-919), due to lack of convincing evidence of efficacy (based on small 28-day study). This Complete Response contains a report for Study H8-MC-GWBJ (GWBJ), in support of the monotherapy indication.

Dr. Valerie Pratt, the FDA medical officer, has also reviewed the last five Period Safety Update Reports (PSURs) that were submitted under NDA 21-773 (PSUR 4, 5, 6, 7 and 8) to address postmarketing emerging safety issues regarding pancreatitis and renal failure associated with exenatide.

3. CMC/Device

There are no new CMC or device issues in the current application.

4. Nonclinical Pharmacology/Toxicology

There are no new non clinical pharmacology / toxicology issues in this application.

5. Clinical Pharmacology/Biopharmaceutics

On March 28, 2007 (NDA 21-773 supplement 009), the applicant submitted exenatide labeling language regarding the use of oral contraceptive (OC) based on study H8O-EW-GWBC entitled “The effect of exenatide on single and multiple doses of oral contraceptive pharmacokinetics in healthy female subjects.” In this single site, open label, three-period, three-sequence, randomized crossover study of 38 healthy females, OC (150 mcg levonorgestrel [LNG] and 30 mcg ethinyl estradiol [EE]) was administered one hour prior and 30 minutes after exenatide. The study data were reviewed by the Office of Clinical Pharmacology and by the Division of Urologic and Reproductive Products (DRUP). Dr. Pratt’s is the review of this study within the Division of Metabolism and Endocrinology Products (DMEP).

In study GWBC, there were no significant changes in pharmacokinetic (PK) parameters when the oral contraceptive was administered an hour prior to exenatide injection. However, the C_{max} of EE and LNG were decreased (45% and 27%, respectively) when the OC was administered 30 minutes after exenatide. The EE trough concentration in that setting (~20% increase compared to the OC taken alone) was similar to that observed in PK studies of other OC products. It is possible that the effect of exenatide on OC pharmacokinetics was confounded by the likely food effect on EE and potential effect on LNG C_{max} values.

DMEP therefore concluded that the *Pharmacokinetics, Drug Interactions* section should be revised to provide a description of the drug-drug interaction study. Furthermore, the Precautions, Drug Interactions section should retain the current recommendation that OC be administered at least one hour prior to exenatide injection. If the applicant wishes to pursue removal of this recommendation, it should provide data on the relative contributions to PK alterations of prior exenatide administration and of the fed state. It is possible that the effect of exenatide may differ somewhat, depending on the type of progestin studied.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The only study submitted under the NDA was study GWBJ. Two studies of 4 weeks duration examining exenatide effects from which reports had been submitted under NDA 21-773 are referred to in the present submission. These studies are not included in the present memorandum.

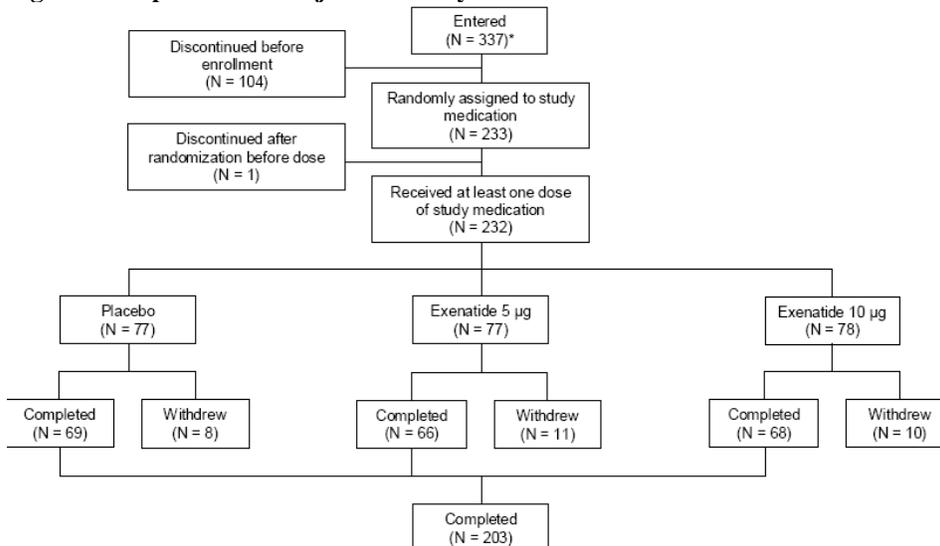
Design and objectives:

GWBJ was a Phase 3, international, double-blind, randomized, three-arm, parallel group trial comparing the safety and efficacy of exenatide 5 µg and 10 µg (both administered subcutaneously [SC] bid) against placebo. The trial had a screening phase, a 2-week placebo run-in phase and a 24-week post-randomization treatment phase. The primary efficacy endpoint was the change in HbA1c from baseline at week 24 in the intent-to-treat (ITT) population, tested under an ANCOVA model with last observation carried forward (LOCF) as the primary method for imputation of missing data. Subjects with T2DM older than 18 years of age, with HbA1c between 6.5 and 10 % (inclusive), BMI 25 – 45 kg/m² (inclusive), and without significant heart failure or coronary disease, renal insufficiency or recent drug-induced weight loss were considered eligible. Subjects randomized to treatment with exenatide 10 µg bid received 5 µg bid for 4 weeks with subsequent uptitration to 10 µg for the remainder of the study.

