CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-919

MEDICAL REVIEW(S)

Medical Officer Safety Memorandum
Division of Metabolic and Endocrine Products

NDA 21-919 (b) (4)

Name of drug: Exenatide (Byetta) subcutaneous injection

Sponsor: Amylin Pharmaceuticals, Inc.

Relevant Exenatide IND/NDAs:

- INDs: 57725, (b) (4)
- NDAs: 21-773

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2D)

Dates of submission: September 11, 2009

Medical Reviewer: Valerie Pratt, M.D.

Medical Team Leaders: Ilan Irony, M.D.

Background: Exenatide injection, an incretin mimetic (specifically, glucagon-like-peptide-1 [GLP-1] analogue), is currently approved to improve glycemic control in patients with type 2 diabetes mellitus (T2D) who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and thiazolidinedione but have not achieved adequate glycemic control. Amylin Pharmaceuticals, Inc. submitted this new drug application supplement to support approval of the 5 and 10 mcg subcutaneous twice daily doses as monotherapy in T2D patients.

There have been rare postmarketing reports of hemorrhagic and necrotizing pancreatitis, sometimes fatal, as well as postmarketing reports of renal failure, sometimes requiring hemodialysis and kidney transplantation, in patients taking exenatide (Byetta). As a result, the exenatide safety labeling was revised and a Risk Evaluation and Mitigation Strategy (REMS) required.

The REMS should include a Medication Guide, Dear Healthcare Professional (DCHP) letter, and timetable for assessments. Postmarketing requirements (PMRs) will include epidemiological and mechanistic (preclinical and clinical) studies as well as analyses of all amylase/lipase data in patients who presented with pain or nausea with or without vomiting.

The sponsor submitted a proposed REMS and supporting document on September 3, 2009. Agency comments were provided via email on September 9, 2009. The sponsor submitted a revised, proposed REMS with a response to the agency's comments on September 11, 2009.

Current submission: The agency's September 9, 2009 comments are in regular type. The sponsor's September 11, 2009 responses are in italics. The responses are acceptable except where noted. The comment to be conveyed to the sponsor is bolded.

- With regard to the REMS proposal:
  (b) (4)
  - In the Dear HCP letter, please delete the paragraph (b) (4) (b) (4) under the Important Limitations of Use as this was deleted from the PI.
    In the Dear HCP letter, the sponsor deleted the paragraph (b) (4) (b) (4) *under the Important Limitations of Use section for consistency with the PI.*
  - In the Dear HCP letter, please delete the last paragraph (b) (4) (b) (4)
    (b) (4)

    COMMENT: The Division of Metabolism and Endocrinology Products does not accept the inclusion of text (b) (4) (b) (4) **in the Dear HCP letter, despite the precedent in other divisions. This letter is being required as part of a REMS to communicate a serious risk about Byetta. The announcement** (b) (4) (b) (4) **detracts from the risk communication.**
- With regard to the REMS supporting document:
  (b) (4)
  - Protocols for the REMS assessment should be submitted for review 90 days (not 60 days) prior to the due date for the first REMS assessment.

The sponsor updated the REMS supporting document to convey that protocols for the REMS assessment will be submitted for review 90 days prior to the due date for the first REMS assessment.

- In the Dear HCP letter, please delete the paragraph (b) (4) (b) (4) under the Important Limitations of Use as this was deleted from the PI.

  See above comments.
- In the Dear HCP letter, please delete the last paragraph (b) (4) (b) (4)

  See above comments.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21919	ORIG-1	AMYLIN PHARMACEUTICALS 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/

VALERIE S PRATT
09/15/2009

ILAN IRONY
09/15/2009

CLINICAL REVIEW

Application Type	NDA 21-919
Submission Number	S-000
Submission Code	N
Letter Date	19-March-2008
Stamp Date	19-March-2008
PDUFA Goal Date	20-September-2008
Reviewer Name	Valerie S. W. Pratt, M.D.
Review Completion Date	20-August-2009
Established Name	Exenatide injection
Proposed Trade Name	Byetta
Therapeutic Class	Incretin mimetic
Applicant	Amylin Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Injection
Dosing Regimen	5 or 10 mcg subcutaneously twice daily
Indication	Treatment of type 2 diabetes mellitus
Intended Population	Adult type 2 diabetics

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of this efficacy supplement.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Because of post-marketing reports of fatal and non-fatal necrotizing and hemorrhagic pancreatitis associated with the use of exenatide and in order to ensure that the benefits of exenatide outweigh this serious risk, I recommend a Risk Evaluation and Mitigation Strategy (REMS), which will consist of a Medication Guide and a timetable for assessments. The sponsor should also continue to submit 15-day reports for cases of suspected pancreatitis, so that we may continue to assess this evolving issue.

In addition, I recommend required postmarketing studies (PMRs) including epidemiological and mechanistic (preclinical and clinical) studies as well as analyses of all amylase/lipase data in patients who presented with pain or nausea with or without vomiting for the following reasons:

- The background rate of acute pancreatitis in the diabetic population is not well understood
- The contribution of exenatide to the incidence of acute pancreatitis in the diabetic population has not been established
- The mechanism by which exenatide may exert this effect is not well understood

I recommend a Dear Health Care Professional (DHCP) letter pertaining to the use of exenatide in patients with renal impairment and end-stage renal disease be included in the REMS, because there have been postmarketing reports of renal failure, sometimes requiring hemodialysis and kidney transplantation. Doctors should be educated to hold exenatide treatment in patients for whom it is not recommended or results in worsening renal function. An FDA safety alert or early communication may create unnecessary panic among the general public.

1.2.2 Required Phase 4 Commitments

The PMRs are as follows:

- Epidemiological study to determine the incidence rate, severity and risk factors for the development of acute pancreatitis as well as hemorrhagic and/or necrotizing pancretitis in exenatide-exposed versus unexposed patients: The goal is to ascertain the background rate and risk factors for the development of acute, hemorrhagic, and necrotizing pancreatitis in the diabetic population treated with other anti-diabetic agents versus the

rate in diabetic patients treated with exenatide in combination with other anti-diabetic agents.

- Mechanistic studies:
  - In vivo preclinical studies to assess possible mechanisms for exenatide-associated pancreatitis, including histopathological assessment of the pancreas
  - A clinical trial investigating the effects of exenatide on cholecystokinin CCK (cerulitide)-stimulated gallbladder emptying (as an indirect measure of a potential impact on the sphincter of Oddi) to assess any non-physiologic effects of exenatide on biliary emptying
- Submission of all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials, including analyses of those data and a systematic analysis of those patients who presented with pain or nausea, with or without vomiting during the treatment phase of those trial.

Please also refer to section 1.2.1 Risk Management Activity above.

We will defer required pediatric studies of exenatide monotherapy in adolescents ages 10-16 years and waive this requirement for children ages 0-9 years. Although type 2 diabetes is increasing in prevalence in the pediatric population, its occurrence in young children is still rare. In addition, an oral antidiabetic agent (like metformin, which is currently the preferred therapy for pediatric type 2 diabetes) is particularly expected to be chosen for the very young over Byetta, which requires twice daily injection. Therefore, Byetta is not likely to be used in a substantial number of pediatric patients below 10 years of age. This is consistent with our approach to the exenatide combination therapy written request.

1.2.3 Other Phase 4 Requests

If the sponsor wishes to pursue removal of the current recommendation that oral contraceptives (OCs) be administered at least one hour prior to exenatide injection, 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 progestin studied.

The sponsor should consider pediatric population PK/PD analysis of exenatide.

1.2.4 Brief Overview of Clinical Program

Exenatide injection, an incretin mimetic (specifically, glucagon-like-peptide-1 [GLP-1] analogue), is currently approved to improve glycemic control in patients with type 2 diabetes mellitus (T2D) who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and thiazolidinedione but have not achieved adequate glycemic control. Amylin Pharmaceuticals, Inc. submitted this new drug application supplement to support approval of the 5 and 10 mcg subcutaneous twice daily doses as monotherapy in T2D patients. This application supplement is based on 24-week data from study H8O-MC-GWBJ (GWBJ), a pivotal phase 3, multicenter, double blind, randomized, three arm, parallel, outpatient clinical trial comparing twice daily exenatide to placebo in 233

randomized, T2D patients. The sponsor also refers to studies 2993-116 and 2993-120 which were submitted with the original exenatide NDA (21-773), when exenatide was first considered for the monotherapy indication and determined to be approvable. Periodic safety reports (PSURs) 5, 6, 7, and 8 are also reviewed as well as renal, pancreatitis, and thyroid safety submissions (August 12 and 15, 2008 and December 19, 2008, respectively).

1.2.5 Efficacy

- The primary objective was to determine if glycemic control as measured by the change in HbA1c from baseline to endpoint with exenatide twice daily (BID) was superior to placebo BID after 24 wks treatment in patients with T2D who had inadequate control with diet and exercise. Only the exenatide groups experienced a statistically significant improvement in HbA1c compared to baseline (7.8%). The LS mean treatment difference relative to placebo at endpoint was -0.5 (95% CI: -0.9, -0.2) (p=0.003) and -0.7 (95% CI: -1.0, -0.3) (p=0.0004) for the exenatide 5 and 10 mcg groups, respectively.
- Among the per protocol population (PP) with baseline HbA1c > 7%, more patients randomized to exenatide 5 mcg (53.2%) and to 10 mcg (47.6%) than patients randomized to placebo (34.1%) had HbA1c ≤ 7% at endpoint. The differences were not statistically significant. Among the PP population with HbA1c > 6.5% at baseline, statistically significantly more patients randomized to exenatide 10 mcg than patients randomized to placebo (41.5% vs. 21.1%) had HbA1c ≤ 6.5% at endpoint (p=0.0178). A greater percentage of exenatide 5 mcg patients (34.9%) than placebo (21.1%) patients had HbA1c ≤ 6.5% at endpoint, although the difference was not statistically significant.
- Exenatide 5 and 10 mcg BID resulted in a greater LS mean change in fasting serum glucose (FSG) from baseline than placebo (-18 and -19 mg/dl vs. -5 mg/dl, respectively). The LS mean treatment difference relative to placebo at endpoint was -12.2 mg/dl (95% CI: -23.22, -1.26) (p=0.0292) and -12.6 mg/dl (95% CI: -24.48, -2.52) (p=0.0161), for the 5 and 10 mcg groups, respectively.
- With the exception of the exenatide 10 mcg treatment group's evening premeal value, both exenatide treatment groups experienced lower self-monitored blood glucose concentrations at all time points and lower daily mean blood glucose concentrations when compared to placebo-treated patients.
- Placebo subjects experienced, on average, a steady decline in body weight beginning at week 4 through the end of the study, with a mean loss of 1.45 kg at week 24 compared to baseline. The LS mean treatment difference relative to placebo at endpoint was -1.3 (95% CI: -2.19, -0.43) and -1.61 (95% CI: -2.49, -0.74) for exenatide 5 and 10 mcg, respectively. These placebo-subtracted reductions in body weight were significant between weeks 8 and 24 (p≤0.0023). Both exenatide groups exhibited significant (p≤0.0090) declines in body weight beginning at week 4 through the end of study, with mean weight loss of 2.7 and 3.2 kg in the 5 and 10 mcg groups respectively. Significant treatment differences were observed at week 16 (p=0.0268) and week 24 (p=0.0037) for the exenatide 5 mcg group and at weeks 8 (p=0.0074) through 24 (p=0.0003) for the exenatide 10 mcg treatment group when compared to placebo (ITT).

- Although baseline BMI did not affect the change in FSG, patients receiving placebo and exenatide 5 mcg with lower BMI values (< 30 kg/m^2) experienced greater LS mean reductions in HbA1c compared with those with higher BMI values (≥ 30 kg/m^2), while LS mean reductions were similar between the two BMI groups in the exenatide 10 mcg group.

GWBJ. LS mean change from baseline to endpoint in HbA1c by baseline BMI (n)		
	BMI < 30 kg/m^2	BMI ≥ 30 kg/m^2
Placebo	-0.52 ± 0.19 (32)	0.04 ± 0.16 (43)
Exenatide 5 mcg	-1.17 ± 0.18 (34)	-0.38 ± 0.16 (42)
Exenatide 10 mcg	-0.88 ± 0.17 (39)	-0.86 ± 0.17 (37)

In graphs of the empirical cumulative distribution of change in HbA1c from baseline to endpoint based on anti-exenatide antibody status of ITT patients, the antibody-negative curve is shifted left suggesting a slight loss in the glycemic effect among antibody-positive patients, compared to patients who remain antibody-negative throughout the duration of the trial (see section 6.1.4.3 Subgroup Analysis).

1.2.6 Safety

The safety analyses are predominantly based on the data from study GWBJ. The main findings from the pivotal study are summarized below:

Deaths: There were no deaths in study GWBJ.

However, postmarketing reports indicate there have been 9 pancreatitis-related deaths in patients treated with exenatide.

Serious adverse events: Four serious adverse events (AEs) were reported in exenatide treated patients in study GWBJ (corneal abscess and iridocyclitis, vaginal bleeding, pregnancy stopped in evolution, and umbilical hernia). The likelihood that exenatide is the causative factor in these AEs is low.

Postmarketing reports indicate that, in addition to the deaths in patients with pancreatitis, there have been 10 cases of necrotizing or hemorrhagic pancreatitis and over 150 cases of renal failure (please refer to sections 7.1.17 and 7.1.25).

Discontinuations due to adverse events: Two exenatide subjects withdrew from study GWBJ due to AEs (nausea and headache).

Gastrointestinal adverse events: As expected with an incretin mimetic, gastrointestinal disorders, including nausea, gastroesophageal reflux disease (GERD), vomiting, and dyspepsia, occurred commonly. In study GWBJ, no patient developed pancreatitis, although one 53 year old subject on exenatide 5 mcg experienced epigastric pain which both pre and postdated exenatide dosing

(weeks 0 and 12). Three of 155 (1.9%) exenatide patients experienced decreased appetite or anorexia.

Hypoglycemia: Hypoglycemia was reported in 3.8% exenatide 10 mcg, 5.2% exenatide 5 mcg, and 1.3% placebo patients. No glucagon injection, intravenous (IV) glucose, or emergency room visits were required.

Adverse events potentially related to anti-exenatide antibody status: Of the 71 exenatide 5 mcg and 73 exenatide 10 mcg patients assessed for antibody status in study GWBJ, 29.6% exenatide 5 mcg and 30.1% exenatide 10 mcg patients were treatment-emergent antibody positive at the last study visit. Adverse events potentially associated with antibody status occurred only in the exenatide 10 mcg group. Within that group, 1 antibody positive patient reported an injection site reaction

Laboratory analyses: There were no important changes from baseline in mean creatinine, ALT, cholesterol, HDL, triglycerides, WBC, and hemoglobin. Mean creatinine clearance decreased 0.07 to 0.08 ml/s in all treatment groups, including placebo. Although the distribution of low, normal, and high creatinine clearance values remained relatively constant in the placebo and exenatide 10 mcg groups, an increase in the percentage of exenatide 5 mcg patients with low creatinine clearance was seen at endpoint compared with baseline (14% vs. 6%). The mean change in creatinine compared to baseline was 0.01, 0.02, and 0.02 mg/dl in the placebo, exenatide 5 mcg, and exenatide 10 mcg treatment groups respectively, suggesting a lack of a drug-dose related effect on creatinine.

The Sponsor has submitted a changes being effected (CBE) supplement requesting the inclusion of language in the label reflecting postmarketing reports of worsened renal function with exenatide. At the agency's request, on August 12, 2008, the sponsor submitted an analysis of renal AEs and out of range renal laboratory values for the six phase 3 placebo-controlled clinical trials that supported the original exenatide NDA 21-773. This submission is reviewed in section 7.1.25. An Office of Surveillance and Epidemiology (OSE) consult on this submission was completed February 23, 2009. OSE's recommendations included the following:

- Alignment of the U.S. product label with the U.K. product label
- Addition of language in the Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections
- Dissemination of the renal dysfunction information to clinicians and the public via a Dear Health Care Professional letter, a Public Health Advisory, and/or MedWatch Safety Alert

A substantial proportion of the renal cases may have resulted from dehydration secondary to vomiting leading to pre-renal and subsequent renal insufficiency. Other cases may represent the progression of renal disease seen in diabetes or the effect of concomitant medications. However, for a few cases, the use of exenatide appears to be the most plausible cause. As a result, the safety labeling pertaining to renal adverse events should be revised, as recommended by OSE, in the new label

A similar percentage of patients in each treatment group had elevated ALT at baseline (placebo 18%, exenatide 5 mcg 17%, exenatide 10 mcg 27%). However, a greater number of patients in the placebo and exenatide 5 mcg treatment groups normalized their ALT by endpoint than those on exenatide 10 mcg treatment. The percentage of patients with abnormal ALT at endpoint in the treatment groups was as follows: placebo 3%, exenatide 5 mcg 8%, exenatide 10 mcg 17%). No dose-related pattern of hepatic adverse events was seen in study GWBJ nor was there a liver abnormality signal in the exenatide studies associated with the original NDA 21-773.

Both exenatide treatment groups had reductions in LDL cholesterol. (Please refer to section 7.1.7.3.1 for the mean changes in the lipid panel from baseline.)

1.2.7 Dosing Regimen and Administration

The sponsor is proposing exenatide 5 and 10 mcg administered subcutaneously (SC) twice daily (BID) within (b) (4) minutes before morning and evening meals as a monotherapy adjunct to diet and exercise to improve glycemic control in adults with T2D. Subjects who tolerate exenatide 5 mcg SC BID for 4 weeks and have not achieved glycemic goals may be up titrated to 10 mcg SC BID. This is the same regimen currently approved for use in combination with some other anti-diabetic drugs.

1.2.8 Drug-Drug Interactions

The sponsor is relying on data included in prior exenatide submissions regarding drug-drug interactions, and has not included new drug-drug interaction data in this efficacy supplement.

1.2.9 Special Populations

Exenatide is intended for use in adult T2D patients. A previous study has shown that mean exenatide clearance is reduced in patients with end-stage renal disease receiving dialysis when compared with healthy subjects (0.9 L/h vs. 9.1 L/h). The current label states that exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment. In addition, the revised label will likely recommend that exenatide not be used in patients with severe renal impairment or end-stage renal disease as well as it be used cautiously in subjects with moderate renal impairment or a history of renal transplantation. The revised label will also likely include a more prominent warning about the potential for renal dysfunction as well as language in the Important Limitations of Use section that the concurrent use of Byetta with insulin has not been studied and cannot be recommended. The limitations of use with respect to insulin is now standard labeling for all anti-diabetics for which there are little or no data for its combined use with insulin.

Postmarketing study 2993-124, "A randomized, single blind, dose rising, placebo controlled, crossover study to evaluate the PK, PD, and tolerability of exenatide in adolescent subjects with T2D" (submit date September 27, 2007), was reviewed by clinical pharmacology reviewer Dr. Manoj Khurana. In study 2993-124, 13 subjects aged 12-16 years received a single 2.5 or 5.0 mcg SC dose of exenatide or placebo followed by a standardized meal. Because there were a

number of subjects in the 2.5 mcg group with exenatide concentrations below the limit of quantification (BLQ), the data from this dose were insufficient to provide reliable PK results. Adequate PK data were obtained from half of the exenatide 5 mcg subjects. Administration of 5 mcg exenatide resulted in mean Cmax of 94.8 pg/mL and AUC0-inf (n=6) of 449.7 pg.h/ml (please refer to section 8.4 Pediatrics).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Amylin Pharmaceuticals, Inc. has submitted this new drug application for the monotherapy use of the incretin mimetic exenatide injection, trade name Byetta. The sponsor proposes use of exenatide as a monotherapy adjunct to diet and exercise to improve glycemic control in adults with T2D. Exenatide is already approved for use in combination with some other anti-diabetic therapies.

2.2 Currently Available Treatment for Indications

Medications currently approved for the treatment of type 2 diabetes mellitus include the following:

- Sulfonylureas
  - Tolazamide (Tolinase)
  - Chlopropramide (Diabinese)
  - Glyburide (Micronase)
  - Glipizide (Glucotrol and Glucotrol XL)
  - Glimepiride (Amaryl)
- Meglitinide analogs: Repaglinide (Prandin)
- D-Phenylalanine: Nateglinide (Starlix)
- Biguanides: Metformin (e.g., Glucophage and Glucophage XR)
- Thiazolidinediones
  - Rosigitazone (Avandia)
  - Pioglitazone (Actos)
- α-Glucosidase inhibitors
  - Acarbose (Precose)
  - Miglitol (Glyset)
- Incretin-mimetics
  - Exenatide (Byetta)
- Amylinomimetics
  - Pramlintide (Symlin)
- Dipeptidyl peptidase 4 inhibitors
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
- Bile acid sequestrants

- Colesevelam (WelChol)
- Dopamine receptor agonists
  - Bromocriptine mesylate (Cycloset)

2.3 Availability of Proposed Active Ingredient in the United States

The FDA has approved exenatide for the following indication: As an adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control.

Exenatide is contraindicated in patients with a known hypersensitivity to it or any of the product components. It is currently not recommended in patients with end-stage renal disease or severe renal impairment. In addition, the revised label will likely recommend that exenatide not be used in patients with severe renal impairment or end-stage renal disease as well as it be used cautiously in subjects with moderate renal impairment or a history of renal transplantation. The revised label will also likely include a more prominent warning about the potential for renal dysfunction as well as language in the Important Limitations of Use section that the concurrent use of Byetta with insulin has not been studied and cannot be recommended. The limitations of use with respect to insulin is now standard labeling for all anti-diabetics for which there are little or no data for its combined use with insulin.

2.4 Important Issues with Pharmacologically Related Products

Exenatide is used to improve glycemic control in T2D patients. Labeled safety concerns with exenatide include:

1. **Acute pancreatitis**
2. **Gastrointestinal side effects**
3. **Hypoglycemia, especially when used in combination with a sulfonylurea**
4. **Hypersensitivity reactions as a result of anti-exenatide antibodies**
5. **Renal failure (labeled as CBE-0; reviewed as part of this submission)**

2.5 Presubmission Regulatory Activity

On June 29, 2004, the sponsor submitted NDA 21-773, which proposed using exenatide for the treatment of type 2 diabetes mellitus in adults. Exenatide was subsequently approved for the indication in subjects taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione.

The single pivotal trial presented by the sponsor in the original NDA for the monotherapy indication 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, or 20 mcg QD). This small study was comprised of 99 subjects with 74 randomized to exenatide. The effect on HbA1c relative to placebo was significant with the exenatide 10 mcg BID dose only. The effects of treatment on serum fructosamine concentration were not significant. Because the trial was not long enough for HbA1c to fully reflect the glycemic effect of exenatide, it was felt that the data were insufficient to fully characterize the effect of an optimal dose of exenatide as monotherapy in the treatment of T2D. As a result, the monotherapy indication was deemed approvable. An end of review teleconference was held September 17, 2007 to discuss the content and format of the complete response to the approvable letter, which required the sponsor to submit data from at least 1 adequate and well-controlled trial of sufficient duration to assess the efficacy (i.e. HbA1c lowering) and safety of exenatide monotherapy in T2D patients.

2.6 Other Relevant Background Information

There has recently been a shift within the Division of Metabolism and Endocrinology Products in terms of indications for antidiabetic drugs. In the past, drugs were indicated for use as monotherapy or in combination with other specified drugs. Now, antidiabetic drugs are indicated as an adjunct to diet and exercise to improve glycemic control. The safety and efficacy of the drug in monotherapy or in combination with other antidiabetic drugs are described in other sections of labeling, as appropriate.

This current submission triggers conversion of the exenatide label into the Physicians Labeling Rule (PLR) format.

Exenatide is approved in 72 countries and marketed in 50 of those.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new chemistry, manufacturing, controls studies were submitted with this NDA. Please Dr. Chien-Hua Niu's review of the original exenatide NDA (21-773) for details.

3.2 Animal Pharmacology/Toxicology

No new pharmacology/toxicology studies were submitted with this NDA. Please see Dr. Tim Hummer's review as well as Dr. John Colerangle's review of the original exenatide NDA (21-773) for details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor has submitted one new clinical study (H8O-MC-GWBJ, also referred to as GWBJ) to support labeling for use as monotherapy. The trial is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study evaluating the efficacy and safety of two exenatide regimens (5 and 10 mcg given BID) over 24 weeks in subjects with T2D who have failed diet and exercise. The primary efficacy assessment is the placebo-corrected change in hemoglobin A1c (HbA1c) from baseline to endpoint with exenatide twice daily.

The sponsor also refers to studies 2993-116 and 2993-120, which were submitted with the original exenatide NDA (21-773) which was reviewed by K. Eddie Gabry on March 29, 2005.

4.2 Tables of Clinical Studies

Table. Tabular listing of clinical trial submitted in the Efficacy Supplement						
Type of Study	**Objective(s) of the Study**	**Study Design and Type of Control**	**Test Product Dosage Regimen**	**Number of Subjects**	**Subjects**	**Duration of Treatment**
H8O-MC-GWBJ						
Efficacy Safety	Primary: Change in HbA1c Secondary: 1. HbA1c ≤7% & ≤6.5% 2. Change in FSG 3. Change in SMBG 4. Change in weight 5. Safety and tolerability 6. Hypoglycemia 7. Change in HOMA & proinsulin/insulin	Multicenter Double-blind Placebo-controlled Randomized Phase 3	5 mcg BID x 4 wk then 5 or 10 mcg BID x 20 wk	233 randomized 203 completed Non-completers: Placebo 9/78 Exenatide 21/155	Adult type 2 diabetics	24 weeks
2993-116 (submitted in the original NDA and previously reviewed)						
Efficacy Safety	Primary: Change in HbA1c Secondary: 1. Safety and tolerability 2. Effect on FPG 3. Effect on serum fructosamine	Randomized Double-blind Placebo-controlled Parallel-group	Exenatide SC: 2.5 mcg BID 5.0 mcg BID 7.5 mcg BID 10.0 mcg BID Placebo SC BID: Equivalent volume/frequency	30 exenatide 9 placebo	Adult type 2 diabetics	28 days
2993-120 (submitted in the original NDA and previously reviewed)						

	Primary: Change in HbA1c Secondary: 1. Safety and tolerability 2. Effect on weight 3. Effect on fasting and postprandial glucose	Randomized Double-blind Placebo-controlled	Exenatide SC: 10 mcg BID 10 mcg QD 20 mcg QD Placebo SC: Equivalent volume/frequency	74 exenatide 25 placebo	Adult type 2 diabetics	28 days
PD = pharmacodynamic; PK = pharmacokinetic; FSG = fasting serum glucose; SMBG = 6-point self-monitored blood glucose; HOMA = homeostasis model assessment analyses; FPG = fasting plasma glucose						

4.3 Review Strategy

I have reviewed clinical trial GWBJ; PSURs 5, 6, 7, and 8; as well as the renal, pancreatitis, and thyroid data submitted August 12 and 15, 2008 and December 19, 2008, respectively. The efficacy assessment is primarily based on the 6-month data from the pivotal phase 3 trial. The safety assessment is based on all of the above listed data.

4.4 Data Quality and Integrity

The study was conduced at 23 study centers in four countries (Romania, India, Russian Federation, and United States). The tables below present the number (%) of patients in each country and the number (%) of patients in each site by treatment groups.

GWBJ. Number (%) of patients in each country

Country	**N**	**%**
India	57	25
Romania	120	53
Russian Federation	31	14
United States	18	8
Total	226	100

GWBJ. Number (%) of patients in each site by treatment groups

COUNTRY	INVID	EX10mcg	EX5mcg	Placebo	Total	Percent
RO	101	23	21	20	64	28%
RO	103	9	9	12	30	13%
IN	309	3	5	6	14	6%
IN	303	3	6	4	13	6%
RO	105	6	2	3	11	5%
RU	202	5	4	2	11	5%
IN	304	5	.	4	9	4%
RU	205	2	4	3	9	4%
US	1	4	1	4	9	4%
IN	300	1	5	2	8	4%
IN	306	3	3	1	7	3%
US	3	1	4	2	7	3%
RO	102	3	3	.	6	3%
RO	104	1	2	3	6	3%
IN	310	1	2	2	5	2%
RU	206	2	1	2	5	2%
RU	200	1	1	2	4	2%
RO	100	.	2	1	3	1%
RU	204	2	.	.	2	1%

GWBJ. Number (%) of patients in each site by treatment groups						
COUNTRY	INVID	EX10mcg	EX5mcg	Placebo	Total	Percent
US	2	1	.	1	2	1%
IN	308	.	.	1	1	0%
PR	4	.	1	.	1	0%
Total		76	76	75	227	100%

NOTE: Puerto Rico is abbreviated "PR" above.

