

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022200Orig1s000

SUMMARY REVIEW



ADDENDUM TO DECISIONAL MEMO

From: Mary H. Parks, M.D.
Deputy Director
Office of Drug Evaluation 2

To: NDA 22-200 Administrative File

Drug Product: Bydureon (extended release exenatide)

Subject: Correction of misstatement in decisional memo dated January 27, 2012

I recently became aware of a typographical error in my decisional memo for NDA 22-200 (Bydureon) dated January 27, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000SumR.pdf. The errors are contained within the following paragraphs on the first and second pages of my memo and are highlighted in red font below:

*The initial submission of Bydureon received a complete response action on March 12, 2010. During this review, FDA only identified the requirement for a REMS with Medication Guide and product quality issues as deficiencies to be remedied. FDA was not made aware of a thorough QT (tQT) study that was conducted for the Canadian regulatory authorities in support of a marketing application for Byetta in that country. The time period during which this tQT study was conducted was between April 23, 2008 and July 21, 2008, well in advance of when Amylin submitted its NDA to FDA for Bydureon. More importantly, FDA was not informed by Amylin that Health Canada considered several findings from tQT study concerning enough such that approval was delayed in Canada because agreement on product labeling could not be reached. **On April 12, 2008**, Health Canada notified FDA of this study and its implications to both Byetta and Bydureon risk assessments.*

*FDA contacted Amylin the following day on **April 13, 2008**, and they confirmed the existence of the study. The study had been conducted outside the U.S. IND and the only information that had been submitted to FDA came in two annual reports in which only the title of this study (“A placebo and positive controlled study of the electrophysiological effects of a single 10 mcg dose of exenatide on the 12 lead electrocardiogram (ECG) QT interval in healthy subjects” – Study GWCI) was reported in a table to the Byetta IND 057725 in annual reports dated April 10, 2009 and April 9, 2010. No results or synopses were provided to either the INDs or NDAs of either Byetta or Bydureon.*

The correct dates for the events described in these two paragraphs are April 12, 2010 and April 13, 2010, respectively. Evidence supporting my correction to this decisional memo can be cited in the Complete Response (CR) letter for NDA 22-200 issued on October 18, 2010, and my accompanying decisional memo for the CR action dated the same day.

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

/s/

MARY H PARKS

09/08/2013

addendum to correct date in decisional memo

**Division Director's Memo**

NDA 22-200

Drug name Bydureon® (exenatide extended-release formulation)

Indication As an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings

Date January 27, 2012

Background

This application is for Bydureon, a long-acting formulation of exenatide, an approved glucagon-like peptide 1 (GLP-1) receptor agonist marketed as an immediate-release formulation under the tradename, Byetta. Both products control hyperglycemia in type 2 diabetes in a glucose-dependent fashion through GLP-1 receptor activation. GLP-1 is an incretin hormone which increases insulin secretion in response to an ingested meal. Because human GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase IV (DPP-IV), it has limited clinical use.

Exenatide is a synthetically manufactured 34-amino acid GLP-1 agonist that has 53% homology with human GLP-1. Agonistic activity at the human GLP-1 receptor is retained with exenatide while being naturally resistant to DPP-IV, allowing for twice-daily administration. Bydureon is comprised of exenatide encapsulated in a biodegradable polymer microsphere. After subcutaneous injection the polymer degrades slowly allowing for the delayed release of exenatide reducing the frequency of injections over Byetta. The recommended dosing regimen for Bydureon is 2 mg once weekly. Amylin manufactures and is the holder of both NDAs for Byetta and Bydureon.

The review and this eventual recommendation for approval of Bydureon has been a long and complicated process, in part due to Amylin's withholding of information on Byetta that FDA deemed to be important to its evaluation of the safety and effectiveness of Bydureon. Although this application was received under Section 505(b)(1) of the FDCA, Amylin requested that FDA rely on the findings of safety and effectiveness of Byetta in support of this NDA. Since the active ingredient for both drug products are identical, this request was granted. However, this agreement would also mean that what knowledge Amylin had of Byetta should have been submitted to FDA in a transparent manner to fully disclose any areas that needed to be considered in the benefit-risk assessment of Bydureon.