Subject Disposition:

Please refer to Figure 1

Figure 1. Disposition of subjects in Study GWBJ



Copied from Figure GWBJ.10.1 from the applicant's GWBJ Study Report

A similar percentage of subjects in each treatment group completed the study. The most frequent reason for subject discontinuation was loss of glucose control, according to investigator discretion.

Demographic and baseline characteristics:

The study was conducted in Romania (53% of subjects), India (25% of subjects), Russia (14% of subjects) and the US (8% of subjects). Please refer to Table 1 for demographic and baseline characteristics of the subjects participating in Study GWBJ.

Table 1. Selected demographic / baseline characteristics of Study GWBJ ITT subjects by treatment group

Variable	Placebo N = 77	Exenatide 5 µg N = 77	Exenatide 10 µg N = 78	Total 232
Age (years) (± SD)	53.2 (± 9.2)	53.7 (± 10.1)	55.2 (± 9.9)	54.0 (± 9.8)
Race / ethnicity (%)				
African	3 (4)	0 (0)	3 (4)	6 (3)
Caucasian	51 (66)	50 (65)	56 (72)	157 (68)
East Asian	1 (1)	0 (0)	0 (0)	1 (0.4)
Hispanic	2 (3)	5 (6)	1 (1)	8 (3)
West Asian	20 (26)	22 (29)	18 (23)	60 (26)
Gender (%)				
Male	42 (55)	40 (52)	48 (61)	130 (56)
Female	35 (45)	37 (48)	30 (38)	102 (44)
Duration T2DM (y) (± SD)	1.3 (1.7)	2.4 (3.4)	2.0 (2.8)	1.9 (2.7)
BMI (kg/m ²) (±SD)	31.6 (4.7)	31.5 (4.7)	30.6 (4.8)	31.3 (4.7)
HbA1c (%) (± SD)	7.8 (0.9)	7.9 (1.0)	7.8 (0.9)	7.8 (0.9)

A few observations are noteworthy:

- Very few subjects (18 of 232) were studied in the US;
- Relative to the proportion of African American patients with T2DM in the United States, the proportion of African American subjects in the study was small (3%) and;
- Subjects in the study had carried the diagnosis of diabetes for < 2 years on average, which make generalization of findings to patients with more prolonged duration of disease more limited. On the other hand, diabetic patients who tend to respond well to a single drug are those who were more recently diagnosed and with less advanced disease.

Primary efficacy endpoint:

Primary analysis

The primary analysis was based on an ANCOVA model with change in HbA1c from baseline to week 24 as the dependent variable and treatment group, screening HbA1c stratum (≤ 8% or > 8%) and baseline as covariates. Results are shown in Table 2.

Table 2. Baseline HbA1c and change from baseline at week 24 by treatment group in the ITT population with LOCF imputation of missing data (ANCOVA model)

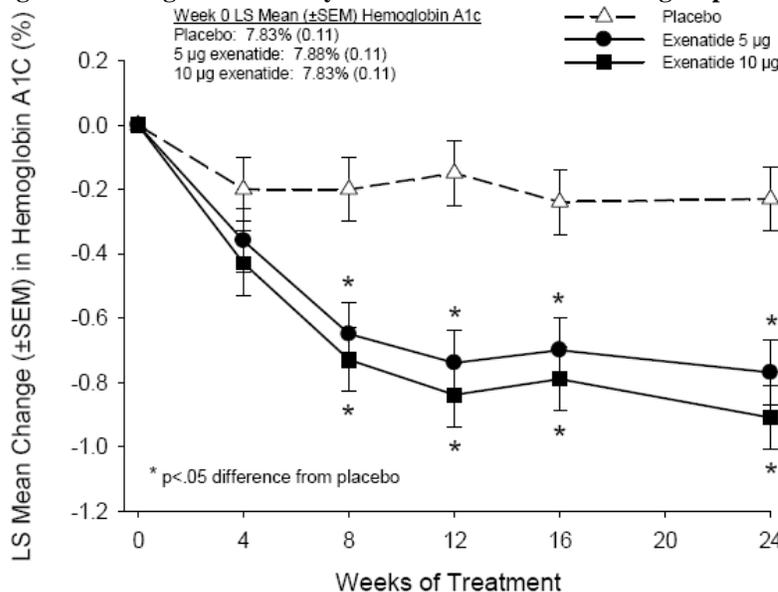
Treatment	Baseline LS Mean	LS Mean Change	p-value	LS Mean difference from placebo in change from baseline at week 24 (± SEM)	p-value
Placebo (n=75)	7.9	-0.2	0.1062		
Exenatide 5 µg (n=76)	7.9	-0.7	0.01	-0.5 % (0.2)	0.003
Exenatide 10 µg (n=76)	7.9	-0.9	< 0.01	-0.7 % (0.2)	0.0004

A statistically significant linear dose effect (p=0.024) was observed, indicating progressive reduction in HbA1c with the 10 µg dose compared to the 5 µg dose.

Other supportive analyses

A sensitivity analysis using a mixed model repeated measures (assuming data are missing at random) also met the primary efficacy endpoint, with a significant effect noted starting on week 8 of the study (Figure 2).

Figure 2. Change in HbA1c by week of visit and treatment group in the ITT population



Copied from the applicant’s Figure GWBJ.11.1 in the clinical study report

Efficacy was also demonstrated through an analysis based on the applicant-defined “per protocol” population. A similar conclusion on efficacy is reached through an alternative analysis using the FDA statistical reviewer-defined “per protocol” population.