A large subset (42%) of the randomized patients were enrolled at study sites 101 and 103. Dr. Lee Pian (biometrics) performed a sensitivity analysis of efficacy to ensure that the findings from these 2 sites were consistent with the findings at the other study sites (please see section 6.1.4.3).

The data from India, Romania, and the Russian Federation may be extrapolated to the United States, although the small percentage of subjects of African and Hispanic descent and large percentage of Asian subjects relative to the United States diabetic population must be noted (2.6%, 3.4%, and 26.3%, respectively).

4.5 Compliance with Good Clinical Practices

The sponsor reports that study H8O-MC-GWBJ (GWBJ) was conducted in accordance with the principles of good clinical practice (GCP), including the ethical review board (ERB) and informed consent.

The table below summarizes the major protocol violations in pivotal study GWBJ. A similar proportion of patients in all treatment groups had each of the major protocol violations, except for incorrect dosing which occurred more commonly in the exenatide treatment groups. The most common major protocol violation was the loss of glucose control, which occurred most often in the placebo group.

GWBJ. Protocol violations by treatment group			
	Placebo (n=78)	**Ex 5 mcg (n=77)**	**Ex 10 mcg (n=78)**
Discontinuation criteria			
Loss of glucose control*	13	7	6
Use of concomitant medication	3	3	6
Inclusion/exclusion criteria			
HbA1c < 6.5% or > 10%	1	0	2
BMI < 25 or > 45 kg/m^2	0	1	3
SBP ≥ 160 mm Hg	0	0	1
ALT > 2.5 x ULN	1	0	0
Incorrect dosing	0	8	6
Total	18 (23.0%)	19 (24.7%)	24 (30.8%)
*Loss of glucose control was defined as either an absolute 1% increase in HbA1c from baseline			

at any visit prior to study termination or HbA1c > 10.5% at week 12 or any time thereafter OR at least 4 capillary fasting glucose levels > 260 mg/dl over 7 consecutive days during home glucose monitoring.

Fourteen subjects were dosed incorrectly during the study. The doses that 5 exenatide 5 mcg subjects and 2 exenatide 10 mcg subjects received were not specified in appendix 16.2.2. Three exenatide 5 mcg subjects received 10 mcg by mistake; the total number of incorrect doses was 1, 4, and 1 respectively. Four exenatide 10 mcg subjects received 5 mcg by mistake; the total number of incorrect doses was 2, 2, 2, and 1, respectively.

4.6 Financial Disclosures

All study GWBJ investigators submitted financial disclosure information and had nothing to report.

As reported in Dr. Gabry's March 29, 2005 review, (b) (4) investigators (b) (6) owned stock in the sponsoring company. (b) (6) transferred 1,025 of 2,975 shares to charitable organizations. As none of these investigators took part in pivotal study GWBJ, the integrity of the key trial was not affected.

5 CLINICAL PHARMACOLOGY

No new clinical pharmacology studies were submitted with this NDA. Please refer to Dr. Manoj Khurana's review as well as Dr. Xiaoxiong (Jim) Wei's review of the original exenatide NDA (21-773) for details.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Treatment of type 2 diabetes mellitus

6.1.1 Methods

This section reviews the pivotal efficacy phase 3 trial GWBJ, a randomized, double blind, placebo controlled, parallel group study comparing exenatide 5 or 10 mcg BID and placebo for the treatment of T2D. Please refer to Dr. K. Eddie Gabry's March 29, 2005 exenatide review (NDA 21-773) of studies 2993-116 and 2993-120.

6.1.2 General Discussion of Endpoints

The primary efficacy assessment in the pivotal phase 3 study is the change in HbA1c from baseline to endpoint after 24 weeks treatment with exenatide or placebo twice daily (BID).

Secondary endpoints included the proportion of subjects achieving HbA1c ≤ 7% and ≤6.5%, change in fasting serum glucose (FSG), change in 6-point self-monitored blood glucose (SMBG, measured before and 2 hours after the three main meals) profile, change in body weight, assessment of safety and tolerability, incidence of hypoglycemic events, and change in beta-cell function and insulin sensitivity as assessed by homeostasis model assessment (HOMA) analyses and the proinsulin/insulin ratio.

HbA1c and glycemic parameters including the change in fasting serum glucose and 6-point self-monitored blood glucose are typically accepted as endpoints to demonstrate the efficacy of investigational antidiabetic products. The other endpoints listed are exploratory.

6.1.3 Study Design

Study H8O-MC-GWBJ is the main trial supporting the efficacy of exenatide as monotherapy.

Study H8O-MC-GWBJ: Safety and efficacy of exenatide as monotherapy in drug-naïve patients with type 2 diabetes

Primary Objective: To test the hypothesis that glycemic control as measured by the change in HbA1c from baseline to endpoint with exenatide BID is superior to placebo BID after 24 wks treatment in patients with T2D who have inadequate control with diet and exercise.

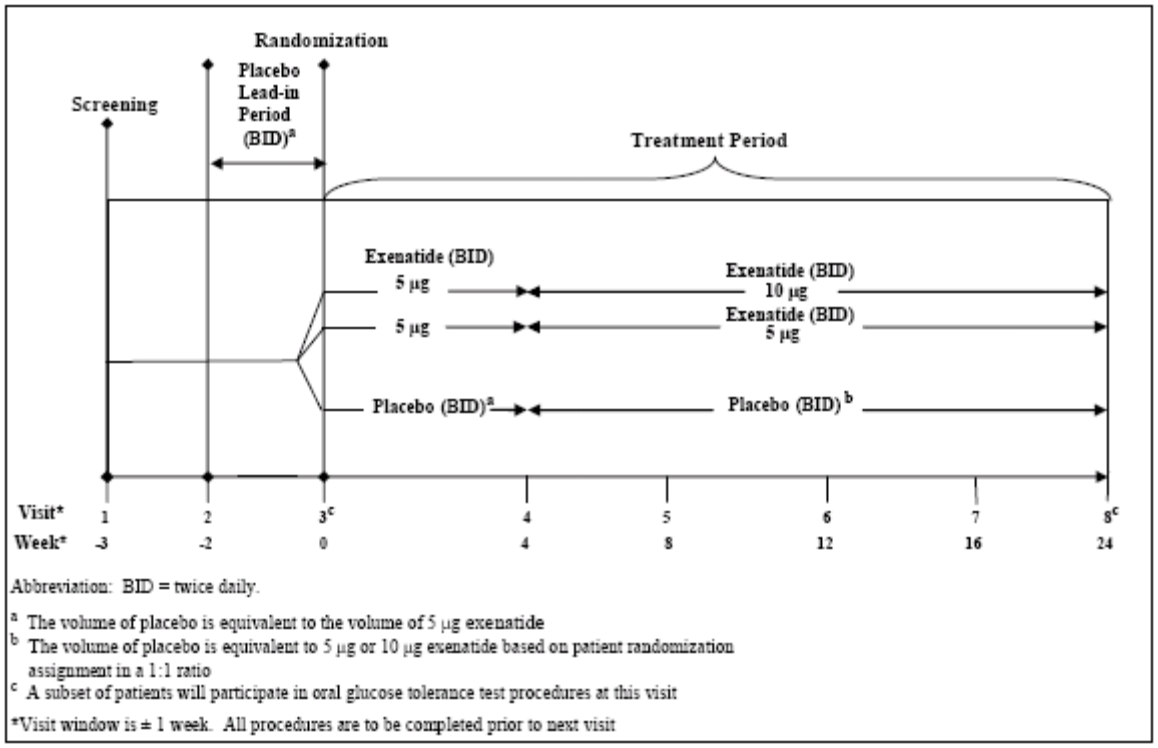
Secondary Objectives: To compare exenatide BID to placebo BID with regard to the following:

- The proportion of subjects achieving HbA1c ≤ 7% and ≤ 6.5%
- Change in fasting serum glucose (FSG)
- Change in 6-point self-monitored blood glucose (SMBG) profile
- Change in body weight
- Assessment of safety and tolerability
- Incidence of hypoglycemic events
- Change in beta-cell function and insulin sensitivity as assessed by homeostasis model assessment (HOMA) analyses and the proinsulin/insulin ratio

Study Design: Multicenter (sites in Romania, Russian Federation, United States, and India), 24-week, phase 3, randomized, double-blind, placebo-controlled, three arm, parallel group, outpatient study comparing exenatide 5 and 10 mcg BID to placebo BID for the treatment of T2D as an adjunct to diet and exercise.

Adult T2D subjects who were inadequately controlled on diet and exercise participated in a 2 week, single blind, placebo run-in period prior to being randomized into one of three treatment arms. During a 4-week initial treatment period, subjects were treated with exenatide 5 mcg subcutaneously (SC) BID or placebo SC BID. Subjects were then assigned to their treatment arm (exenatide 5 or 10 mcg SC BID or placebo SC BID) for the remaining 20-week treatment period. Clinic visits occurred every 4 weeks during treatment.

GWBJ. Study design (Reproduced from Sponsor, NDA 21919, GWBJ study report, page 46)



Vitals, adverse events, and study diaries were collected at every treatment period visit. SMBG was collected at weeks 0, 12, and 24. Lipid, proinsulin, C-peptide, and highly sensitive C-reactive protein levels as well as oral glucose tolerance tests (OGTTs) in a subset of patients were collected at weeks 0 and 24. C-peptide levels were also collected at week 3. HbA1c and glucose levels were collected at weeks -3, 4, 8, 12, and 16; HbA1c was also collected at weeks 0 and 24.

GWBJ. Study schedule (Reproduced from Sponsor, NDA 21919, GWBJ study report, page 53-4)

Visit	1	2	3	4	5	6	7	8	ED
Time relative to Visit 3 (weeks)	-3	-2	0	4	8	12	16	24	
Visit Interval (± weeks)*	1	1	0	1	1	1	1	1	
Informed consent	X								
Patient number assigned	X								
Randomization			X						
Dispense study drug/injection pen		X	X	X	X	X	X		
Collect study drug			X	X	X	X	X	X	X
Collect injection pen								X	X
Dispense glucose meter/ supplies		X							
Instruct on glucose meter/ hypoglycemia/reinforce current diet and exercise plan		X	X	X	X	X	X	X	
Injection/pen training		X	X						
Clinical assessments:									
Pregnancy test	X								
ECG (12-lead)	X								
Medical history	X								
Preexisting conditions	X								
Height	X								
Weight/SBP/DBP/HR	X	X	X	X	X	X	X	X	X
Physical examination	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Distribute study diaries		X	X	X	X	X	X		
Collect study diaries			X	X	X	X	X	X	X
Transfer diary information to CRF:									
6-point SMBG profile			X			X		X	X
Hypoglycemic episodes			X	X	X	X	X	X	X
Injectable therapy dose (day prior to visit)[a]				X	X	X	X	X	X
Chemistry, hematology	X							X	X

Visit	1	2	3	4	5	6	7	8	ED
Time relative to Visit 3 (weeks)	-3	-2	0	4	8	12	16	24	
Visit Interval (± weeks)*	1	1	0	1	1	1	1		
On-site OGTT[b]			X					X	X
Blood insulin[c]			X					X	X
Blood glucose[c]			X					X	X
Laboratory assessments[b]:									
Fasting lipids[d]			X					X	X
Fasting C-peptide	X		X					X	X
Fasting proinsulin			X					X	X
Fasting glucose	X			X	X	X	X		
Highly sensitive C-reactive protein (hsCRP)			X					X	X
Hemoglobin A_{1c}	X		X	X	X	X	X	X	X
Anti-exenatide antibodies			X					X	X
Patient Summary								X	X

Procedures were performed as indicated unless time interval is shaded.

Abbreviations: CRF = case report form; DBP = diastolic blood pressure; ECG = electrocardiogram; ED = early discontinuation visit; HR = heart rate; OGTT = oral glucose tolerance test; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; X = performed at this visit.

[a] Patients did not administer injectable therapy (exenatide or placebo) prior to visiting the study site on the day of visit.

[b] Patients fasted approximately 8 hours prior to visiting the study site.

[c] Blood samples for measurements of blood concentrations of glucose and insulin were drawn immediately before and 30, 60, 120, and 180 minutes following the administration of oral glucose load.

[d] Fasting lipids include total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Low-density lipoprotein cholesterol was calculated.

* All procedures were completed prior to next visit.

Medications were subcutaneously injected 15 minutes before the morning and evening meals.

A total of 233 subjects were randomly assigned to the treatment groups (78 placebo, 155 active drug). Randomization was stratified by investigative site and screening HbA1c (≤ 8% or > 8%). As glycemic rescue criteria was not specified, subjects could be discontinued for loss of glucose control defined as the following:

- 1% increase in HbA1c from baseline at any visit prior to study termination or HbA1c >10.5% at week 12 or anytime thereafter
- At least 4 fingerstick fasting glucose levels >260 mg/dl over 7 consecutive days during home glucose monitoring.

Inclusion criteria:

1. Subjects have T2D based on the disease diagnostic criteria
2. Patients are ≥ 18 years of age.
3. Patients must have been treating their diabetes with diet and exercise therapy consistent with the local standards of medical care, in the opinion of the investigator.
4. Have suboptimal glycemic control as evidenced by an HbA1c between 6.5 to 10% inclusive.
5. Have a body mass index (BMI) of 25 to 45 kg/m^2 inclusive.

Exclusion criteria:

1. Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.
2. Employed by Lilly or Amylin.
3. Have previously completed or withdrawn from this study.
4. Have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
5. Have been treated with any antidiabetic agent.
6. Exclusion criterion (6) applies to females of child-bearing potential (not surgically sterilized and between menarche and 1 year postmenopause) only.
    a. Are breastfeeding
    b. Test positive for pregnancy at the time of enrollment based on a blood serum pregnancy test.
    c. Intend to become pregnant during the study.
    d. Have not practiced a reliable method of birth control for 3 months prior to screening.
    e. Do not agree to continue to use a reliable method of birth control during the study as determined by the investigator.
7. Has poorly controlled blood pressure (≥ 160 mmHg systolic; ≥ 110 mmHg diastolic).
8. Have a known allergy to excipients contained in exenatide.
9. Have a clinically significant history or presence of Class III or IV cardiac disease, coronary artery bypass surgery or angioplasty within the year prior to study inclusion; or is expected to require coronary artery bypass surgery or angioplasty during the course of the study
10. Have a history of renal transplantation or are currently receiving renal dialysis or have an estimated creatinine clearance of < 50 ml/min as estimated by the Cockcroft-Gault equation.
11. Have obvious clinical signs or symptoms of liver disease, chronic hepatitis, or alanine aminotransaminase/serum glutamic pyruvic transaminase (ALT/SGPT) > 2.5 times the upper limit of the reference range.
12. Have known hemoglobinopathy or chronic anemia (hemoglobin concentration < 11.5 g/dl for males < 10.5 g/dl for females).
13. Have a known active proliferative retinopathy or macular edema.
14. Used drugs for weight loss (e.g. orlistat, sibutramine, phenylpropanolamine, or similar over the counter medications) within 3 months of screening.
15. Are currently treated with any of the following excluded medications:
    a. Drugs that directly affect gastrointestinal mobility, including but not limited to metoclopromide, cisapride, and chronic macrolide antibiotics.
    b. Systemic corticosteroids (excluding topical and inhaled preparations) by oral, intravenous, or intramuscular route used regularly (longer than 2 weeks) or used within 2 weeks immediately prior to screening.
16. Patients have less than 5 years of remission history from any malignancy (other than basal cell or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer).
17. Have had an organ transplant.

18. Currently abuses drugs or alcohol or has a history of abuse that in the investigator's opinion would cause the individual to be noncompliant.
19. Fail to satisfy the investigator of suitability to participate for any other reason.

Statistical Plan: Please see Dr. Lee-Ping Pian's statistical review for details. The Sponsor defined two statistical populations:

> Intent-to-treat (ITT) population: All randomized patients who received ≥1 dose of study medication.

Per protocol population (PP): All ITT patients who had at least 12 weeks of exposure to study medication and had no violations of inclusion/exclusion or discontinuation criteria.

Although the PP population may have been better defined as all ITT patients who had at least 20 weeks of exposure to study medication and had no violations of inclusion/exclusion or discontinuation criteria, the statistical reviewer accepted the sponsor's definition, because she performs her own analysis using the ITT and completer populations, not the sponsor-defined PP population.

The sponsor's analysis used the ITT analysis dataset unless otherwise specified. All tests of treatment effects were conducted at a two-sided significance level of 0.05 unless otherwise stated. The last observation carried forward (LOCF) of postbaseline values was used as needed for missing data in change from baseline to endpoint analyses.

Primary efficacy variable: The primary efficacy measure was HbA1c. HbA1c was summarized using descriptive statistics at baseline, each week of visit, and endpoint (LOCF) by treatment group using the ITT, per protocol, and OGTT analysis sets. Actual and change values were summarized using descriptive statistics at each week of visit and endpoint (LOCF) by treatment group using ITT analysis set. The primary analysis was based on an ANCOVA model.

Secondary efficacy variables (see secondary objectives above for the complete list): FSG, body weight, HOMA of insulin sensitivity (HOMA-S), HOMA of beta-cell function (HOMA-B), and lipid, insulin, proinsulin, and C-peptide levels were summarized using descriptive statistics and assessed using a similar model to the primary efficacy measure. SMBG and OGTTs were summarized using descriptive statistics.

Sample size justification: The power computations for this trial were based on a sample size of 258 patients with 86 randomized to receive placebo and 172 randomized to exenatide (86 per arm). Assuming a 30% dropout rate, 60 patients per arm would complete the study. This would provide > 90% power to reject the null hypothesis of no difference among treatments assuming true mean changes in HbA1c of -0.7, -0.5, and 0 for patients receiving exenatide 10 mcg, exenatide 5 mcg, and placebo respectively. This power computation assumed a common standard deviation of 1.0% and two-sided significance level of 0.05. Assuming the same true mean changes in HbA1c, common SD, and two-sided significance level, 60 patients per treatment group would also provide > 90% power to detect a difference between 10 mg

exenatide and placebo treatments and 77% power to detect a difference between 5 mcg exenatide and placebo with a Fisher Protected Testing procedure.

Major Amendments to the Protocol: There were no amendments to the study. The addenda to the study were as follows:

- June 8, 2006: Added adiponectin, tumor necrosis factor-alpha, and plasminogen activator inhibitor-1 measurements to sites in Russia and Romania
- September 1, 2006: Added the estimation of excretion rates of free 8-iso $PGF_{2\alpha}$ and creatinine from first morning urine at weeks 0 and 24 (or early discontinuation) in approximately 75 patients (25 per treatment arm) in Russian and Romania
- October 25, 2006: Because the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommended that glucometers be standardized to plasma glucose concentration, the conversion algorithm changed from whole blood to plasma levels. This recommendation was implemented in Argentina, India, Romania, and Russia. Thus, the values defining hypoglycemia (hypoglycemia [< 64 mg/dl] and severe hypoglycemia [< 54 mg/dl]) were changed in these countries.
- October 25, 2006: Revised the exclusion and discontinuation criteria for sites in Argentina as recommended by the Ministry of Health
- November 6, 2006: Added waist circumference measurements at weeks 0 and 24 (or early discontinuation) to sites in India, as it has been shown to be a more accurate predictor of metabolic syndrome and cardiovascular disease risk factor than BMI in Asian Indians

6.1.4 Efficacy Findings

The Sponsor randomized and treated 233 patients (78 placebo, 155 active drug). One placebo patient discontinued from the study before treatment. Thus, the ITT population is comprised of 232 randomized patients (placebo 77, exenatide 5 mcg 77, 10 mcg exenatide 78). A total of 203 subjects completed the study (69 placebo, 134 active drug). A similar percentage of subjects in each treatment group completed the study (placebo 88.5%; 5 mcg exenatide 85.7%; 10 mcg exenatide 87.2%).

GWBJ. Number of patients in each statistical population

	Number (%) of patients		
Parameters	**Placebo**	**5 mcg Exenatide**	**10 mcg Exenatide**
Intent-to-treat population	77	77	78
Completer population	69 (88.5%)	66 (85.7%)	68 (87.2%)

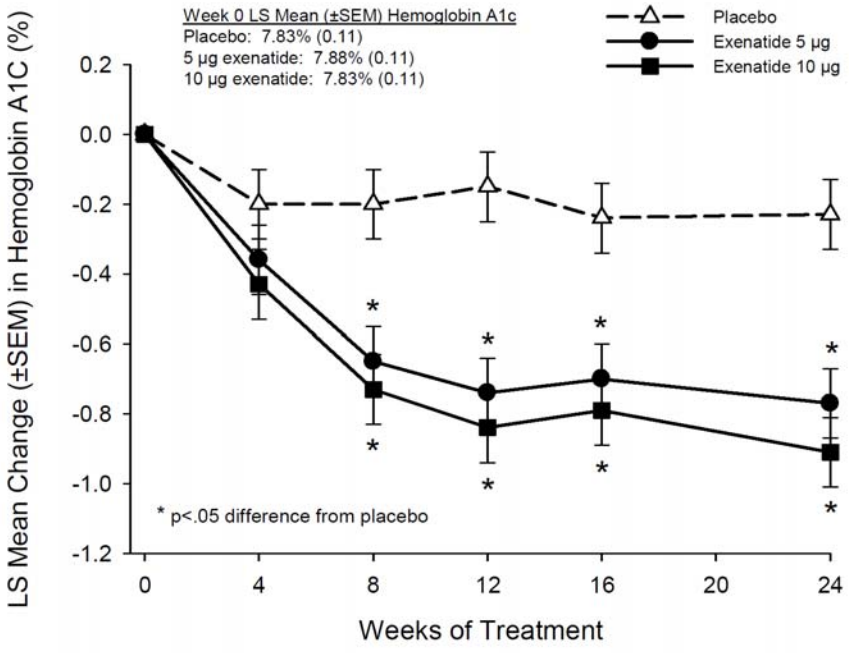
6.1.4.1 Primary efficacy analysis

The primary objective was to determine if glycemic control as measured by the change in HbA1c from baseline to endpoint with exenatide twice daily (BID) was superior to placebo BID after 24

wks treatment in patients with T2D who had inadequate control with diet and exercise. The tables below summarize the mean change in HbA1c from baseline to endpoint (LOCF) in the ITT population. After 24 weeks of treatment, the HbA1c was improved in all three groups. However, only the exenatide groups experienced a statistically significant improvement in HbA1c compared to baseline. Relative to placebo, the LS mean reduction in HbA1c from baseline to endpoint was -0.5% ($p<0.01$) with exenatide 5 mcg and -0.7% ($p<0.001$) with exenatide 10 mcg.

GWBJ. LS Mean change from baseline to endpoint (LOCF) in HbA1c (ITT)			
Treatment	**Baseline LS Mean**	**LS Mean Change**	**p-value**
Placebo (n=75)	7.8	-0.2	0.1062
Exenatide 5 mcg (n=76)	7.9	-0.7	< 0.0001
Exenatide 10 mcg (n=76)	7.8	-0.9	< 0.0001

GWBJ. LS mean treatment difference for HbA1c (ITT)			
	LS Mean	**95% CI**	**p-value**
Baseline			
Ex 5 mcg – Placebo	0.1	(-0.3, 0.4)	0.76
Ex 10 mcg – Placebo	0.0	(-0.3, 0.3)	0.99
Endpoint			
Ex 5 mcg – Placebo	-0.5	(-0.9, -0.2)	0.003
Ex 10 mcg – Placebo	-0.7	(-1.0, -0.3)	0.0004



GWBJ. Change in HbA1c by week of visit (ITT) (Reproduced from sponsor, NDA 21919, GWBJ study report, page 104)

6.1.4.2 Secondary efficacy analysis

6.1.4.2.1 Proportion of patients achieving HbA1c ≤ 7% and ≤ 6.5%

The proportions of patients achieving HbA1c ≤ 7% and ≤ 6.5% are shown below. The minimum inclusion criteria for HbA1c values was 6.5% in study GWBJ. A greater proportion of patients in the exenatide 5 and 10 mcg groups experienced endpoint HbA1c values ≤ 7% and ≤ 6.5% when compared to placebo (54.2% and 52.0% vs. 31.5%; 33.8% and 38.1% vs. 19.1%, respectively). Interestingly, a similar proportion of patients (~50%) dosed with exenatide 5 mcg and 10 mcg achieved HbA1c ≤7%. However, not all of these comparisons were statistically significant. With respect to achieving HbA1c ≤ 7%, neither the exenatide 5 nor 10 mcg dose was statistically significant to placebo when the PP population was used. However, the exenatide 5 and 10 mcg doses resulted in statistically significantly more HbA1c values ≤ 7% compared to placebo when the ITT population was used (p=0.0235 and p=0.0362, respectively). With respect to achieving HbA1c ≤ 6.5%, exenatide 10 mcg, but not the 5 mcg dose, resulted in statistically significantly more reductions in HbA1c below that level when the PP population was used (p=0.0178). These nominal p-values were not adjusted for multiplicity testing.

GWBJ. Number and percent of subjects achieving HbA1c ≤ 7% and ≤ 6.5%				
Treatment	**Baseline HbA1c > 7% & Endpoint HbA1c ≤ 7%**		**Baseline HbA1c > 6.5% & Endpoint HbA1c ≤ 6.5%**	
	n (N)	%	n (N)	%
Placebo	17 (54)	31.5	13 (68)	19.1
Exenatide 5 mcg	26 (48)	54.2	22 (65)	33.8
Exenatide 10 mcg	26 (50)	52.0	24 (63)	38.1
N = number of subjects with baseline > 7% or > 6.5%				

6.1.4.2.2 Change in fasting serum glucose (FSG)

Exenatide 5 and 10 mcg BID resulted in similar significant (p< 0.0001) LS mean reductions in FSG from baseline to endpoint (-18 and -19 mg/dL, respectively). Significant LS mean treatment differences (exenatide – placebo) were observed at endpoint in both exenatide groups.

GWBJ. LS Mean change from baseline to endpoint (LOCF) in FSG (mg/dl) (ITT)			
Treatment	**Baseline LS Mean**	**Mean Change**	**p-value**
Placebo (n=75)	159	-5	0.1926
Exenatide 5 mcg (n=77)	166	-18	< 0.0001
Exenatide 10 mcg	155	-19	< 0.001

(n=76)			

GWBJ. LS mean treatment difference for FSG (mg/dl) (ITT)			
	LS Mean	**95% CI**	**p-value**
Baseline			
Ex 5 mcg – Placebo	7	(-7, 21)	0.3302
Ex 10 mcg – Placebo	-5	(-19, 10)	0.5207
Endpoint			
Ex 5 mcg – Placebo	-12	(-23, -1)	0.0292
Ex 10 mcg – Placebo	-14	(-24, -3)	0.0161

6.1.4.2.3 Change in 6-point self-monitored blood glucose (SMBG) profile

Patients performed SMBG profiles at baseline (week 0) and weeks 12 and 24 (or early discontinuation). Significant mean reductions from baseline were seen in both exenatide treatment groups in the daily mean as well as all time points ($p \leq 0.03$). However, placebo patients only experienced a significant reduction at the midday ($p=0.03$) and evening ($p=0.04$) postprandial time points. With the exception of the exenatide 10 mcg treatment group's evening premeal value, both exenatide treatment groups experienced significantly lower blood glucose concentrations at all time points and the daily mean when compared to placebo-treated patients. As expected for this incretin analog, the postprandial effect on glycemia was greater than the premeal effect. Interestingly, the reductions from baseline for 5 mcg is numerically greater than that with 10 mcg at all timepoints except after the evening meal; there was no dose response.