The initial submission of Bydureon received a complete response action on March 12, 2010. During this review, FDA only identified the requirement for a REMS with Medication Guide and product quality issues as deficiencies to be remedied. FDA was not made aware of a thorough QT (tQT) study that was conducted for the Canadian regulatory authorities in support of a marketing application for Byetta in that country. The time period during which this tQT study was conducted was between April 23, 2008 and July 21, 2008, well in advance of when Amylin submitted its NDA to FDA for Bydureon. More importantly, FDA was not informed by Amylin that Health Canada considered several findings from tQT study concerning enough such that approval was delayed in Canada because agreement on product labeling could not be reached. On April 12, 2008, Health Canada notified FDA of this study and its implications to both Byetta and Bydureon risk assessments.

FDA contacted Amylin the following day on April 13, 2008, and they confirmed the existence of the study. The study had been conducted outside the U.S. IND and the only information that had been submitted to FDA came in two annual reports in which only the title of this study (“A placebo and positive controlled study of the electrophysiological effects of a single 10 mcg dose of exenatide on the 12 lead electrocardiogram (ECG) QT interval in healthy subjects” – Study GWCI) was reported in a table to the Byetta IND 057725 in annual reports dated April 10, 2009 and April 9, 2010. No results or synopses were provided to either the INDs or NDAs of either Byetta or Bydureon.

FDA informed Amylin that this GWCI study should be submitted for review and considered in the resubmission of Bydureon. Amylin resubmitted its Bydureon application on April 22, 2010. Absent from this resubmission were the data from GWCI. Instead, the results and datasets for GWCI were submitted on April 15, and May 13, 2010 to the Byetta IND. Regardless, FDA reviewed it as part of the Bydureon NDA.

On October 18, 2010, a second CR letter was issued citing two new clinical issues which arose as a result of FDA’s review of GWCI. As described in the second CR letter, a significant concentration-QTc relationship for exenatide was noted and it could not be concluded that higher exposures with Bydureon, especially in patients with renal impairment would not adversely affect the QT interval. To address this deficiency, the applicant was told to conduct a tQT study in which Byetta was administered at doses which would approximate exposures to Bydureon. In addition, as a result of a signal for cardiovascular safety from data not disclosed to FDA during its interactions with Amylin at its preNDA meeting and during the initial review cycle of Bydureon, FDA had to reconsider the benefit-risk conclusion of this product with respect to a finding identified in that initial review cycle which was not identified in the first CR letter. This issue centered around whether the to-be-marketed Bydureon product provided similar efficacy as the investigational product.

As stated above, Amylin was relying on the findings of safety and effectiveness of Byetta and had a somewhat abbreviated clinical program for Bydureon to be complemented by the Byetta NDA. Consequently, Amylin had conducted a study comparing an investigational product of Bydureon to Byetta in Study LAR-105 claiming superiority of Bydureon to Byetta: this was the pivotal clinical efficacy and safety trial. Due to changes in the manufacturing site and a scale-up, a different commercial product was proposed for marketing which was not studied in LAR-105. Amylin was required to bridge between the investigational product used in Study LAR-105 and the proposed commercial product. The company did so in a substudy to LAR, referred to as LAR-105c. This substudy had some limitations with regard to duration of assessment and differences between the patients evaluated relative to those studied in LAR-105. However, more importantly, the statistician remarked on the greater deterioration of glycemic control of the commercial product over the investigational product. As noted in the 2nd CR letter, *“The average difference between the two products was 0.2 after 18 weeks of treatment with an accompanying 95% CI for this comparison of 0.0 to 0.3. The lower bound of this 95% CI raises concern that the commercial product may be less effective than the investigational product used in LAR-105. As a result, we can not conclude that the commercial product will provide superior efficacy to the currently marketed Byetta from LAR-105.”*

To address this deficiency, the applicant was told to submit the results of another study comparing Byetta to the commercial product, Study LAR-108.

After receiving its 2nd CR letter, Amylin’s chief medical officer informed the Division that they were committed to providing the agency with an appropriate tQT study to evaluate the effects of higher exenatide drug concentrations on the QT interval and the results of Study 108. However, prior to submitting these data, Amylin took another strategy by submitting a formal dispute resolution request

(FDRR) requesting that FDA approve Bydureon without the results of either these studies. Amylin further requested that the tQT study be a postmarketing required study. The FDRR was denied by Dr. Curtis Rosebraugh and its appeal was denied by Dr. John Jenkins (please appropriate section of action package for their respective decisions).