In a responder analysis using a cutoff proposed by the American Diabetes Association (ADA) of HbA1c of 7%, a greater proportion of subjects with HbA1c > 7% at baseline on exenatide 5 µg (54%) and 10 µg (52%) reached goal compared to the placebo group (31%). Using the International Diabetes Federation and AACE cutoff of HbA1c of 6.5%, more subjects with

HbA1c > 6.5% at baseline in the exenatide groups (34% and 38% in the 5 µg and 10 µg, respectively) reached goal at week 24 compared to placebo (19%).

The applicant conducted an analysis of mean changes in HbA1c by treatment group, based on anti-exenatide antibody status of subjects at the last study visit (week 24 or early discontinuation). The findings are summarized here. Seventy one subjects randomized to exenatide 5 µg group had anti-exenatide antibody titers assessed at the last study visit. Of the 71 subjects, 21 (30%) were anti-exenatide antibody positive. An identical proportion of seroconversion (22 of 73, or 30%) was observed among those subjects randomized to exenatide 10 µg. endpoint (Week 24 or early discontinuation). The mean (SD) change in HbA1c from baseline to endpoint for the exenatide 5 µg treatment group was -0.61 (1.33) % for antibody-positive subjects, and -0.74 (1.08) % for antibody-negative subjects. The mean (SD) change in HbA1c from baseline to endpoint for the exenatide 10 µg group was -0.60 (0.98) % for antibody-positive subjects, and -0.94 (1.02) % for antibody-negative subjects. These results are consistent with findings from the previous trials where exenatide was added on to other background therapies, reported under NDA 21773.

Selected secondary efficacy endpoints:

Fasting Plasma Glucose

Please refer to Table 3 for summary data on the mean change in fasting plasma glucose, by treatment group, in the 24 weeks of Study GWBJ.

Table 3. LS Mean change in fasting plasma glucose (mg/dL) from baseline to week 24 in the ITT population of Study GWBJ

Treatment	Baseline LS Mean	LS Mean Change	p-value	LS Mean difference from placebo in change from baseline at week 24 (± SEM)	p-value
Placebo (n=75)	159	-5	0.1926		
Exenatide 5 µg (n=76)	166	-18	< 0.0001	-12 % (5.6)	0.0292
Exenatide 10 µg (n=76)	155	-19	< 0.0001	-13 % (5.6)	0.0161

The placebo-subtracted reductions in FPG associated with exenatide were not dose-proportional.

Post-prandial glucose: 6-point self monitored blood glucose (SMBG) profile

Subjects performed 2 separate 6-point SMBG profiles (glucose level ac and 2 hours pc around the morning, midday and evening meals) at baseline, Week 12 and Week 24 (please refer to Table 4).

Table 4. LS mean change (SD) from baseline in self-monitored blood glucose values (mg/dL) in the ITT population of Study GWBJ

	LS Mean Change (SD) from baseline in self-monitored blood glucose values (mmol/l)						
	Morning Pre-meal	Morning PP meal	Midday Pre-meal	Midday PP meal	Evening Pre-meal	Evening PP meal	Daily Mean
Placebo (n=77)	-3.8 (4.0)	-7.0 (7.9)	1.4 (4.0)	-9.9 (4.5)	0.7 (4.7)	-9.7 (4.7)	-4.9 (3.6)
Exenatide 5 mcg (n=77)	-19.1 (4.1)	-40.5 (5.0)	-16.2 (4.1)	-30.6 (4.7)	-14.2 (4.9)	-41.6 (4.9)	-27.2 (3.8)
Exenatide 10 mcg (n=78)	-18.7 (4.0)	-38.5 (5.0)	-12.6 (4.1)	-29.0 (4.7)	-10.8 (4.9)	-48.1 (4.9)	-26.9 (3.8)

PP = postprandial

At endpoint, subjects in the exenatide 5 µg treatment group had lower blood glucose concentrations at all timepoints, as well as a lower daily mean glucose, compared with placebo-treated subjects. With the exception of the evening pre-meal, subjects in the exenatide 10 µg treatment group experienced significantly lower blood glucose concentrations at endpoint at all timepoints and the daily mean compared with placebo-treated subjects.

Reviewer comment: The applicant has reported these data with multiple inferential tests showing significant p-values, but these are uncorrected for the high number of comparisons without protection against an inflated type 1 error, so no statistical significance can be ascribed to the data. Therefore, reporting of post-prandial data in labeling, under the Clinical Studies section, will be descriptive only.

Post-prandial glucose: oral glucose tolerance test (oGTT)

The effect of exenatide on the post-prandial excursion of plasma glucose in response to an oGTT was examined in a subset of the population. A group of 104 subjects (45%) underwent a 3-hour oGTT at baseline and at week 24. According to the applicant, this subset reflects the baseline and demographic characteristics of the larger ITT population, except for the absence of West Asian subjects in the oGTT subset. The advantage of this assessment is a more rigorous and uniform testing, and the change in the glucose excursions at the different timepoints of the oGTT would represent a better reflection on the post-prandial incretin effect. The disadvantage is that the oGTT represent an oral incretin response to glucose alone, rather than a more complex meal (Table 5). In addition, Amylin elected to conduct the oGTT in too few subjects (approximately 35 per group) to allow robust conclusions on the exenatide incretin effect. Amylin took a similar approach (a small, selected subgroup for oGTT testing) for the trials under NDA 21773, in support of exenatide as add-on to other background therapies.