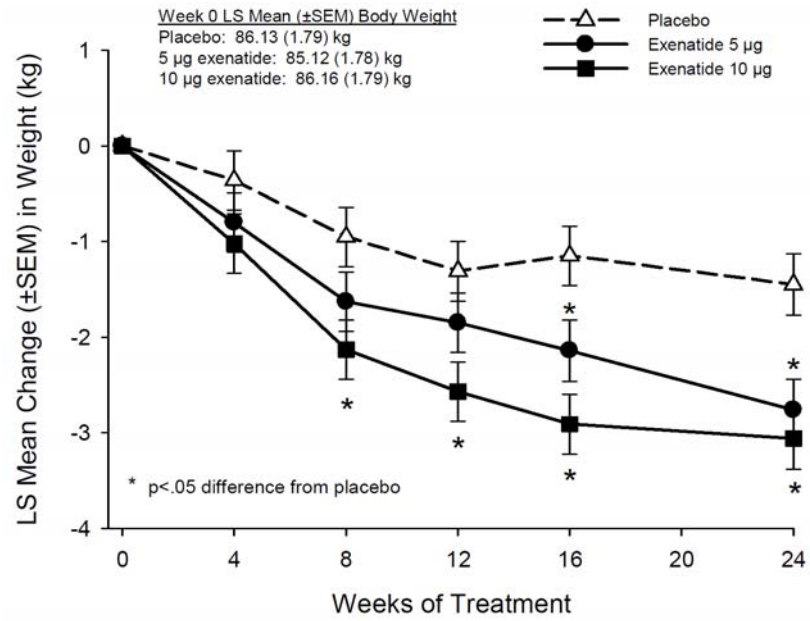
GWBJ. LS mean change (SD) from baseline in self-monitored blood glucose values (mg/dl) (ITT population)							
	LS Mean Change (SD) from baseline in self-monitored blood glucose values (mg/dl)						
	Morning Pre-meal	**Morning PP meal**	**Midday Pre-meal**	**Midday PP meal**	**Evening Pre-meal**	**Evening 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)	-18.72 (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							

6.1.4.2.4 Change in body weight

Placebo subjects experienced, on average, a steady decline in body weight beginning at week 4 through the end of the study, with a mean loss of 1.45 kg at week 24 compared to baseline. The LS mean treatment difference relative to placebo at endpoint was -1.31 (95% CI: -2.19, -0.43) and -1.61 (95% CI: -2.49, -0.74) for exenatide 5 and 10 mcg, respectively.

Greater mean reductions in body weight were seen with both exenatide groups when compared to placebo. There were significant treatment differences observed at week 16 (p=0.0268) and week 24 (p=0.0037) for the exenatide 5 mcg group and at weeks 8 (p=0.0074) through 24 (p=0.0003) for the exenatide 10 mcg treatment group (ITT).

GWBJ. LS Mean change from baseline to endpoint (LOCF) in body weight (kg) (ITT)			
Treatment	**Baseline LS Mean**	**Change**	**p-value**
Placebo (n=69)	86.13	-1.45	< 0.0001
Exenatide 5 mcg (n=66)	85.12	-2.76	< 0.0001
Exenatide 10 mcg (n=69)	86.16	-3.06	< 0.0001



GWBJ. Change in body weight by week of visit (ITT) (Reproduced from sponsor, NDA 21919, GWBJ study report, page 123)

6.1.4.2.5 Change in beta-cell function and insulin sensitivity as assessed by homeostasis model assessment (HOMA) analyses and the proinsulin/insulin ratio

Patient beta-cell function and insulin sensitivity, fasting serum insulin, fasting serum proinsulin, and fasting serum proinsulin/insulin ratio were calculated at baseline (week 0) and endpoint (week 24 or early discontinuation).

No statistically significant differences in fasting serum insulin or proinsulin were observed when exenatide-treated patients were compared to placebo-treated patients from baseline to endpoint.

GWBJ. Fasting serum insulin and proinsulin (pmol/l) log-transformed analysis of treatment differences in change from baseline to endpoint (LOCF) (ITT population)

	Placebo (n=77)	**Ex 5 mcg (n=77)**	**Ex 10 mcg (n=78)**
Insulin			
LS mean of Endpoint:Baseline	0.98	1.18	0.98
LS mean ratio of Ex vs. Placebo		1.20	1.01
95% CI ratio		(0.98, 1.49)	(0.82, 1.23)
p-value		0.0737	0.9594
Proinsulin			
LS mean of Endpoint:Baseline	0.96	0.90	0.81
LS mean ratio of Ex vs. Placebo		0.93	0.84
95% CI ratio		(0.77, 1.13)	(0.69, 1.01)
p-value		0.4914	0.0680

Exenatide 5 mcg patients experienced significant reductions in fasting serum proinsulin/insulin ratio (an indication of beta cell "stress") from baseline compared with placebo patients (22%, p=0.0372). Although exenatide 10 mcg patients experienced improvements (16%) in the proinsulin/insulin ratio, the difference was not statistically significant when compared to placebo patients (p=0.1252).

No treatment differences in HOMA-S (an index of target organ sensitivity) were observed when patients in either exenatide group were compared with placebo patients. However, exenatide 5 and 10 mcg patients showed statistically significant improvements (25% [p=0.0022] and 21% [p=0.0102], respectively) in HOMA-B (an index of pancreatic beta-cell function) at endpoint when compared with placebo patients.

Of note, the above mathematical models are not well-validated surrogates for insulin sensitivity and beta-cell function, and therefore, do not yet rise to a level of evidence to support inclusion in labeling.

6.1.4.3 Subgroup analyses

Demographics

HbA1c and FSG were analyzed based on the patients' gender, age, body mass index (BMI), and anti-exenatide antibody status. Patient age did not significantly affect the change in HbA1c or FSG levels. Although gender did not affect the change in HbA1c levels, a significant ($p<0.10$)

effect of gender was seen on the change in FSG. Female exenatide patients experienced greater LS mean reductions in FSG compared to male exenatide patients. This small difference, however, may be explained by the small number of subjects in each subset.

GWBJ. LS mean change from baseline to endpoint in FSG (mg/dl) by gender (n)		
	Female	Male
Exenatide 5 mcg	-18±6 (37)	-17±5 (40)
Exenatide 10 mcg	-27±6 (30)	-13±5 (46)

Although BMI did not affect the change in FSG, placebo and exenatide 5 mcg patients with lower BMI values (< 30 kg/m^2) experienced greater LS mean reductions in HbA1c compared with those with higher BMI values (≥ 30 kg/m^2), while LS mean reductions were similar between the two BMI groups in the exenatide 10 mcg group.

GWBJ. LS mean change from baseline to endpoint in HbA1c by baseline BMI (n)		
	BMI < 30 kg/m^2	BMI ≥ 30 kg/m^2
Placebo	-0.52 ± 0.19 (32)	0.04 ± 0.16 (43)
Exenatide 5 mcg	-1.17 ± 0.18 (34)	-0.38 ± 0.16 (42)
Exenatide 10 mcg	-0.88 ± 0.17 (39)	-0.86 ± 0.17 (37)

Anti-exenatide antibodies

In the original exenatide NDA 21-773 studies, treatment groups were significantly different in the percentage of patients with anti-exenatide antibodies (range 2-49%). Anti-exenatide antibodies were classified as < 1:125 or ≥ 1:125. Patients in the active treatment groups (exenatide with metformin alone, sulfonylurea (SU) alone, and metformin plus SU) experienced a reduction of HbA1c in both antibody categories compared to placebo. However, the effect was smaller in the antibody titer ≥ 125 patients. Because antibody titer and HbA1c were both outcome variables and not subgroups in the usual sense, caution must be used when interpreting the results below.

NDA 21-773. Mean HbA1c change (%) by antibody titer category (all studies). (Reproduced from Dr. K. Eddie Gabry's March 29, 2005 NDA 21-773 review.)

	Placebo		5 µg		10 µg	
	<125	≥125	<125	≥125	<125	≥125
Metformin alone	n=134	n=1	n=112	n=15	n=113	n=16

Mean (SD)	+0.1 (1.0)	+0.2	-0.4 (1.1)	-0.1 (0.7)	-0.7 (1.0)	-0.5 (1.1)
Median	+0.2	+0.2	-0.5	-0.3	-0.6	-0.3
SFU alone	n=156	n=5	n=131	n=15	n=131	n=27
Mean (SD)	+0.2 (1.0)	-0.8 (1.2)	-0.5 (1.2)	-0.5 (1.3)	-0.8 (1.2)	-0.5 (1.2)
Median	+0.2	-1.1	-0.5	-0.6	-0.7	-0.5
Metformin+SFU	n=290	n=2	n=233	n=48	n=227	n=47
Mean (SD)	+0.3 (1.1)	+0.5 (0.3)	-0.6 (1.1)	-0.2 (1.2)	-0.8 (1.1)	-0.3 (1.3)
Median	+0.2	+0.5	-0.5	-0.2	-0.8	-0.2

In study GWBJ, patients were considered antibody-positive if they had a zero titer or unknown status at baseline and a titer of ≥ 25 dilution at the last visit, or if they had a positive titer at baseline with a ≥ 3-fold increase in titer dilution at the last visit. Of 71 patients treated with exenatide 5 mcg whose antibody status at the last study visit was known, 21 (30%) were anti-exenatide antibody positive. Of 73 patients treated with exenatide 10 mcg whose antibody status at the last study visit was known, 22 (30%) were anti-exenatide antibody positive. Study GWBJ did not measure neutralizing antibodies to exenatide or antibodies to endogenous GLP-1.

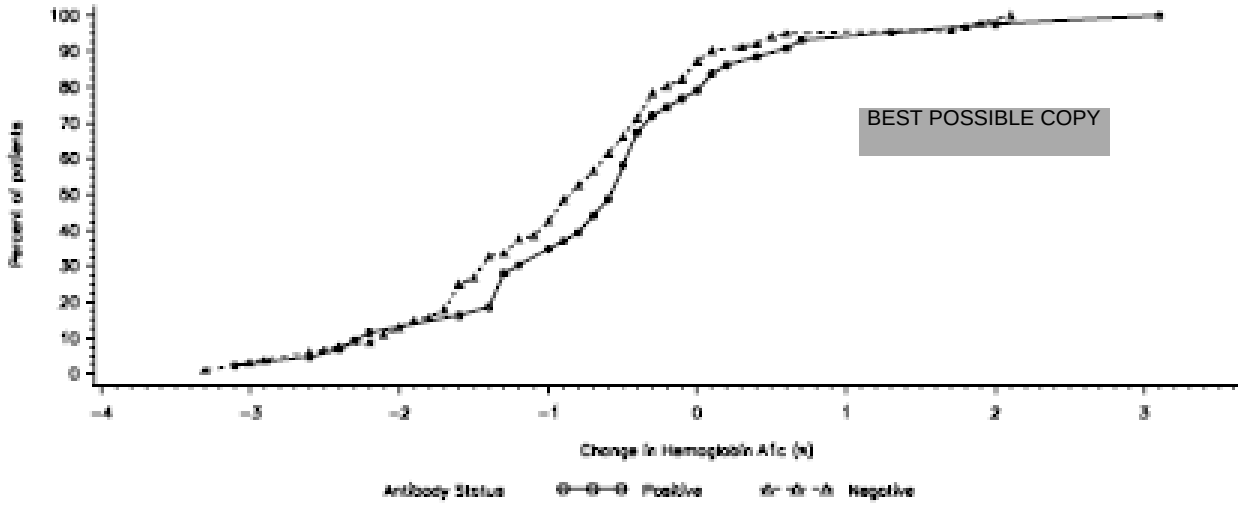
The change in HbA1c and FSG from baseline to endpoint was compared for the anti-exenatide positive and negative patients. The range of mean change in HbA1c (-0.6 to -0.9%) is nearly included within the range of mean change in HbA1c (0.2 to -0.8%) seen in NDA 21-773. In regression models with change in HbA1c and change in FSG as the dependent variables and baseline HbA1c and baseline FSG and antibody status as explanatory variables, no statistically significant associations between change in HbA1c and change in FSG and anti-exenatide antibody status were seen. However, in the table below, it appears that the change in HbA1c and FSG was greater in the antibody negative patients compared to the antibody positive patients, particularly for the exenatide 10 mcg group (this may be partly explained by the poorer baseline glycemic control in the antibody negative patients). Furthermore, in graphs of the empirical cumulative distribution of change in HbA1c from baseline to endpoint based on anti-exenatide antibody status of ITT patients, the antibody-negative curve is shifted left suggesting slight improvement in glycemic control for those patients compared to the antibody-positive patients. Consistent with this, the Precautions section of the current exenatide label states the following: *In a small proportion of patients, the formation of anti-exenatide antibodies at high titers could result in failure to achieve adequate improvement in glycemic control. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.*

NOTE: The time of antibody positivity onset was not assessed by the sponsor.

GWBJ. Mean change (SD) in HbA1c and FSG from baseline to endpoint in exenatide treatment groups by anti-exenatide antibody status

	Exenatide 5 mcg				**Exenatide 10 mcg**			
	Positive		**Negative**		**Positive**		**Negative**	
	Base	Mn chng (SD)	Base	Mn chng (SD)	Base	Mn chng (SD)	Base	Mn chng (SD)
HbA1c (%)	7.64	-0.61	7.92	-0.74 (1.08)	8.78	-0.60 (0.98)	9.26	-0.94 (1.02)

		(1.33)						
FSG (mmol/l)	8.78	0.90 (2.35)	9.26	-1.19 (1.86)	8.29	-0.21 (2.45)	8.74	-1.15 (1.88)
Base=baseline; Mn chng=Mean change								



GWBJ. Empirical cumulative distribution plot of change in HbA1c (%) from baseline to endpoint by anti-exenatide status (ITT population) (Reproduced from sponsor, NDA 21919, study H8O-MC-GWBJ, page 464)

Study Sites

The study was conducted at 23 study centers in four countries (Romania, India, Russian Federation, and United States). As described in Section 4.4, a large subset (42%) of the randomized patients were enrolled at study sites 101 and 103. Descriptive statistics of sites 101 and 103 in Romania were compared to all other sites pooled. (Please refer to Dr. Lee Ping Pian's statistics review for full details.) The HbA1c change from baseline means and medians for the three treatment groups at site 101 and 103 were similar to the corresponding means of all other sites combined.

The mean and median (95% confidence interval) for fasting serum glucose (FSG) change from baseline for investigators 101, 103, and all others pooled were similar. Dose response was not evident for the exenatide 5 and 10 mcg for all investigator groups.

Dr. Lee Ping Pian performed an analysis of covariance (ANCOVA) in HbA1c change from baseline treatment groups, with screening HbA1c stratum (≤ 8% and > 8%) and investigator site as fixed effects and baseline HbA1c as covariate. Investigator sites 101 and 103 were either included or excluded from the analysis. The results (shown below) showed a consistent significance for the overall p-value for all three analyses.

GWBJ. ANCOVA results for HbA1c						
	Placebo	EX 5mcg	Ex 10mcg	overall P	EX 5mcg-Plb	EX10mcg-Plb

GWBJ. ANCOVA results for HbA1c

	Placebo	EX 5mcg	Ex 10mcg	overall P	EX 5mcg-Plb	EX10mcg-Plb
All	-0.2	-0.7	-0.8	0.0005	-0.5	-0.7
	(0.1)	(0.1)	(0.1)		[-0.9, -0.2]	[-1.0, -0.3]
no 101	-0.2	-0.7	-0.8	0.01	-0.5	-0.6
	(0.2)	(0.2)	(0.2)		[-1.0, -0.1]	[-1.1, -0.2]
no 101, 103	-0.3	-0.7	-0.9	0.04	-0.5	-0.7
	(0.2)	(0.2)	(0.2)		[-1.0, 0.05]	[-1.2, -0.1]
101 only	-0.1	-0.7	-0.8	0.03	-0.5	-0.7
	(0.2)	(0.2)	(0.2)		[-1.1, 0.01]	[-1.3, -0.2]
103 only	-0.05	-0.8	-0.7	0.09	-0.8	-0.6
	(0.2)	(0.3)	(0.3)		[-1.5, -0.03]	[-1.4, 0.1]

Thus, both the descriptive statistics and the inferential statistics in HbA1c changes from baseline were consistent with or without sites 101 and 103 in the analysis. The overall p-values were all statistically significant with or without sites 101 and 103.

6.1.5 Clinical Microbiology

Not applicable – exenatide is not an antimicrobial agent.

6.1.6 Efficacy Conclusions

- The primary objective was to determine if glycemic control as measured by the change in HbA1c from baseline to endpoint with exenatide twice daily (BID) was superior to placebo BID after 24 wks treatment in patients with T2D who had inadequate control with diet and exercise. Only the exenatide groups experienced a statistically significant improvement in HbA1c compared to baseline. The LS mean treatment difference (exenatide – placebo) at endpoint was -0.5 (95% CI: -0.87, -0.18) (p=0.0030) and -0.7 (95% CI: -1.01, -0.32) (0.0004) for the exenatide 5 and 10 mcg groups, respectively.
- Among the PP patients with HbA1c > 7%, more exenatide 5 mcg (53.2%) and 10 mcg (47.6%) patients than placebo (34.1%) had HbA1c ≤ 7% at endpoint. The differences were not statistically significant. Among the PP patients with HbA1c > 6.5% at baseline, statistically significantly more (p=0.0178) exenatide 10 mcg patients than placebo patients (41.5% vs. 21.1%) had HbA1c ≤ 6.5% at endpoint. A greater percentage of exenatide 5 mcg patients (34.9%) than placebo patients had HbA1c ≤ 6.5% at endpoint, although the difference was not statistically significant.
- Exenatide 5 and 10 mcg BID resulted in a greater LS mean change in FSG from baseline than placebo (-17.5 and -18.7 mg/dL vs. -5.2 mg/dL, respectively). The FSG LS mean treatment difference relative to placebo at endpoint was -12.2 mg/dL (95% CI: -23.22, -1.26) (p=0.0292) and -12.6 mg/dL (95% CI: -24.48, -2.52) (p=0.0161).

- As expected for this incretin analog, the postprandial effect on glycemia was greater than the premeal effect. With the exception of the exenatide 10 mcg treatment group's evening premeal value, both exenatide treatment groups experienced lower self-monitored blood glucose concentrations at all timepoints and the daily mean when compared to placebo-treated patients. The reduction from baseline for 5 mcg was numerically greater than that with 10 mcg at all timepoints except after the evening meal; there was no dose effect.
- Placebo subjects experienced, on average, a steady decline in body weight beginning at week 4 through the end of the study, with a mean loss of 1.45 kg at week 24 compared to baseline. The LS mean treatment difference relative to placebo at endpoint was -1.31 (95% CI: -2.19, -0.43) and -1.61 (95% CI: -2.49, -0.74) for exenatide 5 and 10 mcg, respectively.
- Although baseline BMI did not affect the change in FSG, placebo and exenatide 5 mcg patients with lower BMI values (< 30 kg/m^2) experienced greater LS mean reductions in HbA1c compared with those with higher BMI values (≥ 30 kg/m^2), while LS mean reductions were similar between the two BMI groups in the exenatide 10 mcg group.
- In regression models with change in HbA1c and change in FSG as the dependent variables and baseline HbA1c and baseline FSG and antibody status as explanatory variables, no statistically significant associations between change in HbA1c and change in FSG and anti-exenatide antibody status were seen. However, in graphs of the empirical cumulative distribution of change in HbA1c from baseline to endpoint based on anti-exenatide antibody status of ITT patients, the antibody-negative curve is shifted left suggesting slight loss in the glycemic effect among antibody-positive patients, compared to patients who remain antibody-negative through the duration of the trial

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In this section, I reviewed the safety data from pivotal study H8O-MC-GWBJ and PSURs 5, 6, 7, and 8. Preferred terms for adverse events were coded using MedDRA version 10.0**.**

7.1.1 Deaths

There were no deaths in study H80-MC-GWBJ.

Postmarketing reports indicate there have been 9 deaths in patients with pancreatitis..

7.1.2 Other Serious Adverse Events

One placebo (1.3%) and four exenatide (1.9%) patients experienced serious adverse events (SAE).

Patient 304-3203 (placebo): 51 year old Asian female with T2D. Five months after starting placebo, the patient was traveling in a transport vehicle when it hit a bridge. She was hospitalized for multiple bruises and abrasions on her body, including her forehead which required stitches.

Patient 104-1202 (exenatide 5 mcg): 66 year old Caucasian male with T2D and a history of cardiac failure, cerebral atrophy, hypertension, ischemic cardiomyopathy, jaundice, and Wallenberg syndrome. After approximately 3 months of study drug use, the patient was hospitalized for one week with the diagnosis of corneal abscess and iridocyclitis. The patient completed the trial.

Patient 300-3013 (exenatide 5 mcg): 44 year old Asian female with T2D and a history of hypertension and hypothyroidism. After approximately 2 months exposure to study drug, the patient experienced vaginal bleeding and while hospitalized had a dilatation and curettage.

Patient 105-1258 (exenatide 10 mcg): 39 year old Caucasian female with T2D and a history of anxiety disorder, dyslipidemia, goiter, hypertension, obesity, menstrual disorder, virilism, and 2 spontaneous abortions. After approximately 4 months exposure to study drug, the patient had two positive urine pregnancy tests (b) (6) Study drug was stopped on May 4, 2007, when she informed the investigator of the positive tests. (b) (6) (b) (6) intravaginal echography revealed a six week pregnancy stopped in evolution the patient was admitted emergently to the hospital for vaginal bleeding and abdominal pain. A surgical abortion was performed. Treatment with study drug was restarted on May 7, 2007.

Patient 101-1073 (exenatide 10 mcg): 69 year old Caucasian female with T2D and history of an umbilical hernia (since 1964), dyslipidemia, extrasystole, spinal osteoarthritis, hypertension, and varicose vein. Prior to receiving study drug on November 16, 2006, examination revealed a large, nonpainful umbilical hernia containing abdominal tissue and intestine. The patient was hospitalized for hernia surgery on (b) (6). The patient did not stop using the drug at any time.

COMMENT: No trend in AEs likely related to exenatide was seen in study GWBJ.

Postmarketing reports indicate that, in addition to the deaths in pancreatitis patients, there have been 10 cases of necrotizing or hemorrhagic pancreatitis and at least 150 cases of renal failure. (Please see sections 7.1.17 and 7.1.25.)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A similar percentage of subjects in each treatment group completed the study (placebo 88.5%, exenatide 5 mcg 85.7%, exenatide 10 mcg 87.2%). The most common reason for study

withdrawal was loss of glucose control, which occurred in a similar percentage of patients in each group (placebo 5.1%, exenatide 5 mcg 3.9%, exenatide 10 mcg 6.4%). Subject decision was the second most common reason for withdrawal; this also occurred at a similar rate in the three treatment groups (placebo 5.1%, exenatide 5 mcg 5.2%, exenatide 10 mcg 2.6%). Of 232 ITT patients, two (0.9%) exenatide 10 mcg subjects discontinued from the study due to AEs. One subject reported headache while the other reported nausea. Three exenatide 5 mcg subjects were withdrawn due to the physician's or sponsor's decision. Although no specific rationale was provided for these physician and sponsor decisions, the following information is reassuring. First, the exenatide 10 mcg group did not have any withdrawals due to physician or sponsor decision. Second, fewer subjects chose to withdraw from the exenatide 10 mcg group when compared to the placebo and exenatide 5 mcg groups.

GWBJ. Summary of patient disposition by treatment group

Disposition	**Placebo N=77 (%)**	**Exenatide 5 mcg N=77 (%)**	**Exenatide 10 mcg N=78 (%)**
Completed	69 (88.5)	66 (85.7)	68 (87.2)
Adverse event	0 (0.0)	0 (0.0)	2 (2.6)
Loss of glucose control	4 (5.1)	3 (3.9)	5 (6.4)
Lost to follow up	1 (1.3)	1 (1.3)	1 (1.3)
Physician decision	0 (0.0)	2 (2.6)	0 (0.0)
Sponsor decision	0 (0.0)	1 (1.3)	0 (0.0)
Subject decision	4 (5.1)	4 (5.2)	2 (2.6)

7.1.3.2 Adverse events associated with dropouts

Patient 206-2300 (exenatide 10 mcg): 69 year old Caucasian female with T2D and a history of hypertension, obesity, hypothyroidism, and a lipid disorder. One day after dose escalation to exenatide 10 mcg, the patient experienced mild nausea which worsened to moderate by the next clinic visit a month later, when she was discontinued from the study. Nausea resolved 3 days later.

Patient 306-3304 (exenatide 10 mcg): 57 year old Asian male with T2D. Approximately 1 month after starting exenatide and one day after increasing the dose to 10 mcg, the patient experienced a severe headache. Approximately 3 weeks later, the patient was discontinued due to this headache.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Gastrointestinal adverse events, including acute pancreatitis

I analyzed the adverse event (AE) dataset for gastrointestinal events. As expected with exenatide, an incretin mimetic, nausea was the most common AE reported (10% of the 10 mcg group, 3% in the 5 mcg group, and 1% in the placebo group). The second most commonly reported AE, in terms of the number of patients, was gastroesophageal reflux disease (3% of

patients in each treatment group). GERD, however, was reported in the same proportion of patients in each treatment group. Vomiting was the third most commonly reported AE, in terms of number of patients (6). The number of both nausea and vomiting events increased with increasing study drug dose. Dyspepsia occurred in five patients, all of whom received exenatide. Eight placebo subjects reported duodenal ulcer, although it was a preexisiting condition for all of them.

No patient developed pancreatitis, although one 53 year old exenatide 5 mcg subject (101-1051) experienced two episodes of epigastric pain at visits 3 and 6 (weeks 0 and 12). The onset of this subject's pain in week 0 prior to exenatide 5 mcg dosing suggests an etiology other than the study drug. (Please also refer to sections 7.1.17 and 7.1.26 which discuss postmarketing events of pancreatitis.)

GWBJ. Adverse gastrointestinal events (number of patients and %) by treatment group

	Total (n=232)	**Ex 10 mcg (n=78)**	**Ex 5 mcg (n=77)**	**Placebo (n=77)**
Abdominal pain upper	2 (1)	0 (0)	2 (1)	0 (0)
Colitis	8 (1)	0 (0)	0 (0)	8 (1)
Colonic polyp	2 (1)	0 (0)	0 (0)	2 (1)
Constipation	4 (1)	4 (1)	0 (0)	0 (0)
Diarrhea	4 (3)	3 (2)	0 (0)	1 (0)
Duodenal ulcer	8 (1)	0 (0)	0 (0)	8 (0)
Dyspepsia	15 (5)	7 (4)	8 (1)	0 (0)
Eructation	3 (1)	3 (1)	0 (0)	0 (0)
Flatulence	1 (1)	0 (0)	1 (1)	0 (0)
Gastric ulcer	8 (1)	0 (0)	8 (1)	0 (1)
Gastritis	16 (2)	8 (1)	0 (0)	8 (1)
Gastrointestinal hemorrhage	1 (1)	0 (0)	0 (0)	1 (1)
Gastro esophageal reflux disease	72 (9)	24 (3)	24 (3)	24 (3)
Hemorrhoid hemorrhage	7 (1)	0 (0)	7 (1)	0 (0)
Hemorrhoids	1 (1)	0 (0)	0 (0)	1 (1)
Nausea	33 (14)	28 (10)	4 (3)	1 (1)
Rectal hemorrhage	1 (1)	0 (0)	0 (0)	1 (1)
Vomiting	13 (6)	8 (3)	5 (3)	0 (0)

A 45 year old placebo patient (002-0052), with a history of T2D, Asperger's disorder, depression, restless leg syndrome, neuropathy, hypercholesterolemia, obesity, and hypothyroidism, experienced a moderately severe gastrointestinal hemorrhage, which did not require hospitalization, 4.5 months after starting placebo.

Three of 155 (1.9%) exenatide patients, but no placebo patients, experienced anorexia or decreased appetite.

- 304-3202 (exenatide 10 mcg): Lost 5.5 kg (7.9%) from 70.0 kg baseline.
- 304-3207 (exenatide 10 mcg): Lost 1.1 (1.3%) kg from 84.3 kg baseline.

