

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 022200/S-008**

***Trade Name:*** BYDUREON

***Generic Name:*** Exenatide Extended-Release For Injectable Suspension

***Sponsor:*** Amylin Pharmaceuticals, LLC

***Approval Date:*** 02/28/2014

***Indications:*** BYDUREON is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

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*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 022200/S-008

**SUPPLEMENT APPROVAL**

Amylin Pharmaceuticals, LLC  
Attention: Cindy Cao, Ph.D.  
Associate Director, CV & Metabolics  
Global Regulatory & Safety Sciences - US  
P.O. Box 4000 (Mail Stop: D22-06)  
Princeton, NJ 08543-4000

Dear Dr. Cao:

Please refer to your Supplemental New Drug Application (sNDA) dated August 29, 2013, received August 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bydureon (exenatide extended-release for injectable suspension).

We acknowledge receipt of your amendments dated October 17, November 14, December 11, 16, and 23, 2013, and February 5, and 24, 2014.

This "Prior Approval" supplemental new drug application proposes a manually operated, single-use, dual-chamber pen presentation of Bydureon (exenatide extended release for injectable suspension).

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide, Instruction for Use for single-dose tray presentation, and Instructions for Use for pen presentation) with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA022200/S-008.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Sincerely,

*{See appended electronic signature page}*

Jean-Marc Guettier, M.D.  
Director (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

### ENCLOSURES:

Prescribing Information

Medication Guide

Instruction for Use for single-dose tray presentation (version approved on January 27, 2012)

Instructions for Use for pen presentation

Carton and Container Labeling for pen presentation

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

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JEAN-MARC P GUETTIER  
02/28/2014

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
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**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BYDUREON safely and effectively. See full prescribing information for BYDUREON.

BYDUREON® (exenatide extended-release for injectable suspension)  
Initial U.S. Approval: 2012

### WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- Exenatide extended-release causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies (5.1).
- BYDUREON is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) (5.1).

## INDICATIONS AND USAGE

BYDUREON is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1.1, 14).

BYDUREON is an extended-release formulation of exenatide. Do not coadminister with BYETTA.

### Important Limitations of Use

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (5.1).
- Should not be used to treat type 1 diabetes or diabetic ketoacidosis (1.2).
- Use with insulin has not been studied and is not recommended (1.2).
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (1.2, 5.2).

## DOSAGE AND ADMINISTRATION

- Administer 2 mg by subcutaneous injection once every seven days (weekly), at any time of day and with or without meals (2.1).
- Administer immediately after the dose is prepared (2.1).

## DOSAGE FORMS AND STRENGTHS

BYDUREON 2 mg exenatide for extended-release injectable suspension has two dosage forms (3):

- BYDUREON single-dose tray containing 2 mg vial
- BYDUREON Pen single-dose 2 mg pen

## CONTRAINDICATIONS

- Do not use for patients with personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4.1).
- Do not use for patients with history of serious hypersensitivity to exenatide or any product components (4.2).

## WARNINGS AND PRECAUTIONS

- Thyroid C-cell tumors in animals: Human relevance unknown. Counsel patients regarding the risk of medullary thyroid carcinoma and the symptoms of thyroid tumors (5.1).
- Pancreatitis: Postmarketing reports with exenatide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies if patient has history of pancreatitis (5.2).
- Hypoglycemia: Increased risk when BYDUREON is used in combination with a sulfonylurea. Consider reducing the sulfonylurea dose (5.3).
- Renal Impairment: Postmarketing reports with exenatide, sometimes requiring hemodialysis and kidney transplantation. Not recommended if patient has severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or moderate renal impairment (5.4, 8.6, 12.3).
- Severe Gastrointestinal Disease: Not recommended in patients with severe gastrointestinal disease (e.g., gastroparesis) (5.5).
- Hypersensitivity: Postmarketing reports with exenatide of serious hypersensitivity reactions (e.g., anaphylaxis and angioedema). In such cases, patients are to discontinue BYDUREON and other suspect medications and promptly seek medical advice (5.7).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug (5.8).

## ADVERSE REACTIONS

- Most common (≥5%) and occurring more frequently than comparator in clinical trials: nausea, diarrhea, headache, vomiting, constipation, injection-site pruritus, injection-site nodule, and dyspepsia (5.3, 6.1).

To report SUSPECTED ADVERSE REACTIONS, contact 1-800-236-9933 and [www.bydureon.com](http://www.bydureon.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- May impact absorption of orally administered medications (7.1, 12.3).
- Warfarin: Postmarketing reports with exenatide of increased INR sometimes associated with bleeding. Monitor INR frequently until stable upon initiation of BYDUREON therapy (6.2, 7.2).

## USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. To report drug exposure during pregnancy call 1-800-633-9081 (8.1).
- Nursing Mothers: Use caution when administering to a nursing woman (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2014

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## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4.1)*, *Warnings and Precautions (5.1)*, and *Nonclinical Toxicology (13.1)*].

## 1 INDICATIONS AND USAGE

BYDUREON is an extended-release formulation of exenatide, administered as an injection once every 7 days (weekly).

### 1.1 Type 2 Diabetes Mellitus

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see *Clinical Studies (14)*].

### 1.2 Important Limitations of Use

Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe BYDUREON only to patients for whom the potential benefits are considered to outweigh the potential risk.

BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

BYDUREON is not a substitute for insulin. BYDUREON 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 BYDUREON with insulin has not been studied and cannot be recommended.

BYDUREON and BYETTA<sup>®</sup> (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYDUREON has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Recommended Dosing**

BYDUREON (2 mg per dose) should be administered once every 7 days (weekly). The dose can be administered at any time of day, with or without meals.

#### **Missed Dose**

If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least 3 days later. Thereafter, patients can resume their usual dosing schedule of once every 7 days (weekly).

If a dose is missed and the next regularly scheduled dose is due 1 or 2 days later, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose.

#### **Changing Weekly Dosing Schedule**

The day of weekly administration can be changed if necessary as long as the last dose was administered 3 or more days before.

## 2.2 Administration

BYDUREON must be injected immediately after the dose is prepared. BYDUREON is administered as a subcutaneous (SC) injection in the abdomen, thigh, or upper arm region. Advise patients to use a different injection site each week when injecting in the same region. BYDUREON must not be administered intravenously or intramuscularly. BYDUREON is intended for patient self-administration.

**Prior to initiation of BYDUREON, patients should be trained by their healthcare professional.** For the BYDUREON Pen, study data demonstrated that training reduced the risk of administration errors such as inadequate mixing or incomplete dosing. Patients using the BYDUREON Pen should be trained on proper mixing and injection technique to ensure the product is adequately mixed and a full dose is delivered. **Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.** The instructions can also be found at [www.bydureon.com](http://www.bydureon.com).

## 2.3 Changing from BYETTA to BYDUREON

Prior treatment with BYETTA is not required when initiating BYDUREON therapy. If the decision is made to start BYDUREON in an appropriate patient already taking BYETTA, BYETTA should be discontinued. Patients changing from BYETTA to BYDUREON may experience transient (approximately 2 weeks) elevations in blood glucose concentrations.

## 3 DOSAGE FORMS AND STRENGTHS

BYDUREON exenatide extended-release for injectable suspension is available as:

- BYDUREON single-dose tray which contains one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe, and two needles (one provided as a spare).
- BYDUREON Pen. Each single-dose pen contains 2 mg of exenatide and diluent, and includes one needle. Each carton contains one spare needle.

**Do not substitute needles or any other components provided with BYDUREON.** See *How Supplied/Storage and Handling (16.1)* for additional information.

## **4 CONTRAINDICATIONS**

### **4.1 Medullary Thyroid Carcinoma**

BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

### **4.2 Hypersensitivity**

BYDUREON is contraindicated in patients with a prior serious hypersensitivity reaction to exenatide or to any of the product components.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Risk of Thyroid C-cell Tumors**

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls [see *Nonclinical Toxicology (13.1)*]. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at  $\geq 2$ -times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON [see *Boxed Warning and Contraindications (4.1)*].

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values  $>50$  ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients

treated with BYDUREON. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation [see *Patient Counseling Information (17)*].

## 5.2 Acute Pancreatitis

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, 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, BYDUREON should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYDUREON should not be restarted. Consider antidiabetic therapies other than BYDUREON in patients with a history of pancreatitis.

## 5.3 Hypoglycemia

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

For additional information on glucose-dependent effects see *Clinical Pharmacology (12.1)*.

