CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-919

SUMMARY REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

NDA #	21-919 (Byetta) 21-995 (Januvia) and 22-055 (Janumet)
Subject	Pancreatitis
Date	June 18, 2009

A. INTRODUCTION

Exenatide (Byetta®) is a synthetically manufactured 34-amino acid glucagon-like peptide 1 (GLP-1) agonist that was originally isolated from the saliva of the Gila monster lizard. GLP-1 is an incretin hormone that increases insulin secretion in response to an ingested meal. Because human GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase IV (DPPIV), it has limited clinical use. Exenatide has 53% homology with human GLP-1 and retains agonistic activity at the human GLP-1 receptor; however, it is naturally resistant to DPP-IV, allowing for a half-life of approximately 4 hrs that is more practical for therapeutic purposes. Exenatide was approved in April 2005 for the treatment of Type 2 diabetes in combination with metformin or sulfonylureas and is available as twice daily subcutaneous injections. In December 2006, exenatide was granted an indication for use in combination with a thiazolidinedione alone or in combination with metformin. This memo accompanies the reviews for NDA 21-919 which seeks the indication for use of exenatide as monotherapy in T2DM.

Currently, exenatide is the only marketed GLP-1 receptor agonist in the United States. Inhibitors of dipeptidyl peptidase IV (DPP4-inhibitors) also affect glucose control through the incretin hormones by prolonging the circulating half-life of endogenous GLP-1. Slight increases in GLP-1 levels are achieved with DPP4-inhibitors; however, pharmacologic levels are only achieved with the GLP-1 receptor agonists. Currently, Januvia (sitagliptin) is the only marketed DPP4-inhibitor in the United States.

The purpose of this Division Director's memo is to discuss the evolving safety signal of pancreatitis and its more severe form of hemorrhagic/necrolytic, observed with exenatide therapy from:

- spontaneous postmarketing adverse event reports (AERS)
- controlled clinical trials
- claims database

In addition, the risk of pancreatitis with sitagliptin will be discussed, as the company (Merck) submitted a changes-being-effected supplement on March 5, 2009, to include reports of pancreatitis under Side Effects: Postmarketing Experience section of the Package Insert for Januvia (sitagliptin) and Janumet (sitagliptin/metformin). As a result, this memo will also accompany several supplements for Januvia and Janumet.

Finally, it has been suggested that pancreatitis may be an emerging safety finding with other the incretin-based therapies. This memo will also summarize the findings from incretin-based therapies in development.

The Office of Surveillance and Epidemiology (OSE) has also been consulted on this safety issue. In my memo I will summarize data reviewed within DMEP and OSE that I have taken into consideration in my labeling recommendation at this juncture for both Byetta and Januvia/Janumet.

B. RISK OF PANCREATITIS ASSOCIATED WITH BYETTA (EXENATIDE)

The risk of pancreatitis associated with exenatide is described from the following sources:

1. Data from spontaneous postmarketing adverse event reports
   a. Periodic Safety Update Reports
   b. FDA's Spontaneous AERS Reports
2. Data from controlled clinical trials
   a. NDA 21-773 (Byetta marketing application and any post-approval controlled trials)
   b. (b) (4) (Exenatide once-weekly NDA currently under review)
3. Data from claims databases
   a. United Healthcare Group
   b. i3 drug safety study
   c. Claims Database study

B1. Data from Spontaneous Postmarketing Adverse Event Reports (AERS)

Since approval, there have been 8 periodic safety update reports (PSURs) submitted by Amylin to this NDA. The PSURs summarize safety information received by Amylin and Eli Lilly from worldwide sources for this production.

B1a. Periodic Safety Update Reports

April 1, 2005 until September 30, 2005 (PSUR 1)

The first postmarketing evaluation for pancreatitis was initiated by Amylin and summarized in its first Periodic Safety Update Report (PSUR 1) submitted on November 30, 2005, which covered a reporting period from April 1, 2005, until September 30, 2005 (~ 5 mos). During this time period there were 8 cases of pancreatitis reported. There were no fatalities and no cases of hemorrhagic or necrotizing pancreatitis reported. According to the applicant, there was an estimated (b) (4) total prescriptions filled during this reporting period based on data from NDCHealth.

October 1, 2005 until March 31, 2006 (PSUR 2) - ~ 11 months since approval

During this reporting period, there were 17 reports of pancreatitis for a cumulative number of 25 cases since approval. **There was one case of necrotizing pancreatitis reported during this time period**. As per the MedWatch report, "this is the first report of necrotizing pancreatitis in a patient receiving exenatide". None of these cases resulted in death. The one case of necrotizing pancreatitis (2006PV007451) occurred on (b) (6) and involved a 46 year-old woman who was started on exenatide 5 mcg bid in November 2005 with dose increased to 10 mcg bid in December 2005. In January 2006, the patient had intense mid-epigastric pain at night which lasted approximately 3 hours then resolved. On (b) (6), the patient had a similar episode and almost fainted. She went to the ER and was found to be hypotensive but responded to IV fluids. A CT scan on (b) (6) revealed an area of hypoperfusion in the pancreas consistent with necrosis. Exenatide was discontinued on January 16, 2006. As per the PSUR, the outcome was reported as resolving.

In this PSUR, the applicant referenced IMS® tracking data and stated that an estimated (b) (4) prescriptions of exenatide were filled in the United States during this reporting period (5.75-fold increase from PSUR 1 reporting period).

April 1, 2006 until September 30, 2006 (PSUR 3) - ~ 17 months since approval

With this PSUR, the cumulative number of pancreatitis cases was 42. One additional case of necrotizing pancreatitis was reported (MRN2006PV014726) involving a 65-year old male with a history of hypertriglyceridemia. Exenatide was initiated in November 2005. On (b) (6) the patient developed abdominal pain and presented to the ER where amylase was elevated at 1660 U/L (upper normal < 100). CT scan revealed acute necrotizing pancreatitis and a 24 cm pancreatic pseudocyst. Patient was intubated

and developed metabolic acidosis later complicated by sepsis and decreased renal function. He was extubated on (b) (6) and re-intubated on (b) (6) due to acute respiratory failure and shock. No fatal cases of pancreatitis was reported in this PSUR.

During this reporting period, approximately (b) (4) total prescriptions of exenatide were filled in the U.S. (11.3-fold increase from PSUR 1 reporting period).

October 1, 2006 until March 31, 2007 (PSUR 4) - ~ 23 months since approval
With this PSUR, the cumulative number of pancreatitis cases was 65. There were no cases of necrotizing or hemorrhagic pancreatitis reported. No fatalities resulting from pancreatitis were reported.

During this reporting period, approximately (b) (4) total prescriptions of exenatide were filled in the U.S. (13.4-fold increase from PSUR 1 reporting period).

