CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-919

OTHER REVIEW(S)

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

CLINICAL INSPECTION SUMMARY

DATE: November 20, 2009

TO: John Bishai, Regulatory Project Manager
Valerie Pratt, M.D., Medical Officer
Division of Metabolism and Endocrinology Products

FROM: Michelle Chuen, M.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: 21-773; 21-919; (b) (4)

IND: (b) (4)

APPLICANT: Amylin Pharmaceuticals, Inc.

DRUG: Exanatide; Exanatide LAR

NME: No

I. BACKGROUND:

The Review Division received a complaint from "a concerned group of Amylin employees" regarding the sponsor. Among the GCP-related issues, the complainants alleged the following:

1. The Vice President stated that it was made clear to her that she would be fired if Byetta received a black box warning for pancreatitis.
2. The data FDA is reviewing may not be the same data generated by the complainant's department.

As this study involved an approved drug product, the inspection was expanded to include evaluation of compliance related to postmarketing adverse event reporting.

The inspection assignment was issued in August 2009 and the inspection was conducted, at Amylin Pharmaceuticals, Inc., in late September 2008. This clinical inspection summary is provided to summarize the results of this inspection at Amylin Pharmaceuticals, Inc. to investigate the complaint.

II. RESULTS:

Name of Contract Research Organization	Protocol #	Inspection Dates	Final Classification
Sponsor: Amylin Pharmaceuticals, Inc. Staci Ellis Director, Regulatory Affairs 9360 Towne Centre Drive San Diego, California 92121	UHC-3	21 Sept-25 Sept 09	Pending (Preliminary classification: NAI for the complaint-related portion of the inspection; VAI for postmarketing adverse event reporting violations)

Key to Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

Sponsor:
Amylin Pharmaceuticals, Inc.
Staci Ellis
Director, Regulatory Affairs
9360 Towne Centre Drive
San Diego, California 92121

a. **What was inspected**: The inspection included review of, but was not limited to, the following: firm's management of studies submitted under NDA 21-919 and (b) (4) (b) (4) in an attempt to confirm the complaint; and review of postmarketing adverse event (PADE) reporting.

b. **General observations/commentary**: The complaint allegations could not be confirmed. No deficiencies were noted in the sponsor's sponsor/monitoring activities. Review of PADE reporting revealed that 7 of 1165 safety reports submitted from 1/09 to 9/09 were reported outside of the 15-day timeframe. Four of the 7 late reports involved late reporting of the initial safety reports. This is a preliminary assessment pending final review from the Division of Compliance Risk Management and Surveillance (DCRMS), which has responsibility for evaluation of the PADE reporting compliance.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication. This is a preliminary assessment pending final review from the Division of Compliance Risk Management and Surveillance (DCRMS), which has responsibility for evaluation of the PADE reporting compliance.

{See appended electronic signature page}

Michelle Chuen, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/

MICHELLE M CHUEN

11/20/2009

I took out "addendum", but I couldn't find the "final" you were referring to. Do you mean the file name? It's just the convention I use when a document is the final version (vs. cis.3.doc, etc.).

CONSTANCE LEWIN

11/23/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Metabolism and Endocrinology Products

Application Number: NDA 21-919

Name of Drug: BYETTA (exenatide) Injection

Applicant: Amylin Pharmaceuticals

Material Reviewed:

Submission Date(s): October 5, 2009

Receipt Date(s): October 5, 2009

Submission Date of Structured Product Labeling (SPL): TBD

Type of Labeling Reviewed: WORD

Background and Summary

On June 29, 2004 Amylin Pharmaceuticals, Inc. submitted an application for BYETTA (exenatide injection) for both, combination therapy and monotherapy use. Review of the application, as amended, yielded the decision to take an approval (AP) action for use of exenatide in combination with metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea to improve glycemic control in patients with type 2 diabetes mellitus. However, an approvable (AE) action was taken for the monotherapy indication. Two different actions for the same application necessitated an administrative split of the application. Therefore, two NDA numbers were given (21-773 for the combination therapy and 21-919 for the monotherapy). This label pertains to NDA 21-919 and is a PLR conversion of the existing combination use label (NDA 21-773). The last label revision made to NDA 21-773 occurred on January 11, 2008.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