## 5.4 Renal Impairment

BYDUREON 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 BYDUREON may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) [see *Use in Specific*

*Populations (8.6) and Clinical Pharmacology (12.3)*]. BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

There have been postmarketing reports of altered renal function with exenatide, 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 exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

## **5.5 Gastrointestinal Disease**

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

## **5.6 Immunogenicity**

Patients may develop antibodies to exenatide following treatment with BYDUREON. Anti-exenatide antibodies were measured in all BYDUREON-treated patients in the five comparator-controlled 24- to 30-week studies of BYDUREON. In 6% of BYDUREON-treated patients, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered [see *Adverse Reactions (6.1)*].

## **5.7 Hypersensitivity**

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

## 5.8 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BYDUREON was assessed in five comparator-controlled trials in patients who entered the studies not achieving adequate glycemic control on their current therapy. In a double-blind 26-week trial, patients on diet and exercise were treated with BYDUREON 2 mg once every 7 days (weekly), sitagliptin 100 mg daily, pioglitazone 45 mg daily, or metformin 2000 mg daily. In a double-blind 26-week trial, patients on metformin were treated with BYDUREON 2 mg once every 7 days (weekly), sitagliptin 100 mg daily, or pioglitazone 45 mg daily. In an open-label 26-week trial, patients on metformin or metformin plus sulfonylurea were treated with BYDUREON 2 mg once every 7 days (weekly) or optimized insulin glargine. In two open-label 24- to 30-week studies, patients on diet and exercise or metformin, a sulfonylurea, a thiazolidinedione, or combination of oral agents were treated with BYDUREON 2 mg once every 7 days (weekly) or BYETTA 10 mcg twice daily.

#### Withdrawals

The incidence of withdrawal due to adverse events was 4.9% (N=45) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients, and 2.0% (N=23) for other comparator-treated patients in the five comparator-controlled 24- to 30-week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5% (N=5) versus 1.5% (N=4) for BYETTA and 0.3% (N=3) for other comparators, injection-site nodule 0.5% (N=5) versus 0.0% for BYETTA and 0.0% for other comparators, diarrhea 0.3% (N=3) versus 0.4% (N=1) for BYETTA and 0.3% (N=3) for other comparators, injection-site reaction 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators, and headache 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators.

## Hypoglycemia

Table 1 summarizes the incidence and rate of minor hypoglycemia in the five comparator-controlled 24- to 30-week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione, or combination of these oral antidiabetic agents. In these trials, an event was classified as minor hypoglycemia if there were symptoms of hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

**Table 1: Incidence (% of Subjects) and Rate (Episodes/Subject Year) of Minor<sup>†</sup> Hypoglycemia in the Monotherapy Trial and in the Combination Therapy Trials**

<b>26-Week Monotherapy Trial</b>	
BYDUREON 2 mg (N = 248)	2.0% (0.05)
Sitagliptin 100 mg (N = 163)	0.0% (0.00)
Pioglitazone 45 mg (N = 163)	0.0% (0.00)
Metformin 2000 mg QD (N = 246)	0.0% (0.00)
<b>26-Week Add-On to Metformin Trial</b>	
BYDUREON 2 mg (N = 160)	1.3% (0.03)
Sitagliptin 100 mg (N = 166)	3.0% (0.12)
Pioglitazone 45 mg (N = 165)	1.2% (0.03)
<b>26-Week Add-On to Metformin or Metformin + Sulfonylurea Trial</b>	
<b>With Concomitant Sulfonylurea Use (N = 136)</b>	
BYDUREON 2 mg (N = 70)	20.0% (1.11)
Titrated Insulin Glargine (N = 66)	43.9% (2.87)
<b>Without Concomitant Sulfonylurea Use (N = 320)</b>	
BYDUREON 2 mg (N = 163)	3.7% (0.11)
Titrated Insulin Glargine <sup>‡</sup> (N = 157)	19.1% (0.64)
<b>24-Week Monotherapy or Add-On to Metformin, a Sulfonylurea, a Thiazolidinedione, or Combination of Oral Agents Trial</b>	
<b>With Concomitant Sulfonylurea Use (N = 74)</b>	
BYDUREON 2 mg (N = 40)	12.5% (0.72)
BYETTA 10 mcg (N = 34)	11.8% (0.31)
<b>Without Concomitant Sulfonylurea Use (N = 178)</b>	
BYDUREON 2 mg (N = 89)	0.0% (0.00)
BYETTA 10 mcg (N = 89)	0.0% (0.00)

**Table 1: Incidence (% of Subjects) and Rate (Episodes/Subject Year) of Minor<sup>†</sup> Hypoglycemia in the Monotherapy Trial and in the Combination Therapy Trials**

<b>30-Week Monotherapy or Add-On to Metformin, a Sulfonylurea, a Thiazolidinedione, or Combination of Oral Agents Trial</b>	
<b>With Concomitant Sulfonylurea Use (N = 107)</b>	
BYDUREON 2 mg (N = 55)	14.5% (0.55)
BYETTA 10 mcg (N = 52)	15.4% (0.37)
<b>Without Concomitant Sulfonylurea Use (N = 186)</b>	
BYDUREON 2 mg (N = 93)	0.0% (0.00)
BYETTA 10 mcg (N = 93)	1.1% (0.02)

N = number of intent-to-treat patients.

Note: Percentages are based on the number of intent-to-treat patients in each treatment group.

<sup>†</sup> Reported event that has symptoms consistent with hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

<sup>‡</sup> Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL. The mean dose of insulin glargine was 10 Units/day at baseline and 31 Units/day at endpoint.

There were no reported events of major hypoglycemia in these five comparator-controlled 24- to 30-week trials. Major hypoglycemia was defined as loss of consciousness, seizure, or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) which resolved after administration of glucagon or glucose or required third-party assistance to resolve because of severe impairment in consciousness or behavior. Patients were to have a concomitant glucose <54 mg/dL.

### Immunogenicity

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies ( $\leq 125$ ) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA<sub>1c</sub>); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies [see *Warnings and Precautions (5.6)*]. In the 30-week trial in which anti-exenatide antibody

assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

A total of 246 patients with antibodies to exenatide in the BYETTA and BYDUREON clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross-reactive antibodies were observed across the range of titers.

## Other Adverse Reactions

### **BYDUREON**

Tables 2 and 3 summarize adverse reactions with an incidence  $\geq 5\%$  reported in the five comparator-controlled 24- to 30-week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione, or combination of these oral antidiabetic agents.

**Table 2: Treatment-Emergent Adverse Reactions Reported in  $\geq 5\%$  of BYDUREON-Treated Patients in Monotherapy Trial**

26-Week Monotherapy Trial				
	BYDUREON 2 mg N = 248 %	Sitagliptin 100 mg N = 163 %	Pioglitazone 45 mg N = 163 %	Metformin 2000 mg N = 246 %
Nausea	11.3	3.7	4.3	6.9
Diarrhea	10.9	5.5	3.7	12.6
Injection-site nodule <sup>†</sup>	10.5	6.7	3.7	10.2
Constipation	8.5	2.5	1.8	3.3
Headache	8.1	9.2	8.0	12.2
Dyspepsia	7.3	1.8	4.9	3.3

N = number of intent-to-treat patients.

Note: Percentages are based on the number of intent-to-treat patients in each treatment group.

<sup>†</sup> Patients in the sitagliptin, pioglitazone, and metformin treatment groups received weekly placebo injections.

**Table 3: Treatment-Emergent Adverse Reactions Reported in  $\geq 5\%$  of BYDUREON-Treated Patients in 24- to 30-Week Add-On Combination Therapy Trials**

<b>26-Week Add-On to Metformin Trial</b>			
	<b>BYDUREON 2 mg N = 160 %</b>	<b>Sitagliptin 100 mg N = 166 %</b>	<b>Pioglitazone 45 mg N = 165 %</b>
Nausea	24.4	9.6	4.8
Diarrhea	20.0	9.6	7.3
Vomiting	11.3	2.4	3.0
Headache	9.4	9.0	5.5
Constipation	6.3	3.6	1.2
Fatigue	5.6	0.6	3.0
Dyspepsia	5.0	3.6	2.4
Decreased appetite	5.0	1.2	0.0
Injection-site pruritus <sup>†</sup>	5.0	4.8	1.2
<b>26-Week Add-On to Metformin or Metformin + Sulfonylurea Trial</b>			
	<b>BYDUREON 2 mg N = 233 %</b>	<b>Insulin Glargine Titrated N = 223 %</b>	
Nausea	12.9	1.3	
Headache	9.9	7.6	
Diarrhea	9.4	4.0	
Injection-site nodule	6.0	0.0	
<b>30-Week Monotherapy or as Add-On to Metformin, a Sulfonylurea, a Thiazolidinedione, or Combination of Oral Agents Trial</b>			
	<b>BYDUREON 2 mg N = 148 %</b>	<b>BYETTA 10 mcg N = 145 %</b>	
Nausea	27.0	33.8	
Diarrhea	16.2	12.4	
Vomiting	10.8	18.6	
Injection-site pruritus	18.2	1.4	
Constipation	10.1	6.2	
Gastroenteritis viral	8.8	5.5	
Gastroesophageal reflux disease	7.4	4.1	
Dyspepsia	7.4	2.1	