On July 28, 2011, Amylin submitted the completed results of both a tQT study and Study LAR-108 in response to the 2nd CR letter. In addition to these studies, the applicant also provided the results of recently completed non-clinical studies with data to be included in labeling for both Byetta and Bydureon.

For the remainder of this memo, I will highlight the findings from Study LAR-108 and the tQT study submitted to address the most recent deficiency items. Please see the reviews from different disciplines for other areas covered with this resubmission.

Clinical Study BCB108 (Source document: 7/27/2011 submission to NDA 22-200, Module 5.3.5.1.3) This was a 24-week, open-label trial comparing the glucose-lowering effects of Byetta to Bydureon. The primary efficacy endpoint was change in HbA1c from baseline to Week 24/study termination and secondary endpoints included but were not limited to: proportion achieving HbA1c < 7%, change in fasting plasma glucose, and change in body weight.

The primary objective of the trial was to demonstrate that the change in HbA1c from baseline was non-inferior between Byetta and Bydureon by a 0.4% margin.

The results of this study were specifically requested for this resubmission because the drug product employed was manufactured at the intended commercial site (West Chester, Ohio), unlike a previously reviewed trial (Study 105), which employed a drug product manufactured at an investigational site (Alkermes). Overall, both trials were similar in study design and patient population, which were patients with T2DM who had been previously treated for at least 2 months on a regimen of diet and exercise alone or a stable regimen of metformin, SU, TZD, or a combination of up to two of these oral medications.

Table 1. Baseline Characteristics of Studies 105 and 108

	Study 105 N=295	Study 108 N=252
Males, N (%)	157 (53.2%)	145 (57.5%)
Mean age, yrs	55	55.6
Mean BMI, kg/m ²	34.9	33.3
Mean HbA1c	8.3	8.4
< 9%, N (%)	216 (73.2%)	178 (71.2%)
≥ 9%, N (%)	79 (26.8%)	72 (28.8%)
Mean duration of diabetes @ screening, yrs	6.7	7.0

Dr. Janice Derr from the Office of Biostatistics reviewed both Studies 105 and 108. Please see her reviews dated December 29, 2009, and September 6, 2011, respectively. Below is a summary of the efficacy results from both of these trials as presented in Dr. Derr's review.

Source of Table: From FDA Statistical Review

TABLE 1 Study BCB108 and Study 105; Primary HbA1c endpoint

	N	Baseline mean HbA1c ± SE	Adjusted mean change from baseline at Week 24 ± SE ¹	Exenatide QW – Byetta Difference in adjusted mean change (95% CI) ¹	P-value
Study BCB108: HbA1c at week 24 as a change from baseline					
All subjects (ITT/LOCF)					
Exenatide QW	123	8.5 ± 0.1	-1.6 ± 0.1	-0.7 (-0.9, -0.4)	<0.001
Byetta	129	8.4 ± 0.1	-0.9 ± 0.1		
Study 105: HbA1c at week 30 as a change from baseline					
All subjects (ITT/LOCF)					
Exenatide LAR	148	8.3 ± 0.1	-1.9 ± 0.1	-0.3 (-0.5, -0.1)	0.002
Byetta	147	8.3 ± 0.1	-1.5 ± 0.1		

Sources: Study BCB108 report, Table 7; Study 105 report, Table 8

In both studies, once-weekly exenatide achieved statistically significantly greater HbA1c reduction than Byetta; however, the treatment difference was greater in Study 108. Although the change from baseline is higher with the investigational formulation (-1.9%) versus the to-be-marketed product (-1.6%), the Byetta response is more pronounced in Study 105 which might have explained the greater treatment effect in Study 108. Study 108 was a 24-week trial whereas Study 105 evaluated efficacy at Week 30. It is not certain if the additional 6 weeks might have made a difference, particularly for the Byetta arm which requires a 4-week titration at the 5 mcg bid dose followed by the maximally approved dose of 10 mcg bid. Patients in Study 108 would have received Byetta 10 mcg bid for only 20 weeks versus 26 weeks in Study 105 and might have achieved greater glycemic control as a result. However, in reviewing the registration trials for Byetta there were several 30-week trials in which efficacy assessments for Byetta administered in the same fashion achieved a change from baseline at Week 30 in HbA1c of 0.9%. These trials were actually noted in Table 2 of Dr. Derr’s original review of Bydureon. So in effect, the efficacy of Byetta in Study 108 is in line with results observed in several earlier trials of longer duration.