- 105-1251 (exenatide 5 mcg): Lost 9.0 kg (10.7%) from 84.0 kg baseline.

7.1.3.3.2 Adverse events potentially related to anti-exenatide antibody status

Patients were considered antibody positive if they had a zero titer or unknown status at baseline and a titer ≥ 1/25 at last study visit, or if they had a positive titer at screening with a ≥ 3 fold increase (three dilutions) at last study visit (week 24 or early discontinuation). Of the 71 exenatide 5 mcg and 73 exenatide 10 mcg patients assessed for antibody status, 21 (29.6%) exenatide 5 mcg and 22 (30.1%) exenatide 10 mcg patients were treatment-emergent antibody positive at the last study visit.

Adverse events potentially indicative of a local or systemic immune reaction were compared between antibody positive and negative subjects at endpoint. Adverse events potentially indicative of an immune reaction were present only in the exenatide 10 mcg group. Because both antibody positive and negative subjects reported these AEs, no clear effect of exenatide antibody status was seen. Furthermore, of the 43 exenatide subjects with positive antibodies at last study visit, only 3 exenatide 10 mcg patients had titers ≥ 1/625. Of these 3 patients, only one (202-2100) reported AEs (nausea and increased alanine aminotransferase), which were likely unrelated to antibody status.

GWBJ. Comparison of adverse events potentially indicative of a local or systemic immune reaction by antibody positive and negative status at endpoint

	Exenatide 5 mcg (n=77)		**Exenatide 10 mcg (n=78)**	
	Positive (n=21)	**Negative (n=50)**	**Positive (n=22)**	**Negative (n=51)**
Asthenia	0	0	0	1
Injection site rash	0	0	1	0
Pain	0	0	0	2
Drug hypersensitivity*	0	0	1	0
Pain in extremity	0	0	0	1
Rash	0	0	1	1
Rash papular	0	0	1	0

*According to the sponsors August 25, 2008 submission, this subject (001-0008) had a moderately severe reaction to Bactrim.

7.1.3.3.3 Hypoglycemia

A hypoglycemic episode was defined as any time a subject felt s/he was experiencing a sign or symptom that is associated with hypoglycemia or had a glucose meter reading <60 mg/dl even if it was not associated with signs, symptoms, or treatment. Severe hypoglycemia was defined as an episode with symptoms consistent with hypoglycemia in which the subject required the assistance of another person and was associated with a glucose meter reading <50 mg/dl or prompt recovery after oral carbohydrate, glucagon, or intravenous glucose.

Four (5.1%) exenatide 10 mcg patients (002-0051, 003-011, 102-1109, 105-1258) , four (5.2%) exenatide 5 mcg patients (003-0105, 003-0107, 300-3005, 004-0152), and one (1.3%) placebo

patient (105-1265) reported a total of 28 hypoglycemic events. One exenatide 10 mcg patient (002-0051) reported 14 hypoglycemic events, although all blood glucose levels were > 3.6 mmol/l (65 mg/dl). One exenatide 10 mcg patients and one 5 mcg patient reported a nocturnal hypoglycemic episode.

Severe hypoglycemia was defined as an episode with symptoms consistent with hypoglycemia in which the patient required assistance from another person and which was associated with either a blood glucose level < 3.0 mmol/l (54 mg/dl) or prompt recovery after oral carbohydrate, glucagon, or IV glucose. Three exenatide 10 mcg patients (003-0111, 102-1109, 105-1258) and one placebo patient (105-1265) experienced blood glucose levels < 3.6 mmol/l (65 mg/dl) that did not require third party assistance. All patients recovered promptly from hypoglycemia. No glucagon injection, intravenous (IV) glucose, or emergency room visits were required.

When treatment exposure in years was taken into account, a statistically significant higher rate of hypoglycemia was observed for patients in the exenatide 10 mcg group (0.52 events/year) when compared with patients in both the exenatide 5 mcg (0.21 events/year, p=0.05) and placebo (0.03 events/year, p=0.006) treatment groups. This difference is attributed to the exenatide 10 mcg patient that reported 14 hypoglycemic episodes during the study. When this exenatide 10 mcg patient is excluded, rates of hypoglycemia are similar between treatment groups (placebo: 1 patient, 1 event; 5 mcg exenatide 4 patients, 7 events; 10 mcg exenatide 2 patients, 3 events). Nocturnal hypoglycemia rates were similar among the three treatment groups.

No subjects with moderate renal impairment were enrolled in study GWBJ. No hypoglycemic events occurred in the 6 placebo, 13 exenatide 5 mcg, or 12 exenatide 10 mcg patients with mild renal impairment.

7.1.3.3.4 Renal failure

The laboratory dataset was analyzed for creatinine values > 132.6 µmol/L (1.5 mg/dL). Only two subjects had creatinine values > 1.5 mg/dL at any time during the study.

- 103-1179 (placebo): Creatinine was 1.51 mg/dL at week -3.
- 101-1085 (exenatide 10 mcg): Baseline creatinine was 113.2 µmol/L (1.3 mg/dL). At week 24, creatinine was 1.7 mg/dL and, on repeat, 1.51 mg/dL.

Thus, only one exenatide subject, whose serum creatinine was 1.3 mg/dl at baseline , had an elevated creatinine level after therapy. The results of study GWBJ do not suggest that exenatide contributes to renal failure, although the study itself was small in size, had a short duration, and excluded subjects at risk for renal failure. (Please also refer to sections 7.1.17 and 7.1.25 which discuss postmarketing events of renal failure and those that occurred in phase 3 placebo-controlled trials.)

NOTE: No neoplasms (benign, malignant, or unspecified), including thyroid, occurred in study GWBJ.

7.1.4 Other Search Strategies

No special search algorithms were utilized in this safety review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were collected at visits 2-8 and early discontinuation. Site personnel recorded any change in the condition(s) and the occurrence and nature of any adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified according to MedDRA 10.0. All adverse events were listed by patient, visit, preferred term, treatment group, severity, and relationship to treatment. Study GWBJ event database had 4,958 adverse events listed. To confirm appropriate coding of adverse terms, I focused on the reports of adverse events in the "Gastrointestinal Disorders" System-Organ-Class, because upper gastrointestinal symptoms are one of the main safety concerns with exenatide. I did not identify significant errors in adverse event categorization or the use of preferred terms.

7.1.5.3 Incidence of common adverse events

Of the 77 placebo patients, approximately 20% reported at least one AE and one patient reported one serious AE. Of the 77 patients on exenatide 5 mcg, approximately 21% experienced at least one AE and two patients reported at least one serious AE. Of the 78 patients on exenatide 10 mcg, approximately 33% experienced at least one AE and one patient reported at least one serious AE. This difference in overall AE rates between the 10 mcg treatment arm and the other treatment arms is driven mostly by the incidence of nausea (13% with 10 mcg, 3% with 5 mcg, and none with placebo-treated patients).

The table below summarizes adverse events experienced by ≥2% of exenatide patients. The cut-off criteria of ≥2% is inherently arbitrary but is commonly used across sponsors and drug categories.

7.1.5.4 Common adverse event tables

GWBJ. Treatment-emergent adverse events (n, %) in ≥ 2% exenatide-treated patients by preferred term

	Placebo (n=77)	**Exenatide 5 mcg (n=77)**	**Exenatide 10 mcg (n=78)**
Patients with ≥ 1 AE (%)	15 (19.5)	16 (20.8)	26 (33.3)
Nausea	0 (0.0)	2 (2.6)	10 (12.8)
Influenza	3 (3.9)	3 (3.9)	5 (6.4)

Nasopharyngitis	1 (1.3)	2 (2.6)	4 (5.1)
Vomiting	0 (0.0)	3 (3.9)	3 (3.8)
Back pain	1 (1.3)	3 (3.9)	2 (2.6)
Diarrhea	0 (0.0)	0 (0.0)	2 (2.6)
Dizziness	0 (0.0)	0 (0.0)	2 (2.6)
Headache	3 (3.9)	4 (5.2)	2 (2.6)
Pain	0 (0.0)	0 (0.0)	2 (2.6)
Pain in extremity	0 (0.0)	0 (0.0)	2 (2.6)
Neck pain	0 (0.0)	2 (2.6)	0 (0.0
Upper respiratory tract infection	3 (3.9)	2 (2.6)	0 (0.0)

7.1.5.5 Identifying common and drug-related adverse events

Based on experience with exenatide as it is currently approved, adverse events of special interest that may be related to study drug include gastrointestinal adverse events including acute pancreatitis; adverse events related to anti-exenatide antibodies; hypoglycemia; and renal failure. All of these conditions are reviewed in detail in Section 7.1.3.3.

A statistically significant increase in thyroid c-cell tumors, including carcinomas, was described in the exenatide once weekly draft report of preclinical rat study REST060229 at exposures ≤ 1x of the anticipated clinical exposure. Rodent c-cell tumors, including carcinomas, have been observed with other GLP-1 formulations that have an overall daily exposure greater than exenatide and formulations that are dosed less frequently than exenatide, although, at this time, exenatide is not suspected of having this effect at clinically relevant doses. No neoplasms (benign, malignant, or unspecified) occurred in study GWBJ. Please also refer to section 7.1.17 Postmarketing experience.

7.1.6 Less Common Adverse Events

See discussions above for the rare, but important adverse events associated with exenatide therapy.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Chemistry and hematology values were measured at weeks -3 (visit 1) and 24 (visit 8) and early discontinuation. Oral glucose tolerance tests and blood insulin and glucose levels were measured at weeks 0 (visit 3) and 24 (visit 8) and early discontinuation. Fasting lipids, proinsulin, highly sensitive C-reactive protein (hsCRP), anti-exenatide antibodies, and C-peptide were measured at weeks 0 and 24 and early discontinuation. Fasting C-peptide was also measured at week -3.

Hemoglobin A1c was measured a weeks -3, 0, 4, 8, 12, 16, and 24 (visits 1, 3, 4, 5, 6, 7, and 8, respectively) and early discontinuation.

The laboratory values of potential clinical importance (PCI) in study GWBJ are shown below. The definitions are acceptable, except for triglycerides (TG) > 600 mg/dL, as studies have shown that TG levels < 600 mg/dL can affect cardiac outcome. Therefore, I analyzed the laboratory dataset for TG > 250 mg/dl. This information is presented in section 7.1.7.3.3.

GWBJ. Criteria for laboratory values of potential clinical importance for subjects with T2D (Reproduced from sponsor NDA 21919 [7/29/08])

Analyte	Values of Potential Clinical Importance
Clinical Chemistry Analytes	
Albumin	L <2.5 g/dL
Alkaline Phosphatase	H >300 U/L
Alanine aminotransferase (ALT [SGPT])	H >3× ULN (IU/L)
Aspartate Aminotransferase (AST [SGOT])	H >3× ULN (IU/L)
Bicarbonate (Serum)	L <18 mEq/L; H >35 mEq/L
Blood Urea Nitrogen (BUN)	H >45 mg/dL
Calcium (Serum)	L <8 mg/dL; H >11 mg/dL
Creatine Kinase (Total)	H >3× ULN (IU/L)
Creatinine (Serum)	H >1.5 mg/dL
Direct Bilirubin [1]	H>1 mg/dL
Gamma Glutamyl Transferase (GGT)	H >3× ULN (IU/L)
Glucose (Plasma or Serum)	L <50 mg/dL; H >450 mg/dL
Phosphorus	L <1.0 mg/dL
Potassium (Serum)	L <3.0 mEq/L; H >5.5 mEq/L
Sodium (Serum)	L <130 mEq/L, H >150 mEq/L
Total Bilirubin	H >2 mg/dL
Uric Acid (Serum)	Males H >10.0 mg/dL; Females H >8.0 mg/dL
Haematology	
Hematocrit	Males <36%, Females <30%
Haemoglobin	Males <12 g/dL; Females <10 g/dL
Platelets	L <75,000 /µL; H >500,000 /µL
White Blood Cell Count (WBC)	L <1,500 cells/µL; H >15,000 cells/µL
Lipid Profile	
Cholesterol, Total	L <100 mg/dL; H >350 mg/dL
Triglycerides	H >600 mg/dL
Urinalysis	
Urine Protein	≥3+ *or* 500 mg/dL
Urine Glucose	≥3+ *or* 500 mg/dL
Urine Ketones	≥3+ or Large
Other	
Haemoglobin A1C-HPLC (Variant)	>12.0%

ALT = alanine transaminase; AST = aspartate transaminase; H = high; L = low; ULN = upper limit of normal.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

I reviewed study H8O-MC-GWBJ's laboratory values.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The table below summarizes the mean (SD) changes from baseline to endpoint in laboratory parameters for Study GWBJ. There were no clinically relevant changes from baseline in creatinine, ALT, cholesterol, HDL, triglycerides, WBC, and hemoglobin. Mean creatinine clearance (estimated using the Cockcroft-Gault equation) decreased 0.07 to 0.08 ml/s in all treatment groups, including placebo. The mean change in creatinine compared to baseline was 0.01, 0.02, and 0.02 mg/dL in the placebo, exenatide 5 mcg, and exenatide 10 mcg treatment groups, respectively. Therefore, there is a lack of a drug dose related effect on creatinine. Both exenatide treatment groups had reductions in LDL.

GWBJ. Mean (SD) change from baseline to endpoint in laboratory parameters (LOCF)						
	Placebo (n=77)		**Ex 5 mcg (n=77)**		**Ex 10 mcg (n=78)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
ALT/SGPT (U/L)	-6.34	15.97	-3.07	13.10	-3.41	15.12
C-reactive protein (mg/L)	-0.79	6.20	-1.05	4.16	0.23	10.62
Cholesterol (mmol/L)	0.20	0.87	0.01	0.84	-0.10	0.92
Creatinine (mg/dL)	0.01	0.11	0.02	0.12	0.02	0.10
Creatinine clearance, estimated (mL/s)	-0.08	0.34	-0.07	0.24	-0.07	0.21
Glucose, fasting (mmol/L)	-0.28	2.54	-1.15	2.05	-0.90	2.08
HDL cholesterol (mmol/L)	0.02	0.20	0.07	0.20	0.01	0.19
Hemoglobin (g/L)	-1.28	7.53	-1.25	8.40	-1.36	7.22
Hemoglobin A1c (%)	-0.15	1.25	-0.70	1.12	-0.83	1.00
LDL cholesterol (mmol/L)	0.09	0.69	-0.09	0.66	-0.10	0.77
Leukocyte count (10^9/L)	-0.16	1.25	-0.10	1.53	-0.21	1.42
Triglycerides (mmol/L)	0.25	1.10	0.04	1.03	0.10	1.02

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Shift tables which summarized the low, normal, and high shifts from baseline to endpoint of critical values for laboratory analytes of potential clinical importance were reviewed for the ITT population. Changes in the distribution of values that differed from baseline or appeared to be treatment related included shifts in ALT, creatinine clearance, HbA1c, and HDL.

Slightly more exenatide 10 mcg subjects had elevated ALT at baseline (placebo 18%, exenatide 5 mcg 17%, exenatide 10 mcg 27%). A greater proportion of patients in the placebo and exenatide 5 mcg treatment groups normalized their ALT by endpoint than those on exenatide 10 mcg treatment. The percentage of patients with abnormal ALT at endpoint in the treatment groups was as follows: placebo 3%, exenatide 5 mcg 8%, exenatide 10 mcg 17%). No dose-related pattern of hepatic adverse events was seen in study GWBJ nor was there a liver abnormality signal in the exenatide studies associated with the original NDA 21-773.

Although the distribution of low, normal, and high creatinine clearance values remained relatively constant in the placebo and exenatide 10 mcg groups, an increase in the percentage of exenatide 5 mcg patients with low creatinine clearance was seen at endpoint compared with baseline (14% vs. 6%). A corresponding shift in creatinine values was not seen. At endpoint, only one subject in each treatment group, including placebo, had an elevated creatinine value.

A greater percentage of exenatide 5 and 10 mcg patients' HDL normalized at endpoint when compared to placebo.

GWBJ. Summary of low, normal, and high shifts from baseline to endpoint of critical values for laboratory analytes of potential clinical importance (ITT)

Laboratory	**Treatment**	**Baseline Values**			**Endpoint Values**		
		Low	**Normal**	**High**	**Low**	**Normal**	**High**
ALT	Placebo	0	58	13	0	69	2
	Ex 5 mcg	0	60	12	0	66	6
	Ex 10 mcg	0	52	19	0	59	12
Creatinine clearance	Placebo	4	55	13	5	55	12
	Ex 5 mcg	4	52	16	10	46	16
	Ex 10 mcg	4	52	15	5	52	14
Creatinine	Placebo	0	71	1	0	71	1
	Ex 5 mcg	0	72	0	0	71	1
	Ex 10 mcg	0	71	0	0	71	1
HDL cholesterol	Placebo	20	51	1	20	50	2
	Ex 5 mcg	29	43	0	20	52	0
	Ex 10 mcg	16	54	0	22	48	0

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Ten randomized patients experienced laboratory values of PCI (placebo 3.9%, exenatide 5 mcg 3.9%, exenatide 10 mcg 5.1%). Among the placebo patients, one had elevated creatinine at screening (133 mmol/L [1.5 mg/dL]) and two had elevated triglyceride (TG) levels at week 24 (8.6 mmol/L [765 mg/dL]; 7.2 mmol/L [639 mg/dL]). One exenatide 5 mcg patient has elevated leukocyte counts at screening and week 24 (15.6 10^9/L). Another exenatide 5 mcg patient had elevated TG at baseline (7.05 mmol/L [624 mg/dL]), while another had low fasting glucose at week 24 (2.7 mmol/L [48.6 mg/dL]). Four exenatide 10 mcg patients experienced clinically relevant laboratory results outside of the critical ranges. These include the following:

- Elevated baseline cholesterol (10.7 mmol/L)
- Elevated creatinine at week 24 (133 mmol/L [1.5 mg/dL]). Baseline creatinine was 106 µmol/L (1.2 mg/dL). - See Section 7.1.3.3.4.
- Low baseline fasting glucose (2.5 mmol/L [45 mg/dL])
- Low cholesterol at week 24 (2.3 mmol/L [88 mg/dL])

GWBJ. Randomized patients with clinically relevant laboratory results outside of critical

ranges								
Inv	**Pat**	**Treat**	**Gender**	**Wk**	**Laboratory test**	**Result**	**Critical limit**	
							Low	**High**
3	107	Ex 5	F	-3	Leukocyte count (10^9/L)	15.6	1.50	15.00
				24	Leukocyte count (10^9/L)	15.6	1.50	15.00
101	1054	Placebo	M	24	Triglycerides (mmol/L)	8.63		6.78
	1056	Ex 5	F	0	Triglycerides (mmol/L)	7.05		6.78
	1060	Placebo	F	24	Triglycerides (mmol/L)	7.21		6.78
	1085	Ex 10	M	24	Creatinine (µmol/L)	150.00		132.60
						133.00		132.60
	1324	Ex 10	M	0	Cholesterol (mg/dL)	413.8	100.5	351.9
102	1109	Ex 10	M	0	Glucose, fasting (mmol/L)	2.50	2.78	24.98
103	1179	Placebo	M	-3	Creatinine (µmol/L)	133.00		132.60
105	1251	Ex 5	M	24	Glucose, fasting (mmol/L)	2.70	2.78	24.98
309	3466	Ex 10	M	24	Cholesterol (mg/dL)	88.2	100.5	351.9
Inv=investigator; Pat=patient; Treat=treatment; Wk=week; M=male; F=female; Ex=exenatide Critical ranges: Triglycerides > 600 mg/dl; Creatinine >1.5 mg/dl; Fasting glucose < 50 or > 450 mg/dl								

Because the sponsor defined the critical triglyceride range loosely, I analyzed the laboratory dataset for triglyceride values > 250 mg/dL. A similar number of patients in each treatment category had at least one TG value > 250 mg/dL (placebo 17 [22%], exenatide 5 mcg 16 [21%], exenatide 10 mcg 17 [22%]). The total number of TG values > 250 mg/dl was also similar in each treatment group (placebo 25 [32%], exenatide 5 mcg 21 [27%], exenatide 10 mcg 25 [32%]). The similar frequency of elevated TG values in three treatment groups suggests this is not a drug effect but likely related to the elevated TG associated with T2D.

A similar percentage of patients in each treatment group were withdrawn for loss of glucose control (placebo 5.1%, exenatide 5 mcg 3.9%, exenatide 10 mcg 6.4%).

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Study GWBJ, blood pressure and heart rate were collected at every visit (weeks -3, -2, 0, 4, 8, 12, 16, 24, and early discontinuation).

7.1.8.2 Standard analyses and explorations of vital signs data

7.1.8.2.1 Analyses focused on measures of central tendencies

Mean blood pressure values improved slightly in the exenatide treatment groups, whereas they were stable in the placebo group.

GWBJ. Mean change in heart rate and blood pressure from baseline to endpoint (ITT)			
	Placebo (n=77)	**Ex 5 mcg (n=77)**	**Ex 10 mcg (n=78)**
Heart rate (BPM)	1	-1	0
Diastolic blood pressure (mm Hg)	0	-1	-3
Systolic blood pressure (mm Hg)	0	-4	-4

7.1.8.2.2 Analyses focused on outliers or shifts from normal to abnormal

Vital signs were analyzed using the following normal ranges:

Systolic blood pressure: 90-140 mm Hg
Diastolic blood pressure: 60-89 mm Hg
Heart rate: 60-100/min

NOTE: The recommended blood pressure for a diabetic is < 130/80 mmHg.

Except for abnormal diastolic blood pressure measurements which occurred more commonly in number and in the number of patients in the placebo group, a similar number of abnormal vital signs occurred in each treatment group and in a similar number of patients within treatment groups.

GWBJ. Number of abnormal vital sign measurements and number of patients with abnormal vital signs by treatment group						
	Number of abnormal vital sign measurements			**Number of patients with abnormal vital signs**		
	Placebo	**Ex 5 mcg**	**Ex 10 mcg**	**Placebo**	**Ex 5 mcg**	**Ex 10 mcg**
Systolic BP	92	64	78	27	28	32
Diastolic BP	83	60	61	38	30	28
Heart rate	13	16	11	7	8	7

7.1.8.2.3 Marked outliers and dropouts for vital sign abnormalities

I analyzed the vitals dataset for systolic blood pressure values > 200 or < 90 mm Hg, diastolic blood pressure values > 110 or < 50 mm Hg, and heart rates < 45 bpm. Only one vital sign measurement was outside of these ranges. A 45 year old Indian male (303-3161) in the exenatide 5 mcg group had a baseline heart rate of 80 bpm, which decreased to 20 bpm at week 4. This value was not repeated and verified. It could be a typographical error, given his normal measurements at week 8. Interestingly, the subject had nearly steady blood pressure measurements of 120/80 mm Hg. He was eventually "lost to follow up." The lack of other subjects with marked vital sign abnormalities, however, is reassuring.

GWBJ. Heart rate and blood pressure for exenatide 5 mcg subject 303-3161					
	Week -3	**Week -2**	**Week 0**	**Week 4**	**Week 8**
Heart rate	64	76	80	20	82
Blood pressure	126/80	120/80	120/80	120/70	120/80

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were only obtained at visit 1 to screen for study eligibility. No ECGs were obtained after exenatide dosing in Study GWBJ.

7.1.10 Immunogenicity

Exenatide may elicit an immune response in humans. A review of adverse events potentially related to anti-exenatide antibody status is in section 7.1.3.3.2.

7.1.11 Human Carcinogenicity

Benign C-cell adenomas were observed in a 104-week carcinogenicity study in male and female rats, but not mice, at doses of 18, 70, or 250 mcg/kg/day. The incidences in female rats were 8% and 5% in the 2 control groups and 14%, 11%, and 23% in the low, medium, and high-dose groups with systemic exposure of 5, 22, and 130 times, respectively, the human exposure resulting form the maximum recommended dose of 20 mcg/d, based on AUC. There is no apparent association between exenatide and cancer in study GWBJ which exposed 155 subjects to exenatide.

A statistically significant increase in thyroid c-cell tumors, including carcinomas, was described in the exenatide once weekly draft report of preclinical rat study REST060229 at exposures ≤ 1x of the anticipated clinical exposure. Rodent c-cell tumors, including carcinomas, have been observed with other GLP-1 formulations that have an overall daily exposure greater than exenatide and formulations that are dosed less frequently than exenatide, although, at this time, exenatide twice-daily is not suspected of having this effect at clinically relevant doses.

7.1.12 Special Safety Studies

There are no special safety studies reported in this efficacy supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No abuse potential or withdrawal phenomena have been described for exenatide.

7.1.14 Human Reproduction and Pregnancy Data

Exenatide is pregnancy category C. It has been shown to cause reduced fetal and neonatal growth as well as skeletal effects in mice at systemic exposures 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/d, based on AUC. There are no adequate and well-controlled studies of exenatide in pregnant women.

Although study GWBJ's inclusion/exclusion criteria required that women of child bearing potential practice a reliable method of birth control for 3 months prior to screening and agree to continue to use a reliable method of birth control during the study, one exenatide 10 mcg patient (105-1258) became pregnant during study GWBJ. This 39 year old Caucasian female had a history of T2D, anxiety disorder, dyslipidemia, goiter, hypertension, obesity, menstrual disorder, virilism, and 2 spontaneous abortions. After approximately 4 months' exposure to study drug, the patient had two positive urine pregnancy tests (b) (6) Study drug was stopped on May 4, 2007, when she informed the investigator of the positive tests. On (b) (6) intravaginal echography revealed a six week pregnancy stopped in evolution. On the patient was admitted emergently to the hospital for vaginal bleeding and severe abdominal pain. A surgical abortion was performed. Treatment with study drug was restarted on May 7, 2007. Because of this patient's history of 2 spontaneous abortions, it is difficult to ascertain the role exenatide may have played in the fetal demise. The currently approved label states that use of exenatide during pregnancy should only be considered if the potential benefit justifies the potential risk to the fetus.

7.1.15 Assessment of Effect on Growth

The safety and effectiveness of exenatide has not been established in the pediatric population.

7.1.16 Overdose Experience

Exenatide overdose (10 times the maximum recommended dose) may result in severe nausea, vomiting, and rapidly declining blood glucose concentrations. No exenatide overdose occurred in study GWBJ.

7.1.17 Postmarketing Experience

The Sponsor submitted 4 Periodic Safety Update Reports (PSURs 5-8), which I reviewed for the following adverse events of special interest: pancreatitis, renal failure, hypersensitivity, and thyroid cancer. As PSUR 4 contained a cumulative review of renal failure, that portion of PSUR 4 is reviewed here as well.

PSUR 4 covers the period form 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 September 30, 2008. PSUR 8 covers the period October 1, 2008 through March 31, 2009. In the PSUR 8 reporting period, approximately (b) (4) pens (b) (4)

(b) (4) were dispensed in the United States. Cumulatively, approximately (b) (4) exenatide pens have been dispensed in the United States and (b) (4) pens have been dispensed worldwide. The table below summarizes spontaneous and clinical trial AEs.

Table. AE summary table (Source: PSUR 8, Appendix 4)

System organ class	Spontaneous/literature/ regulatory bodies			Clinical trial		Total reactions
	Serious	Serious cumulative	Non-serious	Serious	Serious cumulative	Serious + non-serious
Blood & Lymphatic	10	25	7	0	0	17
Cardiac	48	230	15	1	40	64
Congenital, familial, & genetic	1	1	0	0	0	1
Ear & labyrinth	0	2	4	0	0	4
Endocrine	2	7	7	0	0	9
Eye	15	32	32	0	0	47
Gastrointestinal	312	868	765	8	21	1085
General	24	125	376	0	3	400
Hepatobiliary	26	80	29	1	5	56
Immune system	8	67	15	0	0	23
Infections & infestations	35	145	50	1	21	86
Injury, poisoning, and procedural	8	60	119	1	9	128
Investigations	39	137	627	2	4	668
Metabolism & nutrition	48	212	169	0	7	217
Musculoskeletal & connective tissue	9	65	68	0	13	77
Neoplasms benign, malignant, & unspecified	34	108	3	1	10	38
Nervous	51	212	121	1	10	173
Pregnancy, puerperium & perinatal	3	5	0	0	0	3
Psychiatric	9	47	54	0	1	63
Renal & urinary	43	159	10	0	4	53
Reproductive system & breast	0	7	11	0	3	11
Respiratory, thoracic & mediastinal	19	90	40	0	3	59
Skin & subcutaneous tissue	20	60	148	2	3	170
Social circumstances	1	1	2	0	1	3
Surgical & medical	15	64	3	0	0	18
Vascular	15	64	13	0	3	28
Total	**795**	**2873**	**2688**	**18**	**161**	**3501**

NOTE: Please also refer to section 7.1.25 for a review of the August 12, 2008 renal safety information submitted by the sponsor.