Table 5. Change in placebo-subtracted serum glucose (mg/dL) during oGTT from baseline to week 24- LOCF in 104 subjects (subset of Study GWBJ ITT population)

Treatment difference		Fasting	30 Minutes	60 Minutes	120 Minutes	180 Minutes
Exenatide 5 µg	LS Mean	-13.1	-44.3	-46.6	-47.5	-27.2
	SEM	9	13.5	18.4	22.5	22.0
	p-value	0.1456	0.0015	0.0128	0.0379	0.2219
Exenatide 10 µg	LS Mean	-18.7	-41.4	-71.3	-78.7	-61.9
	SEM	8.8	13.1	17.6	22.0	22.1
	p-value	0.0361	0.0022	0.0001	0.0006	0.0063

As seen in the table, the post-“prandial” exenatide effect on glucose is greater than the glucose reduction observed during the fasting state.

Change in body weight

Please refer to Table 6 for results and analyses of changes in body weight by treatment group in Study GWBJ.

Table 6. Change in placebo-subtracted body weight (kg) from baseline to week 24 - repeated measures model in the ITT population (LOCF-imputed for missing data)

Treatment	Baseline LS Mean	LS Mean Change	p-value	LS Mean difference from placebo in change from baseline at week 24 (± SEM)	p-value
Placebo (n=76)	86.1	-1.4	0.1926		
Exenatide 5 µg (n=77)	85.1	-2.8	< 0.0001	-1.3 (0.45)	0.0037
Exenatide 10 µg (n=76)	86.2	-3.1	< 0.0001	-1.6 (0.45)	0.0003

In concordance with the exenatide effect on weight when used in combination with other antidiabetic agents, exenatide caused a statistically significant, although modest, weight loss during the 24 weeks of study GWBJ.

Analyses in Subgroups

Demographic-based subgroup analyses

No remarkable gender or age stratum (< 65 years or ≥ 65 years) effects were noted in the HbA1c and FPG changes from baseline to week 24. Interestingly, subjects with BMI lower than 30 kg/m² at baseline had slightly greater mean reductions in HbA1c and FPG in all groups, including placebo, compared to those subjects with BMI ≥ 30 kg/m². However, there was substantial overlap in the range of effect between the two subgroups to allow any conclusions regarding effects of BMI at baseline. In addition, the analysis does not correlate the effect of exenatide on BMI (i.e., BMI at week 24 – BMI at baseline) and the glycemic effect (HbA1c at week 24 – HbA1c at baseline), which would have been more informative regarding the effect of weight loss on glycemic control in exenatide-treated subjects.

Subgroup analyses based on selected disease baseline characteristics

In addition to interactions with demographic characteristics, the applicant also examined the efficacy of exenatide according to certain baseline morbid characteristics. An interaction with renal function was analyzed due to the importance of renal clearance of exenatide. Subjects with mild renal dysfunction (creatinine clearance ≥ 51 and ≤ 80 mL/min calculated by the Cockcroft-Gault formula) had similar mean HbA1c and FPG reductions from baseline at week 24 as the mean reductions in these parameters among subjects with normal renal function (creatinine clearance > 80 mL/min). The protocol excluded subjects with moderate or severe renal impairment (creatinine clearance ≤ 50 mL/min).

Another analysis conducted by the applicant was to determine whether anti-exenatide antibodies interfered with the efficacy of exenatide (changes in HbA1c and FPG). In both the exenatide 5 μ g and 10 μ g groups, 30% of subjects developed anti-exenatide antibodies by week 24. A small mean loss of effect can be observed for the antibody-positive group compared to the antibody-negative group in both glycemic parameters. Seroconversion was defined as a change from zero or unknown titer at baseline to a titer of ≥ 25 X dilution at the last visit, or if subjects had a positive titer at baseline, as a ≥ 3 -fold increase in titer dilution at the last study visit. One subject in the 5 μ g group and three subjects in the 10 μ g group had titers of anti-exenatide antibodies ≥ 625 X dilution. In the latter three subjects (10 μ g group) the declines in HbA1c from baseline to week 24 were -0.5, -0.4 and -0.5%, values that are below the mean estimate. Additionally we do not have data on long term effects of these antibodies (beyond 6 months) on the glycemic efficacy of exenatide.

Efficacy Conclusions

The data from study GWBJ is supportive of the efficacy of exenatide, when used as monotherapy, to improve glycemic control in subjects with T2DM. The study contains a few limitations in allowing generalization of its findings to the US target population: very few US subjects were enrolled and, among those, very few were African American (compared to the proportion of African American patients with T2DM in the US) and few had a prolonged duration of diabetes. Despite these shortcomings, the data clearly show substantial reduction in HbA1c, FPG and post-prandial glucose compared to placebo, and these effects are dose-proportional.

8. Safety

Scope of Safety Data Reviewed:

Dr. Pratt's review of safety included the safety data from Study GWBJ as well as the review of Periodic Safety Update Reports 4, 5, 6, 7 and 8 under NDA 21-773. Data from these PSUR's were included because the review team felt they were relevant and timely with new observations of serious cases of pancreatitis and renal impairment (the latter in PSUR 4) received by FDA under the MedWatch program.

Deaths:

There were no deaths in Study GWBJ. The 4 PSUR's (5 through 8) listed nine deaths in patients with pancreatitis. The review of the case reports suggests that a number of these patients may have died from causes other than pancreatitis (e.g., leukemia relapse, gastrointestinal bleeding, ischemic bowel, etc). Please refer to Dr. Pratt's review for details.