**Table 3: Treatment-Emergent Adverse Reactions Reported in  $\geq 5\%$  of BYDUREON-Treated Patients in 24- to 30-Week Add-On Combination Therapy Trials**

Injection-site erythema	7.4	0.0	
Fatigue	6.1	3.4	
Headache	6.1	4.8	
Injection-site hematoma	5.4	11.0	
<b>24-Week Monotherapy or as Add-On to Metformin, a Sulfonylurea, a Thiazolidinedione, or Combination of Oral Agents Trial</b>			
	<b>BYDUREON 2 mg N = 129 %</b>	<b>BYETTA 10 mcg N = 123 %</b>	
Nausea	14.0	35.0	
Diarrhea	9.3	4.1	
Injection-site erythema	5.4	2.4	

N = number of intent-to-treat patients.

Note: Percentages are based on the number of intent-to-treat patients in each treatment group.

† Patients in the sitagliptin, pioglitazone, and metformin treatment groups received weekly placebo injections.

Nausea was the most common adverse reaction associated with initiation of treatment with BYDUREON, and usually decreased over time.

### **Injection-Site Reactions**

In the five comparator-controlled 24- to 30-week trials, injection-site reactions were observed more frequently in patients treated with BYDUREON (17.1%) than in patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%), or those patients who received placebo injections (sitagliptin (10.6%), pioglitazone (6.4%), and metformin (13.0%) treatment groups). These reactions for patients treated with BYDUREON were more commonly observed in antibody-positive patients (14.2%) compared with antibody-negative patients (3.1%), with a greater incidence in those with higher titer antibodies [see *Warnings and Precautions (5.6)*]. Incidence of injection-site reactions for patients treated with BYETTA was similar for antibody-positive patients (5.8%) and antibody-negative patients (7.0%). One percent of patients treated with BYDUREON withdrew due to injection-site adverse reactions (injection-site mass, injection-site nodule, injection-site pruritus, and injection-site reaction).

Small, asymptomatic subcutaneous injection-site nodules are seen with the use of BYDUREON. In a separate 15-week study in which information on nodules were collected and analyzed, 24

out of 31 subjects (77%) experienced at least 1 injection-site nodule during treatment; 2 subjects (6.5%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of nodules is consistent with the known properties of the microspheres used in BYDUREON.

## **BYETTA**

In three 30-week controlled trials of BYETTA (N=963) add-on to metformin and/or sulfonylurea, adverse reactions (excluding hypoglycemia) with an incidence of  $\geq 1\%$  and reported more frequently than with placebo included nausea (44% BYETTA, 18% placebo), vomiting (13% BYETTA, 4% placebo), diarrhea (13% BYETTA, 6% placebo), feeling jittery (9% BYETTA, 4% placebo), dizziness (9% BYETTA, 6% placebo), headache (9% BYETTA, 6% placebo), dyspepsia (6% BYETTA, 3% placebo), asthenia (4% BYETTA, 2% placebo), gastroesophageal reflux (3% BYETTA, 1% placebo), hyperhidrosis (3% BYETTA, 1% placebo), and decreased appetite (1% BYETTA, <1% placebo). Similar types of adverse reactions were observed in 24-week and 16-week controlled trials of BYETTA used as monotherapy or as add-on to a thiazolidinedione, with or without metformin, respectively.

## **6.2 Postmarketing Experience**

### **BYETTA**

The following additional adverse reactions have been reported during postapproval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Allergy/Hypersensitivity:* injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema; anaphylactic reaction [see *Warnings and Precautions (5.7)*].

*Drug Interactions:* increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant warfarin use [see *Drug Interactions (7.2)*].

*Gastrointestinal:* nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death [see *Indications and Usage (1.2)* and *Warnings and Precautions (5.2)*].

*Neurologic:* dysgeusia; somnolence

*Renal and Urinary Disorders:* altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction [see *Warnings and Precautions (5.4)*].

*Skin and Subcutaneous Tissue Disorders:* alopecia

## **7 DRUG INTERACTIONS**

### **7.1 Orally Administered Drugs**

Exenatide slows gastric emptying. Therefore, BYDUREON has the potential to reduce the rate of absorption of orally administered drugs. Use caution when administering oral medications with BYDUREON [see *Clinical Pharmacology (12.3)*].

In patients with type 2 diabetes, BYDUREON did not affect the absorption of orally administered acetaminophen to any clinically relevant degree.

### **7.2 Warfarin**

BYDUREON has not been studied with warfarin. However, in a drug interaction study, BYETTA did not have a significant effect on INR [see *Clinical Pharmacology (12.3)*]. There have been postmarketing reports for BYETTA of increased INR with concomitant use of warfarin, sometimes associated with bleeding [see *Adverse Reactions (6.2)*]. In patients taking warfarin, the INR should be monitored more frequently after initiating BYDUREON. Once a stable INR has been documented, the INR can be monitored at the intervals usually recommended for patients on warfarin.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Category C

There are no adequate and well-controlled studies of BYDUREON use in pregnant women. In rats, exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification, and an increased number of neonatal deaths. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1, or 3 mg/kg on gestation days 6, 9, 12, and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1, and 3 mg/kg correspond to systemic exposures of 3, 7, and 17 times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on area under the time-concentration curve (AUC) [see *Nonclinical Toxicology (13.3)*].

Female mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

In developmental toxicity studies, pregnant animals received exenatide, the active ingredient of BYDUREON, subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate, and

skeletal effects at systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

Lactating mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC [see *Nonclinical Toxicology (13.3)*].

### **Pregnancy Registry**

A Pregnancy Registry has been implemented to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

### **8.3 Nursing Mothers**

Exenatide is present in the milk of lactating mice at concentrations less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing. It is not known whether exenatide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for exenatide extended-release in animal studies, a decision should be made whether to discontinue nursing or to discontinue BYDUREON, taking into account the importance of the drug to the mother.

### **8.4 Pediatric Use**

Safety and effectiveness of BYDUREON have not been established in pediatric patients. BYDUREON is not recommended for use in pediatric patients.

### **8.5 Geriatric Use**

In the five comparator-controlled 24- to 30-week trials, BYDUREON was studied in 132 patients (16.6%) who were at least 65 years old and 20 patients who were at least 75 years old. No differences in safety (N=152) and efficacy (N=52) were observed between these patients and younger patients, but the small sample size for patients  $\geq 75$  years old limits conclusions.

In separate trials, BYETTA was studied in 282 patients at least 65 years old and in 16 patients at least 75 years old. No differences in safety and efficacy were observed between these patients and younger patients, but the small sample size for patients  $\geq 75$  years old limits conclusions.

Because elderly patients are more likely to have decreased renal function, use caution when initiating BYDUREON in the elderly.

## 8.6 Renal Impairment

BYDUREON is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance  $< 30$  mL/min) and should be used with caution in patients with renal transplantation. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) [see *Warnings and Precautions (5.4)* and *Clinical Pharmacology (12.3)*].

## 8.7 Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic impairment is not expected to affect blood concentrations of exenatide [see *Clinical Pharmacology (12.3)*].

## 10 OVERDOSAGE

There were no reports of overdose in the five comparator-controlled 24- to 30-week trials of BYDUREON. Effects of overdoses with BYETTA in clinical studies included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations, including severe hypoglycemia requiring parenteral glucose administration. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

## 11 DESCRIPTION

BYDUREON (exenatide extended-release for injectable suspension) is supplied as a sterile powder to be suspended in diluent and administered by subcutaneous injection. Exenatide is a 39-amino acid synthetic peptide amide with an empirical formula of  $C_{184}H_{282}N_{50}O_{60}S$  and a molecular weight of 4186.6 Daltons. The amino acid sequence for exenatide is shown below.

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH<sub>2</sub>

BYDUREON is a white to off-white powder that is available in a dosage strength of 2 mg exenatide per vial or per pen. Exenatide is incorporated in an extended-release microsphere formulation containing the 50:50 poly(D,L-lactide-co-glycolide) polymer (37.2 mg per dose) along with sucrose (0.8 mg per dose). The powder must be suspended in the diluent prior to injection.