Pancreatitis

The age-standardized incidence of pancreatitis (per 100,000 person-years) for the general United States population in 2000 was 38.1 (14.5 biliary, 8.4 alcoholic, 15.3 idiopathic). The age-standardized incidence rate of acute pancreatitis rose by 32% between 1994 and 2001 (Fray et al. 2006). While most patients with pancreatitis experience mild, self-limited disease, 15-20%

experience hemorrhagic or necrotizing pancreatitis (Forsmark and Baillie 2007; Frossard and Steer 2008). Age, obesity, and comorbid illness are risk factors for severe disease.

At the sponsor's request, Ingenix conducted epidemiologic investigations using an insurance claims database to better understand the incidence of pancreatitis in the diabetes population. The current use of exenatide was not associated with an increased rate of likely acute pancreatitis (adjusted RR 0.9%; 95% CI 0.6-1.3) compared with current use of other antidiabetic medications. Another Ingenix study entitled the "Association of exenatide and sitagliptin with acute pancreatitis in claims-based active drug safety surveillance system" was submitted by the sponsor in draft manuscript form on November 15, 2008. The study objective was to estimate the risk of acute pancreatitis among users of exenatide and sitagliptin compared to metformin and glyburide. Cases were those who were hospitalized with the primary diagnosis of acute pancreatitis. After excluding patients with claims suggestive of prior history of pancreatic disease in the 6 months prior to initiation of exenatide, sitagliptin, or the comparator drugs, the study population included 27,966 exenatide initiators, 16,276 sitagliptin initiators, and approximately equal numbers of metformin and glyburide controls. The sponsor's main finding was "no increased risk of acute pancreatitis associated with use of either exenatide or sitagliptin in comparison to metformin or glyburide." The estimated relative risk of acute pancreatitis among initiators of exenatide (RR 1.0, 95% CI: 0.6-1.7) and sitagliptin (RR 1.0; 95% CI: 0.5-2.0) was comparable to their matched comparison cohorts.

However, in his December 31, 2008 review, Dr. Syed Ahmad, from the Office of Surveillance and Epidemiology (OSE), rejected the conclusion that the risk with exenatide might be similar to other antidiabetic drugs for the following reasons:

- The outcome of pancreatitis was an ICD-defined outcome and as such the more serious and potentially fatal hemorrhagic/necrotizing pancreatitis cases cannot be specified and separated.
- The i3 Aperio study lacked validation of the outcomes by a thorough medical record review.
- i3 Aperio is an active surveillance tool with many methodological caveats and, therefore, more suitable for hypothesis generation and not confirmatory studies.
- A search in the AERS database at that time did not identify any case of acute necrotizing/hemorrhagic pancreatitis in association with sitagliptin. (Currently, however, 2 cases of hemorrhagic or necrotizing pancreatitis have been identified in association with sitagliptin.)
- Acute pancreatitis is a serious and potentially life-threatening event with a high case fatality rate. Thus, according to Dr. Ahmad, it "seems reasonable" to highlight the risk of acute pancreatitis to the level of a boxed warning.

As stated above, OSE is more concerned about communicating the incidence of hemorrhagic and necrotizing pancreatitis in exenatide-treated patients than the incidence of less severe acute edematous pancreatitis. As seen in the table below using data previously compiled by OSE, the frequency of hemorrhagic or necrotizing pancreatitis is highest with exenatide when compared with other antidiabetic medication, despite its being a less commonly used medication.

Prescription use of antidiabetic medications (1995-2006) compared to frequency of hemorrhagic and necrotizing pancreatitis cases (Source: OSE)			
	Total	% Rx Total	Cases of hemorrhagic or necrotizing pancreatitis
Metformin, single-entry	(b) (4)		4
Glimeperide, single-entry			3
Nateglinide			0
Exenatide			6 (see above)
Pramlinitide			0
*Values are in thousands, ad			

In PSURs 5, 6, and 7, the sponsor used the following MedDRA preferred terms to search for pancreatitis events: blood amylase abnormal, blood amylase increased, lipase abnormal, lipase increased, oedematous pancreatitis, pancreatic enzyme abnormality, pancreatic enzyme abnormal, pancreatic enzyme increased, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis haemorrhagic, pancreatitis necrotizing, pancreatitis relapsing, and urine amylase increased. In PSUR 8, the sponsor also included hereditary pancreatitis and ischemic pancreatitis. Cumulatively, there have been 639 cases of pancreatitis through March 31, 2009. The cumulative pancreatitis events as of August 31, 2008, according to the sponsor's cumulative review which was submitted in PSUR 7, were as follows:

PSUR 7. Pancreatitis events reported as of August 31, 2008	
MedDRA preferred terms	**Number of events**
Pancreatitis	251
Pancreatitis acute	79
Pancreatitis necrotizing	8
Pancreatitis hemorrhagic	1
Pancreatitis chronic	4
Pancreatitis relapsing	2
Total events	**345**

Pancreatitis occurs in exenatide-treated patients with almost similar frequency in men and women. Although pancreatitis cases have been reported worldwide, the majority of cases (87%) were reported from the United States, where the majority of exenatide exposure occurs. Time to onset varies. Events are most common in middle-aged patients, although this is also the population most likely to use exenatide as it is currently not recommended in children.

PSURs 5-8. Review of relevant pancreatitis information*				
	PSUR 8	**PSUR 7**	**PSUR 6**	**PSUR 5**
Age range in years (mean)	29-83 (58)	21-79 (58)	34-76 (56)	42-76 (56)
Female:Male ratio	1.3:1	1.3:1	1.1:1	1.3:1
Time to onset in days	2-1095 (294)	2-870 (271)	1-930 (237)	2-332 (115)

(mean)				
Cases with 2+ events	*	*	6	1
Fatalities	3	1	3	1
*Information not provided. Category may not be applicable.				

The sponsor convened 2 external expert panels (1 each in the US and EU) to provide further assessment of the pancreatitis cases in exenatide-treated patients. The panels developed a scale of objective clinical, laboratory, and imaging criteria to assess the likelihood of the diagnosis of acute pancreatitis. The cases were then categorized into definite, probable, possible, unlikely, or indeterminate categories based on the diagnosis assessment. For evaluation of relatedness to exenatide, categories included definite, possible, possible with a more likely alternative etiology, unlikely, and indeterminate. Any case with incomplete data was assessed as a possible likelihood of causality.

When assessing the validity of the diagnosis, the panels considered classic symptoms (sudden onset, severe, persistent pain often radiating to the back), laboratory data (amylase and lipase > 3x ULN), and imaging results. When assessing the etiology, the panels considered drug-induced, gallstone, excessive alcohol, severe hypertriglyceridemia (> 1000 mg/dL), and pancreatic tumors. The results of these assessments are shown below.

PSUR 7. Certainty of diagnosis by likelihood of causality (Reproduced from the sponsor)

Certainty of Diagnosis	Likelihood of Causality					
	Definite	Possible*	Possible with more likely alternative etiology	Unlikely	Indeterminate†	**Total**
	n (by row %, ***by column %***, **by total %** respectively)					
Definite	**0**	**34** (73.9, ***13.0***, **10.3**)	**9** (19.6, ***20.9***, **2.7**)	**3** (6.5, ***13.0***, **0.9**)	**0**	**46 (13.9)**
Probable	**0**	**49** (75.4, ***18.7***, **14.8**)	**11** (16.9, ***25.6***, **3.3**)	**5** (7.7, ***21.7***, **1.5**)	**0**	**65 (19.7)**
Possible	**0**	**69** (76.7, ***26.3***, **20.9**)	**12** (13.3, ***27.9***, **3.6**)	**9** (10.0, ***39.1***, **2.7**)	**0**	**90 (27.3)**
Indeterminate*	**0**	**110** (85.3, ***42.0***, **33.3**)	**11** (8.5, ***25.6***, **3.3**)	**6** (4.7, ***26.1***, **1.8**)	**2** (1.6, ***100***, **0.6**)	**129 (39.1)**
Total	**0**	**262 (79.4)**	**43 (13.0)**	**23 (7.0)**	**2 (0.6)**	**330 (100)**

** the majority of indeterminate cases were considered possibly related despite insufficient data; † due to lack of information*

Approximately half (155/330, 47.0%) of reported cases were probably or possibly pancreatitis. The majority of reported cases (262/330, 79.4%) were possibly related to exenatide. Of the 330 postmarketing cases of pancreatitis (through August 31, 2008), 129 were determined to be indeterminate due to insufficient information to make an assessment and were excluded from further analysis by the sponsor.

Of the remaining 201 cases with a definite, probably, or possible diagnosis, 166 (82.5%) reported abdominal pain. A total of 113 (56.2%) had amylase and/or lipase elevation > 3x ULN. A total of 88 (43.7%) of cases had imaging results consistent with pancreatitis.

A total of 167 (83.1%) of cases provided medical history. Of these, 115 (68.9%) reported at least one confounding factor or possible alternative etiology, which are shown below.

PSUR 7. Incidence of factors which confound the diagnosis of pancreatitis (N=167)	
Confounding factors	**Number (%) of cases**

History of pancreatitis	16 (9.6)
Cholelithiasis/cholecystitis	37 (22.2)
Hypertriglyceridemia	49 (29.3)
Excessive alcohol use	13 (7.8)

Of the 201 cases, 178 provided information about concomitant medications. A total of 166 (166/178, 93.3%) cases reported the concomitant use of at least one drug associated with the development of pancreatitis. The most frequently reported concomitant medications were metformin (115), hydrochlorothiazide (39), furosemide (22), ACE inhibitors (71), and statins (82).

Of the 201 cases, 170 reported the case outcome at the time of reporting. Five of the 201 cases died. (A total of 6 fatalities were reported as one was categorized as indeterminate and did not meet criteria for this section.) Of the fatal cases, 1 cause of death was attributed to pancreatitis. The other 4 deaths were attributed to metabolic acidosis, respiratory failure, gastrointestinal bleed, and leukemia.

Review of the PSUR 8 (October 1, 2008 – March 31, 2009) and the Cumulative Review of Pancreatitis (through August 31, 2008) submitted in PSUR 7 identified nine postmarketing cases of fatal pancreatitis:

- **US200705005536:** 66 year old female with a history of diabetes, peripheral vascular disease, and hypertension experienced a fatal case of acute pancreatitis. The patient began exenatide 5 mcg BID in October 2006 which was increased to 10 mcg BID in November. Six months after starting exenatide, the patient was diagnosed with acute pancreatitis and exenatide was discontinued. When she was admitted to the hospital (b) (6) a computerized axial tomography (CT) study showed mild infiltrative changes and a small loculated fluid collection at the pancreatoduodenal groove, suggesting possible "grooved" pancreatitis with pseudocyst formation. Her amylase and lipase on the day of the CT study were 116 and 153, respectively. Her gallbladder was removed laproscopically during the hospitalization. She was discharged (b) (6). On (b) (6), the patient was readmitted for right upper quadrant and epigastric pain for 2 months. On (b) (6), her amylase and lipase levels were 105 (normal) and 52 (normal 22-51), respectively. On (b) (6), the patient died due to metabolic acidosis due to ischemic stomach, liver, and small intestine due to "peripheral vascular disease due to diabetes mellitus and hypertension".
    - **COMMENT: A definite case of pancreatitis, although death appears to be the result of ischemic bowel disease.**
- **US200711005127:** 45 year old female who, while taking exenatide, was admitted to the intensive care unit and died from acute pancreatitis. A physician reported that the patient's concomitant medications were not likely related to the event. The reporting physician assessed the acute pancreatitis as related to exenatide. Additional information was not provided.
    - **COMMENT: Incomplete information was provided.**

- **US200711005991:** 47 year old male with a history of T2D, hypertension, hyperlipidemia, morbid obesity (444 pounds), gastroenteritis, and ventral hernia repair had hemorrhagic pancreatitis and died (b) (6). The patient began exenatide 5 mcg BID on June 13, 2007 and increased his dose to 10 mcg one month later. On September 5, 2007, he experienced severe upper abdominal pain with sweating followed by multiple episodes of nausea and vomiting. On (b) (6), he presented at the emergency department with these symptoms. His abdomen at that time was obese, soft, with hypoactive bowel sounds, and tender to palpation in the right and left upper and mid epigastric regions. Blood work was significant for the following: WBC 24,400 cells/µL, glucose 476 mg/dL, AST 370 U/L, ALT 236 U/L, total bilirubin 2.5 mg/dL, lipase > 12,000 U/L, and carbon dioxide 17 mEq/L. The patient's (b) (6) ultrasound, which was limited due to obesity, showed fatty changes in the liver and multiple mobile echogenic stones within the gallbladder with thickened wall suggesting acute cholecystitis. The (b) (6) CT scan, which was limited by the patient's body habitus, showed a mildly large pancreatic head, unremarkable gallbladder, mildly fatty liver, narrowing at the L1-2 disk, mild ascites, and probable mild lingular atelectasis. He was admitted to telemetry and given bowel rest, fluids, hydromorphone, ondansetron, piperacillin, imipenem, total parenteral nutrition (TPN), and insulin. He was noted to have good pain control, stable vital signs, and a steady gait. However, on the morning of (b) (6), he had a syncopal episode while trying to stand after using the commode. He was unresponsive, pulseless, and hypoxic when CPR was initiated. He was later pronounced dead as he was still without a pulse. Autopsy showed a gallbladder with 50 black stones (< 4 mm each), 440 g hemorrhagic and necrotic pancreas (normal 75-150 g), but no common bile duct blockage. A 50% occlusion of the left anterior descending coronary artery, hepatic steatosis, and hemorrhagic gastritis.
    - **COMMENT: This is a definite case of pancreatitis. Multiple gallstones were seen although the common bile duct was not blocked. The subject died of cardiorespiratory arrest after a syncopal episode.**
- **US200802002837:** 72 year old male with a history of gallstones, T2D, hypertension, hyperlipidemia including hypertriglyceridemia, coronary artery disease, diverticular disease, peripheral vascular disease, anxiety, strawberry allergy, angioplasty of the right superficial femoral artery, and weekly social alcohol use. Concomitant medications included metformin, rosiglitazone, felodipine, ramipril, fenofibrate, furosemide, acetylsalicylic acid, calcium, hydrocodone, and paracetamol. The patient began exenatide in the Fall 2006. After a few weeks of use, he developed abdominal pain and discontinued exenatide use in 2006. The stomach pain resolved, although treatment details were not provided. On (b) (6), the patient presented at the emergency department with epigastric pain which radiated to the back and was associated with vomiting. CT scan showed acute pancreatitis with an enlarged head and neck, punctate calcifications, and induration. The common duct was normal and without stones. There were pancreatic stones suggestive of chronic changes, gallstones and sludge with a normal gallbladder, and a left renal cyst. He was admitted for gallstone pancreatitis and treated. On (b) (6), he became acutely short of breath with decreased oxygen saturation. Chest x-ray showed lower lobe atelectasis and pulmonary vascular congestion with edema. Although a pulmonary embolus was not ruled out, it was felt that the

hypoxia was likely due to acute respiratory distress syndrome associated with pancreatitis. A CT scan on an unreported date showed multiple large bilateral pulmonary emboli and a necrotic body of the pancreas. On (b) (6), abdominal pain increased and urine output decreased. Amylase was 1140 and lipase 5082. The patient was moved to the intensive care unit (ICU). Blood sugars were 300-400 mg/dL; the patient was treated with insulin. Right lower extremity duplex, on an unreported date, showed superficial femoral vein thrombus occluding the popliteal vein. The patient was treated with IV heparin and an inferior vena cava (IVC) Greenfield filter (b) (6). (b) (6) (b) (6), CT showed unchanged pancreatitis with increased ascites and bilateral pleural effusions. On (b) (6), the patient was discharged to a skilled nursing facility to follow up with surgery for gallbladder removal. On (b) (6), the patient presented to the ER complaining of fever, increasing abdominal girth, inability to eat, and weakness. His abdomen was distended, mildly tender, and with a fluid wave. Lower extremity edema was present bilaterally, although calves were nontender. Amylase was reported as 354 and 348 and lipase as 463 and 131 that day. A CT scan showed necrotizing chronic pancreatitis with phlegmon and cystic changes around the neck. He was diagnosed with vancomycin resistant enterococci in the stool and Klebsiella Enterobacter in the urine. On (b) (6) the patient's oxygen saturation was 93% on room air. On an unreported date, he had shortness of breath and was found to have pulmonary emboli. Respiratory support was provided including eventually mechanical ventilation. As serum albumin levels were critically low, albumin transfusions were given. Therapeutic paracenteses were performed to reduce ascites. On (b) (6), it was decided not to continue mechanical ventilation and the patient expired shortly thereafter.

  - **COMMENT: A definite case of pancreatitis, although the subject had a history of gallstone pancreatitis and had gallstones on CT. The patient discontinued exenatide approximately 4 months prior to pancreatitis onset. He expired after discontinuation of mechanical ventilator with a history of pulmonary emboli.**

- **US200804001305:** 58 year old female, with a history of acute myelogenous leukemia status post allogenic matched unrelated bone marrow transplant (b) (6) and steroid induced diabetes which was also treated with metformin, who had acute pancreatitis and died (b) (6) from a leukemia relapse. On January 2, 2008, the patient was started on exenatide 5 mcg BID. She did not monitor her blood sugars. On (b) (6), she was admitted for acute pancreatitis and diabetic ketoacidosis. Lab values were as follows: lipase 9023, glucose 807, cholesterol 267, WBC 13.7. Her elevated liver enzymes were attributed to graft versus host disease. Exenatide was discontinued on January 23. She recovered with treatment. On (b) (6), her labs were lipase 79, glucose 51, alkaline phosphatase 120, ALT 120, AST 82, triglycerides 282, cholesterol 284, and WBC 9.2. On (b) (6), the patient died from a leukemia relapse.
  - **COMMENT: The subject died from leukemia relapse.**
- **US200806002509:** 56 year old male, with a history of diabetes on the concomitant medications fenofibrate, metformin, ezetimbe/simvastatin, amlodipine/benazepril, was started on exenatide 5 mcg BID in May 2007 and increased to 10 mcg BID in June. In May 2008, HbA1c was 6.3%. In (b) (6), after stopping his exenatide for 2-4 days on

vacation, the patient developed sudden onset abdominal pain. He was admitted for gallstone pancreatitis. He had a cholecystectomy and was discharged (b) (4). One to two days later, he returned to the hospital with abdominal pain. The hospital course and treatment were not provided. While hospitalized, he died due to gastrointestinal bleeding.

  - **COMMENT: The subject died from gastrointestinal bleeding, after a cholecystectomy for gallstone pancreatitis.**

- **GB20081103650:** CT scan results revealed edematous pancreatitis with extensive peripancreatic stranding and multiple gallstones. Amylase was modestly elevated (132, nl 1-100). Lipase level was not reported. Upon recovery, the patient experienced cardiac arrest and died. Autopsy showed the cause of death was acute myocardial infarction, ischemic heart disease, and pancreatitis secondary to gallstones.
  - **COMMENT: Pancreatitis was secondary to gallstones.**
- **US200903001316:** The subject had 2 episodes of pancreatitis. The first involved nausea, vomiting, and abdominal pain with no reports of enzyme elevation or diagnostic testing. The second episode involved similar symptoms with a normal amylase level and CT scan results that were negative for pancreatitis. The patient died the next day. The cause of death, according to the sponsor, was unknown.
  - **COMMENT: Laboratory results and imaging do not support a diagnosis of pancreatitis.**
- **US200812002439:** The report described death due to pancreatitis but no other details were provided.
  - **COMMENT: Incomplete information was provided.**

Ten cases of necrotizing pancreatitis were reported through March 31, 2009, according to PSUR 8 and the Cumulative Review of Pancreatitis submitted in PSUR 7. One case (US200802002837) was fatal and was previously described. The remaining 9 cases are described below.

- **US200602000669:** 46 year old female with a history of metabolic syndrome and hypertriglyceridemia who was started on exenatide 5 mcg BID in November 2005 and increased to 10 mcg BID one month later. During the week of January 9, 2006, the patient experienced mid-epigastric pain at night which lasted 3 hours and resolved. The patient then experienced another episode of abdominal pain with nausea and vomiting. On (b) (6), the patient presented to the ER after almost fainting at home. Her blood pressure was reported as 70 mm/Hg. She was treated with fluids, and her blood pressure improved. The patient's amylase and lipase were elevated. She was admitted for acute pancreatitis that day and exenatide was discontinued. A CT scan on approximately (b) (6) showed an area of pancreatic hypoperfusion consistent with necrosis. At the time of last report, the patient was hospitalized in stable condition.
- **US200606002001:** 65 year old male, with a history of T2D and hypertriglyceridemia, who began exenatide 5 mcg BID on November 10, 2005 and increased to 10 mcg BID one month later. Concomitant medications included hydrochlorothiazide, metformin, lisinopril, Arthrotec, Vytorin, Anaprox, and colchicine. On (b) (6), the patient developed abdominal pain and was admitted for acute necrotizing pancreatitis. Amylase

was 1660 U/L. CT scan showed acute necrotizing pancreatitis with a 24 cm pseudocyst. Exenatide was probably discontinued upon hospital admission, according to the reporting physician. During the hospitalization, the patient was intubated and extubated twice, started on antibiotics for fever and sepsis, and developed decreased renal function and a pancreatic phlegmon. CT scans later showed that the "pancreatitis had improved." The patient was discharged from the hospital (b) (6) in stable condition. It is not clear from the report if the patient was transferred to a long-term respiratory care facility.

- **US200801003034:** 69 year old male with a history of diabetes mellitus, obesity, hypertension, increased cholesterol, hypertriglyceridemia, rare alcohol use, prostate cancer status post external radiation therapy, allergic rhinitis, benign prostatic hyperplasia, degenerative joint disease, depression, acute coronary disease, transient, ischemic attack, peripheral vascular disease, and inguinal hernia repair. Concomitant medications included mometasone furoate, ramipril, rosiglitazone maleate, diazepam, fexofenadine hydrochloride, fenofibrate, atorvastatin calcium, acetylsalicylic acid with and without dipyridamole, rabeprazole sodium, buproprion hydrochloride, montelukast, tamsulosin hydrochloride, amlodipine, metformin, folic acid, and sitagliptin.

  The patient began exenatide 10 mcg BID on July 3, 2006. On April 27, 2007, the patient had diarrhea and nausea without vomiting. On (b) (6) after starting exenatide, he had dull, constant, diffuse, nonradiating abdominal pain which was worse over the epigastric region. A CT scan of the abdomen showed scattered atelectasis, fatty infiltration of the liver, a 1 cm hypodense lesion in the upper right pole of the left kidney likely a cyst, an enlarged pancreas with decreased enhancement, marked edema of retroperitoneal fat surrounding the pancreas, no peripancreatic fluid, and mild small bowel ileus. The patient was admitted for acute pancreatitis (b) (6), (b) (6). Lipase was 6820 U/L (Normal: 8-74 U/L). The patient was intubated upon admission. A nasogastric tube was placed for the abdominal ileus. Exenatide was discontinued in April 2007. (b) (6) lipase had decreased to 1112 U/L. On (b) (6) (b) (6), a right upper quadrant ultrasound revealed no cholelithiasis or acute cholecystitis, no biliary distention, a fatty liver, and minimal perihepatic fluid. On the same day, a hepatobiliary iminodiacetic acid (HIDA) scan was consistent with acute high-grade common bile duct obstruction, lipase was 723 U/L, bilirubin 2.5 mg/dL, creatinine 1.5 mg/dL (Normal: 0.5-1.3 mg/dl), and triglycerides 150 mg/dL. (b) (6) an endoscopic retrograde cholangiopancreatography (ERCP) was performed. During the procedure, the patient was mildly tachypneic with an oxygen saturation of 92% but the pancreatic duct was cannulated. A cholangiogram noted a narrowing of the lumen of the common bile duct. A stent was placed with drainage of bile. The physician noted that the ERCP may exacerbate his pancreatitis further. (b) (6) bilirubin was 1.5 mg/dL. (b) (6) a CT scan showed new atelectasis and small left pleural effusion, new ascites, increasing peripancreatic inflammatory changes with patchy vascular enhancement of the head and tail and no enhancement of the pancreatic head suggesting possible pancreatic necrosis, and a new ileus with increased bowel distension. (b) (6) (b) (6) the CT was repeated revealing increased peripancreatic fluid density structure compressing the posterior stomach, decrease in trace ascites, inhomogenous pancreatic

enhancement compatible with necrotizing pancreatitis. He was transferred out of the ICU (b) (6), at which time he had a 7.2 x 9.3 cm fluid collection increasing in size, sepsis, bradycardia, and hypotension required dopamine. (b) (6), the pseudocyst was drained by CT-guidance and showed an infection with gram positive cocci. The patient was electively taken to the operating room for exploration and debridement of the infected pancreatic pseudocyst. On an unreported day after surgery, the patient was again intubated, transferred to the ICU, and abdomen drained with bilateral active drains which showed gram negative rods and gram positive cocci in pairs and chains. He was treated with linezolid, meropenem, and fluconazole. He was later extubated, transferred out of the ICU, and his active drains changed to gravity-draining catheters. He was then diagnosed with clostridium difficile colitis and treated with vancomycin. (b) (6) (b) (6) he was discharged home with home health nursing, physical therapy, and a peripherally inserted central catheter (PICC) for antibiotics.

- **US200802002764:** 55 year old male with a history of T2D, 3-4 alcoholic drinks per week, obesity, hypertension, cholecystitis, and hyperlipidemia. Concomitant medications included fenofibrate, omega-3 triglycerides, atorvastatin, nicotinic acid, metoprolol, acetylsalicylic acid, doxazosin, furosemide, hydrochlorothiazide, eplerenone, ramipril, and insulin 75/25 mix. The patient received exenatide 10 mcg BID on April 1, 2007. After starting exenatide, his weight increased from 330 to 462 pounds. On March 3, 2008, his weight was 305 pounds. Sometime after starting exenatide, the patient had severe diarrhea. After four days, he went to the ER for pain and diarrhea. Amylase at that time was approximately 1000; he was admitted for acute pancreatitis. An MRI scan showed no gallstones or bile sludge. A HIDA scan showed poor gallbladder function. The patient was given hydration, nothing by mouth, and medications were discontinued; he and his laboratory values improved after 24 hours. All of the medications except for hydrochlorothiazide were later restarted. (b) (6) the patient was readmitted with acute pancreatitis and severe epigastric pain; exenatide was discontinued on November 3. His laboratories were as follows: amylase 443, lipase 4421, AST 569, ALT 411, lactate dehydrogenase 664. (b) (6) an MRI showed pancreatitis with fluid/edema on the pancreas, bilateral atelectasis and pleural effusions, ascites, and a "negative appearing gallbladder…and common bile duct". (b) (6) CT scan showed worsening of diffuse acute pancreatitis with a thick band of fluid cloaking the ventral aspect of the pancreas with involvement of the lesser sac and stomach which was a pseudocyst as well as stable ascites, increased atelectasis and pleural effusions, and flank edema. (b) (6) CT scan showed severe interval deterioration in fulminant pancreatitis with associated inflammatory changes and an enlarging lesser sac pseudocyst. (b) (6) CT scan showed persistent moderate left pleural effusion with bibasilar atelectasis (greater on left), increased very large pseudocyst that invaded the stomach, mild worsening in the intense pancreatic and peripancreatic inflammation, edema, and probably partial necrosis of the pancreas, increased ascites, and worsened adynamic ileus. (b) (6) CT showed that the pseudocyst increased from 5.8 to 6.7 cm. He was discharged (b) (6). On (b) (6) his triglycerides were 84. He recovered from the acute necrotizing pancreatitis (although the pseudocyst was still palpable), atelectasis, and pericardial effusion. He was recovering from anasarca.