April 1, 2007 until September 30, 2007 (PSUR 5) - ~ 29 months since approval
With this PSUR, the cumulative number of pancreatitis cases was 90; 25 cases limited to this reporting period. There was one fatality associated with the pancreatitis report (US200705005536); no cases of necrotizing or hemorrhagic pancreatitis. The fatal case involved a 66-year old female who had a history of peripheral vascular disease and hypertension. Six months after initiating treatment with exenatide the patient was diagnosed with acute pancreatitis and drug was discontinued. She was hospitalized two weeks later and CT scan showed mild infiltrative changes, small loculated fluid collection at the pancreatoduodenal groove with possible diagnoses including grooved pancreatitis with pseudocyst formation. Amylase was reportedly normal at 116. Lipase was 153 (normal 22-51). Patient underwent laparoscopic cholecystectomy while hospitalized and was discharged but was readmitted 17 days later with complaints of RUQ pain and epigastric pain. Her amylase and lipase levels were 105 and 52, respectively. The patient died four days later. No autopsy was performed.

During this reporting period, approximately (b) (4) total prescriptions of exenatide were filled in the U.S. (14.3-fold increase from PSUR 1 reporting period).

October 1, 2007 until March 31, 2008 (PSUR 6) - ~35 months since approval ***(OF NOTE – 1ST FDA ALERT WENT OUT IN OCTOBER 2007)***
During this 6-month reporting time period, there were 125 cases of pancreatitis reported representing a 5-fold increase in reports compared to the previous reporting period for PSUR 5. For those cases with outcome data (n=86), there were 3 fatalities. There were four cases of necrotizing pancreatitis (US200802002837, US200801003034, US200802002764, and US200712001764). There was one case of hemorrhagic pancreatitis (US200711005991).

During this reporting period, approximately (b) (4) total prescriptions of exenatide were filled in the U.S. (15.1-fold increase from PSUR 1 reporting period).

April 1, 2008 until September 30, 208 (PSUR 7) - ~ 41 months since approval ***(OF NOTE – 2nd FDA ALERT WENT OUT IN AUGUST 2008)***
During this 6-month reporting time period, there were 66 cases of pancreatitis reported. There was one fatality involving a 72-year old female who underwent a right hemi-colectomy and cholecystectomy for Stage IV adenocarcinoma of the colon with biliary obstruction and resultant pancreatitis.

During this reporting period, approximately (b) (4) total prescriptions of exenatide were filled in the U.S. (14.7-fold increase from PSUR 1 reporting period)

October 1, 2008 until March 31, 2009 (PSUR 8) - ~ 47 months since approval

During this 6-month reporting time period, there were 247 cases of pancreatitis reported. There were 3 fatalities. There were 3 other cases reported as necrotizing, necrotizing and hemorrhagic, and hemorrhagic. None of these cases was associated with a fatal outcome.

During this reporting period, approximately (b) (4) total prescriptions of exenatide were filled in the U.S. (12.9-fold increase from PSUR 1 reporting period)

B1b. FDA's Spontaneous Adverse Event Reports
Concurrent with the PSUR submissions, OSE conducted a review of the FDA's spontaneous Adverse Events Reporting System (AERS).

On **July 12, 2007**, OSE provided its first consult on the matter of exenatide-associated pancreatitis. In Dr. Swann's review, a search of AERS was conducted for domestic cases with "serious only" outcome identified for the following MedDRA terms:

- High Level Term (HLT) – acute and chronic pancreatitis and
- Preferred terms (PT) blood amylase increased, lipase increased and pancreatic enzymes increased

Cases were then selected if:
1. Clinical diagnosis of acute pancreatitis OR
2. If case report had no mention of clinical diagnosis of acute pancreatitis but had two of the three following criteria (a plus b <u>or</u> c) then the case was evaluated as "acute pancreatitis"
    a) severe and sudden midepigastric abdominal pain,
    b) increase serum amylase (normal 30-170 U/L) and/or lipase (normal 7-60 U/L)
    c) confirmatory diagnostic imaging (US, CT or other imaging techniques)

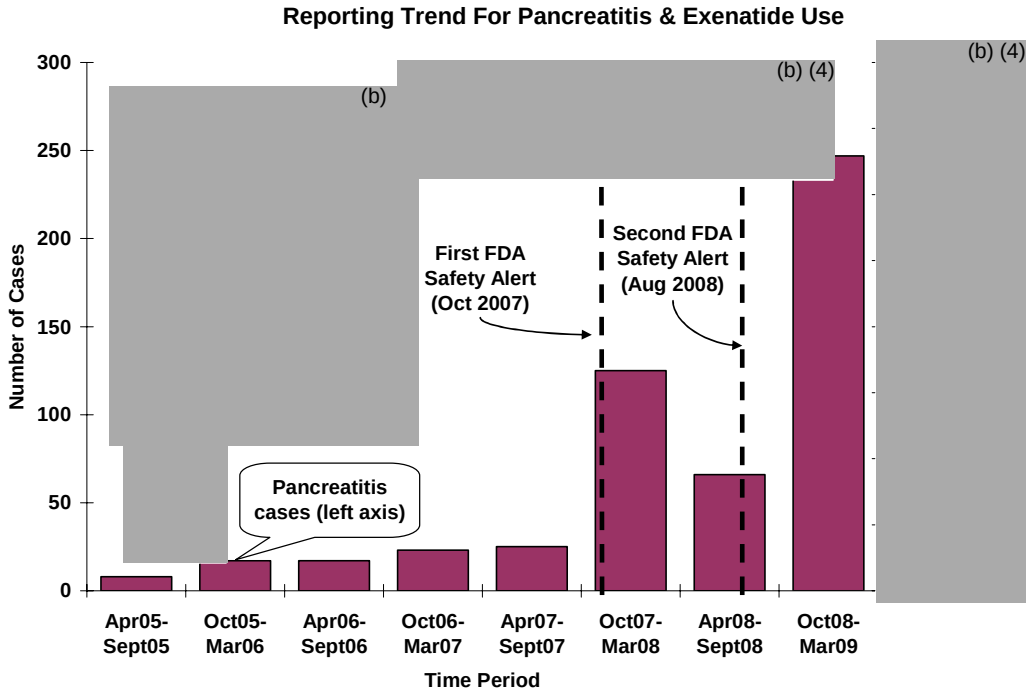
In this first consult the time period of AERS search was from April 28, 2005 until December 31, 2006. Dr. Swann identified 30 unique cases meeting the selection criteria; there were no cases of hemorrhagic or necrotizing pancreatitis in this series. Overall, this first consult corresponded with the cumulative reports from the company's PSUR reports 1-4 which had a cumulative number of 65 pancreatitis cases reported. There were 2 cases of necrotizing pancreatitis reported by the firm that were not mentioned in this OSE report. These were subsequently identified in the 2nd consult. The <u>final</u> OSE recommendation in this first consult was a bolded WARNING for pancreatitis. Of note, Dr. Ahmed provided a memo to the file with a dissenting recommendation for a Boxed Warning. After negotiations with the firm involving both DMEP and OSE/DDRE, the labeling was updated to include bolded language in the PRECAUTIONS section. This was accepted by both DMEP and DDRE since an NDA for monotherapy use was under review at that time that would result in PLR change to the label. This would effectively place this in the WARNINGS section as there is no distinction between Warnings and Precautions under the PLR format.