This label is a PLR conversion based on new data submitted to NDA 21-919 in addition to data used for the original combination approval. Since the approval for the combination use of BYETTA (NDA 21-773), a number of adverse events have been reported through the AERS database citing cases of acute pancreatitis, hemorrhagic and necrotizing pancreatitis, hypoglycemia, and renal impairment. As a result, the aforementioned were addressed in this PLR conversion under the Warnings and Precautions section. Please note that this PLR label will be used for both NDA 21-773 (combination therapy) and 21-919 (monotherapy). Upon approval, all future submission will be directed to NDA 21-773, thereby reuniting the combination and monotherapy back unto the original application.

NOTED CHANGES:

1. **Under INDICATIONS AND USAGE**
   - **Type 2 Diabetes Mellitus**
     BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
   - **Important Limitations of Use**
     BYETTA is not a substitute for insulin. BYETTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

     The concurrent use of BYETTA with insulin has not been studied and cannot be recommended.

Under WARNINGS AND PRECAUTIONS

2. **Acute Pancreatitis**

   Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

3. Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea (hypoglycemia can also occur when other antidiabetic agents are used in combination with a sulfonylurea). Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

For additional information on glucose dependent effects see *Mechanism of Action (12.1)*.

4. Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation *[see Use in Specific Populations (8.6)]*. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

5. Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

6. Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA, consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals. In a small proportion of patients, the formation of antibodies to

exenatide 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 *[see Adverse Reactions (6.1)]*.

7. Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice *[see Adverse Reactions (6.2)]*.

The following issues/deficiencies have been identified and should be communicated to the labeling for its proposed labeling.

- We note that SPL has not been submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. Please submit PLR compliant SPL by (DATE).

John Bishai, Ph.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Enid Galliers
Chief, Project Management Staff

Drafted: John Bishai/10.28.09
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21919	ORIG-1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION

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/s/

POOJA DHARIA
11/17/2009
Entered on behalf of John Bishai

JOHN M BISHAI
11/17/2009

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred randomized and controlled pediatric study under Pediatric Research Equity Act (PREA) to evalute the efficacy and safety of exenatide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	NA
Study/Clinical trial Completion Date:	NA
Final Report Submission Date:	12/31/2010
Other: NA	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☒ Prior clinical experience indicates safety
   ☒ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   Exenatide monotherapy is ready for approval for use in adults. However, the pediatric studies have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Deferred pediatric study required under PREA in pediatric patients ages 10 to 16 years with type 2 diabetes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled clinical trial evaluating the efficacy and safety of exenatide in pediatric patients ages 10 to 16 years.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Subpopulation: Pediatric patients ages 10-16 years with type 2 diabetes mellitus

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An adequately powered epidemiological study to determine the incidence rate, severity and risk factors for the development of acute pancreatitis, including the more severe forms of hemorrhagic and necrotizing pancreatitis, in exenatide-exposed versus unexposed patients.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	NA
Study/Clinical trial Completion Date:	NA
Final Report Submission Date:	11/30/2009
Other: NA	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Postmarketing reports suggest an association between exenatide and acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis. Preclinical studies do not provide any signal of a pancreatitis risk, and a biological mechanism for such an association has not been determined. The background rate of pancreatitis in type 2 diabetes mellitus patients is purported to be as much as 3-fold higher than the rate in the general population. It is unclear if the association between exenatide use and pancreatitis is simply a reflection of this higher background rate, or whether it is causally associated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   The goal is to ascertain the background rate and risk factors for the development of acute pancreatitis, including the severe forms, 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.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An epidemiological study using a large claims database study with medical record retrieval capability and validation of all cases to determine the incidence rate, severity and risk factors for the development of acute pancreatitis, including the more severe forms of hemorrhagic and necrotizing pancreatitis, in exenatide-exposed versus unexposed patients.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Epidemiologic queries using i3 Aperio to assess the relative risk of pancreatic cancer and thyroid neoplasm among patients using Byetta and those using metformin or glyburide. Thyroid neoplasm assessment will also include benign and malignant diagnosis event stratification.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	NA
Study/Clinical trial Completion Date:	NA
Final Report Submission Date:	03/31/2010
Other: NA	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