Serious Adverse Events:

Four subjects in the exenatide-treated groups had non-fatal SAEs: corneal abscess and iridocyclitis leading to hospitalization (subject on 5 µg bid), hospitalization for dilation and curettage due to vaginal bleeding (subject on 5 µg bid); abnormal pregnancy and surgical abortion (exenatide 10 µg bid); and hospitalization for umbilical hernia surgery diagnosed before study entry.

Postmarketing reports indicate that, in addition to the pancreatitis-related deaths, there have been 10 cases of necrotizing pancreatitis and at least 166 cases of renal failure (further described under Section 11. Postmarketing Data in this review).

Adverse Events leading to discontinuation: Two subjects in the exenatide 10 µg bid group in Study GWBJ discontinued due to AEs: one with headache and the other with nausea.

Adverse Events:

The most common AE reported was nausea (3% in the exenatide 5 µg bid group and 13% in the exenatide 10 µg bid group). This AE was followed in decreasing frequency by influenza, nasopharyngitis, vomiting, headache and back pain.

Adverse Events of Special Interest:

In addition to AEs leading to study discontinuation, the applicant considered 2 types of AEs as of special interest: GI events (due to its prior experience with exenatide in prior Phase 3 studies) and hypoglycemia (a potential problem in T2DM with most products, particularly when used in combination). The review team also analyzed injection site reactions and any safety repercussions of anti-exenatide antibodies in subjects who became seropositive during the study.

Combined GI AEs

Three of 155 exenatide-treated subjects had anorexia and weight loss: 2 in the 10 µg group and one in the 5 µg group. The events of anorexia / decreased appetite were mild to moderate. Weight loss in these subjects were as follows: 5.5 kg in one subject with anorexia on 10 µg, 9 kg in one subject with anorexia in the 5 µg group and 1.1 kg in one subject with decreased appetite in the 10 µg group. No placebo-treated subjects had treatment emergent AEs of weight loss or anorexia in the study.

Reviewer comment: Exenatide and other GLP-1 analogs are being developed for an obesity indication.

Nausea was the most common AE reported (10% of the 10 µg group, 3% in the 5 µg group, and 1% in the placebo group). The second most commonly reported AE was gastroesophageal

reflux disease (GERD) (3% of subjects in each treatment group). Vomiting was the third most commonly reported AE. The combined frequency of nausea and vomiting events increased proportional to the exenatide dose. Dyspepsia occurred in five patients, all of whom received exenatide.

Please refer to the Postmarketing Data, in Section 11 of this review, for important new data on serious episodes of pancreatitis.

Hypoglycemia

Very few subjects experienced and reported symptoms of hypoglycemia, with similar frequencies among the groups. Three subjects on exenatide 10 µg, 4 subjects on exenatide 5 µg and one subject on placebo reported at least one episode. One of the 3 subjects on exenatide 10 µg reported 14 episodes of hypoglycemia, all of them associated with blood glucose levels > 65 mg/dL. No episodes of severe hypoglycemia were reported in the general safety population or among those subjects with mild renal insufficiency.

Injection site reaction

One subject on exenatide 10 µg had a moderate intensity rash at the exenatide injection site. The rash resolved while the subject continued treatment with exenatide. The only relevant information about this event is that it occurred in a subject who developed anti-exenatide antibodies at Week 24 (titer 1/125 X dilution).

Safety issues related to anti-exenatide antibodies

No safety issues were identified.

Laboratory Evaluations

In analyses of laboratory parameters focused on measures of central tendency, there were no important changes from baseline in mean serum creatinine, estimated creatinine clearance, ALT, cholesterol, HDL, triglycerides and WBC. Mean (\pm SD) serum hemoglobin decreased from baseline to week 24 in all 3 groups, not dose-proportional between the exenatide groups: -1.28 (\pm 7.5) g/L for placebo, -1.25 (\pm 8.4) g/L for exenatide 5 µg, and -1.36 (7.2) g/dL for the exenatide 10 µg group.

Analyses of outliers and laboratory values of clinical importance yielded unremarkable results.

Vital Signs

There were small mean reductions in systolic blood pressure (SBP), diastolic blood pressure (SDP), and heart rate (HR) from baseline to endpoint identified among subjects in the exenatide treatment groups compared with those in the placebo treatment group. These are likely to be not clinically meaningful. Mean reductions in SBP, SDP, and HR were experienced by exenatide 5 µg treated subjects (-3.56 mmHg, -0.53 mmHg, -0.57 bpm) and exenatide 10 µg-treated subjects (-4.25 mmHg, -2.92 mmHg, -0.11 bpm) compared with slight mean increases in placebo-treated subjects (0.08 mmHg, 0.12 mmHg, 0.70 bpm).

Electrocardiograms

ECGs were only recorded at the screening visit, in order to determine eligibility.

Safety Update

The four month safety update for this NDA was waived because the ongoing studies were either for a different indication or blinded such that the data obtained would be of limited use.

Postmarketing data

Dr. Pratt has reviewed the 5 most recent Periodic Safety Update Report (PSUR) 4 through 8. The following AEs were the focus of the review: pancreatitis, renal failure, hypersensitivity, and thyroid tumors.

PSUR 4 covers the period from October 1, 2006 through March 31, 2007. PSUR 5 covers the period from April 1, 2007 through September 30, 2007. PSUR 6 covers the period from October 1, 2007 through March 31, 2008. PSUR 7 covers the period from April 1, 2008 through June 30, 2008. PSUR 8 covers the period October 1, 2008 through March 31, 2009. Parallel to an increase in the number of prescriptions, the number of reported AEs in all SOCs has increased substantially, particularly in PSUR 7 (3 months only). One possible explanation for the recent increased AE reporting rate is the revised product labeling (January 2008) and the public and health care providers attention to exenatide safety following FDA safety alerts (October 2007 and August 2008).