I also noted that the baseline use of TZDs, alone or in combination, was higher in the Bydureon group (17.1%) compared to Byetta (9.8%). All patients had to have been on an effective dose of rosiglitazone or pioglitazone for at least 2 months prior to screening. As it may take 6 months for the maximal effect of TZDs to be observed, an analysis of efficacy by the different background therapies at baseline was evaluated to ensure that the superiority findings were not related to the imbalance in TZD use. Bydureon resulted in greater HbA1c reduction than Byetta in all subgroups including patients treated with diet and exercise alone, metformin alone, SU alone or metformin plus SU. Hence, the differential use of TZDs at baseline did not appear to bias the findings towards superiority for Bydureon.

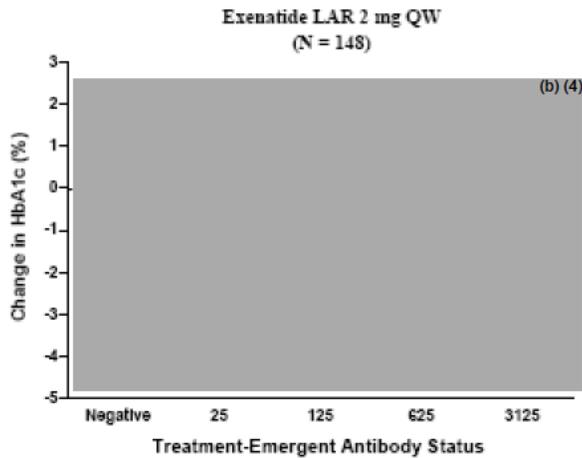
There were two items noted in the original statistical review of Bydureon that I want to address in this memo. In Study 105, Dr. Derr expressed concern of a potential for bias due to unblinded adjustment of sulfonylurea dose prior to the primary efficacy evaluation. While this concern was alleviated by several sensitivity analyses performed of that study, I inquired if a similar concern arose for Study 108. Figure 6B from her review showed a similar response in HbA1c reduction by baseline SU use/non-use with a p-value for treatment interaction of 0.470, hence the adjustments in SU dosing did not appear to affect the overall results in Study 108. The second concern was related to the comparison of the investigational drug product and to-be-marketed product in Study LAR 105c. Because the mean baseline of patients enrolled in this substudy was 6.8 and the substudy was merely evaluating whether this degree of control could be sustained, the efficacy of patients with higher baseline HbA1c could not be determined. In Study 108, patients were stratified by baseline HbA1c < or ≥ 9% and a similar efficacy response was

observed in both subgroups (Please see Table 6 from Dr. Derr’s review). Consequently, Study 108 provided sufficient evidence of efficacy in patients with more poorly controlled type 2 diabetes. Overall, Study 108 was an adequate and well-controlled study employing the to-be-marketed product. The efficacy results of the Byetta arm were internally consistent with previously conducted trials reviewed by FDA and a systematic review for bias towards showing non-inferiority and superiority did not identify any.

In my previous review of this NDA (dated October 18, 2010), I noted that there were 9 patients in Study 105 treated with exenatide LAR 2 mg QW who had high antibody titers in which there appeared to be a trend towards lower efficacy as depicted below:

Source: CSR for Study 105

Figure 31. Change in HbA1c (%) at Week 30 by Anti-Exenatide Antibody Titer at Last Visit on or Prior to Week 30 (Study 2993LAR-105; Intent-to-Treat Population [N = 295])



It is interesting to note that in Study 108 there were 28 patients treated with Bydureon who had high Ab titers (≥ 625) and a similar pattern of reduced efficacy is noted compared to patients with no or low positive titers. Bydureon-treated patients with high titers had a mean HbA1c reduction of 1.0% versus 1.7% in those with no or low titers. In addition, more patients in the Bydureon group (28/128; 22%) versus Byetta (9/122; 7%) developed high Ab titers. This observation should be included in labeling.