The diluent for the BYDUREON vial is supplied in a prefilled syringe within each single-dose tray. The diluent for the BYDUREON Pen is contained within each single-dose pen. Each configuration contains sufficient diluent to deliver 0.65 mL. The diluent is a clear, colorless to pale-yellow solution composed of carboxymethylcellulose sodium (19 mg), polysorbate 20 (0.63 mg), sodium phosphate monobasic monohydrate (0.61 mg), sodium phosphate dibasic heptahydrate (0.51 mg), sodium chloride (4.1 mg), and water for injection. Sodium hydroxide may be added during manufacture of BYDUREON Pen for pH adjustment.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Incretins, such as glucagon-like peptide-1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut. BYDUREON is a GLP-1 receptor agonist that enhances glucose-dependent insulin secretion by the pancreatic beta-cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide is a GLP-1 receptor agonist that has been shown to bind and activate the human GLP-1 receptor *in vitro*. This leads to an increase in both glucose-dependent synthesis of insulin and *in vivo* secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic AMP and/or other intracellular signaling pathways. Exenatide promotes insulin release from pancreatic beta-cells in the presence of elevated glucose concentrations.

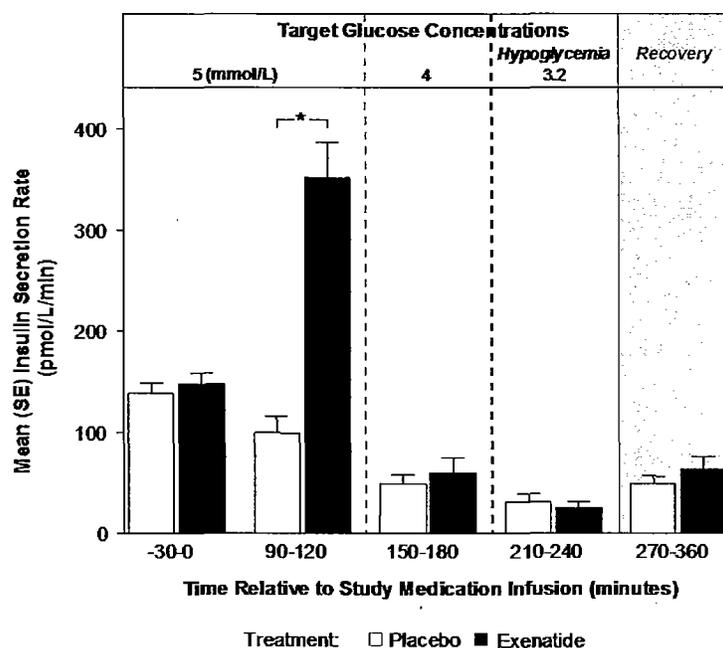
## 12.2 Pharmacodynamics

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through the actions described below.

### Glucose-Dependent Insulin Secretion

The effect of exenatide infusion on glucose-dependent insulin secretion rates (ISR) was investigated in 11 healthy subjects. In these healthy subjects, on average, the ISR response was glucose-dependent (Figure 1). Exenatide did not impair the normal glucagon response to hypoglycemia.

**Figure 1:** Mean (SE) Insulin Secretion Rates During Infusion of Exenatide or Placebo by Treatment, Time, and Glycemic Condition in Healthy Subjects



SE = standard error.

Notes: 5 mmol = 90 mg/dL, 4 mmol/L = 72 mg/dL, 3.2 mmol/L = 58 mg/dL; Study medication infusion was started at time = 0 minutes.

Statistical assessments were for the last 30 minutes of each glycemic step, during which the target glucose concentrations were maintained.

\*  $p < 0.05$ , exenatide treatment relative to placebo.

## **Glucagon Secretion**

In patients with type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia.

## **Gastric Emptying**

Exenatide slows gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

## **Food Intake**

Infusion of exenatide in 8 healthy subjects resulted in a 19% decrease in caloric intake following an *ad libitum* meal.

## **Fasting and Postprandial Glucose**

In a separate 15-week controlled study where fasting glucose was assessed on a weekly basis, BYDUREON treatment resulted in a mean reduction in fasting glucose of 17 mg/dL following 2 weeks of therapy with full effect on fasting glucose not observed until approximately 9 weeks.

In a 30-week controlled study of exenatide extended-release compared to BYETTA, postprandial glucose levels were measured during a mixed meal tolerance test in a subset of patients with type 2 diabetes mellitus. Following treatment for 14 weeks, when steady-state concentrations had been achieved (approximately 280-310 pg/mL), the LS mean change from baseline was significantly greater with BYETTA (-126 mg/dL) than exenatide extended-release (-96 mg/dL).

## **Cardiac Electrophysiology**

The effect of exenatide at therapeutic (253 pg/mL) and supratherapeutic (627 pg/mL) concentrations, following an intravenous infusion on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg) three-period crossover thorough QT study in 74 healthy subjects. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on population correction method (QTcP) was below 10 ms. Therefore, exenatide was not associated with prolongation of the QTc interval at therapeutic and supratherapeutic concentrations.

## 12.3 Pharmacokinetics

### Absorption

Following a single dose of BYDUREON, exenatide is released from the microspheres over approximately 10 weeks. There is an initial period of release of surface-bound exenatide followed by a gradual release of exenatide from the microspheres, which results in two subsequent peaks of exenatide in plasma at around week 2 and week 6 to 7, respectively, representing the hydration and erosion of the microspheres.

Following initiation of once every 7 days (weekly) administration of 2 mg BYDUREON, gradual increase in the plasma exenatide concentration is observed over 6 to 7 weeks. After 6 to 7 weeks, mean exenatide concentrations of approximately 300 pg/mL were maintained over once every 7 days (weekly) dosing intervals indicating that steady state was achieved.

### Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of BYETTA is 28.3 L and is expected to remain unchanged for BYDUREON.

### Metabolism and Elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. The mean apparent clearance of exenatide in humans is 9.1 L/hour and is independent of the dose. Approximately 10 weeks after discontinuation of BYDUREON therapy, plasma exenatide concentrations generally fall below the minimal detectable concentration of 10 pg/mL.

### Drug Interactions

#### *Acetaminophen*

When 1000 mg acetaminophen tablets were administered, either with or without a meal, following 14 weeks of BYDUREON therapy (2 mg weekly), no significant changes in acetaminophen AUC were observed compared to the control period. Acetaminophen  $C_{max}$  decreased by 16% (fasting) and 5% (fed) and  $T_{max}$  was increased from approximately 1 hour in the control period to 1.4 hours (fasting) and 1.3 hours (fed).

The following drug interactions have been studied using BYETTA. The potential for drug-drug interaction with BYDUREON is expected to be similar to that of BYETTA.

### ***Digoxin***

Administration of repeated doses of BYETTA 30 minutes before oral digoxin (0.25 mg once daily) decreased the  $C_{max}$  of digoxin by 17% and delayed the  $T_{max}$  of digoxin by approximately 2.5 hours; however, the overall steady-state pharmacokinetic exposure (e.g., AUC) of digoxin was not changed.

### ***Lovastatin***

Administration of BYETTA (10 mcg twice daily) 30 minutes before a single oral dose of lovastatin (40 mg) decreased the AUC and  $C_{max}$  of lovastatin by approximately 40% and 28%, respectively, and delayed the  $T_{max}$  by about 4 hours compared with lovastatin administered alone. In the 30-week controlled clinical trials of BYETTA, the use of BYETTA in patients already receiving HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles compared to baseline.

### ***Lisinopril***

In patients with mild to moderate hypertension stabilized on lisinopril (5-20 mg/day), BYETTA (10 mcg twice daily) did not alter steady-state  $C_{max}$  or AUC of lisinopril. Lisinopril steady-state  $T_{max}$  was delayed by 2 hours. There were no changes in 24-hour mean systolic and diastolic blood pressure.

### ***Oral Contraceptives***

The effect of BYETTA (10 mcg twice daily) on single and on multiple doses of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) was studied in healthy female subjects. Repeated daily doses of the oral contraceptive (OC) given 30 minutes after BYETTA administration decreased the  $C_{max}$  of ethinyl estradiol and levonorgestrel by 45% and 27%, respectively, and delayed the  $T_{max}$  of ethinyl estradiol and levonorgestrel by 3.0 hours and 3.5 hours, respectively, as compared to the oral contraceptive administered alone. Administration of repeated daily doses of the OC one hour prior to BYETTA administration decreased the mean  $C_{max}$  of ethinyl estradiol by 15%, but the mean  $C_{max}$  of levonorgestrel was not significantly changed as compared to when the OC was given alone. BYETTA did not alter the mean trough

concentrations of levonorgestrel after repeated daily dosing of the oral contraceptive for both regimens. However, the mean trough concentration of ethinyl estradiol was increased by 20% when the OC was administered 30 minutes after BYETTA administration injection as compared to when the OC was given alone. The effect of BYETTA on OC pharmacokinetics is confounded by the possible food effect on OC in this study [see *Drug Interactions (7.1)*].