Pancreatitis

A total of 639 cases of pancreatitis have been identified in the five PSURs, but the number includes also chronic, ischemic and hereditary cases. In October 2007 FDA issued a safety alert related to the emerging risk of pancreatitis. As of August 31, 2008, 8 cases of necrotizing and 1 case of hemorrhagic pancreatitis have been reported. The majority (87%) of the pancreatitis reports came from the U.S. From market approval in 2005 to August 2008, six U.S. cases of hemorrhagic or necrotizing pancreatitis associated with exenatide use were reported to AERS. In August 2008 FDA issued a second safety alert, this time to communicate the risk of necrotizing and / or hemorrhagic pancreatitis, which had resulted in two deaths. A sponsor-assembled panel of experts created a scale to assess the likelihood of the diagnosis of acute pancreatitis and the relatedness to exenatide treatment. The panel reviewed 330 cases that had been reported through August 31st, 2008. Of these, 129 were considered to contain insufficient information to ascertain a diagnosis. One hundred and fifty five of 330 cases (47%) were deemed probably or possibly pancreatitis and almost 80% (262/330) were deemed possibly related to exenatide. Please refer to Dr. Pratt's review for further details on the Amylin-assembled expert panel report.

In addition to the PSURs containing reports of pancreatitis, Amylin submitted for review two epidemiologic studies conducted at the applicant's request by Ingenix, based on a claims-based surveillance system. These studies were not designed to identify cases of necrotizing or hemorrhagic pancreatitis. Based on the conclusions from the studies, the reporting rate of pancreatitis associated with exenatide was no higher than background for the diabetic population ("observed to expected analysis"), and the reporting rate of pancreatitis associated

with exenatide and sitagliptin combined was similar to the reporting rate associated with metformin and glyburide combined (i3 Aperia) (“drug against drug analysis”). DMEP requested a review of these studies by OSE. OSE’s conclusion was that the study using the i3 Aperia claims-based data had significant limitations and does not allow a conclusion that exenatide exhibits a risk profile for pancreatitis similar to other antidiabetic drugs. Furthermore, OSE focused their review on cases of necrotizing and / or hemorrhagic pancreatitis, where the AERS reports show higher numbers of cases associated with exenatide. Thus, OSE has recommended elevation of pancreatitis in the exenatide label to a Boxed Warning. However, subsequent to filing the review, the OSE director and the director of the Office of Drug Evaluation II came to an agreement to add pancreatitis as an interim labeling change under Warnings and Precautions, until the review of the required epidemiologic study is submitted and reviewed. For further detail, please refer to the OSE reviews and to Dr. Pratt’s review.

The pancreatitis issue has been addressed in ongoing discussions with OSE and with the applicant regarding the appropriate placement in labeling and an updated Risk Mitigation and Evaluation Strategy (REMS). DMEP, OSE and the applicant have agreed to add wording on pancreatitis (including the complicated cases) under Warnings and Precautions. The REMS for pancreatitis will include a Medication Guide and a timetable for assessments. At the time of this writing, final discussions with the applicant are ongoing regarding details of the above.

Renal failure

PSUR 4

According to the applicant’s analyses, including a broad range of MedDRA preferred terms related to renal failure, 58 cases were identified from the initial marketing approval in the US (April 2005) until March 2007 (end of the reporting period for PSUR 4).

Slightly more than half (55%) of the cases were female; the average age was 61 years in the 53 cases that reported age. A majority of these patients (32, 55%) took concomitant medications known to affect kidney function, including diuretics, NSAIDs, ACE inhibitors and angiotensin receptor blockers. Of these 32, 16 (50%) patients were dehydrated, hypovolemic, or hypotensive. An additional 4 patients had dehydration without associated gastrointestinal symptoms. Other reported risk factors included pancreatitis (five patients including one necrotizing), sepsis (two patients), rhabdomyolysis (two patients), and nephrolithiasis (one patient).

Five of the 58 patients had an event coded as renal tubular necrosis; four of these had renal failure or insufficiency as well as nausea and vomiting. Three of these four patients as well as the remaining fifth patient had dehydration and/or hypotension. Three of these five patients also used medications known to affect renal function. In total, 48 of the 58 (83%) cases had at least one of the above risk factors known to affect renal function. Little information was provided for the 10 cases without a documented renal function risk factor. One patient had a history of “mild renal problems” with a baseline creatinine of 2.0 mg/dL. Two other patients had “low grade renal failure” (serum creatinine 1.4 mg/dl) or “chronic renal insufficiency” (serum creatinine 2.1 mg/dL). One patient experienced renal failure associated with an allergic reaction. Of the 58 patients, 33 recovered or experienced improvement. Only five cases had ongoing renal failure at the last report. No outcome information was supplied in the majority of remaining cases. Of the 58 cases, ten had to go on hemodialysis. Most of these

cases were confounded (acute renal failure, rhabdomyolysis post-trauma, etc). Five of the seven cases with sufficient information for an assessment experienced rapid improvement without chronic need for renal replacement therapy.

In order to capture renal failure as screened by laboratory abnormalities, MedDRA terms related to creatinine, BUN, glomerular filtration rate, etc were employed. Twenty eight cumulative cases met these preferred terms. This group of patients with abnormal renal laboratories generally had less information reported and small increases in creatinine (often \leq 2.5 mg/dL) than those with adverse renal events.