- **COMMENT: Positive rechallenge.**

- **US200807002087:** Patient had necrosis around the pancreatic tail and a dilated common bile duct without the presence of stones.
- **US200808006124:** Patient was hospitalized twice for pancreatitis. On the first admission, gall bladder ultrasound showed numerous small gallstones. The patient underwent a cholecystectomy. Exenatide was discontinued but restarted at discharge. The patient was hospitalized with necrotizing pancreatitis 9 days later. The subject had abdominal pain. Pancreatic enzymes were modestly elevated (amylase 136 [nl 28-100] and lipase 163 [13-60]). No imaging information was provided. Past medical history included gallstones, alcohol abuse, and hypertriglyceridemia. Concomitant medications included hydrochlorothiazide, valsartan, and fenofibrate. The patient recovered.
- **US20005000184:** Patient had a diagnosis of necrotizing pancreatitis and multiorgan failure consistent with the diagnosis.
- **US200811001739:** MRI results revealed necrotizing pancreatitis but enzyme levels were not reported. The patient remained hospitalized at the time of the report.
- **US200811004931:** MRI results were consistent with hemorrhagic, necrotizing pancreatitis. Amylase was 284 and triglycerides were 797. The patient was recovering at the time of the report.

One case of hemorrhagic pancreatitis (US200711005991) had a fatal outcome and was previously described. Another subject (US200812004072) reportedly developed hemorrhagic pancreatitis and was hospitalized, although no information was provided on symptoms, enzyme levels, or diagnostic testing.

NDA 21-919. Cases of fatal, necrotizing, and hemorrhagic pancreatitis described in PSUR 8 and PSUR 7's Cumulative Review of Pancreatitis

ID	Pancreatitis	Risk factors and related information
US200705005536	Fatal	Gallbladder removed (b)(6). Pain persisted in (b)(6) when amylase & lipase were not significantly elevated and pt died due to metabolic acidosis secondary to peripheral vascular disease and ischemia.
US200711005127	Fatal	
US200711005991	Fatal hemorrhagic	History of hyperlipidemia. US + gallstones and cholecystitis. Fatal syncopal episode.
US200802002837	Fatal necrotizing	History of gallstones, hyperlipidemia, & social ETOH use. + Pulmonary emboli. Pt expired after discontinuation of mechanical ventilator.
US200804001305	Fatal	History of steroid use. Died from leukemia relapse.
US200806002509	Fatal	Stopped exenatide use 2-4 d earlier. Gallstone pancreatitis treated with cholecystectomy. Died during readmission for GI bleeding.
GB20081103650	Fatal	Died of cardiac acute MI, ischemic heart disease, and pancreatitis secondary to gallstones.
US200903001316	Fatal	Labs and imaging not provided to support diagnosis.
US200812002439	Fatal	
US200602000669	Necrotizing	History of hypertriglyceridemia
US200606002001	Necrotizing	History of hypertriglyceridemia and thiazide use.
US200801003034	Necrotizing	History of hypertriglyceridemia and rare ETOH use. US negative for gallstones & cholecystitis, but HIDA c/w common bile duct obstruction which was relieved by ERCP.
US200802002764	Necrotizing	History of ETOH use, cholecystitis, hyperlipidemia, and thiazide use.

		Positive rechallenge without thiazide. Normal gallbladder and common bile duct at that time.
US200807002087	Necrotizing	
US200808006124	Necrotizing	Had cholecystectomy for gallstone pancreatitis. Necrotizing pancreatitis diagnosed 9 days later.
US20005000184	Necrotizing	
US200811001739	Necrotizing	
US200811004931	Necrotizing	
US200812004072	Hemorrhagic	Labs and imaging not provided to support diagnosis.

There were 12 cases representing possible positive rechallenges with reported subsequent episodes of pancreatitis. Nine of these cases specified discontinuation and reinitiation of exenatide and are described below. Three additional cases (US200808004389, US200808002002, and US200609004314) described patients experiencing ≥ 2 episodes of pancreatitis and specified the discontinuation of exenatide but lacked precise information on when and/or whether exenatide was stopped and/or reinitiated. Detailed information on concomitant medications was not always provided.

- **US200710004228:** 34 year old female with severe pain and vomiting 1 year after starting exenatide. She was diagnosed with pancreatitis when triglyceride levels were > 1000 mg/dL. Exenatide was discontinued, she recovered, and exenatide was restarted 1 week later. She was hospitalized 3 times for pancreatitis. Each time, exenatide was discontinued, medications were changed, and she resumed exenatide upon discharge. The fifth time she had pancreatitis, her triglycerides were 4600 mg/dL.
- **US200805003754:** 56 year male who developed pancreatitis 5 months after starting exenatide, which was then discontinued. The patient recovered, he resumed exenatide, and was diagnosed with a second case of pancreatitis 12 months later. Exenatide was discontinued, he recovered, it was resumed, and he experienced a third case of pancreatitis 5 months later.
- **US200804005536:** 75 year old female who experienced epigastric pain and pancreatitis, from which she recovered. She was treated with furosemide for leg swelling and developed pancreatitis 1 month later. Exenatide was discontinued and she recovered. Within 2 weeks, exenatide was restarted and discontinued within 1 month. After discontinuing exenatide, she experienced a third episode of pancreatitis.
- **US200805002912** developed pancreatitis while on exenatide, which was discontinued. The pancreatitis resolved. Exenatide was reinitiated and the pancreatitis recurred.
- **US200802002764:** 55 year old male with a history of chronic cholecystitis on fenofibrate, atorvastatin, furosemide, hydrochlorothiazide, and ramipril, developed pancreatitis with pseudocyst. All medications were discontinued and he recovered. Pancreatitis later recurred with amylase and lipase elevation after resuming medications, except for hydrochlorothiazide.
- **US200710004471:** 59 year old female developed pancreatitis, from which she recovered. Exenatide was resumed, but the status of atorvastatin, fenofibrate, and olmesartan was not provided. Ten months later when pancreatic enzymes were normal, she developed abdominal pain. CT scan showed inflammatory changes and a fluid collection suggestive of a small pseudocyst.

- **US200810001928:** After using exenatide for approximately 3 months, the patient experienced abdominal pain with normal pancreatic enzymes. Exenatide was discontinued. The pancreatitis resolved. Approximately 3 months later, exenatide was reinitiated and within 2 weeks, pancreatic enzymes were elevated (amylase 138 and lipase 288). She was diagnosed with pancreatitis and exenatide was discontinued. Two months later, ultrasound showed mild-moderate chronic pancreatitis. Eight months after discontinuing exenatide, amylase and lipase were 53 and 258, respectively.
- **US200811004879:** Patient experienced abdominal tenderness and was diagnosed with pancreatitis approximately 2 years after starting exenatide. No enzyme levels or diagnostic testing were provided. The pancreatitis resolved and exenatide was discontinued. Two months later, exenatide was restarted and within 4 weeks amylase and lipase levels were elevated (values not provided). Exenatide was discontinued and the pancreatic enzymes normalized.
- **US200811004298:** The patient experienced pancreatitis. Exenatide was discontinued and later restarted. The patient then experienced elevated lipase. No further details were provided. Exenatide was continued.

The PSUR 7's Cumulative Review of Pancreatitis (through August 31, 2008) described 29 patients with possible negative rechallenge or resolution of pancreatitis with continued exenatide use. The cases were as follows:

- 21 patients continued exenatide throughout an episode of pancreatitis with resolution documented during continued treatment
- 5 patients who discontinued exenatide during an initial episode of pancreatitis restarted exenatide at the same dose with no reported recurrence
- 3 patients who discontinued exenatide during an initial episode of pancreatitis restarted exenatide at a lower dose with no reported recurrence

In summary, pancreatitis has been reported in association with exenatide. Although patients may have risk factors including a history of pancreatitis, cholelithiasis, alcohol abuse, elevated triglycerides or the use of medications known to cause pancreatitis, these factors do not fully explain the frequency of necrotizing and hemorrhagic pancreatitis reports, which exceeds that of other antidiabetic therapies, including metformin which is prescribed to significantly more patients.

On June 26, 2008, OSE reviewed the cases of hemorrhagic and necrotizing pancreatitis, reported between April 2005 (market approval) and March 31, 2008 that were associated with exenatide use. Six hemorrhagic or necrotizing pancreatitis cases were described, all of which required hospitalization. Two cases resulted in death even after the discontinuation of exenatide. As of August 1, 2008, two more cases of severe hemorrhagic and necrotizing pancreatitis had been reported to the Adverse Event Reporting System (AERS). Based on the Adverse Event Reporting System (AERS) analyses and the serious nature of this AE, the Division of Adverse Event Analysis I (DAEAI) recommended communicating this information to the public and healthcare professionals as well as a boxed warning in the exenatide label.

On August 18, 2008, an updated exenatide health care professional sheet was released. It read as follows: *Since issuing Information for Healthcare Professionals in October 2007, FDA has received reports of 6 cases of hemorrhagic or necrotizing pancreatitis in patients taking Byetta. Byetta is a medicine given by subcutaneous injection to help treat adults with type 2 diabetes. Of the 6 cases of hemorrhagic or necrotizing pancreatitis, all patients required hospitalization, two patients died and four patients were recovering at time of reporting. Byetta was discontinued in all 6 cases.*

Byetta and other potentially suspect drugs should be promptly discontinued if pancreatitis is suspected. There are no signs or symptoms that distinguish acute hemorrhagic or necrotizing pancreatitis associated with Byetta from the less severe form of pancreatitis. If pancreatitis is confirmed, initiate appropriate treatment and carefully monitor the patient until recovery. Byetta should not be restarted. Consider antidiabetic therapies other than Byetta in patients with a history of pancreatitis.

FDA is working with the maker of Byetta, Amylin Pharmaceuticals, Inc., to add stronger and more prominent warnings in the product label about the risk of acute hemorrhagic or necrotizing pancreatitis.

The safety labeling pertaining to pancreatitis should be revised to reflect a potentially fatal risk and its placement within the label elevated. A combined DMEP-OSE Regulatory Briefing was held on April 24, 2009 to discuss this topic. The wording and placement of the pancreatitis safety labeling are currently under internal discussion, with some of the reviewers in OSE favoring a boxed warning while others in OSE and those in DMEP favoring placement under the Warnings and Precautions.

It is the opinion of this reviewer that the pancreatitis language should be placed in the Warnings and Precautions section. While I acknowledge the seriousness of hemorrhagic and/or necrotizing pancreatitis, the cases occur rarely and are often confounded by patients' past medical histories and concomitant medications. There is uncertainty about the frequency of pancreatitis, including the severe forms, in the diabetic population, especially in patients on anti-diabetic medications (e.g. sitagliptin). In the exenatide patient population, pancreatitis case reports were partly stimulated by 2 FDA alerts on this subject.

The revised exenatide label will include a new Highlight section in accordance with the Physicians Labeling Rule. As a result, the pancreatitis safety language will be prominently displayed at the beginning of the label. This in combination with the conversion of the patient package insert (PPI) to a medication guide and a further communication plan will educate patients and physicians about the risk of hemorrhagic and/or necrotizing pancreatitis associated with exenatide. Furthermore, postmarketing requirements will include epidemiologic, mechanistic, and clinical evaluations to better answer the lingering questions described above. If at that time data supports the need to further elevate the warning, a boxed warning could then be considered.

Renal failure

PSURs 4 and 5 reviewed renal failure as a special topic. PSUR 4 reviewed acute renal failure cumulatively from the initial marketing of exenatide in the United States (April 2005). The sponsor used the following MedDRA preferred terms for this review: renal failure acute, renal failure chronic (worsening cases), renal failure, renal impairment, and renal tubular necrosis. This resulted in cases with a range of creatinine values (1.4 - 13 mg/dL) and level of severity (change in creatinine from 1.0 to 1.4 mg/dL to requiring hemodialysis). The analysis revealed 14 health care professional (HCP)–confirmed cases of renal failure and 12 HCP-confirmed cases of altered renal laboratory function in the PSUR 4 reporting period. The most commonly reported events in the reporting period was renal failure acute (6 cases) and blood creatinine increased (10 cases).

Cumulatively, there were 58 cases with events reported as renal failure or a similar term. 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 (n=32 [55%]) took concomitant medications known to affect kidney function. 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 (5 patients including 1 [MRN 2006PV014726] necrotizing), sepsis (2 patients), rhabdomyolysis (2 patients), and nephrolithiasis (1 patient). In total, 48 of the 58 (83%) cases had at least one of the above risk factors known to affect renal function.

PSUR 4. Number (%) of cases (N=58) reporting use of concomitant medications known to affect kidney function

Concomitant medication	**Number of cases**
Diuretics	24 (41%)
NSAIDs	14 (24%)
ACE inhibitors	19 (32%)
Angiotensin receptor blockers	6 (10%)

Five of the 58 patients had an event coded as renal tubular necrosis (2005PV001263. 2005PV002504, 2005PV004605, 2006PV008192, 2006PV017862); 4 of these had renal failure or insufficiency as well as nausea and vomiting. Three of these 4 patients as well as the remaining fifth patient had dehydration and/or hypotension. The majority of these patients (3 of 5) also used medications known to affect renal function.

According to the sponsor, 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” (creatinine of 1.4 mg/dL) or “chronic renal insufficiency” (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.

Regarding the cases of abnormal renal laboratory function for which renal failure or a similar term was not reported, there were 12 HCP-confirmed cases in the PSUR 4 reporting period and 28 HCP-confirmed cases cumulatively. MedDRA preferred terms for these cases included blood creatinine increased, blood urea increased, glomerular filtration rate decreased, creatinine renal clearance decreased, azotaemia, and renal function test abnormal. Of the cases with gender and age reported, 52% were female and the average age was 61.2 years. This group of patients with abnormal renal laboratory results generally had less information reported and small increases in creatinine (often ≤ 2.5 mg/dL) than those with adverse renal events.

Of the 28 patients with abnormal renal laboratory results, 18 (64%) reported renal function risk factors. Fifteen of the 28 (54%) patients used concomitant medications known to affect the kidney. Eight (29%) had nausea, vomiting, or diarrhea; 5 of these 8 also reported dehydration and 2 also reported hypotension. Most of the remaining 10 patients without risk factors had very limited information provided, according to the sponsor.

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.

Of the 10 cases that underwent or were scheduled for hemodialysis, 9 cases had a renal failure event and one case had increased blood creatinine. Eight (80%) of these cases used one or more concomitant medication known to affect renal function. Five (50%) cases involved nausea, vomiting, and/or diarrhea. One case each involved rhabdomyolysis following trauma and pancreatitis. One patient had chronic renal insufficiency and was planning hemodialysis prior to exenatide use. The outcomes of hemodialysis varied and are shown below.

PSUR 4. Outcome of renal cases*	
Hemodialysis outcome	**# Cases**
ARF resolved with ≤3 hemodialysis sessions	2
Resolution	1
Discharged ≤ 4 days after dialysis initiation	2
Hospitalized with multiorgan dysfunction on dialysis 4 days after its initiation	1
End stage renal disease secondary to T2D needing chronic dialysis	1
Little or no outcome information provided	3
*One additional case involved a patient receiving chronic hemodialysis, whose nephropathy did not worsen after exenatide but underwent renal transplant	

In summary, the cumulative analysis of exenatide-associated renal failure in PSUR 4 suggests the following:

- The majority of exenatide-associated renal failure cases are also associated with the concomitant use of medicines known to alter renal function and/or symptoms associated with dehydration.
- Exenatide-associated renal failure occurs with similar incidence in males and females with an average reported age of 61 years.

- Analysis of this adverse event is complicated by incomplete reports as well as patients' history of diabetes, which may predispose them to renal insufficiency.
- When an outcome was provided, 83% (39/47) of cases experienced improvement or resolution of renal failure.
- Of the 7 hemodialysis cases with sufficient outcome data presented, 5 (71%) experienced rapid improvement. One required chronic hemodialysis due to T2D-induced nephropathy. One patient remained hospitalized with multiorgan dysfunction without a clear cause.

PSUR 4. Number (%) of renal failure cases with known renal failure risk factors (April 2005 – March 31, 2007)	
Reported renal risk factor	**Cases (N=86)**
Concomitant medication	47 (54%)
Symptoms associated with dehydration/hypovolemia	44 (51%)
Either one of the above risk factors	65 (76%)
Other risk factors	
Pancreatitis	5 (6%)
Sepsis	2 (2%)
Rhabdomyolysis	2 (2%)
Nephrolithiasis	1 (1%)

Using a collection of terms related to renal failure in PSUR 5, 28 healthcare professional (HCP) and 25 consumer cases of renal events were reported from April 1, 2007 to September 30, 2007. Two HCP cases were excluded as one was reported in the previous period and one had nonspecific coding. The sponsor focused its analysis on the 26 HCP cases, one of which (GB20070802995) was a fatal case of cardiac failure congestive and renal failure.

PSURs 5. Review of relevant renal failure information from HCP reported cases	
	PSUR 5
Age range in years (average)	23-80 (60)
Male:Female ratio	1.9:1
Time to onset in days (mean)	1-378 (61)
Fatalities	1

NOTE: PSUR 5, when compared to PSUR 4, reported an increased male:female ratio but similar average age.

Of these 26 cases, 17 were acute renal failure or worsened chronic renal failure or similar, and 9 were reportedly abnormal laboratory values. Similarly to PSUR 4, 13 (50%) cases reported nausea, vomiting, diarrhea, dehydration, or volume depletion, and 14 (54%) cases reported the use of concomitant medications known to affect renal function. 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 3 cases which worsened or did not recover were followed for a short period of time.

Renal cases of interest reported in PSUR 5 include the following:

- **GB200708002995:** 60 year old male fatal case of congestive heart failure and renal failure. Past medical history included obesity, diabetes, pre-existing heart disease, and rosiglitazone use. Concomitant medications included metformin, glargine, and pioglitazone. The patient began exenatide 5 mcg SC BID on July 30, 2007; as he failed to attend the training session, he may have misused the drug. (b) (6), he was admitted to the hospital with congestive heart failure and died. On an unknown date, he also developed nausea, vomiting, lactic acidosis, and possibly renal failure.
- **US200705005981:** 57 year old female with the past medical history of T2D, mild hypertension, and dylipidemia. Concomitant medications included metformin, valsartan, and atorvastatin. In the Fall of 2006, the patient began exenatide 5 mcg SC BID and experienced 27 pounds weight loss and nausea. (b) (6), the patient was hospitalized for acute renal failure; exenatide, metformin, and valsartan were discontinued. Laboratory data (b) (6) included serum creatinine 1.0 mg/dL, creatinine clearance (CrCl) < 30 ml/min, and HbA1c 8.9%. (b) (6) (b) (6) serum creatinine was 8.5 mg/dL, blood urea nitrogen (BUN) 39, and CrCl < 10 ml/min. Urinalysis showed 1+ proteinuria and hematuria with microalbumin. Kidney ultrasound and antibody studies were negative. (b) (6) kidney biopsy showed "tubular vacuolization consistent with diabetes." The patient required several weeks of hemodialysis. (b) (6) serum creatinine was 1.3 mg/dL and the diagnosis was stage 3 chronic kidney disease (CKD). The patient was recovering. Exenatide was not restarted; the patient was treated with glargine.
- **US200704003102:** 51 year old male who started exenatide 5 mcg BID and then increased the dose to 10 mcg BID. In 2007 approximately 1 week after the increase, the patient had nausea and vomiting and was admitted to the hospital where exenatide was discontinued. According to the Medwatch report, severe nausea and vomiting led to dehydration and then acute renal failure. He then experienced elevated potassium, cardiac and respiratory arrest. He was resuscitated and received dialysis and mechanical ventilation in the critical care unit. (b) (6), the patient recovered, was up and talking, and was to be transferred to a rehabilitation facility.
- **US200705000179:** 69 year old female, who while taking metformin, began exenatide 5 mcg BID in December 2005 and later increased the dose to 10 mcg BID. On March 26, 2007, there were reportedly no issues. The patient then experienced viral diarrhea and vomiting. She was hospitalized with acute renal failure and received hemodialysis. Continuation of exenatide was not provided; she had not recovered.

PSURs 6, 7, and 8's data were presented by system organ class rather than as an adverse event of special interest. In PSURs 6-8, a total of 144 reactions (56 serious) were categorized as "renal and urinary disorders". As the SOC title suggests, not all of these adverse events were cases of renal failure. PSUR 8 described 1 fatal event of acute renal failure. IT200901002604 was a 62 year old male with T2D, myocardial necrosis, hypertensive cardiomyopathy, myocardial ischemia, and obesity. The patient began exenatide 5 mcg daily and increased to 20 mcg daily 1

month later. On an unknown date reported as "after 15 days", the patient experienced left side pain and was diagnosed with left calyceal-pyelic dilation and the presence of hyperechogenic spots per abdominal ultrasound. Exenatide was discontinued approximately 11 weeks after initiation due to general malaise and the patient was hospitalized "after a few days" with acute renal insufficiency. He received hemodialysis as treatment. Approximately 3 weeks later, he died due to acute renal insufficiency.

NOTE: Please also refer to section 7.1.25 which reviews the analysis of renal AEs and out of range renal laboratory values for the six phase 3 placebo-controlled clinical trials that supported the original exenatide NDA 21-773, which the sponsor submitted on August 12, 2008.

On September 20, 2007, the sponsor submitted a changes being effected (CBE) labeling supplement pertaining to renal safety. It included the following language in the label:

(b) (4)

As no mechanism for renal toxicity has been identified and renal failure continues to be reported in patients using exenatide, an OSE consult was placed to aid the division in determining the appropriateness of the CBE labeling change. The consult, which was completed February 23, 2009, agreed with the supplement language as it relates to renal adverse events. It also contained the following recommendations:

- Alignment of the U.S. product label with the U.K. product label
  - A recommendation that exenatide not be used in patients with a history of renal transplantation, moderate or severe renal impairment, or kidney failure
  - Warning against concurrent use with insulin
- Addition of language describing the postmarketing cases of acute renal failure, some of this resulted in kidney transplantation or worsening of renal transplant function, to the Warnings and Precautions/Renal Impairment section
- Addition of the adverse event terms "kidney transplant" and "kidney transplant dysfunction" in the Adverse Reactions/Post-Marketing Experience/Renal and Urinary Disorders section
- Addition of language to the Patient Counseling Information section

- The dissemination of this renal dysfunction information to clinicians and the public via a Dear Health Care Professional letter, a Public Health Advisory, and/or MedWatch Safety Alert

A substantial proportion of the renal cases may have resulted from dehydration secondary to vomiting leading to pre-renal and subsequent renal insufficiency. Other cases may represent the progression of renal disease seen in diabetes or the effect of concomitant medications. However, for a few cases, the use of exenatide appears to be the most plausible cause. As a result, the safety labeling pertaining to renal adverse events should be revised.

I agree with OSE that exenatide should not be used in patients with severe renal impairment or end-stage renal disease; postmarketing adverse event language should be added to the label; and the United States' and United Kingdom's labels should be more aligned. However, due to limited clinical experience with subjects with a history of moderate renal impairment or renal transplant and subjects concurrently using insulin, I disagree with OSE's recommendations for these populations. Instead, I recommend that exenatide be used cautiously in subjects with moderate renal impairment or a history of renal transplant; this is more consistent with the United Kingdom's moderate renal impairment language. As discussed above, I recommend dissemination of the renal dysfunction information to clinicians via a DCHP letter. In addition, I believe the recommendation against the concurrent use of exenatide and insulin should be placed in the Important Limitations of Use section, rather than Warnings and Precautions; this is consistent with now standard labeling for all anti-diabetics for which there are little or no data for combined use with insulin.

Hypersensitivity

A total of 28 HCP and 10 consumer cases of anaphylactic reaction were reported in PSUR 7's Cumulative Review of Anaphylactic Reactions (40 total events). With an estimated exposure of nearly 1 million patients, the reporting rate of anaphylactic reaction is < 0.01%. Five cases were reported as life threatening; none were fatal. Of the 30 cases which reported the patient's age, the age range was 29-67 years (mean 49 years). The female:male ratio was 2.2:1. 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. Two cases described patients without a history of exenatide exposure who, after initiating exenatide, developed a hypersensitivity reaction within 7 days. The sponsor suggests these may have been anaphylactoid reactions (i.e., non-IgE mediated mechanism of mast cell/basophil activation), although supportive data were not provided. The signs and symptoms of anaphylactic reactions reported included anaphylactic shock, syncope/loss of consciousness, shortness of breath, angioedema, urticaria, rash, itching, and swelling. Two additional cases of anaphylactic shock occurred during PSUR 8's reporting period (October 1, 2008 – March 31, 2009).

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

Thyroid cancer

In the 104-week carcinogenicity study, benign thyroid C-cell adenomas were observed in female rats at all exenatide doses (18, 70, and 250 µg/kg/d SC injection). The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups with systemic exposures of 5, 22, and 130 times, respectively, the human exposure resulting from the maximum recommended dose of 20 µg/day, based on plasma area under the curve (AUC).

On April 2, 2009, an Advisory Committee convened to discuss the potential risk of medullary thyroid (c-cell) cancer based on rodent carcinogenicity studies of liraglutide, another GLP-1 analogue with a longer duration of action than exenatide twice daily.

A draft report of the 104-week rat carcigenicity study with the exenatide once weekly formulation indicated a statistically significant increase in thyroid c-cell tumors in female and male rats. The incidence of c-cell carcinomas was also significantly increased in the high dose female group, and a numerical increase in c-cell carcinomas was observed in low, mid, and high dose males. However, a 104-week carcigenogenicity study in mice at doses of 18, 70, and 250 µg/kg/d SC injection showed no evidence of tumor (systemic exposure up to 95x the human exposure). Because the PK profile of exenatide once weekly is quite different from exenatide (Byetta) and the longer duration of action may be the basis for a possible increased risk of medullary thyroid cancer, it is currently thought that this information is not relevant to short acting exenatide.

Nonetheless, PSUR 8 included a cumulative review of thyroid cancer. Spontaneous reports were searched using the following terms: thyroid neoplasm, thyroid neoplasms benign, and thyroid neoplasms malignant. Ten cases of thyroid cancer were reported through March 31, 2009. All were reported in the United States. The 3 cases which contained a pathologic description were papillary thyroid cancer; no cases of medullary thyroid cancer have been reported. Nine cases provided the patient's age, which ranged from 43-69 years (average 56 years). Female to male ratio was 3.5:1. The time to onset was determined in 7 cases. Excluding one case of recurrent, metastatic thyroid cancer, the time to onset ranged from 0-16 months (mean 4 months).

Although the reporting rate for newly diagnosed thyroid cancers with exenatide cannot be directly compared to the background incidence rate of thyroid cancers in the US, the reporting rate is significantly lower (0.9 cases/100,000 patient-years versus 8.4/100,000 patient-years). None of the postmarketing cases of thyroid cancer described medullary cancer of c-cell origin. Therefore, no new clinical thyroid tumor safety labeling is needed at this time. The sponsor plans to continue to monitor this risk, including measuring calcitonin every 12 weeks in all clinical studies of exenatide once weekly, consulting with thyroid cancer experts regarding these findings, and continuing targeted surveillance for all clinical trial and postmarketing cases.

On December 19, 2008, the sponsor responded to an October 31, 2008 request for an analysis of clinical and postmarketing cases of thyroid cancer observed in subjects treated with exenatide. As PSUR 8's more recent cumulative analysis of postmarketing cases was reviewed above, only

the clinical trial cases are discussed here. As of September 30, 2008, there were no cases of thyroid cancer in the completed, controlled clinical trials of exenatide.

7.1.17.1 Study type and design/patient enumeration

Pivotal study H8O-MC-GWBJ is a 24-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study. Type 2 diabetics who had inadequate glycemic control with diet and exercise participated in a 2 week, single blind, placebo lead-in period before being randomized to exenatide or placebo. A total of 232 subjects were evaluable for safety (155 of whom received exenatide).