A pre-clincal study conducted in the HIP rat (a rodent model of diabetes) described adverse exocrine pancreatic effects expressed as necrotizing pancreatitis. The study concluded that drugs, such as Byetta, that directly or indirectly enhance GLP1 activity may increase the risk of pancreatitis and pancreatic cancer with long-term treatment. The background rate of pancreatitis in type 2 diabetes mellitus patients is purported to be as much as 3-fold higher than the rate in the general population. The background rate of pancreatic cancer is higher in diabetics and in obese individuals. It is unclear if the purported association between exenatide use and pancreatitis and pancreatic cancer is simply a reflection of these higher background rates, or whether they are causally associated.

Certain long-acting GLP1 analogs have been associated with medullary thyroid cancer findings in rodents (both rats and mice). MTC was not seen in pre-clinical studies with Byetta. However, an outside report cited a disproportionate number of cases of thyroid neoplasms in the AERS database associated with the use of Byetta.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A pre-clincal study conducted in the HIP rat (a rodent model of diabetes) described adverse exocrine pancreatic effects expressed as necrotizing pancreatitis. The study concluded that drugs, such as Byetta, that directly or indirectly enhance GLP1 activity may increase the risk of pancreatitis and pancreatic cancer with long-term treatment. The background rate of pancreatitis in type 2 diabetes mellitus patients is purported to be as much as 3-fold higher than the rate in the general population. The background rate of pancreatic cancer is higher in diabetics and in obese individuals. It is unclear if the purported association between exenatide use and pancreatitis and pancreatic cancer is simply a reflection of these higher background rates, or whether they are causally associated.

Certain long-acting GLP1 analogs have been associated with medullary thyroid cancer findings in rodents (both rats and mice). MTC was not seen in pre-clinical studies with Byetta. However, an outside report cited a disproportionate number of cases of thyroid neoplasms in the AERS database associated with the use of Byetta.