Of the 28 patients with abnormal renal laboratories, 18 (64%) reported risk factors associated with renal impairment. Fifteen of the 28 (54%) patients used concomitant medications known to affect renal function. Eight (29%) had nausea, vomiting, or diarrhea; five of these eight also reported dehydration and two also reported hypotension. Most of the remaining 10 patients without risk factors had very limited information provided, according to the applicant. Seven of the 28 cases had resolved or were resolving. Three cases were ongoing at last report. The majority of the remaining cases had no outcome information provided.

PSUR 5

An additional 26 unique cases were reported by healthcare providers from April 7, 2007 to September 30, 2007. One subject died from CHF and renal failure.

Of these 26 cases, 17 were acute renal failure or worsened chronic renal failure or similar, and nine were reportedly abnormal laboratory values. In 13 (50%) cases, nausea, vomiting, diarrhea, dehydration, or volume depletion was reported. In 14 cases (54%), concomitant medications known to affect renal function were used. In total, 19 (73%) cases were associated with possible dehydration or concomitant medications which may affect renal function. Of the 13 cases for which an outcome was reported, 10 (77%) recovered or were recovering. The remaining three cases which worsened or did not recover were followed for a short period of time.

PSUR 6

PSUR 6's data were presented by system organ class and did not lend itself to a review of the preferred terms suggestive of renal failure.

PSUR 7

Using a search using the same preferred MedDRA terms used for PSUR 5, 29 cases were identified, but with no narratives and little information about them.

Applicant's documents submitted in response to FDA request

On 8/12/08, the applicant submitted an analysis of integrated renal safety data from five exenatide Phase 3 studies, including Study GWBJ. The analysis included AEs and prespecified laboratory abnormalities. A total of 1473 subjects were treated with exenatide and 905 subjects were treated with placebo, for study duration ranging from 16 to 30 weeks. The groups had similar demographic characteristics, as well as baseline renal laboratory values (BUN, creatinine and estimated creatinine clearance).

The mean change in BUN from baseline to endpoint increased slightly in the placebo group but decreased slightly in the exenatide groups (0.3 vs. -0.2 mg/dl). The clinical significance of this small difference is not clear. The mean change in creatinine from baseline to endpoint

was similar in both the placebo and exenatide group (0.00 vs. 0.01 mg/dl). In addition, the percentage of subjects with either BUN or creatinine elevations above specified thresholds of clinical importance was small and similar among the treatment groups.

Labeling actions

On 9/27/07 the applicant proposed a CBE supplement for inclusion of renal safety data under Precautions and Adverse Reactions (prior to the implementation of the Physician Labeling Rule, where Warnings and Precautions are combined in the same section). DMEP requested an OSE consult regarding this labeling supplement. OSE recommends adding the postmarketing findings of renal function impairment to Warnings and Precautions, and a recommendation against the use of exenatide in patients with moderate or severe renal impairment and renal transplantation. The information also should be conveyed under Adverse Reactions – Postmarketing experience, and in the Patient Counseling Information. I agree with these OSE recommendations.

In addition to the above recommendations, OSE also recommended a labeling change to add a warning against concurrent use of exenatide with insulin. The recommendation was based on several AERS case reports describing patients treated with insulin for whom exenatide therapy was added to improve glycemic control, as an “off label” approach and who experienced deterioration of renal function, including one case which required renal transplantation. OSE also argues that the United Kingdom label states that use of Byetta® with “insulin cannot be recommended” and that “Byetta® should not be used in type 2 diabetic patients who require insulin therapy due to beta cell failure.”

The current exenatide label simply states that exenatide has not been studied with insulin. Recently approved antidiabetic products not evaluated with concomitant insulin therapy had their labels approved under the Physician Labeling Rule format. DMEP has required applicants to acknowledge the lack of trial data supporting use of these products with insulin under “Important Limitations of Use” section of the label, as appropriate. In my view, the cases reported represent insulin-using patients with long standing diabetes and likely with variable degrees of nephropathy and renal impairment, and not a new specific drug-drug interaction in which the combination of insulin and exenatide could be particularly harmful to the kidney. My interpretation of the wording in the United Kingdom label is that lack of safety and efficacy data preclude a recommendation for exenatide use with insulin, and an acknowledgment that in diabetic patients with beta cell failure exenatide may not exert any additional benefit beyond that provided by insulin treatment. Therefore, my recommendation is that the revised exenatide label cites the lack of supporting data under Section 1 (Indications and Usage) Subsection 1.2 Important Limitations of Use, and I disagree with OSE’s recommendation to add a Warning against exenatide use with insulin.

In addition to changes in labeling, DMEP will require a REMS related to the issue of renal failure to include the Medication Guide and a timetable for assessments as mentioned above, and specifically for this issue, a communication plan through a letter to health care providers to alert them of the postmarketing association of acute renal failure and use of exenatide.

Hypersensitivity

Hypersensitivity was reviewed as a topic of special interest in PSUR 5 through 8. A total of 40 events of severe hypersensitivity or anaphylaxis have been reported by health care professionals and consumers.

Five cases were reported as life threatening; none were fatal. Time to onset for the 26 cases which reported this information ranged from 1 day to 1 year. Fifteen of 38 cases had a history of drug allergy, unspecified allergy, and / or anaphylactic reaction. The majority of reports (n=27 [71%]) did not describe alternative etiologies or complicating factors. Two cases described a positive rechallenge. The signs and symptoms of anaphylactic reactions reported included anaphylactic shock, syncope/loss of consciousness, shortness of breath, angioedema, urticaria, rash, itching, and swelling.