Table 17. BCB108: Change in HbA1c (%) by intrinsic subpopulations

Subgroup	Study BCB108 (24 Weeks)					
	Exenatide Once Weekly 2 mg			BYETTA 10 mcg BID [1]		
	N	Mean (SE) Baseline (%)	LS Mean (SE) Change (%) [2]	N	Mean (SE) Baseline (%)	LS Mean (SE) Change (%) [2]
Overall Population	128	8.5 (0.1)	-1.6 (0.1)	122	8.4 (0.1)	-0.9 (0.1)
Gender						
Male	77	8.6 (0.1)	-1.6 (0.1)	68	8.4 (0.1)	-0.8 (0.2)
Female	51	8.4 (0.2)	-1.5 (0.2)	54	8.4 (0.2)	-1.0 (0.2)
Age (Screening)						
<65 Years	102	8.5 (0.1)	-1.5 (0.1)	101	8.5 (0.1)	-0.9 (0.1)
≥65 Years	26	8.3 (0.2)	-1.9 (0.2)	21	7.9 (0.2)	-1.3 (0.2)
Race						
Caucasian	81	8.4 (0.1)	-1.8 (0.1)	68	8.2 (0.1)	-1.1 (0.1)
Hispanic	37	8.7 (0.2)	-1.1 (0.2)	41	8.5 (0.2)	-0.7 (0.2)
Renal Function (Baseline)						
Normal [3]	63	8.9 (0.2)	-1.6 (0.2)	59	8.5 (0.2)	-0.8 (0.2)
Mild Impairment [3]	56	8.2 (0.1)	-1.4 (0.2)	55	8.3 (0.1)	-1.0 (0.2)
Moderate Impairment [3]	8	7.9 (0.2)	-1.5 (0.3)	8	8.0 (0.2)	-0.9 (0.3)
BMI Stratum (Baseline)						
<30 kg/m ²	39	8.7 (0.2)	-1.8 (0.2)	45	8.5 (0.2)	-0.7 (0.2)
≥30 kg/m ²	89	8.4 (0.1)	-1.5 (0.1)	77	8.3 (0.1)	-1.0 (0.1)
Antibody Status [4]						
Negative Titer	44	8.3 (0.1)	-1.7 (0.2)	57	8.2 (0.1)	-0.9 (0.2)
Low Positive Titer (≤125)	51	8.6 (0.2)	-1.7 (0.2)	46	8.4 (0.2)	-0.9 (0.2)
Higher Titer (≥625)	28	8.5 (0.2)	-1.0 (0.3)	9	8.3 (0.4)	-0.8 (0.5)

Source: Summary of Clinical Efficacy Table 14

Please see reviews of Dr. Pratt dated 2/22/10, 9/15/2010, and 12/12/2011 for a thorough discussion of the safety findings in this application. In general, a similar safety profile to that of Byetta was observed and product labeling will differ only slightly on safety findings. A CV meta-analysis of exenatide trials was previously reviewed by Dr. Fiona Callahan. No excess CV risk was identified but these trials were not prospectively evaluated for CV safety in a high-risk patient population. I note that Amylin is conducting a CV outcomes trial with Bydureon. As was done for Byetta, this trial will be listed as a PMR for this NDA.

Pancreatitis

Initial reports of pancreatitis associated with exenatide use came in the 1st periodic safety update report in 2005. Subsequently, more cases were reported resulting in an FDA safety alert issued in October 2007 followed by a second one in August 2008 as a result of some cases being of the severe form of necrotizing or hemorrhagic pancreatitis. Since 2005, several epidemiologic and nonclinical studies have been conducted to further investigate this risk. Results have been inconsistent and in the majority of cases, negative for a signal of excess risk.

As Bydureon is a long-acting form of exenatide, cases of pancreatitis were carefully scrutinized in this NDA. Review of safety was not limited to only Study 108 and the tQT study but also included data from 6 other studies (See Table 18 in Dr. Pratt's 2011 review). A total of 9 cases of pancreatitis were reported in the data submitted with the original NDA and resubmissions. Five of these occurred in completed, controlled studies and four occurred in ongoing trials. Dr. Pratt has summarized these cases on pages 67-68 of her most recent review. The exposure-adjusted rate for pancreatitis was 4.4 events per 1000 subject-yrs for Bydureon, 6.6 for sitagliptin, and 13.9 for pioglitazone. It should be noted that one of the cases in a pioglitazone-treated patient was described as necrotizing. Four additional cases occurred in Bydureon patients in ongoing trials.