### **Warfarin**

Administration of warfarin (25 mg) 35 minutes after repeated doses of BYETTA (5 mcg twice daily on days 1-2 and 10 mcg twice daily on days 3-9) in healthy volunteers delayed warfarin  $T_{max}$  by approximately 2 hours. No clinically relevant effects on  $C_{max}$  or AUC of *S*- and *R*-enantiomers of warfarin were observed. BYETTA did not significantly alter the pharmacodynamic properties (e.g., international normalized ratio) of warfarin [see *Drug Interactions (7.2)*].

### **Specific Populations**

#### **Renal Impairment**

BYDUREON has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease receiving dialysis. Population pharmacokinetic analysis of renally impaired patients receiving 2 mg BYDUREON indicate that there is a 62% and 33% increase in exposure in moderate (N=10) and mild (N=56) renally impaired patients, respectively, as compared to patients with normal renal function (N=84).

In a study of BYETTA in subjects with end-stage renal disease receiving dialysis, mean exenatide exposure increased by 3.4-fold compared to that of subjects with normal renal function [see *Use in Specific Populations (8.6)*].

#### **Hepatic Impairment**

BYDUREON has not been studied in patients with acute or chronic hepatic impairment [see *Use in Specific Populations (8.7)*].

## **Age**

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide [see *Use in Specific Populations (8.5)*].

## **Gender**

Population pharmacokinetic analysis suggests that gender does not influence the steady-state concentrations of exenatide following BYDUREON administration.

## **Race**

There were no apparent differences in steady-state concentrations of exenatide among Caucasian, Hispanic, and Black patients following BYDUREON administration.

## **Body Mass Index**

Population pharmacokinetic analysis of patients with body mass indices (BMI)  $\geq 30$  kg/m<sup>2</sup> and  $< 30$  kg/m<sup>2</sup> suggests that BMI has no significant effect on the pharmacokinetics of exenatide.

## **Pediatric**

BYDUREON has not been studied in pediatric patients [see *Use in Specific Populations (8.4)*].

# **13 NONCLINICAL TOXICOLOGY**

## **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

A 104-week carcinogenicity study was conducted with exenatide extended-release in male and female rats at doses of 0.3, 1.0, and 3.0 mg/kg (2-, 9-, and 26-times human systemic exposure based on AUC, respectively) administered by subcutaneous injection every other week. A statistically significant increase in thyroid C-cell tumor incidence was observed in both males and females. The incidence of C-cell adenomas was statistically significantly increased at all doses (27%-31%) in females and at 1.0 and 3.0 mg/kg (46% and 47%, respectively) in males compared with the control group (13% for males and 7% for females). A statistically significantly higher incidence of C-cell carcinomas occurred in the high-dose group females (6%), while numerically higher incidences of 3%, 7%, and 4% (nonstatistically significant versus

controls) were noted in the low-, mid-, and high-dose group males compared with the control group (0% for both males and females). An increase in benign fibromas was seen in the skin subcutis at injection sites of males given 3 mg/kg. No treatment-related injection-site fibrosarcomas were observed at any dose. The human relevance of these findings is currently unknown.

A 104-week carcinogenicity study was conducted with exenatide, the active ingredient in BYDUREON, in male and female rats at doses of 18, 70, or 250 mcg/kg/day (3-, 6-, and 27-times human systemic exposure based on AUC, respectively) administered by once-daily bolus subcutaneous injection. Benign thyroid C-cell adenomas were observed in female rats at all exenatide doses. The incidences in female rats were 8% and 5% in the two control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups.

In a 104-week carcinogenicity study with exenatide, the active ingredient in BYDUREON, in male and female mice at doses of 18, 70, or 250 mcg/kg/day administered by once-daily bolus subcutaneous injection, no evidence of tumors was observed at doses up to 250 mcg/kg/day, a systemic exposure up to 16 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. The carcinogenicity of exenatide extended-release has not been evaluated in mice.

BYDUREON and exenatide, the active ingredient in BYDUREON, were not mutagenic or clastogenic, with or without metabolic activation, in the Ames bacterial mutagenicity assay or chromosomal aberration assay in Chinese hamster ovary cells. Exenatide was negative in the *in vivo* mouse micronucleus assay.

In mouse fertility studies with exenatide, the active ingredient in BYDUREON, at twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day, males were treated for 4 weeks prior to and throughout mating, and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 760 mcg/kg/day, a systemic exposure 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

### **13.3 Reproductive and Developmental Toxicology**

A rat embryo-fetal developmental toxicity study was conducted with exenatide extended-release. A complete reproductive and developmental toxicity program was conducted with exenatide, the active ingredient in BYDUREON.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1, or 3 mg/kg on gestation days 6, 9, 12, and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1, and 3 mg/kg correspond to systemic exposures of 3, 7, and 17 times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

In female mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, beginning 2 weeks prior to and throughout mating until gestation day 7, there were no adverse fetal effects at doses up to 760 mcg/kg/day, systemic exposures up to 148 times the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant mice given twice-daily subcutaneous doses of 6, 68, 460, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 15 (organogenesis), cleft palate (some with holes), and irregular fetal skeletal ossification of rib and skull bones were observed at 6 mcg/kg/day, a systemic exposure equal to the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant rabbits given twice-daily subcutaneous doses of 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through 18 (organogenesis), irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a systemic exposure 4 times the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

In pregnant mice given twice-daily subcutaneous doses of 6, 68, or 760 mcg/kg/day exenatide, the active ingredient in BYDUREON, from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths was observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a systemic exposure equal to the human exposure resulting from the maximum recommended dose of 2 mg/day, based on AUC.

## **14 CLINICAL STUDIES**

BYDUREON has been studied as monotherapy and in combination with metformin, a sulfonyleurea, a thiazolidinedione, a combination of metformin and a sulfonyleurea, or a combination of metformin and a thiazolidinedione.

## 14.1 24-Week Comparator-Controlled Study

A 24-week, randomized, open-label trial was conducted to compare the safety and efficacy of BYDUREON to BYETTA in patients with type 2 diabetes and inadequate glycemic control with diet and exercise alone or with oral antidiabetic therapy, including metformin, a sulfonylurea, a thiazolidinedione, or combination of two of those therapies.

A total of 252 patients were studied: 149 (59%) were Caucasian, 78 (31%) Hispanic, 15 (6%) Black, and 10 (4%) Asian. Patients were treated with diet and exercise alone (19%), a single oral antidiabetic agent (47%), or combination therapy of oral antidiabetic agents (35%). The mean baseline HbA<sub>1c</sub> was 8.4%. Patients were randomly assigned to receive BYDUREON 2 mg once every 7 days (weekly) or BYETTA (10 mcg twice daily), in addition to existing oral antidiabetic agents. Patients assigned to BYETTA initiated treatment with 5 mcg twice daily then increased the dose to 10 mcg twice daily after 4 weeks.

The primary endpoint was change in HbA<sub>1c</sub> from baseline to Week 24 (or the last value at time of early discontinuation). Change in body weight was a secondary endpoint. Twenty-four week study results are summarized in Table 4.

**Table 4: Results of 24-Week Trial of BYDUREON**

	<b>BYDUREON 2 mg</b>	<b>BYETTA 10 mcg*</b>
<b>Intent-to-Treat Population (N)</b>	129	123
<b>HbA<sub>1c</sub> (%)</b>		
Mean Baseline	8.5	8.4
Mean Change at Week 24 <sup>†</sup>	-1.6	-0.9
Difference from BYETTA <sup>†</sup> [95% CI]	-0.7 [-0.9, -0.4] <sup>¶</sup>	
<b>Percentage Achieving HbA<sub>1c</sub> &lt;7% at Week 24 (%)</b>	58 <sup>¶</sup>	30

**Table 4: Results of 24-Week Trial of BYDUREON**

	BYDUREON 2 mg	BYETTA 10 mcg*
<b>Fasting Plasma Glucose (mg/dL)</b>		
Mean Baseline	173	168
Mean Change at Week 24	-25	-5
Difference from BYETTA <sup>†</sup> [95% CI]	-20 [-31, -10] <sup>¶</sup>	

N = number of patients in each treatment group.

Note: mean change is least squares mean change.