The purpose of the proposed epidemiologic study is to look for possible signals of pancreatic or thyroid cancer associated with long-term exposure to Byetta.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Epidemiologic queries using i3 Aperio to assess the relative risk of pancreatic cancer and thyroid neoplasm among patients using Byetta and those using metformin or glyburide. Thyroid neoplasm assessment will also include benign and malignant diagnosis event stratification.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A 3-month pancreatic safety study in a diabetic rodent model treated with Byetta.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	03/31/2010
Study/Clinical trial Completion Date:	06/30/2010
Final Report Submission Date:	01/31/2011
Other: NA	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Byetta is a marketed drug. Prior clinical experience indicates safety. This animal study is being requested to explore potential mechanisms involved in the clinical pancreatitis signal observed post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Postmarketing reports suggest an association between exenatide and acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis. Nonclinical studies do not provide any signal of a pancreatitis risk and biological mechanisms for such an association have not been determined. The purpose of this study is to explore possible mechanisms for exenatide-associated pancreatitis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An animal study to assess pancreatic safety in a diabetes model, e.g., Zucker rat following treatment with exenatide. This is a model of insulin resistant diabetes whereby free fatty acids stimulate over-production of insulin. The endpoints for this study should include pancreas/pancreatic ductal histopathology, assessment of pancreatic ductal proliferation, e.g., KI67, amylase/lipase, insulin and plasma glucose.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Submission of all amylase and lipase data obtained in ongoing, terminated, and completed clinical trials, including analyses of those data. Also provide a systematic analysis of amylase and lipase data from those patients who presented with abdominal pain or nausea, with or without vomiting during the treatment phase of those trials.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	NA
Study/Clinical trial Completion Date:	10/27/2009
Final Report Submission Date:	03/31/2010
Other: NA	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Postmarketing reports suggest an association between exenatide and acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis. Preclinical studies do not provide any signal of a pancreatitis risk, and a biological mechanism for such an association has not been determined. The background rate of pancreatitis in type 2 diabetes mellitus patients is purported to be as much as 3-fold higher than the rate in the general population. It is unclear if the association between exenatide use and pancreatitis is simply a reflection of this higher background rate, or whether it is causally associated. Additionally, preliminary clinical data suggests transient asymptomatic elevations in amylase and lipase in both exenatide-exposed and unexposed patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Uncertainty remains regarding the effect of exenatide on amylase and lipase levels in general - whether there are particular patients who may have an increased baseline risk of pancreatitis; whether monitoring of amylase and lipase levels in asymptomatic subjects is predictive of who will develop acute pancreatitis; whether cases of acute pancreatitis are related to exenatide itself versus exenatide in combination with other anti-diabetic agents; whether the population prescribed exenatide is at greater risk for pancreatitis because they have higher BMIs (given the beneficial effect of exenatide in promoting weight loss). These applications are both for a new approval (exenatide monotherapy) and for post-approval (exenatide combination therapy). The new safety information is post-marketing cases of acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor has multiple ongoing clincial trials of its long-acting preparation (exenatide LAR) and has incorporated amylase and lipase monitoring into those protocols. The division wants to ensure the timely submission and analysis of those data to inform future labeling decisions.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A clinical trial investigating the effects of exenatide on 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.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	NA
Study/Clinical trial Completion Date:	NA
Final Report Submission Date:	12/31/2010
Other: NA	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☒ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☒ Theoretical concern
   - ☐ Other

   Postmarketing reports suggest an association between exenatide and acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis. Preclinical studies do not provide any signal of a pancreatitis risk, and a biological mechanism for such an association has not been determined.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   To assess any effect of exenatide on the sphincter of Oddi and gall bladder emptying as a possible mechanism for exenatide-associated acute pancreatitis.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial investigating the effects of exenatide on 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.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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

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/s/

AMY G EGAN
10/30/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 20, 2009
To:	Mary Parks, M.D., Director, Division of Metabolic and Endocrine Drug Products, OND
Thru:	Solomon Iyasu, M.D., Director, Division of Epidemiology, OSE
From:	Diane K. Wysowski, Ph.D., Epidemiologist, Division of Epidemiology, OSE
Subject:	Postmarketing Requirement for Exenatide
Drug Name(s):	Exenatide (Byetta)
Submission Number:	Safety Information Amendment
Application Type/Number:	NDA 21-919
Applicant/sponsor:	Amylin Pharmaceuticals
OSE RCM #:	2009-1046 (continued)

1 INTRODUCTION

Reports of acute pancreatitis and hemorrhagic and necrotizing pancreatitis related to the use of exenatide (Byetta), a drug indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus, have been the subject of consults, communications, regulatory action, and discussion within the FDA.

To study the association between exenatide and acute pancreatitis, Amylin Pharmaceuticals commissioned the i3 Drug Safety staff to perform "A Retrospective Cohort Study of Acute Pancreatitis in Relation to the Use of Byetta and Other Antidiabetic Drugs." The "revised first interim report" dated December 31, 2008, was sent to DMEP in January, 2009. DMEP sent a written consult request, dated May 15, 2009, to the Office of Surveillance and Epidemiology (OSE) that was forwarded to the Division of Epidemiology (DEPI). It requested:

- comments on the interim results,
- comments on the protocol design and planned medical chart review and whether it will provide a reasonable assessment of acute pancreatitis and hemorrhagic or necrotizing pancreatitis for Byetta and other anti-diabetic agents, and
- a proposal for a more appropriate epidemiological study design to evaluate the risk of acute pancreatitis and hemorrhagic or necrotizing pancreatitis that can be conducted by this or another applicant as a postmarketing study requirement *if the currently described study design is judged inadequate*.