A history of severe hypersensitivity to exenatide or any product components is currently listed as a contraindication to the use of this drug.

Thyroid tumors

A spontaneous review by the applicant for thyroid tumors was conducted in PSUR 6. This was prompted by findings of higher rates of benign C-cell adenomas in rats compared to control animals in 2-year carcinogenicity studies. Other GLP-1 analogs have been linked to thyroid carcinomas in rodents.

PSUR 8 included a cumulative review of thyroid cancer / tumors. Search terms included the following: thyroid neoplasms (benign or malignant), parathyroid tumor (benign or malignant), and thyroid mass. Ten cases were reported. All were within the United States. None were reported as medullary cancer of the thyroid. No cases were reported from exenatide clinical trials. No new thyroid tumor safety labeling is needed at this time.

Safety Conclusions

New important safety issues emerging during the review cycle for this NDA are the serious cases of pancreatitis (including fatal cases and life-threatening cases of necrotizing and / or hemorrhagic pancreatitis) and issues related to renal failure. These issues did not arise from the review of Study GWBJ submitted in the application in support of a monotherapy indication, but rather from the review of postmarketing reports under the applicant's PSURs and the reports from MedWatch / AERS.

After internal discussions between DMEP and OSE, as well as discussion with the applicant, the plan to address the emerging safety issues includes:

- Labeling changes, to elevate pancreatitis to Warnings and Precautions as an interim measure pending the submission of the epidemiologic study in the 3rd quarter 2009;
- Labeling changes, to communicate the risk of renal failure associated with exenatide, also under Warnings and Precautions;
- REMS which includes a medication guide, a timetable for assessment for both pancreatitis and acute renal failure and a communication plan (a "Dear Health Care Provider" letter to be sent by Amylin) for the issue of acute renal failure
- Postmarketing required studies to:
 - i. Continue to evaluate the risk of pancreatitis and complicated pancreatitis (necrotizing and / or hemorrhagic forms) in the diabetic population and among users of exenatide;
 - ii. Conduct mechanistic preclinical studies on effects of exenatide in animal models of diabetes, including histopathology;
 - iii. Conduct mechanistic clinical trial on the effects of exenatide on gallbladder motility and emptying.

9. Advisory Committee Meeting

DMEP did not call for an Advisory Committee meeting to discuss this Complete Response to NDA 219191.

10. Pediatrics

Efficacy and safety of exenatide have not been established in the pediatric population, a segment in which the rate of T2DM is growing worldwide. Children and adolescents are likely to be treated with exenatide. At the original approval of exenatide as add-on to other antidiabetic agents in April 2005, FDA has waived the requirement for a pediatric safety and efficacy study in children ages 0 to 11 years, and deferred a study in children and adolescents age 12 to 16 years. An approved written request dated September 8th, 2006 includes a pediatric study to include children and adolescents in the age range 10 -16 years (inclusive). As part of the written request, results of a PK / PD placebo-controlled, crossover, single dose study were submitted to FDA by the applicant on September 9th, 2007. The applicant had requested labeling changes to reflect the results of the PK / PD study. In the internal discussion between DMEP and the Pediatric Review Committee, a decision was reached to not include the PK /PD results, as the data show no compelling issues of public safety in that population and their inclusion in labeling could be seen as an implied indication, without support data from an adequately controlled safety and efficacy study. Since Amylin is already conducting a study in the 10 – 16 years old pediatric group, DMEP may include an updated PREA requirement for the study in the same age range.

11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues, other than those covered in other parts of this review document.

12. Labeling

At the time of this writing, the labeling is being finalized with agreement on the major points between DMEP and Amylin. The major issue under discussion was the appropriate placement of the new postmarketing data on complicated cases of pancreatitis (necrotizing and / or hemorrhagic), and to a lesser extent, a discussion of appropriate labeling for postmarketing findings of acute renal failure.

Other items that have been discussed revolved around the following issues:

- Whether to display results of post-prandial glycemic effects in a small subgroup of the overall population studied;
- Removal of statistical inferential testing (p-values) from representation of data obtained under multiple comparisons, post-hoc and without protection against overall inflation of the type 1 error;

- Whether to display data regarding analysis based on proportion of subjects in each treatment group achieving glycemic targets recommended by organizations other than the American Diabetes Association ($HbA1c \leq 6.5\%$ supported by the American Association of Clinical Endocrinologist and the International Diabetes Federation);
- Clinical Pharmacology issues regarding the drug-drug interaction data with oral contraceptives and with drugs of narrow therapeutic index, warfarin in particular.

13. Recommendations/Risk Benefit Assessment

Efficacy of exenatide in subjects not adequately controlled with diet and exercise alone has been demonstrated through the study submitted in this application. DMEP has determined that the appropriate section to convey data supporting the use of an antidiabetic product is the Clinical Studies section of that product's label, rather than as a separate indication. Therefore, the significant glycemic effects of exenatide in monotherapy will be added to the label.

In addition to the review of findings from study GWBJ, the review of postmarketing safety data from the applicant's PSURs and other reports regarding new information on complicated cases of pancreatitis and renal failure will be summarized in the Warnings and Precautions of the label.

REMS including a Medication Guide and a communication plan are being finalized with the applicant at the time of this writing, and postmarketing required studies are being discussed with the applicant.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICA LS INC	BYETTA (EXENATIDE) INJECTION

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

/s/

ILAN IRONY
08/20/2009

MARY H PARKS
08/21/2009