In conclusion, the review of the Bydureon clinical development program did not identify a greater signal of risk for Bydureon over other comparators. Regardless, it remains difficult to establish definitively that an agent whose pharmacologic effect targets pancreatic cells and further affects gastrointestinal physiology is absent of any risk for pancreatitis. I agree with Dr. Pratt that similar language approved in Byetta's labeling discussing the risks of pancreatitis should carry over into the Bydureon label and any Byetta PMRs related to this risk should also be extended to Bydureon.

Hypersensitivity Reactions

Antibodies to exenatide developed in more patients treated with Bydureon than Byetta. Antibody positive patients had a higher incidence of immune-related adverse events. The majority of these events were administration site reactions including injection site erythema followed by musculoskeletal and connective tissue disorders of which arthralgia was the predominant complaint.

BCB112 (thorough QT study)

Please see review of the Interdisciplinary Review Team for QT Studies dated November 28, 2011.

Prior to initiating the pivotal tQT study, Amylin conducted a pilot study to determine if higher exposures to exenatide which approximated Bydureon exposure in patients with renal impairment could be achieved through an infusion of exenatide and that these high drug levels could be tolerated by study participants. The pivotal tQT study, Study BCB112, incorporated a similar dosing scheme and achieved suprathreshold target that was several fold higher than steady state concentrations expected with therapeutic doses of Bydureon.

This study was a randomized, placebo-controlled, and positive-controlled (moxifloxacin), 3-period, crossover design. Placebo and exenatide infusions were blinded; moxifloxacin was not. Three steady state concentrations were targeted: ~ 200 pg/mL, 300 pg/mL and 500 pg/mL over the course of 3 days. ECGs were obtained at multiple timepoints including those which would cover the steady state PK profile of exenatide.

The upper limit of the 2-sided 90% CI for LS Mean difference in Change from Baseline in QT interval corrected for heart rate was below 10 msec at all time points and at all targeted exenatide concentration. Positive control arm yielded expected increase in QT interval relative to placebo; hence, the study had adequate assay sensitivity to detect an effect on QT prolongation with exenatide.

Below is a summary of the findings from the pivotal tQT study.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Exenatide (~200pg/mL, ~300pg/mL and ~500pg/mL) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcP}$ (ms)	90% CI (ms)
Exenatide (~200pg/mL)	9	5.0	(3.7, 6.3)
Exenatide (~300pg/mL)	9	3.6	(2.3, 5.0)
Exenatide (~500pg/mL)	9	2.7	(1.4, 4.0)
Moxifloxacin 400 mg*	3	11.4	(9.0, 13.8)

* Multiple endpoint adjustment was applied for 3 timepoints.

No significant effect on QT interval was observed with exenatide, including at drug levels within the range that would be expected when patients with renal impairment are exposed to Bydureon (~ 500 pg/mL).

Post-marketing Requirements

As noted in Dr. Pratt’s review, the prolonged activation of GLP-1 receptor by Bydureon raises similar concerns of C-cell hyperplasia and risks for neoplasm as was observed in the nonclinical development program for another approved long-acting GLP-1 receptor agonist, liraglutide. Consequently, several nonclinical studies will be required of this NDA to better understand the relevance of C-cell hyperplasia on tumor progression and whether the finding is reversible, the role of GLP-1 receptor activation on development of C-cell hyperplasia, and differences/similarities of GLP-1 receptor expression across human and rodent thyroid C-cells. In addition to the nonclinical PMRs, the applicant will be required to establish a medullary thyroid carcinoma case series registry and labeling will be similar to liraglutide with respect to contraindications, boxed warning and recommendations against initial therapy in drug-naïve patients. Finally, the applicant is required to conduct a prospective cardiovascular outcomes trial to address the FDA’s 2008 Guidance for CV risk assessment.

Conclusions and Overall Recommendations

With this 3rd submission, the applicant has addressed all the deficiencies identified in previous reviews. Bydureon has been shown to effectively lower HbA1c to a greater extent than Byetta. A second tQT study which achieved higher exenatide drug exposures in study participants than a previously conducted study (GWCI) provided sufficient evidence that Bydureon does not pose a serious risk of QT prolongation.

This application can be approved pending agreement reached on labeling.

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

/s/

MARY H PARKS
01/27/2012