The first two requests were addressed in the DEPI consult dated June 16, 2009, that was sent to DMEP; however, it was agreed by DEPI and DMEP that because of time constraints, the third request for the provision of a study proposal or alternative study designs (if needed) would not be addressed at that time.

The DMEP staff has indicated that now they would like to receive from the DEPI staff a proposal for a "more appropriate epidemiological study design to evaluate the risk of acute pancreatitis."

2 MATERIALS REVIEWED

The consult date June 16, 2009, entitled a "Review of the Revised First Interim Report of a 'Retrospective Cohort Study of Acute Pancreatitis in Relation to Use of Byetta and other Antidiabetic Agents' " and selected parts of the first interim report were reviewed again to provide the following comments:.

3 REVIEWER'S COMMENTS

The previous consult on this retrospective cohort study identified many limitations and made some suggestions for improvement; however, as the DEPI reviewer, I stated that I was in favor of the study being continued. It appears to meet DMEP's criteria for a post-marketing requirement.

An important step in the study that had not yet been initiated at the time of the first interim study report was the verification of incident cases of acute pancreatitis and hemorrhagic and/or necrotizing pancreatitis following the use of exenatide and other anti-

diabetic agents based on medical record review. With verification of cases, the i3Drug Safety research staff conducting the study will be able to determine incidence rates. Also, the researchers should be able to conduct their planned nested case-control study of acute pancreatitis (and hemorrhagic and/or necrotizing pancreatitis) to determine risk factors. Indeed, the study protocol states that "Subsequent analyses will include a nested case-control study that utilized covariate data from the medical charts derived from around the time of acute pancreatitis cases and contemporaneously for controls."

Highlighted in the initial DEPI review was the subject of study power. The revised first interim report of this study stated that 952 potential cases of acute pancreatitis will need to be validated by medical record review. If we assume that 900 cases meet the case definition, and that severe pancreatitis constitutes 20% of cases (1,2), 180 severe cases would be expected among all the diabetes cohorts. However, a DEPI staff member who attended the August, 2009, International Conference on Pharmacoepidemiology recently stated that presenters of this study reported a much lower validation rate of acute pancreatitis of only about 40%-50%. Assuming accuracy of this statement, only about 380-475 cases would be validated acute pancreatitis cases and some 75-95 cases would be severe among the different treatment cohorts.

Since the actual number of validated cases of hemorrhagic and necrotizing pancreatitis will not be known until case adjudication is completed, it is unknown at this time if the number of cases will be adequate to perform any analyses. If sample size for hemorrhagic and necrotizing pancreatitis is found to be inadequate, the FDA should consider asking the researchers if increasing the sample size by adding the year 2008 to the period of study would offer a sufficient number of cases.

Even if this study is not able to identify sufficient numbers of hemorrhagic or necrotizing pancreatitis, I believe that the study would be worth finishing in an attempt to determine if an association exists between the development of acute pancreatitis and initiation of exenatide and/or other antidiabetic drugs and to estimate the rate of these events in this population (i.e., persons who are mostly <65 years of age with commerical health insurance).

The researchers developed propensity scores for exenatide initiation relative to initiation of other antidiabetic medication or membership in the non-diabetes cohort separately. It is expected that the propensity scores would be used in the nested case-control analyses.

In addition, I suggest that any validated cases of hemorrhagic and/or necrotizing pancreatitis be described by age, sex, body mass index, antidiabetic and other concomitant drugs, severity and duration of diabetes, previous medical conditions, etc. to determine if these individuals appear to be "end-stage" diabetics.

4 SUMMARY

The current study should be able to provide rates for pancreatitis within a population of individuals who are mostly < 65 years of age with commercial health insurance. It is also likely to capture cases of hemorrhagic and/or necrotizing pancreatitis. Although it may be adequate to estimate the differential risk for acute pancreatitis among selected antidiabetic agents, it may not be large enough to estimate the differential risk for hemorrhagic and/or necrotizing pancreatitis among selected antidiabetic agents. If

sample size for hemorrhagic and necrotizing pancreatitis is found to be inadequate, the FDA should consider asking the researchers if increasing the sample size by adding the year 2008 to the period of study would offer a sufficient number of cases.