7.1.17.2 Demographics

Most patients in study GWBJ were Caucasian (>64%) and West Asian (>23%) with approximately 56% men and 44% women. The mean baseline age, BMI, and HbA1c were similar between treatment groups. The majority of patients were Romanian or Indian. Nationalities were distributed similarly between treatment groups.

GWBJ. Baseline characteristics

Characteristic	Placebo (N=77)	Ex 5 mcg (N=77)	Ex 10 mcg (N=78)
Age, mean (SD)	53.25 (9.25)	53.68 (10.15)	55.21 (9.90)
Race, n (%)			
African	3 (3.9)	0 (0.0)	3 (3.8)
Caucasian	51 (66.2)	50 (64.9)	56 (71.8)
Hispanic	2 (2.6)	5 (6.5)	1 (1.3)
Asian	21 (27.3)	22 (28.6)	18 (23.1)
Male (%)	42 (54.5)	40 (51.9)	48 (61.5)
Mean duration of diabetes (years)	1.30	2.39	2.02
BMI (kg/m^2), mean (SD)	31.61 (4.67)	31.52 (4.70)	30.65 (4.83)
HbA1c, mean (SD)	7.82 (0.86)	7.88 (0.96)	7.83 (0.95)
HbA1c > 8% (%)	33 (42.9)	34 (44.2)	34 (43.6)

GWBJ. Summary of patients by country

	Placebo	Exenatide 5 mcg	Exenatide 10 mcg
India	22	22	18
Romania	40	39	42
Russia	9	10	12
United States	7	6	6

I searched the list of concomitant medications used during study GWBJ for the following drugs with a known exenatide interaction: acetaminophen, digoxin, lisinopril, lovastatin, oral antibiotics, oral contraceptives, and warfarin (please refer to section 8.2 Drug-Drug Interactions).

Although no warfarin-related listing was seen, drug classes pertaining to the other listed drugs were present on the list of concomitant medications. The frequency of their use is shown below. There were no clinically important imbalances between the treatment groups with regard to these medications or any of the other concomitant medications.

GWBJ. Relevant concomitant drug therapy using during the study by drug treatment group (N [%]) (ITT population)

	Placebo (n=77)	**Ex 5 mcg (n=77)**	**Ex 10 mcg (n=78)**
Other analgesics & antipyretics	1 (1.3)	2 (2.6)	1 (1.3)
ACE inhibitor, plain	20 (26.0)	28 (36.4)	27 (34.6)
Digitalis glycosides	0 (0.0)	1 (1.3)	0 (0.0)
HMG CoA reductase inhibitors	9 (11.7)	14 (18.2)	18 (23.1)
Total related to antibiotics	14 (18.2)	16 (20.8)	17 (21.9)
Antibiotics	2 (2.6)	0 (0.0)	1 (1.3)
Antiinfectives	1 (1.3)	0 (0.0)	2 (2.6)
Penicillin with extended spectrum	0 (0.0)	1 (1.3)	2 (2.6)
Tetracycline	1 (1.3)	1 (1.3)	1 (1.3)
First-generation cephalosporins	1 (1.3)	0 (0.0)	0 (0.0)
Fluoroquinolones	0 (0.0)	0 (0.0)	1 (1.3)
Sulfonamides, plain	9 (11.7)	14 (18.2)	10 (12.8)
Total related to oral contraceptives	3 (3.9)	2 (2.6)	0 (0.0)
Progestin & estrogen, fixed combination	2 (2.6)	1 (1.3)	0 (0.0)
Progestin & estrogen, sequential preparation	1 (1.3)	1 (1.3)	0 (0.0)

7.1.17.3 Extent of exposure (dose/duration)

The intent to treat population was composed of 77 placebo, 77 exenatide 5 mcg, and 78 exenatide 10 mcg subjects, who took ≥ 1 dose of study drug. These adult T2D subjects, who were inadequately controlled on diet and exercise, participated in a 2 week, single blind, placebo run-in period prior to being randomized into a treatment arm. During a 4 week initial treatment period, subjects were treated with exenatide 5 mcg subcutaneously (SC) BID or placebo SC BID. Subjects were then assigned to their previously randomized treatment arm (exenatide 5 or 10 mcg SC BID or placebo SC BID) for the remaining 20 week treatment period. No specific study data were collected for assessment of treatment compliance. In total, 203 of 232 ITT patients completed 24 weeks of study treatment with similar percentages in each treatment group completing the study (placebo 88.5%, 5 mcg exenatide 85.7%, 10 mcg exenatide 87.2%).

GWBJ. Number and percentage of patients who completed the study by treatment group

	Placebo (n=77)	**Exenatide 5 mcg (n=77)**	**Exenatide 10 mcg (n=78)**
Completed	69 (88.5%)	66 (85.7%)	68 (87.2%)
Withdrew	8 (10.4%)	11 (14.3%)	10 (12.8%)

7.1.17.4 Dosages not taken on schedule

No specific study data were collected for assessment of treatment compliance. However, 8/77 10.3%) exenatide 5 mcg and 6/78 (7.7%) exenatide 10 mcg subjects took at least one incorrect exenatide dose (e.g., interchanged 5 for 10 mcg or vice versa) during the study. No placebo subjects were misdosed.

7.1.18 Description of Secondary Clinical Data Sources Used to Evaluate Safety

PSURs 5, 6, 7, and 8 and a portion of PSUR 4 were discussed in section 7.1.17.

7.1.19 Adequacy of Overall Clinical Experience

The exenatide monotherapy clinical development program is adequate with respect to the number of patients studied and the duration of exposure and follows the guidelines previously agreed to by the Division. Study GWBJ was conducted in type 2 diabetic patients, who are the target population for the proposed indication.

7.1.20 Adequacy of Special Animal and/or In Vitro Testing

According to Dr. Hummer (pharmacology-toxicology reviewer), the exenatide monotherapy indication is supported by previous animal and *in vitro* testing. There does not appear to be a renal toxicity signal in exenatide animal studies. In the 6 month subcutaneous rat study, a small statistically significant increase (up to 36%) in mean serum BUN was noted for female rats, with no correlative histopathology findings. In the 28 day intranasal rat study, a small statistically significant increase in mean serum BUN (25%) was seen in high dose males only, with no correlative histopathology.

In the 91 day monkey study, a statistically significant increase in BUN was observed in the low and mid dose animals, but not the high dose. There were no microscopic findings in the kidney. In the 9 month monkey study, tubular dilatation was observed in 1/6, 1/6, 3/6, and 2/6 males at 0, low, mid, and high doses. No changes in mean clinical chemistry parameters were observed.

7.1.21 Adequacy of Routine Clinical Testing

The sponsor adequately evaluated hematology and chemistry parameters in study GWBJ, given the understanding of exenatide at the time. Amylase and lipase levels were not routinely measured in the study. However, the pancreatitis and PSUR submissions since have enabled detailed reviews on the subject.

No post-treatment electrocardiograms were collected in study GWBJ. As the original review of exenatide did not note any effect of exenatide on ECG parameters, this is acceptable.

7.1.22 Adequacy of Metabolic, Clearance, and Interaction Workup

The sponsor has performed adequate testing in this arena, as discussed in previous exenatide submissions. However, if the sponsor wishes to pursue removal of the current recommendation that oral contraceptives (OCs) be administered at least one hour prior to exenatide injection, 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 progestin studied.

7.1.23 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor has performed adequate assessments of the adverse events known to be associated with exenatide therapy in study GWBJ at the time of study planning. Amylase and lipase were not measured in study GWBJ.

7.1.24 Assessment of Quality and Completeness of Data

The data from pivotal study GWBJ were complete and of good quality.

7.1.25 Additional Submissions, Including Safety Update

PSURs 5, 6, 7, and 8 and a portion of PSUR 4 were discussed in section 7.1.17. 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.

On August 12 and 15, 2008, the sponsor submitted additional renal and pancreatitis safety data as requested. These submissions included the following additional information:

- August 12, 2008:
  - Response to FDA request for (renal) information
  - Clinical analysis of renal AEs
- August 15, 2008
  - Executive summary of pancreatitis
  - Medwatch reports with fatal outcome and necrotizing and hemorrhagic pancreatitis cases

The pancreatitis information was reviewed in section 7.1.17 Postmarketing Experience. The renal safety submission is reviewed below.

Renal safety submission (August 12, 2008): As requested, the sponsor submitted an analysis of renal AEs and out of range renal laboratory values for the six phase 3 placebo-controlled clinical trials that supported the original exenatide NDA 21-773. Studies 2993-112, 2993-113, and 2993-115 were the pivotal studies submitted with the original exenatide NDA (21-773, serial 000). The study reports for H80-MC-GWAP, -GWBQ, and –GWBJ were submitted to NDA 21-773

(February 27, 2006), IND 57,725 (February 25, 2007), and NDA 21-919 (March 19, 2008), respectively. No phase 4 placebo-controlled studies have been conducted with exenatide.

Table 1: Summary of Placebo-Controlled Studies of BYETTA (exenatide injection)

Study	Concomitant Antidiabetic Medication(s)	Duration [1]	Number of ITT Subjects	
			Placebo	BYETTA [2]
2993-112	Metformin	30 Weeks	113	223
2993-113	Sulfonylurea	30 Weeks	123	254
2993-115	Metformin + Sulfonylurea	30 Weeks	247	486
H8O-MC-GWAP	TZD or TZD + Metformin	16 Weeks	112	121
H8O-MC-GWBA	Metformin or Metformin + Sulfonylurea	16 Weeks	233	234
H8O-MC-GWBJ	None (Diet and Exercise Only)	24 Weeks	77	155
Total	—	—	**905**	**1473**

ITT = intent-to-treat; TZD = thiazolidinedione.
Note: All studies included in the analysis were designated as Phase 3.
[1] Duration of treatment with randomized study medication following placebo lead-in period (4-week lead-in for 30-week trials, 2-week lead-in for 16- and 24-week trials).
[2] Includes treatment with BYETTA 5 mcg BID for duration of study, or 4 weeks of BYETTA 5 mcg BID followed by BYETTA 10 mcg BID for remainder of study.

NOTE: Reproduced from the sponsor's 8/12/08 submission

The demographic and baseline characteristics were similar between treatment groups, when these six studies were pooled. The percentage of subjects (2-16%) with abnormal BUN, creatinine, and/or urine protein at baseline was similar between treatment groups in each individual study.

Table 2: Key Demographic Characteristics by Treatment (Placebo-Controlled Studies of BYETTA [exenatide injection] Intent-to-Treat Population [N = 2378])

Baseline Characteristic	Placebo (N = 905)	BYETTA (N = 1473)
Gender (n [%])		
Female	421 (46.5)	646 (43.9)
Male	484 (53.5)	827 (56.1)
Mean (SD) Age (years)	54.7 (9.8)	54.6 (10.1)
Mean (SD) Duration of Diabetes (years)	7.3 (5.8)	7.0 (5.9)

Note: Age and duration of diabetes were calculated from screening date.
- Percentages are based on the number of subjects in each treatment group.
Cross-Reference: Supporting Data Summary 1.

NOTE: Reproduced from the sponsor's 8/12/08 submission

8/12/08 Renal data. Mean demographic and baseline characteristics (SD) of the ITT population in placebo-controlled exenatide studies		
	Placebo (n=905)	Exenatide (n=1473)
Baseline BUN (mg/dl)*	16.0 (4.8)	16.3 (5.2)
Baseline creatinine (mg/dl)	0.8 (0.2)	0.9 (0.2)
Baseline Cockroft-Gault creatinine clearance (ml/m)	123.8 (43.64)	126.4 (46.1)
***NOTE: BUN and urine protein were only measured in studies 2993-112, -113, and**		

-115 (placebo n=483, exenatide n=963).

8/12/08 Renal data. Baseline abnormal laboratory findings (n[%])		
	Placebo (n=905)	Exenatide (n=1473)
BUN*	29 (6.0)	65 (6.7)
Creatinine	20 (2.2)	24 (1.6)
Urine protein (1+ or higher)*	77 (15.9)	154 (16.0)
***NOTE: BUN and urine protein were only measured in studies 2993-112, -113, and -115 (placebo n=483, exenatide n=963)**		

Normal and high BUN and creatinine ranges were determined by the testing laboratory. The laboratory values of potential clinical importance (PCI) were defined by the sponsor (BUN > 45 mg/dL; creatinine > 1.6 mg/dL for males or > 1.4 mg/dl for females) and are appropriate.

The mean change in BUN from baseline to endpoint increased in the placebo group but decreased 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).

Table 4: Change in Blood Urea Nitrogen and Creatinine Concentrations by Treatment from Baseline to Study Termination (Placebo-Controlled Studies of BYETTA [exenatide injection]; Intent-to-Treat Population [N = 2378])

Analyte / Statistic	Placebo	BYETTA 5 mcg	BYETTA 10 mcg	BYETTA All
BUN	**N = 483**	**N = 480**	**N = 483**	**N = 963**
Mean (SD) Baseline (mg/dL)	16.0 (4.8)	16.2 (5.2)	16.5 (5.2)	16.3 (5.2)
Mean (SD) Change from Baseline to Study Termination (mg/dL)	0.3 (4.1)	-0.1 (4.1)	-0.3 (3.7)	-0.2 (3.9)
Creatinine	**N = 905**	**N = 557**	**N = 916**	**N = 1473**
Mean (SD) Baseline (mg/dL)	0.84 (0.21)	0.87 (0.21)	0.84 (0.20)	0.85 (0.21)
Mean (SD) Change from Baseline to Study Termination (mg/dL)	0.00 (0.11)	0.01 (0.13)	0.01 (0.13)	0.01 (0.13)

BUN = blood urea nitrogen; SD = standard deviation.
Note: BUN was only tested in Studies 2993-112, 2993-113, and 2993-115.
NOTE: Reproduced from the sponsor's 8/12/08 submission

Individual and pooled phase 3 studies were analyzed for any post-treatment BUN or creatinine level above the upper limit of the normal range. The incidence of these abnormalities was similar between treatment groups, except for study 2993-113. Study 2993-113 was a 30-week, double-blind, efficacy, and safety study in 377 type 2 diabetics using sulfonylureas. In this study, proportionally more exenatide 10 mcg subjects had an elevated creatinine level (13.18% vs. 6.5% and 4.8%) post-treatment. However, this trend was not seen in the other five phase 3 studies which enrolled a total of 2,001 ITT subjects, nor was a similar trend seen when study 2993-113 was analyzed for creatinine levels of PCI (placebo 2.4%, exenatide 5 mcg 3.2%, exenatide 10 mcg 3.9%).

8/12/08 Renal data. Number (n/N) and percent (%) of ITT subjects with any post-treatment BUN above the upper limit of the normal range			
	Placebo (N=483)	Ex 5 mcg (N=480)	Ex 10 mcg (N=483)
All studies	83/483 (17.2)	76/480 (15.8)	79/483 (16.4
2993-112	10/113 (8.9)	13/110 (11.8)	14/113 (12.4)
2993-113	24/123 (19.5)	16/125 (12.8)	21/129 (16.3)
2993-115	49/247 (19.8)	47/245 (19.2)	44/241 (18.3)

8/12/08 Renal data. Number (n/N) and percent (%) of ITT subjects with any post-treatment creatinine above the high limit of the normal range			
	Placebo (N=905)	Ex 5 mcg (N=557)	Ex 10 mcg (N=916)
All studies	41/905 (4.5)	39/557 (7.0)	46/916 (5.0
2993-112	4/113 (3.5)	10/110 (9.1)	4/113 (3.5)
2993-113	8/123 (6.5)	6/125 (4.8)	17/129 (13.2)
2993-115	22/247 (8.9)	20/245 (8.2)	21/241 (8.7)
H8O-MC-GWAP	5/112 (4.5)		1/121 (0.8)
H8O-MC-GWBA	0/233 (0.0)		1/234 (0.4)
H8O-MC-GWBJ	2/77 (2.6)	3/77 (3.9)	2/78 (2.6)

The incidence of BUN and creatinine measurements of PCI was small and similar between treatment groups when studies were analyzed individually and pooled.

8/12/08 Renal data. Number (n/N) and percent (%) of ITT subjects with any post-treatment BUN or creatinine outside the limit for potential clinical importance			
	Placebo (N=905)	Ex 5 mcg (N=557)	Ex 10 mcg (N=916)
All 3 studies which measured BUN	1/483 (0.2)	3/480 (0.6)	2/483 (0.4)
All 6 studies which measured creatinine	11/905 (1.2)	7/557 (1.3)	12/916 (1.3)

Shifts from baseline BUN and creatinine laboratory grade were evaluated. Although the percentage of patients with a shift from a normal baseline to high or PCI post-baseline BUN or creatinine value was similar, slightly more exenatide patients experienced elevated creatinine, albeit in a non-dose-dependent manner (placebo 2.5%, exenatide 5 mcg 5.2%, exenatide 10 mcg 4.7%).

8/12/08 Renal data. Percent of subjects with shift from normal baseline to high or PCI post-baseline BUN grade						
	Placebo (N=483)		Ex 5 mcg (N=480)		Ex 10 mcg (N=483)	
	High	PCI	High	PCI	High	PCI
All studies	12.2	0.2	11.9	0.0	9.1	0.0
2993-112	1.9	0.0	1.7	0.0	1.5	0.0
2993-113	3.5	0.0	2.3	0.0	2.1	0.0
2993-115	6.8	0.2	7.9	0.0	5.6	0.0

8/12/08 Renal data. Percent of subjects with shift from normal baseline to high or PCI post-baseline creatinine grade						
	Placebo (N=905)		Ex 5 mcg (N=557)		Ex 10 mcg (N=916)	
	High	PCI	High	PCI	High	PCI
All studies	2.2	0.3	4.7	0.5	2.8	1.8
2993-112	0.1	0.0	0.9	0.4	0.2	0.1
2993-113	0.4	0.0	0.0	0.2	1.0	0.3
2993-115	1.2	0.3	3.2	0.0	1.5	0.2
H8O-MC-GWAP	0.4	0.0	0.0	0.0	0.1	0.0
H8O-MC-GWBA	0.0	0.0	0.0	0.0	0.0	0.1
H8O-MC-GWBJ	0.0	0.0	0.5	0.0	0.0	0.1

Significant elevations in BUN and creatinine were defined by the sponsor as any post-treatment increase from baseline ≥ 10 mg/d L for BUN or ≥ 0.8 mg/dL for creatinine. The number of subjects with significant elevations was similar between treatment groups.

8/12/08 Renal data. Percentage subjects with significant elevations* in BUN and creatinine				
	Placebo	Ex 5 mcg	Ex 10 mg	Ex 5 + 10 mcg
BUN	5.0	5.4	3.7	4.6
Creatinine	0.0	0.2	0.0	0.1
* Defined as any post-treatment increase from baseline ≥ 10 mg/dl for BUN or ≥ 0.8 mg/dl for creatinine				

Renal adverse events (AEs) in the phase 3 placebo-controlled studies of exenatide were analyzed by the sponsor using the search terms listed below. The incidence of renal AEs was similar between treatment groups (placebo 1.0%, exenatide 0.7%). Only one case of increased creatinine in an exenatide 10 mcg subject was assessed by the sponsor as related to study drug. No cases requiring hemodialysis were reported. The range of duration of treatment prior to AE onset was 1-211 days (mean 71.8 days).

Table 7: Summary of Treatment-Emergent Renal Adverse Events by Preferred Term and Treatment (Placebo-Controlled Studies of BYETTA [exenatide injection]; Intent-to-Treat Population [N = 2378])

	Placebo (N = 905)		BYETTA (N = 1473)	
	Subject	Events	Subject	Events
Preferred Term [1]	**n (%)**	**n**	**n (%)**	**n**
All Renal Adverse Events	**9 (1.0)**	**10**	**10 (0.7)**	**11**
Blood creatinine increased	2 (0.2)	2	2 (0.1)	2
Blood urea increased	2 (0.2)	2	0 (0.0)	0
Diabetic nephropathy	0 (0.0)	0	1 (0.1)	1
Protein urine present	0 (0.0)	0	3 (0.2)	3
Proteinuria	4 (0.4)	4	3 (0.2)	3
Renal failure	1 (0.1)	1	0 (0.0)	0
Renal failure acute	1 (0.1)	1	0 (0.0)	0
Renal function test abnormal	0 (0.0)	0	1 (0.1)	2

Note: Percentages are based on the number of subjects in each treatment group. Subjects experiencing multiple events are only counted once.

[1] MedDRA v11.0 preferred terms included in the analysis were: Acute prerenal failure, Albuminuria, Anuria, Azotaemia, Blood creatinine abnormal, **Blood creatinine increased**, Blood urea abnormal, **Blood urea increased**, Blood urea nitrogen/creatinine ratio increased, Creatinine renal clearance decreased, Diabetic end stage renal disease, **Diabetic nephropathy**, Dialysis, Glomerular filtration rate abnormal, Glomerular filtration rate decreased, Haemodialysis, Haemolytic uraemic syndrome, Hepatorenal failure, Hepatorenal syndrome, Hypercreatininaemia, Nephritis, Nephritis interstitial, Nephropathy toxic, Oedema due to renal disease, Oliguria, Peritoneal dialysis, Postrenal failure, **Protein urine present**, **Proteinuria**, **Renal failure**, **Renal failure acute**, Renal failure chronic, **Renal function test abnormal**, Renal impairment, Renal tubular disorder, Renal tubular necrosis, Tubulointerstitial nephritis, Urea renal clearance decreased, Urine output decreased. Terms identified in the search are indicated in **bold**.

NOTE: Reproduced from the sponsor's 8/12/08 submission

Exenatide and placebo subjects experienced 15.4 and 24.6 events per 1000 subject-years. Although the rate of renal AEs was higher in the exenatide 10 mcg than 5 mcg group, both were lower than the placebo group (18.9 and 10.7 vs. 24.6 events/1000 subject-years). However, the wide 95% confidence intervals which overlap between the three groups limit the conclusions that can be drawn.

8/12/08 Renal data. Exposure-adjusted incidence rate for renal impairment analysis in phase 3 placebo-controlled exenatide studies				
	Placebo (N=905)	Ex 5 mcg (N=557)	Ex 10 mcg (N=916)	Ex 5 + 10 mcg (1473)
n/N (%)	9/905 (0.99)	3/557 (0.54)	7/916 (0.76)	10/1473 (0.68)
Total exposure years*	365.6	280.3	370.4	650.8
Rate	24.6	10.7	18.9	15.4
95% CI	(11.3, 47.7)	(2.2, 31.3)	(7.6, 38.9)	(7.4, 28.3)
*See Table 1 in this section for the duration of the individual studies.				

7.1.26 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety analyses are predominantly based on the data from study GWBJ. The main findings from the pivotal study are summarized below:

Deaths: There were no deaths in study GWBJ.

Serious adverse events: Four serious adverse events (AEs) were reported in exenatide treated patients in study GWBJ (corneal abscess and iridocyclitis, vaginal bleeding, pregnancy stopped in evolution, and umbilical hernia). The likelihood that the SAEs are attributable to exenatide is low.

Postmarketing reports indicate that, in addition to the pancreatitis-related deaths, there have been 10 cases of necrotizing or hemorrhagic pancreatitis and over 150 cases of renal failure (please refer to sections 7.1.17 and 7.1.25).

Discontinuations due to adverse events: Two exenatide subjects withdrew due to AEs (nausea and headache).

Gastrointestinal adverse events: As expected with an incretin mimetic, gastrointestinal disorders, including nausea, gastroesophageal reflux disease (GERD), vomiting, and dyspepsia, occurred commonly. In study GWBJ, no patient developed pancreatitis, although one 53 year old exenatide 5 mcg subject experienced epigastric pain which both pre and postdated exenatide dosing (weeks 0 and 12). Three of 155 (1.9%) exenatide patients experienced decreased appetite or anorexia.

Hypoglycemia: Hypoglycemia was reported in 3.8% of exenatide 10 mcg, 5.2% of exenatide 5 mcg, and 1.3% of placebo patients. No glucagon injection, intravenous (IV) glucose, or emergency room visits were required.

Adverse events potentially related to anti-exenatide antibody status: Of the 71 exenatide 5 mcg and 73 exenatide 10 mcg patients assessed for antibody status in study GWBJ, 29.6% of exenatide 5 mcg and 30.1% of exenatide 10 mcg patients were treatment-emergent antibody positive at the last study visit. Adverse events potentially associated with antibody status occurred only in the exenatide 10 mcg group. Within that group, 1 antibody positive patient reported an injection site reaction. Because both antibody positive and negative subjects reported AEs potentially indicative of an immune system reaction, no clear effect of exenatide antibody status was seen.

Laboratory analyses: There were no important changes from baseline in mean creatinine, ALT, cholesterol, HDL, triglycerides, WBC, and hemoglobin. Mean creatinine clearance decreased 4.2-4.8 ml/min in all treatment groups, including placebo. Although the distribution of low, normal, and high creatinine clearance values remained relatively constant in the placebo and exenatide 10 mcg groups, an increase in the percentage of exenatide 5 mcg patients with low

creatinine clearance was seen at endpoint compared with baseline (14% vs. 6%). The mean change in serum creatinine compared to baseline was 0.01, 0.02, and 0.02 mg/dL in the placebo, exenatide 5 mcg, and exenatide 10 mcg treatment groups respectively, suggesting a lack of a drug-dose related effect on creatinine.

The Sponsor has submitted a changes being effected (CBE) supplement requesting the inclusion of language in the label reflecting postmarketing reports of worsened renal function with exenatide. At the agency's request, on August 12, 2008, the sponsor submitted an analysis of renal AEs and out of range renal laboratory values for the six phase 3 placebo-controlled clinical trials that supported the original exenatide NDA 21-773. This submission is reviewed in section 7.1.25. An Office of Surveillance and Epidemiology (OSE) consult on this submission was completed February 23, 2009. OSE's recommendations included the following:

- Alignment of the U.S. product label with the U.K. product label
- Addition of language in the Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections
- Dissemination of the renal dysfunction information to clinicians and the public via a Dear Health Care Professional letter, a Public Health Advisory, and/or MedWatch Safety Alert

A similar percentage of patients in each treatment group had elevated ALT at baseline (placebo, 18%; exenatide 5 mcg, 17%; exenatide 10 mcg, 27%). However, a greater number of patients in the placebo and exenatide 5 mcg treatment groups normalized their ALT by endpoint than those on exenatide 10 mcg treatment. The percentage of patients with abnormal ALT at endpoint in the treatment groups was as follows: placebo, 3%; exenatide 5 mcg, 8%; exenatide 10 mcg, 17%). No dose-related pattern of hepatic adverse events was seen in study GWBJ nor was there a liver abnormality signal in the exenatide studies associated with the original NDA 21-773.

Both exenatide treatment groups had reductions in LDL cholesterol, which were small and likely not clinically relevant. (Please refer to section 7.1.7.3.1 for the mean changes in the lipid panel from baseline.)

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The exenatide 5 and 10 mcg SQ BID regimens are currently approved to improve glycemic control in patients with T2D who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and thiazolidinedione but have not achieved adequate glycemic control. The sponsor submitted this new drug application to support approval of the 5 and 10 mcg subcutaneous twice daily doses as monotherapy in T2D patients.

In study GWBJ, exenatide was administered subcutaneously twice daily within 15 minutes before morning and evening meals. This is in general agreement with the twice daily dosing at any time within the 60-minute period before the morning and evening meals (or before the two

main meals of the day, approximately 6 hours or more apart) that is recommended in the current exenatide label.

Study GWBJ also excluded patients with a history of renal transplantation, currently receiving renal dialysis, or with an estimated creatinine clearance of < 50 mL/min as estimated by the Cockcroft-Gault equation. The current label, however, suggests that only end-stage renal disease patients receiving dialysis experience a clinically significant reduction in mean exenatide clearance. As discussed in section 7.1.17, the renal safety language will be revised in the new label.