On **June 26, 2008**, a second consult was completed by Dr. Swann which covered the reporting time period of April 2005 until March 31, 2008 (end of PSUR 6). The search strategy was different from the initial consult in that now ALL AERS outcomes were searched, both foreign and domestic cases were pulled, and in addition to the HLTs of acute and chronic pancreatitis, the Preferred Terms, pancreatitis hemorrhagic and pancreatitis necrotizing were included. Cases were selected if there was the following:
1) Clinical diagnosis of hemorrhagic or necrotizing AND
2) Temporal relationship between exenatide therapy and pancreatitis event

In this consult, Dr. Swann identified 242 crude reports of pancreatitis. No individual review of the reports was conducted so this number may have included duplicates. Applying the PTs for selection of more severe cases, 6 cases of necrotizing or hemorrhagic pancreatitis were identified. Two of these reports included fatal outcome. Based on these 6 cases of HNP, OSE recommended a boxed warning for exenatide. This was DDRE's final recommendation, reiterated in an updated consulted on **March 4, 2009.**

The findings from this 2nd consult also mirrored the company's PSURs 1-6. Both the company and OSE's consult noted the marked increase in reports of pancreatitis in the 6th reporting period (company) and 4th quarter (OSE) which was subsequent to the first FDA safety alert, suggestive of stimulated reporting (Figure 1 below). The sharpest rise in prescription usage occurred between October 2005 and October 2006. Although there was a continued increase in estimated prescriptions filled until September 2008, this increase was less pronounced. Despite this marked increase in exenatide use, the number of pancreatitis reports appears stable during the October 2005-September 2007 time period. In contrast, the steep increase in number of cases reported in October 2007-March 2008 occurred during a time period in which prescriptions filled for exenatide were at a plateau. This observation would suggest that the increased reporting was influenced more by the FDA safety alerts than by increased market use of the drug.

Figure 1.



Although there was a marked increase in number of pancreatitis reports that was temporally related to the FDA safety alerts, the proportion of HNP cases reported did not appear to change over time. From the published literature, approximately 10-25% of acute pancreatitis cases present in its more severe form with gland necrosis (necrotizing pancreatitis).[1,2] In Table 1, the proportion of all pancreatitis cases reported for exenatide which presented as necrotizing or hemorrhagic was less than 6%. Even when the absolute number of pancreatitis cases rose exponentially following greater public awareness of this safety concern, the percentage of the more severe cases did not increase. This finding lends some credence to Amylin's argument that some of the reports of necrotizing/hemorrhagic pancreatitis represent the spectrum of this disease, and not evidence that exenatide directly causes more severe pancreatitis. However, I would note that if exenatide increases the risk of pancreatitis over the general background rate

[1] Hughes SJ et al. Necrotizing Pancreatitis. *Gastroenterol Clin N Am.* 36(2007):313-232.
[2] Haney JC et al. Necrotizing Pancreatitis: diagnosis and management. *Surg Clin N Am*. 87(2007): 1431-1446.

in the diabetic population or more than other anti-diabetic therapies, then one would expect an increased risk for necrotizing/hemorrhagic pancreatitis.

Table 1. Reports of Pancreatitis and More Severe Cases of Hemorrhagic/Necrotizing (HNP) Since Approval Relative to Prescription Usage Data Based on PSUR data

	PSUR1 4/05-9/05	PSUR 2 10/05-3/06	PSUR 3 4/06-9/06	PSUR 4 10/06-3/07	PSUR 5 4/07-9/07	PSUR 6 10/07-3/08	PSUR 7 4/08-9/08	PSUR 8 10/08-3/09
# cases	8	17	17	23	25	125	66	247
#HNP	0	1	1	0	0	5	0	3
% HNP/all cases	--	5.9%	5.9%	--	--	4%	--	1.2%
total Rx								(b) (4)

I would note that during this ongoing review, discrepancies in number of reports obtained from PSUR and AERS were noted. This may reflect direct submissions of AEs to FDA although there were also cases identified by the manufacturer not noted in the OSE consult. For completeness, the following table (provided by Dr. Amy Egan, DMEP's Deputy Director Safety) lists all cases of necrotizing/hemorrhagic pancreatitis that FDA is aware of as of July 20, 2009. Rows highlighted in yellow represent events occurring after the 1st FDA alert. All but 2 fell into this category.

Table 2. Reports of HNP for Byetta as of July 20, 2009 (n=16)

ISR#	MFR#	Event Date	Report Date	Interval b/w Event and Report Date	Event before FDA safety alert/Report submitted after alert
5122511	200606002001	5/3/06	9/25/06	5 mos	N
5491558	200801003034	4/28/07	10/19/07	5 mos	Y
5532976	200807002087	11/9/07	11/29/07	20 days	N
5628720	No Amylin Report	1/24/08	2/15/08	1 mos	N
5574629	200711005991	9/6/07	12/26/07	3 mos	N
5581487	No Amylin Report	10/29/07	1/3/08	2 mos	N
5987291	200808006124	8/7/08	12/??/08	4 mos	?
5928511	200810003877	Unk.	10/16/08	?	?
5660764	200802002764	4/??/07	3/3/08	1 yr	Y
5957236	200811001739	??/??/07	11/7/08	? 1 yr	?
5987276	200811004931	10/??/08	1/12/09	4 mos	N
6015469	200812004072	1/??/08	12/11/08	1 yr	N
5734010	200905000184	10/??/06	4/??/08	? 1.5 yrs	Y
5534562	No Amylin report	5/19/2007	12/4/2007	6 mos	Y
No OSE report	200602000669	1/16/2006	1/23/2006	15 day	N
No OSE report	200802002837	4/??/07	4/16/2008	1 yr	Y

B2. Data from Controlled Clinical Trials

B2a. Exenatide NDA 21-773

A total of 2252 patients were studied in the clinical development program supporting the NDA submission. The majority of these were in the Phase 1 and 2 clinical trials. There were three Phase 3 pivotal trials which were 30-weeks in duration, preceded by a 4-week placebo lead-in period. At the end of this lead-in period, patients were randomized to receive exenatide 5 ug bid (Groups A or B) or placebo (Groups C or D) in a 2:2:1:1 randomization scheme for 4 weeks in a double-blinded fashion. Subsequent to this 4-week period, patients in Group B were titrated to exenatide 10 ug bid whereas Groups A, C, and D remained on their originally assigned treatments. This period remained double-blinded and was 26

weeks in duration. At the end of 30 weeks, patients remaining in the study had the option of entering a 22-week, open-label uncontrolled extension trial.