\* BYETTA 5 mcg twice daily before the morning and evening meals for 4 weeks followed by 10 mcg twice daily for 20 weeks.

† Least squares (LS) means are adjusted for baseline HbA<sub>1c</sub> strata, background antihyperglycemic therapy, and baseline value of the dependent variable (if applicable).

¶ p<0.001, treatment vs comparator.

Reductions from mean baseline (97/94 kg) in body weight were observed in both BYDUREON (-2.3 kg) and BYETTA (-1.4 kg) treatment groups.

BYDUREON did not have adverse effects on blood pressure. An LS mean increase from baseline (74 beats per minute) in heart rate of 4 beats per minute was observed with BYDUREON treatment and 2 beats per minute with BYETTA treatment. The long-term effects of the increase in pulse rate have not been established [see *Warnings and Precautions* (5.8)].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

BYDUREON (exenatide extended-release for injectable suspension) for once every 7 days (weekly) subcutaneous administration is supplied as:

BYDUREON single-dose tray, supplied in cartons that contain four single-dose trays (NDC 66780-219-04). Each single-dose tray contains:

- One vial containing 2 mg exenatide (as a white to off-white powder)
- One prefilled syringe delivering 0.65 mL diluent
- One vial connector
- Two custom needles (23G, 5/16") specific to this delivery system (one is a spare needle)

BYDUREON Pen, supplied in cartons that contain four single-dose pens and one spare needle (NDC 66780-222-04). Each single-dose pen contains:

- One pen containing 2 mg of exenatide (as a white to off-white powder) and delivering 0.65 mL diluent.
- One custom needle (23G, 9/32") specific to this delivery system.

Do **not** substitute needles or any other components provided with BYDUREON.

## **16.2 Storage and Handling**

- BYDUREON should be stored in the refrigerator at 36°F to 46°F (2°C to 8°C), up to the expiration date or until preparing for use. BYDUREON should not be used past the expiration date. The expiration date can be found on the carton, on the cover of the single-dose tray, or on the pen label.
- Do not freeze BYDUREON. Do not use BYDUREON if it has been frozen. Protect from light.
- BYDUREON single-dose tray can be kept at room temperature not to exceed 77°F (25°C) [see USP Controlled Room Temperature] for no more than a total of 4 weeks, if needed.
- Use the diluent only if it is clear and free of particulate matter.
- After suspension, the mixture should be white to off-white and cloudy.
- BYDUREON must be administered immediately after the exenatide powder is suspended in the diluent.
- Use a puncture-resistant container to discard BYDUREON with the needle still attached. Do not reuse or share needles or syringes.
- Keep out of the reach of children.

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide. **Prior to initiation of BYDUREON, patients should be trained by their healthcare professional.**

Inform patients about the potential risks and benefits of BYDUREON and of alternative modes of therapy. Also inform patients about the importance of diabetes self-management practices, such as regular physical activity, adhering to meal planning, periodic blood glucose monitoring and HbA<sub>1c</sub> testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications.

### 17.1 Risk of Thyroid C-cell Tumors

Inform patients that exenatide extended-release causes benign and malignant thyroid C-cell tumors in rats and that the human relevance of this finding is unknown. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) [see *Warnings and Precautions (5.1)*].

### 17.2 Risk of Pancreatitis

Inform patients treated with BYDUREON of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue BYDUREON promptly and contact their healthcare provider if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.2)*].

### 17.3 Risk of Hypoglycemia

The risk of hypoglycemia is increased when BYDUREON is used in combination with an agent that induces hypoglycemia, such as a sulfonylurea [see *Warnings and Precautions (5.3)*]. Explain the symptoms, treatment, and conditions that predispose to the development of hypoglycemia. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating BYDUREON therapy, particularly when concomitantly administered with a sulfonylurea [see *Warnings and Precautions (5.3)*].

## **17.4 Risk of Renal Impairment**

Inform patients treated with BYDUREON of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs [see *Warnings and Precautions (5.4)*].

## **17.5 Risk of Hypersensitivity Reactions**

Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of exenatide. If symptoms of hypersensitivity reactions occur, patients must stop taking BYDUREON and seek medical advice promptly [see *Warnings and Precautions (5.7)*].

## **17.6 Use in Pregnancy**

Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant [see *Use in Specific Populations (8.1)*].

## **17.7 Instructions**

Patients should be trained on how to use BYDUREON properly prior to self-administration. Instruct patients on proper mixing and injection technique to ensure the product is adequately mixed and a full dose is delivered. Refer patients to the accompanying Instructions for Use for complete administration instructions with illustrations.

Each dose of BYDUREON should be administered as a subcutaneous injection at any time on the dosing day, with or without meals. Patients should be informed that the day of once every 7 days (weekly) administration can be changed if necessary as long as the last dose was administered 3 or more days before. If a dose is missed, it should be administered as soon as noticed, provided the next regularly scheduled dose is due at least 3 days later. Thereafter, patients can resume their usual once every 7 days (weekly) dosing schedule. If a dose is missed and the next regularly scheduled dose is due in 1 or 2 days, the patient should not administer the missed dose and instead resume BYDUREON with the next regularly scheduled dose [see *Dosage and Administration (2.1)*].

Counsel patients that they should never share BYDUREON with another person, even if the needle is changed. Sharing of BYDUREON or needles between patients may pose a risk of transmission of infection.

If a patient is currently taking BYETTA, it should be discontinued upon starting BYDUREON. Patients formerly on BYETTA who start BYDUREON may experience transient elevations in blood glucose concentrations, which generally improve within the first 2 weeks after initiation of therapy [see *Dosage and Administration (2.3)* and *Clinical Studies (14.1)*].

Treatment with BYDUREON may also result in nausea, particularly upon initiation of therapy [see *Adverse Reactions (6)*].

Inform patients about the importance of proper storage of BYDUREON, injection technique, and dosing [see *Dosage and Administration (2)* and *How Supplied/Storage and Handling (16)*].

The patient should read the BYDUREON Medication Guide and the Instructions for Use before starting BYDUREON therapy and review them each time the prescription is refilled.

Manufactured for:  
AstraZeneca Pharmaceuticals LP  
Wilmington, DE 19850

By:  
Amylin Ohio LLC  
West Chester, OH 45071

BYDUREON is a registered trademark of the AstraZeneca group of companies.

## Medication Guide

### **BYDUREON® (by-DUR-ee-on) (exenatide extended-release for injectable suspension)**

Read this Medication Guide before you start using BYDUREON and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

#### **What is the most important information I should know about BYDUREON?**

##### **Serious side effects may happen in people who use BYDUREON, including:**

- 1. Possible thyroid tumors, including cancer.** During the drug testing process, the medicine in BYDUREON caused rats to develop tumors of the thyroid gland. Some of these tumors were cancers. It is not known if BYDUREON will cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people.
  - Before you start using BYDUREON, tell your healthcare provider if you or any of your family members have had thyroid cancer, especially medullary thyroid cancer, or Multiple Endocrine Neoplasia syndrome type 2. **Do not** use BYDUREON if you or any of your family members have medullary thyroid cancer, or if you have Multiple Endocrine Neoplasia syndrome type 2. People with these conditions already have a higher chance of developing medullary thyroid cancer in general and should not use BYDUREON.
  - While using BYDUREON, tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.
- 2. Inflammation of the pancreas (pancreatitis),** which may be severe and lead to death.

##### **Before using BYDUREON, tell your healthcare provider if you have had:**

- pancreatitis
- stones in your gallbladder (gallstones)

- a history of alcoholism
- high blood triglyceride levels

These medical conditions can make you more likely to get pancreatitis. It is not known if having these conditions will lead to a higher chance of getting pancreatitis while taking BYDUREON.

**Stop using BYDUREON and call your healthcare provider right away if** you have pain in your stomach area (abdomen) that is severe, and will not go away. The pain may happen with or without vomiting. The pain may be felt going from your abdomen through to your back. This type of pain may be a symptom of pancreatitis.

### **What is BYDUREON?**

- BYDUREON is an injectable prescription medicine that may improve blood sugar (glucose) in adults with type 2 diabetes mellitus, and should be used along with diet and exercise.
- BYDUREON is a long-acting form of the medication contained in BYETTA. **Do not** use BYDUREON and BYETTA together.
- BYDUREON is not recommended as the first choice of medication for treating diabetes.
- BYDUREON is not insulin.
- It is not known if BYDUREON is safe and effective when used with insulin.
- BYDUREON is not for use in people with type 1 diabetes or people with a condition caused by very high blood sugar (diabetic ketoacidosis).
- It is not known if BYDUREON is safe and effective in children. BYDUREON is not recommended for use in children.
- It is not known if BYDUREON is safe and effective in people who have a history of pancreatitis.
- BYDUREON has not been studied in people who have severe kidney problems.