I suggest that the study be continued. For validated cases of acute pancreatitis and for cases of hemorrhagic and/or necrotizing pancreatitis, the planned nested case-control study (within the retrospective cohort study) should be carried out to identify risk factors.

In addition, I suggest that any validated cases of hemorrhagic and/or necrotizing pancreatitis be described by age, sex, body mass index, antidiabetic and other concomitant drugs, severity and duration of diabetes, previous medical conditions, etc. to determine if these individuals appear to be "end-stage" diabetics.

Diane K. Wysowski, Ph.D.

cc: SwannJ/GreenL/AviganM/DPV1

EganA/BishaiJ/PrattV/MahoneyKM/JoffeH/ColmanE/ParksM/DMEP

AhmadSR/WysowskiD/BrinkerA/IyasuS/DEPI

5 REFERENCES

1. Haas S, Singer MW. Differential diagnosis and therapy of acute pancreatitis. (Abstract in English). Praxis (Bern 1994). 2002;91(39):1595-1602.

2. Pitchumoni CS, Patel NM, Shah P. Factors influencing mortality in acute pancreatitis: can we alter them? J Clin Gastroenterol 2005;39(9):798-814.

3. Fagenholz PJ, Castillo CF, Harris NS, Pelletier AJ, Camargo CA Jr. Increasing United States hospital admissions for acute pancreatitis, 1988-2003. Ann Epidemiol 2007:17(7):491-497.

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/s/

DIANE K WYSOWSKI
08/21/2009

SOLOMON IYASU
08/21/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 23, 2009
To:	Mary Parks, MD, Director
	Division of Metabolism and Endocrinology Products (DMEP)
Through:	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide) #2
Drug Name(s):	BYETTA (exenatide) Injection
Application Type/Number:	NDA 21-919
Applicant/sponsor:	Amylin Pharmaceuticals, Inc.
OSE RCM #:	2008-1511

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for BYETTA (exenatide) Injection. Please let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. DRISK previously reviewed the proposed BYETTA MG and Risk Evaluation and Mitigation Strategy (REMS) on December 5, 2008, and provided an Addendum to this review also on December 5, 2008.

2 MATERIAL REVIEWED

- Draft BYETTA (exenatide) Injection Prescribing Information (PI) submitted March 19, 2008, revised by the Review Division throughout the current review cycle, and provided to DRISK on July 16, 2009.
- Draft BYETTA (exenatide) Injection Medication Guide (MG) originally submitted on September 11, 2008, further revised and provided to DMEP on July 7, 2009. DRISK reviewed the July 7, 2009 version of the MG obtained from the DMEP eRoom on July 19, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

We have the following clarification in response to the Applicant's inquiry about the rationale for the proposed font type and size:

- We do not object to the use of 12 point font. The Medication Guide regulations set forth in 21 CFR 208 require a 10 point font. The use of 12 point font is actually desirable because patients with diabetes may have visual impairment. DRISK has routinely commented in review memos regarding use of fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. In 2008, the American Society of Consultant Pharmacists Foundation in collaboration with the American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. Information was previously included in our review memo dated December 5,

2008 regarding this publication and our re-formatting of the proposed MG document.

- We routinely re-format patient labeling using APHont with an 11 point font size in our reviews. Since some patient labeling materials end up being excessive in length, the use of APHont with 11 point font size can help to improve readability while also keeping the length of the patient labeling a reasonable length.

Please let us know if you have any questions.

19 page(s) have been Withheld in Full immediately following this page as B4 (CCI/TS)

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

/s/

Sharon Mills
7/23/2009 12:26:09 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
7/23/2009 01:10:39 PM
DRUG SAFETY OFFICE REVIEWER