Table 3. Pre-marketing Exposure

	Exenatide	Placebo
Total exposed	1857	805
Less than 6 months	1017	
At least 6 months	840	
At least 12 months*	272	
Patient-yrs exposure		

*All exposures beyond 7 months are from open-label, uncontrolled studies

Since its approval, cumulative experience with postmarketing clinical trial has provided greater patient exposure data. As of August 31, 2008, 4980 patients have participated in 41 completed trials: 3331 received exenatide, 991 received placebo, and 658 received active comparators (insulin). The cumulative exposure in patient-years is summarized below.

Table 4. Total Exposure from All Controlled Clinical Trials up to August 31, 2008

	Exenatide	Insulin	Placebo
	N=3331 3065 pt-yrs	N=658 397 pt-yrs	N=991 374 pt-yrs
Number of Subjects with at least 24, 52, or 78 Weeks of Exposure			
>=24 weeks	n=1823 2733 pt-yrs	n=459 341 pt-yrs	n=417 235 pt-yrs
>=52 weeks	n=1070 2254 pt-yrs	N=134 135 pt-yrs	n=0
>=78 weeks	n=645 1761 pt-yrs	n=0	n=0

In this cumulative clinical trial database there were 9 cases of pancreatitis: 7 in exenatide, 1 in placebo, and 1 in insulin. None of these cases was characterized as hemorrhagic or necrotizing. The following table summarizes these findings.

Table 5. Rate of Pancreatitis Observed in Combined Completed Controlled Clinical Trials (data cut-off date 8/31/08)

	Exenatide	Placebo	Insulin
Total Patients	3331	991	658
Total w/ event	7	1	1
Incidence Rate per 1000 pt-yrs	2.3	2.7	2.5
95% CI	(0.9, 4.7)	(0.1, 14.9)	(0.1, 14.0)

From the controlled clinical trials, the risk of pancreatitis was similar to control. This is reassuring; however, I would note that the number of patients evaluated in the combined controlled clinical trial program is small compared to exposures that can be evaluated in the post-marketing setting which would provide a better estimate of pancreatitis risk for exenatide relative to other anti-diabetic therapies.

B2b. Data from Bydureon (b) (4)

Amylin submitted an NDA for a once-weekly formulation of exenatide with the proposed tradename, Bydureon, on May 4, 2009. As of the data cut-off date of November 15, 2008, there were 11 completed

or ongoing clinical studies under this (b) (4); approximately 985 subjects have been exposed to exenatide once weekly with approximately 350 treated for at least 6 months.

This NDA is still under review; (b) (4)

(b) (4)

(b) (4)

B3. Data from Claims Database

B3a. United Healthcare Claims Database

With their 2nd PSUR submission, Amylin and Lilly described their plans to further investigate the risk of pancreatitis in the diabetes population based on a retrospective observational database study utilizing data from the United HealthCare (UHC) claims database. In its 3rd PSUR submission, the company summarized the key finding of an increased risk of acute pancreatitis in the diabetic population versus the non-diabetic population. This study noted a 3.74-fold greater incidence of acute pancreatitis in patients with T2DM than that observed in the non-diabetic cohort. The annualized incidence rate of acute pancreatitis in T2DM calculated from this study was 107.8 events/100,000 pt-years. The annualized incidence rate of acute pancreatitis in the non-diabetic cohort was 28.8 events/100,000 pt-yrs. At that time, the spontaneous pancreatitis reporting rate for exenatide was approximately 29-35 events/100,000 pt-yrs leading to the company's conclusion that the risk of pancreatitis associated with exenatide did not exceed the background rate of pancreatitis for T2DM.

B3b. i3 drug safety study

The company commissioned a second retrospective observational database to assess the incidence of pancreatitis in patients with T2DM using exenatide relative to the incidence in patients with T2DM not using exenatide. This is the i3 drug safety study which included a population of patients with at least 9 months of continuous enrollment in the participating health insurance plans between September 1, 2004 and December 31, 2007. The following cohorts were identified:

- Patients who initiated therapy with exenatide
- Patients who initiated therapy with other anti-diabetic drugs
- Patients without claims associated with diabeties

The study outcome of interest was *likely acute pancreatitis* identified in the insurance claims, defined as an ER visit or hospitalization with a primary discharge diagnosis of acute pancreatitis. A medical chart review is also planned to obtain more detailed information about each outcome of interest.

An interim report for this study was submitted to FDA on December 31, 2008 suggesting a similar rate of *likely acute pancreatitis* diagnoses for exenatide vs other anti-diabetic drugs. For current users of exenatide versus other anti-diabetic drugs, the adjusted RR (95% CI) for *likely acute pancreatitis* was 0.9 (95% CI 0.6-1.3). A similar finding was observed for recent users in both cohorts. There was a non-significant higher RR for past users. Similar to the UHC claims database study, a higher rate of *likely acute pancreatitis* diagnoses was observed in the two diabetic cohorts compared to the non-diabetic cohort.

DMEP submitted a formal consult to OSE requesting:

1. Comments on the interim results
2. 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
3. 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.

This consult was completed on June 16, 2009 by Dr. Diane Wysowski. She noted that the sample size of this study is unlikely to answer the question of whether exenatide is associated with hemorrhagic or

necrotizing pancreatitis although the medical chart review will likely be able to identify these cases that would not be captured by ICD-9 codes. She states further that "even if this study is not able to identify any cases of hemorrhagic or necrotizing pancreatitis, [she] believes 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". Critiques/comments on the study design were also provided and have been forwarded accordingly to the firm.

B3c. Claims Database Study

Coincident with the submission of this interim report was the publication of an analysis of data from an insurance claims database from June 2005 to June 2008 to estimate risk and relative risk of acute pancreatitis among patients using incretin-based diabetes therapies (exenatide and sitagliptin) compared to patients treated with other anti-diabetic therapies.[3] This study reported no difference in acute pancreatitis between exenatide or sitagliptin with metformin/glyburide use.

Table 6. Summary of Pancreatitis Risk from Claims Database Study[3]

	No. of Cases	No. Patients	Absolute risk (%)	Relative Risk	95% CI
Drug pair 1					
Exenatide	37	27,996	0.13	1.0	0.6-1.7
Metformin/glyburide	36	27,983	0.13	1.0	Ref
Drug pair 2					
Sitagliptin	19	16,267	0.12	1.0	0.5-2.0
Metformin/glyburide	19	16,281	0.12	1.0	Ref

Although much more limited in its study design, including the absence of any medical chart review, these results are aligned with the interim results from the i3 drug safety study that is scheduled for study completion in September 2009.

C. RISK OF PANCREATITIS ASSOCIATED WITH JANUVIA (SITAGLIPTIN)

With exception for the preceding section discussing data from claims databases, this memo has primarily focused on the risk of pancreatitis associated with exenatide therapy. On March 5, 2009, Merck submitted a Changes Being Effected (CBE) supplement proposing to include the term *pancreatitis* under Side Effects: Postmarketing Experience section of the Package Insert for Januvia (sitagliptin) and Janumet (sitagliptin/metformin).