8.2 Drug-Drug Interactions

The sponsor relies on data included in prior exenatide submissions regarding drug-drug interactions, and has not included drug-drug interaction data in this efficacy supplement. Note, exenatide's effect on the T_{max} of other drugs is likely related to the known GLP-1 effect on slowing gastric emptying. Drugs known to interact with exenatide include the following:

- Digoxin: Coadministration of repeated doses of exenatide 10 mcg BID decreased the C_{max} of oral digoxin (0.25 mg QD) by 17% and delayed the T_{max} by approximately 2.5 hours, although the overall steady-state PK exposure (AUC) was not changed.
- Lovastatin: Lovastatin AUC and C_{max} were decreased approximately 40% and 28% respectively and T_{max} was delayed about 4 hours when exenatide 10 mcg BID was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 30 week controlled clinical trials of exenatide, the use of exenatide in patients already receiving HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles compared to baseline.
- Lisinopril: In patients with mild to moderate hypertension stabilized on lisinopril 5 to 20 mg/day, exenatide 10 mcg BID did not alter steady-state C_{max} or AUC of lisinopril. Lisinopril steady-state T_{max} was delayed by 2 hours. There were no changes in 24 hour mean blood pressure.
- Acetaminophen: When 1000 mg acetaminophen elixir was given to exenatide 10 mcg BID (0 hour) and 1, 2, 4 hours after exenatide injection, acetaminophen AUCs were decreased by 21%, 23%, 24%, and 14% respectively. C_{max} was decreased by 37%, 56%, 54%, and 41% respectively. T_{max} was increased from 0.6 hours in the control period to 0.9, 4.2, 3.3, and 1.6 hours respectively. Acetaminophen AUC, C_{max}, and T_{max} were not significantly changed when acetaminophen was given 1 hour before exenatide injection.
- Warfarin: Coadministration of repeat doses of exenatide (5 mcg BID on days 1-2 and 10 mcg BID on days 3-9) in healthy volunteers, delayed warfarin (25 mg) T_{max} by about 2 hours. No clinical relevant effects on C_{max} or AUC of S- and R-enantiomers of warfarin were observed. Exenatide did not change the pharmacodynamic properties of warfarin. However, there are postmarketing reports of increased INR sometimes associated with bleeding with the concomitant use of warfarin and exenatide.

On March 28, 2007 (NDA 21-773 supplement 009), the sponsor submitted exenatide labeling language regarding the use of oral contraceptives based on study H8O-EW-GWBC "The effect of exenatide on single and multiple doses oral contraceptive pharmacokinetics in healthy female

subjects." In this single site, open label, three period, three sequence, randomized crossover study of 38 healthy females, oral contraceptives (150 mcg levonorgestril [LNG] and 30 mcg ethinyl estradiol [EE]) was administered one hour prior and 30 minutes after exenatide. The study was reviewed by clinical pharmacology and the Division of Urologic and Reproductive Products (DRUP).

In study GWBC, there were no significant changes in PK parameters when the OC was administered an hour prior to exenatide injection. However, the Cmax 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.

The division 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 OCs be administered at least one hour prior to exenatide injection. If the sponsor 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 progestin studied.

8.3 Special Populations

Exenatide is intended for use in T2D patients, such as those who enrolled in study GWBJ. As mentioned above, exenatide should not be used in patients with end-stage renal disease receiving dialysis nor in subjects with severe renal impairment; it should be used cautiously in subjects with moderate renal impairment or a history of renal transplantation. Study GWBJ excluded patients with obvious signs of liver disease. No pharmacokinetic study has been performed in patients with acute or chronic hepatic insufficiency, although hepatic dysfunction is not expected to affect blood concentrations because exenatide is primarily renally cleared.

The mean age of patients included in study GWBJ was approximately 54 years, and excluded patients under 18 years of age. Previous population PK analysis of patients (22 – 73 years) suggests that age does not influence the PK properties of exenatide among adult patients.

The revised label will also include language in the Important Limitations of Use section that the concurrent use of Byetta with insulin has not been studied and cannot be recommended. The limitations of use with respect to insulin is now standard labeling for all anti-diabetics for which there are little or no data for its combined use with insulin.

8.4 Pediatrics

The proposed indication sought in this efficacy supplement is restricted to adult T2D patients. The efficacy and safety of exenatide have not been established in the pediatric population. Due to the scant number of patients under the age of 12 years with T2D who would be available to participate in a clinical trial, a waiver of the pediatric research requirement was obtained for exenatide in children 0-11 years. Study 2993-124, "A randomized, single blind, dose rising, placebo controlled crossover study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of exenatide in adolescent subjects with type 2 diabetes mellitus (T2D)," was conducted in adolescents 12-16 years old and submitted to NDA 21-773 on September 9, 2007.

In study 2993-124, 13 subjects received a single 2.5 or 5.0 mcg SC dose of exenatide or placebo followed by a standardized meal. Because there were a number of subjects in the 2.5 mcg group with exenatide concentrations below the limit of quantification (BLQ), the data from this dose was insufficient to provide reliable PK data. Adequate PK data were obtained from half of the exenatide 5 mcg subjects. These preliminary dose-exposure data are shown below.

Study 2993-124. Pharmacokinetic data for exenatide 5 mcg in subjects aged 10-16 years

Parameter	**C_{max} (pg/ml)**	**T_{max} (h)**	**$T_{1/2}$ (h)**	**AUC_{0-inf} (pg.h/ml)**	**AUC_{0-t} (pg.h/ml)**	**CL/F (l/h)**	**V/F (L)**
N	12	12	6	6	12	6	6
Mean	94.8	2.3	1.7	449.7	316.7	13.8	34.2
SD	50.9	0.9	0.4	246.3	176.4	6.3	21.1

There was a statistically significant, dose related decrease in postprandial plasma glucose, compared to placebo as measured by $AUC_{15\text{-}180min}$, although, again, the number of 2.5 mcg subjects with exenatide concentrations BLQ made it difficult to establish the exposure-response relationship for exenatide from this pediatric study.

A total of 9 treatment-emergent AEs were reported and are listed below. No episodes or symptoms of hypoglycemia occurred. One subject (44002) experienced 6 of the 9 treatment-emergent AEs. This subject experienced a serious hyperglycemia and was withdrawn from the study.

Study 2993-124. Treatment-emergent AEs (ITT population, n=13)

Subject	**Treatment**	**Adverse event**	**Event < 24 h after administration?**
43905	Ex 5 mcg	Pharyngeal erythema	Yes
44001	N/A	Headache	No
	N/A	Headache	No
44002	N/A*	Hyperglycemia	No*
	Ex 2.5 mcg	Dehydration	Yes
		Ketonuria	Yes
		Nausea	Yes

		Vomiting	Yes
		Abdominal pain upper	Yes
* Although hyperglycemia was > 24 hours after exenatide administration, start stop date for this AE (Sept 21-22, 2006) was the same as the other AEs recorded for subject 44002			

As discussed at the Pediatric Review Committee (PeRC), this PK information will not be added to the label because it does not show a public health risk and describing the data would be considered a de facto indication.

8.5 Advisory Committee Meeting

Not applicable – this efficacy supplement did not go to Advisory Committee.

8.6 Postmarketing Risk Management Plan

On January 22, 2009, DMEP, OSE, and the sponsor engaged in labeling discussion for NDAs 21-773 and 21-919. The proper section of labeling intended to convey the risk of severe forms of pancreatitis associated with exenatide was discussed. On February 13, 2009, the sponsor proposed to notify healthcare providers (HCP), pharmacists, and patients of the following:

- Necrotizing and hemorrhagic pancreatitis, including fatalities, have been reported in patients treated with exenatide
- How to distinguish the common gastrointestinal symptoms of exenatide from the hallmark symptom of pancreatitis (i.e. severe and persistent abdominal pain)
- Patients with symptoms of pancreatitis should seek advice from their doctor and discontinue exenatide
- HCPs should evaluate patients in a timely manner when these symptoms develop (e.g. measure amylase/lipase to ascertain whether they are 3x upper limit of normal and, if appropriate, perform imaging)
- Exenatide should not be restarted if pancreatitis occurs

The sponsor proposed reaching those educational goals in the amended Risk Evaluation and Mitigation Strategy (REMS) with the following communication tools: (Items marked by an asterisk [*] indicate tools outside of the sponsor's standard practice.)

- HCP and pharmacists
    - Package insert
    - Medication guide
    - Dear HCP or Dear Pharmacist Letter to be mailed to approximately 136,000 medical and allied medical professionals and hand-delivered to approximately 60,000 HCP*
    - A HCP's Guide to Prescribing exenatide*
    - Pancreatitis disease state backgrounder*
    - Educational web conference with exenatide Speaker Bureau on pancreatitis (HCPs only)
    - Letter to Clinical Investigators (HCPs only)

  - Update to HCP and pharmacist-related promotional materials
  - Product call center Q&A and medical information letter(s)
- Patients
  - Medication guide
  - Pharmacist letter mailed to patients to include pancreatitis education*
  - Update patient-related promotional materials including Patient Starter Kit
  - Product call center Q&A
  - Patient Initiation Guide (handed to new patients by their HCP)*

The sponsor also proposed the following studies:

- Studies to evaluate risk factors for susceptibility
  - Continued evaluation of spontaneous reports, including clinical study cases
  - Epidemiologic claims studies such as the UHC 3 study (interim report submitted January 5, 2009) and ongoing IMS (Pharmetrics) claims database study
  - Possible exploration of other pancreatitis databases
- Studies to help identify the physiological mechanism which results in pancreatitis, including the severe form
  - Analysis of amylase and lipase data in ongoing studies of exenatide once weekly
  - In vivo preclinical studies using models of pancreatitis in normal and diabetic animals
  - Gallbladder emptying study in humans: The effect of CCK (cerulitide)-stimulated gallbladder emptying study (as an indirect measure of the effect on the sphincter of Oddi) is currently being studied in Europe to assess any non-physiologic affects of exenatide on biliary emptying.

It is my opinion that, while I would not discourage the sponsor from making additional pancreatitis-related communications, because 2 FDA alerts have been released on the subject, it may be more beneficial if the sponsor released its communications after completion of one or more PMRs when more information on the subject is known. According to the sponsor's August 6, 2009 submission, results from the UHC-3 Retrospective Cohort Study of Acute Pancreatitis in Relation to Use of Byetta and Other Antidiabetic Agents and animal studies of the effect of exenatide on pancreatitis should be available later this year.

Please also refer to section 9.3 Recommendation on Postmarketing Actions.

9 OVERALL ASSESSMENT

9.1 Conclusions

Please see Section 6.1.6 (efficacy conclusions), Section 7.3 (safety conclusions), and Section 9.2 (recommendation on regulatory action) for details.

In summary, the sponsor has achieved the pre-defined efficacy endpoint, which was to demonstrate that glycemic control, as measured by the change in HbA1c from baseline to endpoint, with exenatide BID is superior to placebo BID after 24 weeks of treatment in patients with T2D who are experiencing inadequate control through diet and exercise. The concern that the previously completed monotherapy study was insufficient to fully characterize the effect of an optimal dose of exenatide has been adequately addressed by the data obtained from study GWBJ which enrolled 232 subjects for a 24 week treatment period. I therefore recommend approval of this efficacy supplement, inclusion of the key endpoint results to the Clinical Studies section, as well as revision of the safety language to reflect our current understanding of the risks associated with exenatide use.

However, because of post-marketing reports of fatal and non-fatal necrotizing and hemorrhagic pancreatitis associated with the use of exenatide and in order to ensure that the benefits of exenatide outweigh this serious risk, I recommend a Risk Evaluation and Mitigation Strategy (REMS), which will consist of a Medication Guide and a timetable for assessments, as well as the Post-Marketing Requirements (PMRs) described below. The details of these elements are being discussed between DMEP, OSE and the sponsor.

I recommend a Dear Health Care Professional (DHCP) letter pertaining to the use of exenatide in patients with renal impairment and end-stage renal disease be included in the REMS, because there have been postmarketing reports of renal failure, sometimes requiring hemodialysis and kidney transplantation. Doctors should be educated to hold exenatide treatment in patients for whom it is not recommended or results in worsening renal function. An FDA safety alert or early communication may create unnecessary panic among the general public.

9.2 Recommendation on Regulatory Action

Based on my conclusions above, I am recommending approval of this efficacy supplement.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Because of post-marketing reports of fatal and non-fatal necrotizing and hemorrhagic pancreatitis associated with the use of exenatide and in order to ensure that the benefits of exenatide outweigh this serious risk, I am recommending a Risk Evaluation and Mitigation Strategy (REMS), which will consist of a Medication Guide and a timetable for assessments. The sponsor should also continue to submit 15-day reports for cases of suspected pancreatitis, so that we may continue to assess this evolving issue.

In addition, I recommend required postmarketing studies (PMRs) include epidemiological and mechanistic (both preclinical and clinical) studies as well as analyses of all amylase/lipase data and patients who presented with pain or nausea with or without vomiting for the following reasons:

- The background rate of acute pancreatitis in the diabetic population is not well understood
- The contribution of exenatide to the incidence of acute pancreatitis in the diabetic population has not been established
- The mechanism by which exenatide may exert this effect is not well understood

I recommend a Dear Health Care Professional (DHCP) letter pertaining to the use of exenatide in patients with renal impairment and end-stage renal disease be included in the REMS, because there have been postmarketing reports of renal failure, sometimes requiring hemodialysis and kidney transplantation. Doctors should be educated to hold exenatide treatment in patients for whom it is not recommended or results in worsening renal function. An FDA safety alert or early communication may create unnecessary panic among the general public.

9.3.2 Required Phase 4 Commitments

The PMRs are as follows:

- Epidemiological study to determine the incidence rate, severity and risk factors for the development of acute as well as hemorrhagic and/or necrotizing pancreatitis in exenatide-exposed versus unexposed patients: The goal is to ascertain the background rate and risk factors for the development of acute, hemorrhagic, and necrotizing pancreatitis, in the diabetic population treated with other anti-diabetic agents versus the rate in diabetic patients treated with exenatide in combination with other anti-diabetic agents.
- Mechanistic studies:
    - In vivo preclinical studies to assess possible mechanisms for exenatide-associated pancreatitis, including histopathological assessment of the pancreas
    - A clinical trial investigating the effects of exenatide on cholecystokinin (CCK) cerulitide-stimulated gallbladder emptying (as an indirect measure of a potential impact on the sphincter of Oddi) to assess any non-physiologic effects of exenatide on biliary emptying
- Submission of all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials, including analyses of those data and a systemic analysis of those who presented with pain or nausea with or without vomiting during the treatment phase of those trial.

Please also refer to section 9.3.1 Risk Management Activity above.

We agree with the sponsor's proposal to defer required pediatric studies of exenatide monotherapy in adolescents aged 10-16 years and we agree to waive this requirement for children aged 0-9 years. This is consistent with our approach to the exenatide combination therapy written request.

9.3.3 Other Phase 4 Requests

If the sponsor wishes to pursue removal of the current recommendation that oral contraceptives (OCs) be administered at least one hour prior to exenatide injection, 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 progestin studied.

The sponsor should consider pediatric population PK/PD analysis of exenatide.

9.4 Labeling Review

Please see the label for my proposed changes and the rationale underlying those changes.

9.5 Comments to Applicant

Please refer to the comments contained in sections 9.3.1 – 9.3.3 as well as the changes to the proposed label.

10 APPENDIX

Not applicable.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21773	SAFETYRPT 13	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA 21773	SAFETYRPT 15	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA 21773	SAFETYRPT 16	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA 21773	SAFETYRPT 17	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA 21773	SUPPL 11	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION
NDA 21919	ORIG 1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION

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/s/

VALERIE S PRATT
08/20/2009

ILAN IRONY
08/20/2009

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

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Memorandum author:	Robert J. Meyer, MD, Director, ODE II
Date:	Wednesday, April 27, 2005
NDA:	21-773 (21-919)
Sponsor:	Amylin Pharmaceuticals
Proprietary Name:	BYETTA (exenatide injection)
Date of submission:	June 29th, 2004
Regulatory Due Date:	April 29th, 2005

Introduction: This is a first in its class, new molecular entity that is intended to improve glycemic control in type 2 diabetes. Exenatide's primary mechanism of action is dependant on pancreatic beta cell function, and therefore the drug would have little to no beneficial effect in type 1 diabetes. Exenatide is a 39-amino acid polypeptide that was originally discovered in the salivary secretions of the Gila Monster lizard (Heloderma suspectum). It acts pharmacologically much like a human incretin (which are secreted by the gut). Exenatide has substantial overlap in amino acid sequence with human glucagon-like polypeptide-1 (or GLP-1) at 53% homology and binds to the same receptor in an equipotent fashion. GLP-1 itself is very short-lived, but exenatide is not susceptible to the same enzymatic degradation as is GLP-1 and therefore has a more durable, pharmacologically useful duration of action. Exenatide increases glucose-dependant insulin synthesis and secretion and inhibits glucagon secretion. It also delays gastric emptying and has a mild anorectic effect. Interestingly, in animals, there are some data to suggest exenatide and other incretins may promote beta-cell preservation and increase beta-cell mass (including preclinical data done for this program), though this phenomenon has not been adequately established in humans.

Amylin Pharmaceuticals carried out reasonably extensive investigations of this drug as an add-on therapy to metphormin and/or sulfonylureas in patients who are not adequately controlled on those oral agents alone. While they also sought approval of BYETTA as monotherapy to improve glycemic control, it was clear that this part of the development program was rudimentary and did not adequately address issues related to efficacy and the method of use in those subjects. Therefore, the NDA has been administratively split, with the monotherapy indication now being assigned the number NDA 21-919.

This memorandum will summarize the information and recommendations for both applications and will serve as the official signatory document. However, please also see Dr. David Orloff's Division Director memorandum for other summary information.

Chemistry/ Microbiology/Device

Exenatide is a synthetic peptide that, as BYETTA, is presented as a preserved, sterile solution for subcutaneous injection by a pre-filled "pen" device that utilizes either 1.2 or 2.4 mL cartridges. The pens are designed to deliver either 5 or 10 mcg doses. There are two drug substance manufacturers, Mallinckrodt and Bachem, both with adequate DMFs. Neither the device consult nor the microbiologic consult raised any significant issues. The CMC team feels this product is approvable. One interesting issue that need not be resolved pre-approval is whether this product is more properly called exenatide or exenatide acetate, as it is not clear if the molecule exists as the free acid, or if it is associated with the acetate salt. The site inspections are acceptable and there is an overall acceptable recommendation for this application on the EERs.

Pharmacology/Toxicology

A full toxicologic program was conducted in support of the approval of this medication, which is intended for chronic use. The toxicologic profile of exenatide is rather unremarkable, with some evidence of body weight changes and parotid gland inflammation (as well as beta-cell hyperplastic changes). The tests for mutagenesis and clastogenesis were negative, though the carcinogenicity studies showed thyroid C-cell adenomas in female rats. These lesions occur at doses far in excess of the maximum expected human exposure, and since there was no mutagenic signal, the dose-threshold can be sc. The reproductive toxicology studies showed little effects of the drug, though there was some impairment of fetal growth and minor skeletal changes in exposed animals at doses 3 fold in excess of the human exposure. The Pharm-Tox team recommends approval with appropriate language in the labeling.

Biopharmaceutics

This drug is given subcutaneously twice daily (as three times daily did not appear to increase the efficacy as assessed by HgbA1c). The drug has been shown to be effective when administered in the pre-meal setting and that is how it will be recommended for use. Its half-life ranges from 1.5 to 3.5 hours. The drug is primarily cleared renally, with a clearance value of approximately 9 L/hr. The drug is reasonably unaffected by mild or moderate renal impairment, but its pharmacokinetics are significantly impacted in end-stage renal disease and therefore its use is not recommended in this population. The drug is dose proportional over the relevant range (5 to 10 mcg) for AUC, but slightly less than proportional for Cmax.

While not appreciably metabolized by hepatic mechanisms, due to its effect on GI motility (and perhaps via other mechanisms), there are some notable drug-drug considerations with exenatide. For instance, exenatide decreases the bioavailability of lovastatin and acetaminophen. The PK effect on lovastatin was not apparent in terms of pharmacodynamics in the clinical trials, since patients on lovastatin and exenatide did not show identifiable lipid changes compared to placebo patients. Though not formally studied, there is a concern that exenatide could affect the efficacy of oral contraceptives, given its effect on other drugs and given OCP's pharmacokinetics.

As for pharmacodynamics, Type 2 diabetics have nearly absent first-phase insulin secretion (very early spike) in response to a glucose load. Exenatide therapy partially to almost fully corrects the first-phase insulin secretion response and leads to higher insulin levels in the second phase than in normals (and certainly untreated type 2's).

Clinical / Statistical

See Dr. Gabray's medical officer and Dr. Pian's statistical reviews and Dr. Orloff's memo for detailed discussions of the clinical program and findings. In short, the sponsor conducted three 7-month trials of exenatide to demonstrate the **efficacy** of exenatide as add on therapy to metformin, sulfonylureas, or both (one trial for each add-on condition) for type-2 patients inadequately controlled on the oral agent(s). These studies enrolled a total population of 1446 subjects, with reasonable demographic distribution. Each of these studies showed remarkably similar results, with mean decreases of HgbA1c of around 0.5% for the 5 mcg dose and about 0.9% for the 10 mcg dose. This effect on lowering of A1c appears durable out to one year from extension data. In the 7-month trials, about 30% of patients achieved A1c's below 7% with the lower dose in these studies, and 40% with the higher dose (compared with about 10% in placebo). Attributable weight loss was not as clearly dose related, but there was a mean weight loss with active treatment of about 0.5 – 2 kgs more than that seen on average in placebo.

The monotherapy indication was only supported by one, small phase-2 study that was designed to assess changes in HgbA1c and fructosamine (the more appropriate endpoint for a short-term study). This study was only 6 weeks total (4 weeks of treatment) and enrolled only 99 subjects. Changes in the HgbA1c were not consistently significant and changes in the fructosamine were not significant. While it would be expected that exenatide would work as monotherapy in type 2 diabetes, this database is inadequate to prove this and, more importantly, to establish the best way to dose the drug for this use.

As for **safety**, the drug has shown a reasonable safety profile. The most common adverse event is nausea, occurring in upwards of 50% of patients treated with the 10 mcg BID dose. This nausea does appear to abate somewhat with continued use. Also notable is the occurrence of excess hypoglycemia, particularly when used with sulfonylureas. Overall, 20% of exenatide patients reported at least one episode, compared to 8% in the control groups. This phenomenon, not surprisingly, did show dose-responsiveness. However, only one of the reported hypoglycemic episodes was classified as "severe" (i.e., requiring the intervention of a second party) but still resolved with an oral snack. Labeling will need to caution about this and recommend possible lowering of the sulfonylurea dose when instituting exenatide therapy.

The sponsor assessed patients for the development of anti-exenatide antibodies. Forty-four percent of patients exposed to the drug in the 7-month trials developed antibodies, with 86% of these having only weak titers. Of the remaining 14% high-titer patients (6% of all exposed patients), only half showed an apparent diminution in glycemic control that might be attributable to the antibodies. The low antibody patients appeared to have no

atrtributable changes in glycemic control. The antibodies appeared to have no other consequences.

There were 4 pregnancies during the trials, 2 occurring in women on oral contraceptives. While the pregnancies that were carried to term were uneventful, it is notable to have two of these four represented apparent OCP failures. Given the notable effect of exenatide on absorption of certain drugs, we need to obtain a phase-4 commitment from Amylin to better explore the PK interactions of this drug with OCPs. In the meanwhile, some caution in this regard should be placed in labeling.

DSI Audits
4 clinical sites were inspected by FDA, all considered to have performed sufficiently well in clinical study management and record keeping to be acceptable for consideration. There is no evidence of systemic data issues. One site in a long-term controlled study (Dr. Nath, from Beth Israel, Yonkers, NY) was excluded by Amylin due to inadequate data documentation procedures found during a company-directed audit. The sponsor handled this appropriately (see pg. 40 of Dr. Gabray's review for details).

Financial disclosure
The sponsor met the expectations with regard to assessing and disclosing potential financial conflicts of interest. The review team did not feel that the investigators with financial interests had substantial sway over the conduct and results of the studies and conclude that the financial information does not raise undue concern over data integrity.

DMETS/nomenclature
DMETS has recommended against the name BYETTA due to several potential confusions (e.g., Diabeta, Zyrtec, Zebeta, Bijuva, Viagra). However, as Dr. Orloff's memo states, few of these pose substantial risk to the patients and none of them are similar dosage forms, with all but the Bijuva being oral dosage forms and the latter being a vaginal cream. The DMETS recommendations on labeling were considered in the labeling negotiations with the sponsor. As previously stated, there is some debate amongst the CMC team if the established name is more properly exenatide injection or exenatide acetate injection. This can be resolved post-approval, as it is a technicality that should be settled, but has no safety or efficacy bearing in the meantime.

Labeling
Satisfactory labeling, including instructions on the use of the pen device, has been arrived at for NDA 21-773 with the sponsor. The monotherapy indication and related materials have been removed from the label.

Recommendation
This drug, under NDA 21-773, should be approved for the treatment of type 2 diabetes as adjunctive therapy to those patients already taking metphormin and/or sulfonylureas but not adequately controlled with the oral agent(s) alone. The sponsor will need to provide additional data from one or more clinical trials to gain an indication for monotherapy,

both to show efficacy definitively and, perhaps more importantly, to determine optimal dosing/method of use. Given the efficacy of exenatide in the add-on setting and the mechanism of action of this drug (which is not dependant on the presence of the oral agents) and the findings in the small, brief phase 2 study, if the additional monotherapy study is thorough in design, I do not see the need for replication. One well-designed and conducted study should be adequate. However, pending results from such a study or studies, NDA 21-919 will be deemed approvable.

The analysis of the safety data did not reveal any issues that would require special risk minimization activities for NDA 21-773. We are asking for phase 4 commitments both for pediatrics (only down to age 12, since this is type 2 diabetes) and to further explore the potential pharmacokinetic interactions between exenatide therapy and oral contraceptives.

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Robert Meyer
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MEDICAL OFFICER

M E M O R A N D U M

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)
NDA 21-919 (monotherapy)
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.

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		
Treatment	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. The effect on HbA1c relative to placebo was significant with the exenatide 10 mcg BID dose only. The effects of treatment on serum fructosamine concentration were not significant relative to placebo. I concur with Dr. Gabry that this study and these data are insufficient to fully characterize the effect of an optimal dose of exenatide as monotherapy in the treatment of DM2. Additional investigations, which conceivably could be done without placebo but with several doses of exenatide, of sufficient duration to assess the full extent and durability of effect on HbA1c, are needed to support approval and inform labeling for to monotherapy.

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

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, a 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 or 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

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 filling process is under (b) (4) and a recommendation that if not, a particular (b) (4) degradation product be monitored during storage.
3. Information on (b) (4) leachables in the solution (b) (4) (b) (4) prior to filling. I have spoken with Dr. Fraser about whether this is necessary, given that all prefilled cartridges (e.g., for growth hormone or insulin) are (b) (4). He considers this a GMP issue. This has not been included in the letter.
4. An agreement to withdraw from distribution out-of-spec lots and to report to the Agency. This is also a GMP issue and has not been included in the letter.
5. Finally, the ONDC reviewer disagrees with the sponsor that there is adequate information to conclude that the established name should be "exenatide injection" rather than (b) (4) and believes a study is necessary to substantiate this sponsor's "claim" in this regard. He proposes that such a study should be aimed at demonstrating that exenatide exists primarily as the free acid rather than the acetate salt. Pending review by Dr. Duffy, the requested study, to involve exhaustive lyophilization performed at laboratory scale followed by analytical characterization of the material for acetate content, is not included in the action letter.

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.

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, Bijuva, and Viagra. As all but Bijuva are oral dosage forms (Bijuva 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

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 (b) (4) (b) (4) 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. Improved beta cell function persistent after discontinuation of exenatide has not been established and this, therefore, is an implied claim of impact on the natural history of beta cell function in DM2.

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 Cmax has been added. In addition, language has been added stating that the impact of exenatide on the absorption and effecitiveness of oral contraceptives has not bee 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.

NDA 21-919, proposing the use of exenatide as monotherapy in patients with DM2 should be "approvable" pending further data on efficacy from adequate and well-controlled investigation(s), specifically of sufficient duration to determine the magnitude of the expected effect of the drug on glycemic control as assessed by change in HbA1c.

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/s/

David Orloff
4/25/05 03:07:51 PM
MEDICAL OFFICER

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