### **Who should not use BYDUREON?**

#### **Do not use BYDUREON if:**

- you or any of your family members have a history of medullary thyroid cancer.
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumors in more than one gland in their body.

- you are allergic to exenatide or any of the ingredients in BYDUREON. See the end of this Medication Guide for a complete list of ingredients in BYDUREON. Symptoms of a severe allergic reaction may include:
  - swelling of your face, lips, tongue, or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat

Talk to your healthcare provider before using this medicine if you have any of these conditions.

## **What should I tell my healthcare provider before using BYDUREON?**

### **Before using BYDUREON, tell your healthcare provider if you:**

- have any of the conditions listed in the section “**What is the most important information I should know about BYDUREON?**”
- have severe problems with your stomach such as slow emptying of your stomach (gastroparesis) or problems digesting food.
- have or have had kidney problems, or have had a kidney transplant.
- have any other medical conditions.
- are pregnant or are planning to become pregnant. It is not known if BYDUREON may harm your unborn baby. Tell your healthcare provider if you become pregnant while taking BYDUREON.

**Pregnancy Registry:** There is a registry for women who use BYDUREON during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. If you use BYDUREON at any time during pregnancy, you may enroll in this registry by calling 1-800-633-9081.

- are breastfeeding or plan to breastfeed. It is not known if BYDUREON passes into your breast milk. You and your healthcare provider should decide if you will use BYDUREON or breastfeed. You should not do both without talking with your healthcare provider first.

**Tell your healthcare provider about all of the medicines you take,** including prescription and over-the-counter medicines, vitamins, and herbal supplements. BYDUREON may affect the way some medicines work and some other medicines may affect the way BYDUREON works.

Especially tell your healthcare provider if you take:

- other diabetes medicines, especially insulin or a sulfonylurea
- any medicine taken by mouth
- warfarin sodium (Coumadin<sup>®</sup>, Jantoven<sup>®</sup>)

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

## **How should I use BYDUREON?**

**For detailed instructions, see the Instructions for Use that comes with your BYDUREON.**

- BYDUREON comes as a single-dose tray or as a single-dose pen. Your healthcare provider will prescribe the BYDUREON that is best for you.
- **Your healthcare provider should teach you how to use BYDUREON before you use it for the first time.** If you have any questions or do not understand the instructions, talk with your healthcare provider or pharmacist.
- Pay special attention to mixing BYDUREON well, as shown in the Instructions for Use.
- After injecting with the BYDUREON Pen, make sure you hold the needle in your skin for 10 seconds, to get the full dose.
- Use BYDUREON exactly as your healthcare provider tells you to.
- BYDUREON is injected once every seven days (weekly) any time during the day.
- BYDUREON is a subcutaneous injection. Inject BYDUREON into your skin exactly the way your healthcare provider told you to. You can use the injection in your stomach area (abdomen), your thigh, or the back of your upper arm. Each week you can use the same area of your body. But be sure to choose a different injection site in that area.
- You can use BYDUREON with or without food.
- **If you miss a dose of BYDUREON, it should be used as soon as you remember, provided the next regularly scheduled dose is due at least 3 days later.**
- **If you miss a dose of BYDUREON and the next regularly scheduled dose is due 1 or 2 days later, do not use the missed dose. Use BYDUREON on the next regularly scheduled day.**
- **Do not** use 2 doses of BYDUREON less than 3 days apart.

- If you want to change your dosing day, you can. Your new dosing day must be at least 3 days after your last dose.
- BYDUREON must be injected right after you mix it.
- **If you are taking BYETTA and your healthcare provider prescribed BYDUREON, you should follow your healthcare provider's instructions about when to stop taking BYETTA and when to start taking BYDUREON.** BYETTA is a different form of the same medicine that is in BYDUREON, so do not take BYETTA when you are taking BYDUREON. When you first change from BYETTA to BYDUREON, your blood sugar levels may be higher than usual and should get better in about 2 weeks.
- Inject your dose of BYDUREON under the skin (subcutaneous injection), as you are told to by your healthcare provider. **Do not inject BYDUREON into a vein or muscle.**
- **Do not** share your BYDUREON with another person even if the needle is changed. Sharing your tray or pen with another person can cause you or someone else to get an infection.
- Follow your healthcare provider's instructions for diet, exercise, how often to test your blood sugar, and when to get your HbA<sub>1c</sub> checked. If you see your blood sugar increasing during treatment with BYDUREON, talk to your healthcare provider because you may need to adjust your current treatment plan for your diabetes.
- Talk to your healthcare provider about how to manage high blood sugar (hyperglycemia) and low blood sugar (hypoglycemia), and how to recognize problems that can happen with your diabetes.

### **What are the possible side effects of BYDUREON?**

#### **BYDUREON can cause serious side effects, including:**

- **See "What is the most important information I should know about BYDUREON?"**
- **Low blood sugar (hypoglycemia).** Your risk for getting low blood sugar is higher if you use BYDUREON with another medicine that can cause low blood sugar, such as a sulfonylurea. The dose of your sulfonylurea medicine may need to be lowered while you use BYDUREON. Signs and symptoms of low blood sugar may include:
  - shakiness
  - sweating

- headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heartbeat
  - feeling jittery
- **Kidney problems (kidney failure).** BYDUREON may cause nausea, vomiting or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure, which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration. Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that will not go away, or if you cannot drink liquids by mouth.
  - **Severe allergic reactions.** Severe allergic reactions can happen with BYDUREON. Stop using BYDUREON, and get medical help right away if you have any symptom of a severe allergic reaction. See "**Who should not use BYDUREON?**"

**The most common side effects of BYDUREON include:**

- nausea
- diarrhea
- headache
- vomiting
- constipation
- itching at the injection site
- a small bump (nodule) at the injection site
- indigestion

Nausea is most common when you first start using BYDUREON, but decreases over time in most people as their body gets used to the medicine.

Talk to your healthcare provider about any side effect that bothers you or does not go away.

These are not all the side effects of BYDUREON. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store BYDUREON?**

- Store BYDUREON in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** use BYDUREON past the expiration date printed on the BYDUREON carton, single-dose tray cover, or pen label. The expiration date is labeled *EXP* and can be found on the paper cover of the single-dose tray or single-dose pen.
- **Do not** freeze BYDUREON. **Do not** use BYDUREON if it has been frozen.
- Keep BYDUREON within its sealed tray until ready for use.
- Protect BYDUREON from light until you are ready to prepare and use your dose.
- If needed, you can keep BYDUREON single-dose tray out of the refrigerator at 68°F to 77°F (20°C to 25°C) for up to 4 weeks.
- See the Instructions for Use for information about how to throw away your used BYDUREON parts.

**Keep BYDUREON, and all medicines, out of the reach of children.**

### **General information about safe and effective use of BYDUREON**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BYDUREON for a condition for which it was not prescribed. Do not give your BYDUREON to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about BYDUREON. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about BYDUREON that is written for healthcare professionals.

For more information about BYDUREON, go to [www.BYDUREON.com](http://www.BYDUREON.com) or call 1-877-700-7365.

### **What are the ingredients in BYDUREON?**

#### **Contents of the powder:**

**Active Ingredient:** exenatide

**Inactive Ingredients:** polylactide-co-glycolide and sucrose

**Contents of liquid (diluent):**

**Inactive Ingredients:** carboxymethylcellulose sodium, polysorbate 20, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, water for injection. Sodium hydroxide may be added during manufacture of BYDUREON Pen for pH adjustment.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

BYDUREON is a registered trademark and BYETTA is a registered trademark of the AstraZeneca group of companies. All other marks are the marks of their respective owners.

Manufactured for:  
AstraZeneca Pharmaceuticals LP  
Wilmington, DE 19850

By:  
Amylin Ohio LLC  
West Chester, OH 45071

Revised: February 2014

**Instructions for Use**  
**BYDUREON® (by-DUR-ee-on)**  
**exenatide extended-release**  
**for injectable suspension**

Read the BYDUREON Medication Guide for important safety information.