Merck searched its database for reports mapping to PTs of pancreatitis/acute pancreatitis, blood amylase increase, lipase increase, and hyperlipasaemia associated with use of sitagliptin or sitagliptin/metformin. The time period of this search was from market introduction (December 2006 – Januvia was approved October 2006) until February 3, 2009 – an approximate 26 months post-launch reporting period for Januvia.

There were 108 reports with PTs pancreatitis/acute pancreatitis and 34 reports with the less specific PTs of amylase and lipase increase or hyperlipasaemia. The company focused only on the 108 reports due to paucity of information in the latter category. The following characteristics of these 108 reports were summarized:

[3] Dore, DD et al. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. *Current Medical Research and Opinion*. 2009;25(4):1019-1027.

Table 7. Characteristics Summarized by Merck for 108 Reports of Pancreatitis/Acute Pancreatitis from December 2006-February 2009

Proportion in U.S.	91/108 (84%)
Median Age (range)	64 years (36-88)
Gender	Reported in 93/108 (86%) of reports
Female	41/93 (44%)
Male	52/93 (56%)
Time to Onset	Reported in 51/108 (47%) of reports
Median days	56 days
Range	1-682 days

Merck's review of these 108 reports was further narrowed down as follows:

- 38/108 (35%) lacked sufficient information for full assessment
- 52/108 (48%) provided some information on history, concomitant medications, clinical course but lacked imaging studies
- **18/108 (17%) cases had confirmatory imaging studies**

In this CBE submission, necrotizing pancreatitis was described in one patient. This case is summarized below.

> *<u>WAES 0810DEU0004 (received by manufacturer on December 8, 2008)</u>*
> *50-year old female hospitalized on* (b) (6) *for left thoracic pain. Was treated with metformin and glimepiride at that time but with inadequate control (HbA1c 10.4%).* (b) (6) (b) (6) *report states last dose of metformin was taken that morning and patient was placed on metformin/sitagliptin that evening (1000mg/50mg bid). During this hospital stay serum lipase was 138 U/L, amylase 30 U/L. Patient was discharged on* (b) (6)*.*
>
> *On September 9, 2008, patient developed exhaustion and weakness ("was not able to leave the bed"). Metformin/sitagliptin was discontinued that day and metformin reinitiated. On September 11, 2008, the patient had liquid stools and on* (b) (6) *nausea, vomiting, and acute abdominal pain were reported. She was hospitalized that day with lipase 15,416 U/L, amylase 238 U/L, and WBC 11,600. She was admitted to the ICU. Ultrasound on* (b) (6) *revealed steatosis hepatic, no intrahepatic or extrahepatic vessel enlargement. Gallbladder was concrement-free.* (b) (6)*r* (b) (6) *abdominal CT revealed an enlarged inflammatory conglomerate in transition area between pancreatic corpus and head, including duodenum and infiltration in liver hilus and a large pseudocyst. Necroses were seen until caudal area reaching caudal pole of the kidney. The report stated "bile ducts were not enlarged, gallbladder was well-defined and there was no indication for an inflammatory process"; however, in a later sentence the report read "stomach was decidedly dilated including inflammatory involvement of duodenum, which was most likely cause by a passage obstruction".* (b) (6)*, another abdominal US showed a 5 cm echo-poor space-occupying lesion in transition area between pancreatic corpus and head, possibly corresponding to a cystic lesion in the context of a necrotizing pancretitis.*
>
> *Patient was discharge on* (b) (6)*. Reporting physician felt that acute pancreatitis was possibly related to therapy with metformin/sitagliptin and that patient had no previous "bile duct disease".*

FDA also received a MEDWATCH report (ISR #5526739-2) on January 9, 2009 with limited information. The following verbatim text from this report is stated below:

Pt was obese and had 2 or 3 recurrent pancreatitis prior to Januvia therapy. Had history of alcohol abuse. Autopsy showed hemorrhagic pancreatitis, thus on the cause of death list. This physician didn't believe the death was caused by Januvia.

FDA inquired of Merck whether it had received this report and had any follow-up information. The company said this case corresponds to WAES 0709USA04017 was initially reported on September 24, 2007. Merck has requested follow-up information on the autopsy report and as of April 30, 2009, no additional information has been provided.

In its March 4, 2009, reiterating its recommendation for a boxed warning for Byetta, the following table was provided as evidence that the risk of pancreatitis, in particular hemorrhagic/necrotizing, was greater with exenatide than sitagliptin and pramlintide, 2 drugs with similar marketing times to exenatide. At that time, OSE acknowledged that the consult for sitagliptin was still ongoing.

Table 8. Reporting rate of HNP in association with exenatide And selected newer antidiabetic agents

Products (Approval date)	Estimated dispensed prescriptions	Mean days of therapy	Total # of reports since marketing	Person-years of exposure	Reporting rate – per million person years
Sitagliptin (10/06)	(b) (4)	33	0	651,682	0
Pramlintide (03/05)		27	0	43,866	0
Exenatide (04/05)		30	12	657,534	18

In July 2007, OSE provided its first consult on the matter of exenatide-associated pancreatitis in response to a proposed labeling change by Amylin. In its first PSUR (April 1, 2005-Sept 30, 2005) covering 6 months post-approval, there were 8 cases of pancreatitis or acute pancreatitis reported for exenatide. In the second PSUR covering the reporting period of October 1, 2005-March 31, 2006, an additional 6 months post-approval, there were 17 additional cases of pancreatitis reported for exenatide. In Merck's CBE submission, it was noted that in the 6 month period post-approval, there were 11 cases of pancreatitis/acute pancreatitis reported and in the subsequent 6-month period, an additional 12 cases were reported for sitagliptin.

Table 9. Comparison of Reports of Pancreatitis for Exenatide and Sitagliptin 12-months Post-approval

	Exenatide[a]	**Sitagliptin[b]**
1st 6-month period post-approval	4/1/05-9/30/05	12/06-5/07
	8 cases	11 cases
2nd 6-month period post approval	10/1/05-3/31/06	6/07-11/07
	17 cases	12 cases

[a]Data based on OSE consult dated July 12, 2007

[b]Data based on Merck's CBE submission on March 3, 2009

In two sequential 6-month periods post-approval, there were a total of 25 cases of pancreatitis/acute pancreatitis reported with exenatide use compared to 23 cases reported with sitagliptin use, suggesting very little difference in the raw count of cases. However, because these data are provided by several different sources, it is important to understand what search criteria were applied to capture these reports.

OSE evaluated AERS cases that were *domestic and serious only*. In addition, the following MedDRA terms were applied:

- HLT – acute and chronic pancreatitis
- PT – blood amylase increase, lipase increased, and pancreatic enzymes increased

As noted above under the section discussing the Merck CBE submission, similar preferred terms were used to map on AE reports for sitagliptin. Merck, however, provided global reports so its analysis was not limited to domestic only, as in OSE's consult. However, 84% of the sitagliptin cases were from the U.S. (n=91) so for all intents and purposes, the majority of the cases in both of these databases are domestic.

OSE further refined its search by applying the following selection criteria to <u>unduplicated</u> cases:

1. Clinical diagnosis of acute pancreatitis, OR
2. If case report had no mention of clinical diagnosis of acute pancreatitis but had two of the three following criteria (a plus b <u>or</u> c) then the case was evaluated as "acute pancreatitis"
   a) severe and sudden midepigastric abdominal pain
   b) increased serum amylase (normal 30-170 U/L) and/or lipase (normal 7-60 U/L)
   c) confirmatory diagnostic imaging (including US, CT or other imaging techniques)

This resulted in the identification of **48 cases** associated with exenatide use during the reporting period of April 28, 2005 through December 31, 2006 (20 months). OSE further refined its search by doing a hands-on review in which alternative explanations could be applied to eliminate cases. 18 cases were eliminated with a remaining 30 index cases for exenatide. For the purposes of this memo, I will focus on the 48 cases.

In Merck's CBE submission, the applicant reported **108 unduplicated cases** with preferred terms pancreatitis/acute pancreatitis identified during a period of December 2006 through February 3, 2009. By selecting out cases with this PT, this maps to the first selection criteria used by OSE (report included a clinical diagnosis of acute pancreatitis). Focusing only on the first 20 months post-approval for Januvia so that one is looking at a comparable post-approval time interval for both exenatide and sitagliptin, there were **56 cases** reported with sitagliptin use. If we assume approximately 84% of these reports are domestic, then we might estimate 47 cases of pancreatitis associated with sitagliptin use, a number that is not too different from the 48 identified by OSE during the same post-approval surveillance time interval. The following table compares the two drugs and the reports of pancreatitis. It would appear that even before OSE's completed consult of sitagliptin's CBE, one can conclude that the raw counts of pancreatitis in an identical post-marketing time perioid were the same between these two products lending some credence to the i3 drug safety interim report and the claims database study.

Table 10. Comparison of Reports of Pancreatitis for Exenatide and Sitagliptin 20-months post approval

	Exenatide[a]	**Sitagliptin[b]**
Unduplicated reports of pancreatitis during 20-month period post-approval/launch	48 domestic	56 total (estimated 47 domestic since 84% of all reports are U.S.)
Imaging study confirming	11	18

diagnosis

[a]Data based on OSE consult dated July 12, 2007
[b]Data based on Merck's CBE submission on March 3, 2009

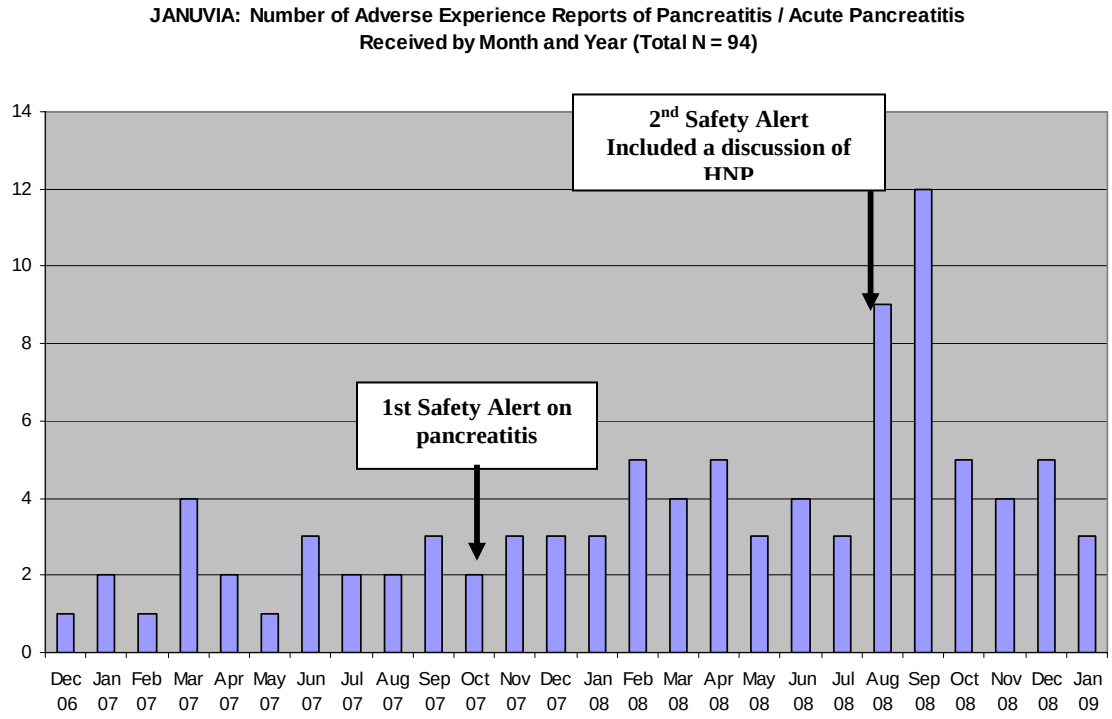
Between June 17 and 19, 2009, OSE provided 3 consults on the issue of sitagliptin-associated pancreatitis. In the consult primarily authored by Dr. Yinghua Wang, a search strategy identical to that used for exenatide was applied for sitagliptin for the time period from market approval until February 9, 2009. For Januvia (approved 10/16/06) this represents an approximate 28-month period and for Janumet (approved 3/20/07) this represents an approximate 23-month period.

Dr. Wang identified 88 cases meeting the selection criteria. There were no fatalities; however, 58 of these cases required hospitalization and 4 of these were admitted to the ICU. Two cases of necrotizing pancreatitis were identified in her review. One case was summarized above involving a 50-year old female. The 2nd case had not been identified in the review of Merck's CBE. This case (ISR 6064466) involved a 43-year old male who was admitted to the hospital with nausea, vomiting and epigastric pain. Lipase and amylase were not notably elevated but CT scan showed > 50% pancreatic necrosis and a normal gallbladder.

The post-marketing timeframe in which Dr. Wang has summarized the AERS data for Januvia corresponds with data from PSURs 1-5 for Exenatide (April 2005-Sept 2007). During that time frame, there were a total of 90 cases of pancreatitis reported for exenatide, 2 of these cases were necrotizing (see Table 1). Again the similarity in raw counts of pancreatitis and HNP during a similar post-marketing period is evident (sitagliptin 88 vs exenatide 90; both had 2 cases of HNP).

The impact of FDA safety alerts on reporting of adverse events for the drug of interest and other drugs within the same class has been described in the published literature.[4,5] To evaluate whether there has been a changed in pattern of pancreatitis reports for Januvia coinciding with the FDA safety alerts for exenatide, the following figure plots the number of pancreatitis reports submitted to the manufacturer over time, as summarized in their CBE submission. Superimposed on this plot are the time points in which the FDA safety alerts for exenatide were issued. There was not an appreciable change in the number of reports received after the first safety alert. However, the number of reports increase 3 to 4-fold from July 2008 over the next two months following the 2nd safety alert which updated the initial alert to discuss the 6 cases of necrotizing and hemorrhagic pancreatitis. Also of interest is that all three necrotizing pancreatitis cases for Januvia occurred <u>after</u> the 2nd FDA safety alert.

[4] McAdams M, Staffa J, Dal Pan G. Estimating the extent of reporting to FDA: a case study of statin-associated rhabdomyolysis. *Pharmacoepidemiol Drug Saf.* 2008 Mar 17(3):229-39.
[5] Motola D et al. Influence of regulatory measures on the rate of spontaneous adverse drug reaction reporting in Italy. *Drug Saf* 2008;31(7):609-16.



None of the comparisons between exenatide and sitagliptin, up until this point, can be construed as a comparison of risk since postmarketing reports only represent a numerator in any risk calculation. And even as a numerator, there is much uncertainty surrounding the actual number of cases as this is a voluntary reporting system which can be influenced by many factors.

To better assess risk, OSE calculated reporting rates for both exenatide and sitagliptin (other anti-diabetic therapies were included but sitagliptin will be the primary focus of this memo). Different reporting rates and conclusions were made and separate reviews finalized to reflect differing opinions on the risk of these two drugs. While all calculations yielded a 2-fold higher reporting rate with exenatide compared to sitagliptin, Dr. Ahmad is in favor of placing language on the risk of pancreatitis associated with sitagliptin under Adverse Reactions whereas other reviewers with concurrence from Drs. Brinker, Avigan, and Iyasu are in favor of such placement under Warnings and Precautions. I note that Dr. Brinker has written a separate memo in which he discusses the impact of the FDA safety alerts on stimulated reporting and concluded that "given the limitations of spontaneous adverse event reports, the observed reporting rates (for sitagliptin and exenatide) are considered to be similar" and that this "suggests a similar course of regulatory action for sitaglipin as undertaken for exenatide".

OSE has also provided an updated table comparing the rates of hemorrhagic and necrotizing pancreatitis between exenatide and sitagliptin, as it is now evident that Table 8 is inaccurate since HNP cases have also been reported with sitagliptin. In their June 19, 2009 consult for sitagliptin the update reporting rates for HNP are as follows:

Table 11. Reporting Rate of HNP in Association with Sitagliptin, Exenatide, and Pramlintide (adapted from Dr. Wang's OSE consult)

Products (approval date)	Estimated dispensed Rx (b) (4)	Mean Days of Therapy	Ttl # of Reports since marketing	Person-yrs exposure	Reporting rate per million person-yrs
Sitagliptin (10/06)		33	1	969,131	1
Exenatide (4/05)		30	12	683,191	18
Pramlintide (3/05)		27	0	52688	0

This table excludes foreign reports since prescription usage data are limited to the U.S. Of note, there were 2 foreign reports for sitagliptin and none for exenatide at the time of the OSE consult completion. On July 16, 2009, FDA received information from Merck in response to a request from DMEP. In this submission a fourth case of necrotizing pancreatitis was reported for sitagliptin. The narrative is as follows:

> WAES 0906FRA00083 (follow-up received on 10-Jul-2009) described a 59 year old male with history of pancreas divisum, hypertension, hypercholesterolemia and diabetic nephropathy with no history of alcoholism. On 27-Jan-2009, the patient was placed on therapy with sitagliptin 100 mg daily for diabetes and on amlodipine. Concomitant therapy included metformin, glimepiride, atorvastatin and perindopril. He was hospitalized (b) (6) for necrotizing pancreatitis. Therapy with sitagliptin was discontinued. Biliary magnetic resonance imaging showed pancreas divisum. CT scan showed necrotizing pancreatitis. Hepatic and biliary ultrasound was normal (no lithiasis). Necrotizing pancreatitis resolved slowly. No further information is expected.

It is conceivable that FDA will continue to receive more cases of HNP for sitagliptin, if there is a rise in reporting for pancreatitis.

D. PANCREATITIS SAFETY EVALUATION WITH OTHER INCRETIN-BASED THERAPIES IN DEVELOPMENT

D1. Nonclinical data

There has been recent interest in whether incretin-based therapies are associated with an elevated risk of pancreatitis. A recent e-publication in *Diabetes* by Butler et al. involving a transgenic rat model reported increased pancreatic ductal proliferation (8/8) and ductal metaplasia (2/8) in transgenic animals treated with sitagliptin alone that was reduced when sitagliptin was coadministered with metformin. A report of hemorrhagic pancreatitis was reported in one transgenic rat treated with sitagliptin alone. This study was a 3-month study involving treatment groups of 8 animals. This study was reviewed by Dr. Todd Bourcier, supervisory pharmacologist/toxicologist in DMEP. In his review dated May 15, 2009, Dr. Bourcier also summarized the extensive nonclinical pharmacology/toxicology program for sitaglipin in which rats treated out to 2 years at exposures ranging from 6x-62x higher than clinical exposure, based on AUC, revealed no adverse effect of drug treatment based on histopathological evaluation. Unlike the Butler study, these 2-year rat studies studied treatment groups of 50 animals per sex. For one carcinogenicity study, there were 500 animals studied compared to 40 transgenic animals evaluated by Butler et al. Similarly, there has been no signal for pancreatitis from the non-clinical toxicology program supporting of exenatide dosed at multiples above clinical exposure.

Aside from the inconsistent findings between the transgenic animal model study and the nonclinical program supporting the marketing application for sitagliptin, Dr. Bourcier points out that the animal model used by Butler et al. is one that expresses human IAPP transgene (HIP rats). IAPP is the acronym for Islet Amyloid Polypeptide or amylin, a peptide that is co-secreted with insulin from the beta-cells. These animals develop diabetes as a result of amyloid deposition in the pancreas. It is unclear what the

relevance of the findings from the HIP rat study is to humans and the overall results should be interpreted with caution. No conclusion that biological plausibility for sitagliptin-induced pancreatitis has been established should be made based on this single study. The pharmtox discipline is currently evaluating whether diabetic animal models can be evaluated in the nonclinical assessment of pancreatitis for incretin-based therapies.

D2. Liraglutide

This NDA is still under review; however, it was recently presented at an advisory committee meeting on April 2, 2009. In the background materials provided by the applicant, a total of nine cases of pancreatitis were reported (8 in liraglutide group and 1 in control group). There was one fatal case in the liraglutide report. Notable is that pancreatitis was not diagnosed clinically but during a post-mortem examination. Follow-up report from a pathologist included a statement that the patient was found dead and that improper storage conditions may account for some of the pathology findings. The rates of pancreatitis were summarized by subject years of exposure to reflect differential randomization scheme and treatment exposure. Overall, there was a numeric imbalance suggesting a higher risk of pancreatitis associated with liraglutide than comparators.

Table 12. Pancreatitis in Liraglutide Program

Treatment group	Rate per 1000 subject-years of exposure
Total liraglutide	2.2
Placebo	0
Active comparator	0.9
Total comparator (active plus placebo)	0.6

This numeric imbalance observed with liraglutide in its NDA is concerning and should be reflected in labeling, should this application be approved. I would note that the overall exposure for exenatide from all controlled clinical trials exceeds liraglutide and no imbalance in pancreatitis was noted (see Section B1b); however, the imbalance in the liraglutide program should raise the possibility that pancreatitis may be a risk associated with incretin-based therapies that requires continued evaluation.

E. DISCUSSION

Since the first PSUR for exenatide was provided to the FDA on November 2005, the postmarketing signal for pancreatitis associated with exenatide has continued to evolve from many data sources. A similar finding is not noted in all these different data sources. Not surprisingly, this has resulted in divergent opinions within OND and OSE on what is the appropriate risk communication for exenatide and now, sitagliptin. All parties, including Amylin, are in agreement that the label must include a discussion of pancreatitis and the more severe cases of hemorrhagic and necrotizing pancreatitis. The disagreement is in the placement of that language in the label. OSE's recommendation to elevate the pancreatitis language to be a Boxed Warning is based on an observation of more reports of severe pancreatitis associated with exenatide use than other anti-diabetic drugs.

Amylin has argued that stimulated reporting of pancreatitis secondary to two FDA alerts has resulted in some reports containing the more severe forms found in approximately 15-25% of the spectrum of acute pancreatitis as opposed to evidence of an increase risk of exenatide-induced hemorrhagic/necrotizing pancreatitis. From Figure 1 in my memo, I believe there is evidence to suggest that the rise in reporting of pancreatitis is correlated with the increased publicity surrounding this issue. It also appears that this increased public awareness for exenatide has influenced the pattern of reporting for sitagliptin. From Table 1, it appears that the number of reports for hemorrhagic/necrotizing pancreatitis falls within the expected percentage of all pancreatitis cases noted in the published literature. Of particular interest is that upon reviewing the individual reports for HNP, there appears to be a delayed reporting for several of these cases. That is, the event date for HNP for some of these patients occurred prior to the FDA alerts.

However, the FDA did not receive the reports until after October 2007 (See Table 2), which suggests that the FDA alerts prompted reporting of these events many months after it occurred (one case was reported 1 ½ yrs after the event) and one can not conclude that the risk of HNP has somehow now increased. Furthermore, in reviewing these cases, there is little evidence to suggest that the severe cases were the result of the patient's delay in seeking medical attention. Many of the cases presented acutely and HNP was diagnosed within 24 hrs of initial symptoms. While HNP is a serious event, I believe that there are too few cases of HNP to discern a difference in risk between exenatide and other anti-diabetic therapies, particularly if these data are derived from AERS for which there are factors influencing the rate of reporting.

Amylin has also argued that type 2 diabetes is associated with a higher risk of pancreatitis than the general population and that what is observed with exenatide from postmarketing reports reflects the underlying risk of diabetes. Evidence for this comes from several publications[6,7] and more recently from the claims database studies, United Healthcare group and the i3 drug safety. In addition, the claims database studies suggest a similar rate of pancreatitis between exenatide and other anti-diabetic therapies. If indeed the reports of pancreatitis for exenatide (or sitagliptin) reflect the underlying disease, not the drug, it can be argued that no language for pancreatitis should be included in labeling. This would be akin to requiring anti-diabetics to include retinopathy or nephropathy in their labels. However, I am not convinced that such a conclusion can be made, particularly given the imbalance in pancreatitis rates observed in the liraglutide NDA. With the currently available data, I would focus on whether the risk of acute pancreatitis associated with exenatide is different from other anti-diabetics. If indeed the risk of acute pancreatitis is higher with exenatide over other anti-diabetics then by extension, the risk of observing more severe forms of hemorrhagic and necrotizing pancreatitis will be higher with exenatide than other anti-diabetics. Such a finding would support my conclusion for a boxed warning for exenatide.

However, the currently available data provide conflicting evidence of risk for pancreatitis between exenatide and other anti-diabetic therapies. From the claims database studies, the risk of acute pancreatitis does not appear different between exenatide and other anti-diabetic therapies. Until recently, the only data source for such a conclusion came from AERS. However, it is becoming apparent that reports of pancreatitis are also increasing with sitagliptin and as of July 15, 2009, OSE was notified of another report of necrotizing pancreatitis associated with sitagliptin use. Given the limitations of AERS reporting and the changing pattern of reporting in such a short timespan that may have been influenced by FDA's public safety alerts, I can not make a conclusion that exenatide is different from other anti-diabetics based on AERS alone. In particular, I believe the degree of risk for exenatide and sitagliptin based on AERS is not sufficiently different that in concurrence with a statement made by Dr. Brinker in his consult, I believe a similar regulatory course of action should be taken for both these drugs.

At this time, the regulatory course of action that I am recommending takes into consideration the ongoing retrospective observational study (i3 drug safety study) which is scheduled to be submitted to the FDA in September 2009. This study will provide information on the risk of acute pancreatitis between exenatide, sitagliptin, other anti-diabetic drugs, and the cohort of patients without diabetes. Because it will include medical chart reviews, it will also provide assurances that any necrotizing or hemorrhagic pancreatitis cases will be noted.

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[6] Blomgren KB et al. Obesity and treatment of diabetes with glyburide may both be risk factors for acute pancreatitis. *Diabetes Care*. 2002; 25(2):298-302.

[7] Noel RA et al. Increased risk of pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care.* 2009;32(5):834-838.

F. RECOMMENDATIONS

I am recommending that for both Byetta and Januvia/Janumet, the prescribing information includes a discussion of reports of acute pancreatitis, including necrotizing and hemorrhagic cases under Warnings and Precautions. Unresolved issues include:

1. Is the risk of pancreatitis with exenatide greater than other anti-diabetics?
2. Is the risk of pancreatitis with sitagliptin greater than other anti-diabetics?
3. What is the risk of pancreatitis between exenatide and sitagliptin?

These 3 questions are being asked in the i3 drug safety study with final results scheduled for submission to FDA in September 2009. These data will better inform FDA on whether a boxed warning is warranted for either exenatide or sitagliptin and should therefore be made a required study under the Food and Drug Administration Amendments Act (FDAAA) to ensure timely submission to the agency.

The incretin-based anti-diabetic therapies may be associated with a higher risk for pancreatic adverse events. Mechanistic studies on the effect of these therapies on bile duct flow and the sphinctor of Oddi have been proposed by Amylin. Similar studies should also be undertaken by Merck for sitagliptin and Novo Nordisk for liraglutide. Should liraglutide be approved, OSE should consider the 3rd question in DMEP's consult for the i3 drug safety study. Specifically, DMEP had requested OSE to *"provide 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 possibility that signals for pancreatitis observed from AERS reflects an increased risk to patients with type 2 diabetes should not be dismissed. If the i3 drug safety study results show similar risk of acute pancreatitis across all cohorts for diabetes therapies and an increase risk over the non-diabetic cohort, a discussion should be undertaken on whether other anti-diabetic therapies need to have updated labeling.

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/

MARY H PARKS
11/01/2009