**Your Step-by-Step Guide**

**CAUTION: Keep guide and medicine out of the reach of children.**

**If you have questions about taking BYDUREON® (exenatide extended-release for injectable suspension)**

- Refer to the **Common Questions and Answers** section
- Call **1-877-700-7365**
- Visit **www.BYDUREON.com**

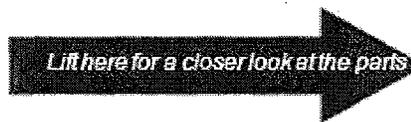
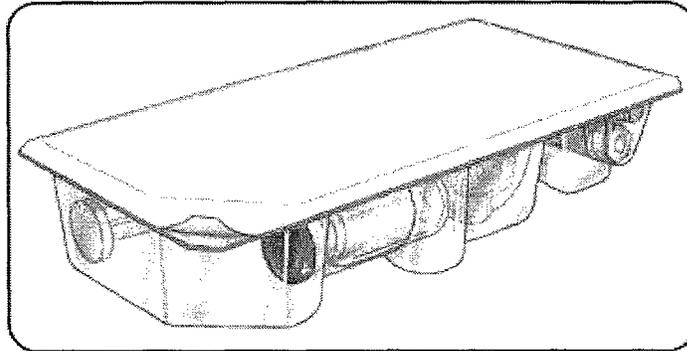
**IMPORTANT:**

**Read this Instructions for Use before you start using BYDUREON and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.**

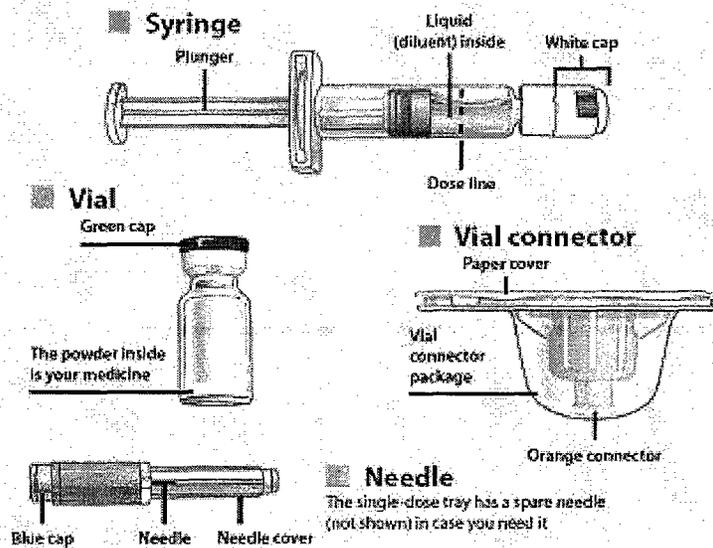
**Consider marking your calendar to remind yourself to take your injection once every seven days (weekly).**

## Your guide to the parts

- Single-dose tray

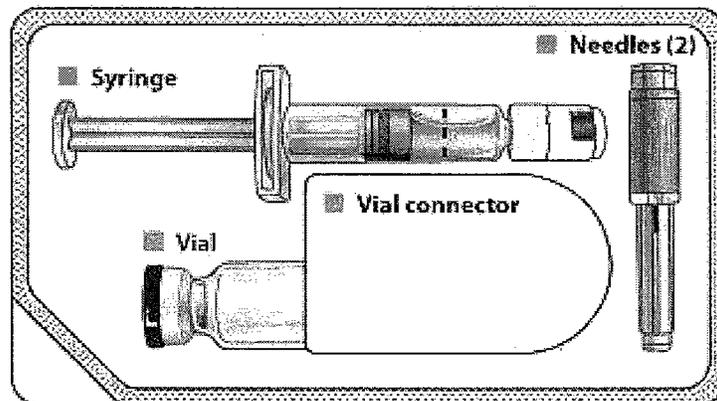


**Keep this flap open so you can refer to it as you go through the steps.**



## Your guide to the parts

- Single-dose tray



## What's Inside

To take the correct dose, read **each** page so that you do **every** step in order.

This step-by-step guide is divided into 4 sections:

- Getting Started
- Connecting the Parts
- Mixing the Medicine and Filling the Syringe
- Injecting the Medicine

For **Common Questions and Answers**, see page 32.

## How to store your single-dose trays of BYDUREON

- Store your BYDUREON in the refrigerator at 36°F to 46°F (2°C to 8°C).
- If needed, you can keep your BYDUREON tray out of the refrigerator at 68°F to 77°F (20°C to 25°C) for up to 4 weeks.
- Protect BYDUREON from light until you are ready to prepare and use your dose.
- Do not freeze BYDUREON trays.
- Do not use BYDUREON past the expiration date. The expiration date is labeled *EXP* and can be found on the paper cover of each tray.
- Keep BYDUREON, and all medicines, out of the reach of children.

1.

## Getting Started

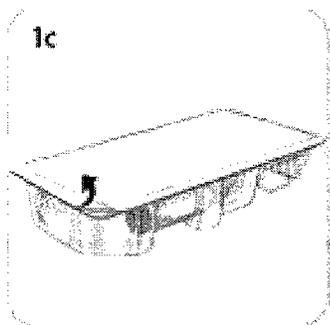
### Helpful Hints

- Try to be patient. It can take time to get used to giving yourself injections
- Set aside enough time to complete all the steps without stopping
- As you do the steps, it can be helpful to read the directions aloud

#### 1a) Take a single-dose tray from the refrigerator.

**You will also need a puncture-resistant container with a lid to hold used needles and syringes.** This is not included in the tray. You may use a red biohazard container, a hard plastic container (such as an empty detergent bottle), or a metal container (such as an empty coffee can). Ask your healthcare provider how to safely throw away used needles and the container. There may be state and local laws about this. Do not throw the container in your household trash or try to recycle it.

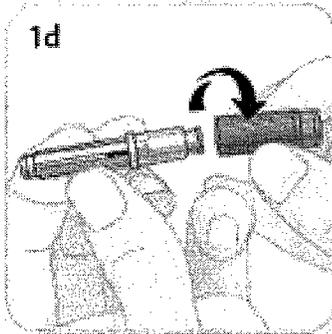
#### 1b) Wash your hands. Prepare to clean your injection site with soap and water or an alcohol swab prior to injecting your medicine.



#### Peel back the paper cover to open.

Remove the syringe. The liquid in the syringe should be clear with no particles in it. It is okay if there are bubbles.

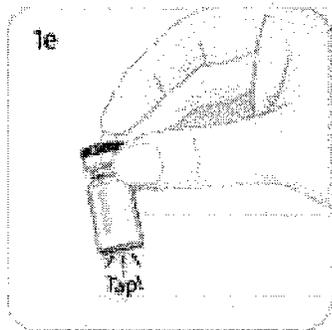
Place the needle, vial connector package, vial, and syringe on a clean, flat surface.



**Pick up the needle, and twist off the blue cap.**

Set the covered needle aside. You will use it later.

There is a spare needle in the tray if you need it.



**Pick up the vial.**

**Tap the vial several times against a hard surface to loosen the powder.**

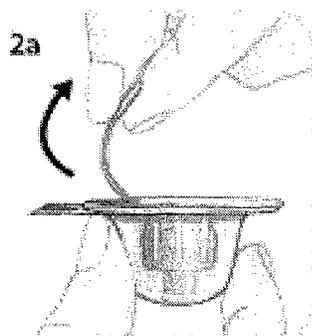


**Use your thumb to remove the green cap.**

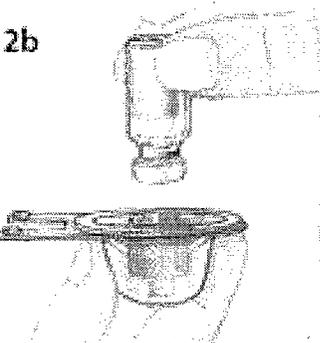
Put the vial aside.

2.

### Connecting the Parts

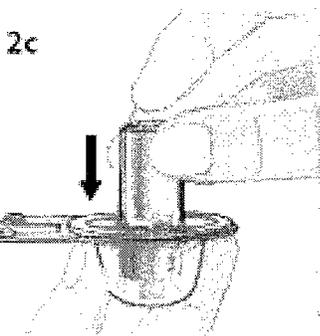


**Pick up the vial connector package and peel off the paper cover. Do not touch the orange connector inside.**



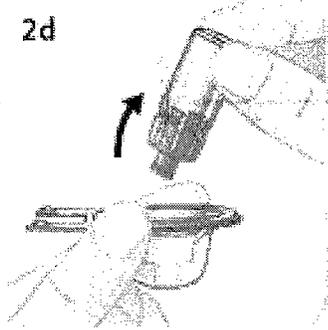
**Hold the vial connector package.**

**In your other hand, hold the vial.**



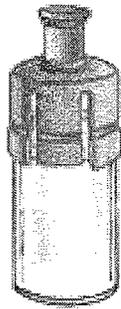
**Press the top of the vial firmly into the orange connector.**

2d



**Then lift the vial with the orange connector now attached out of the clear package.**

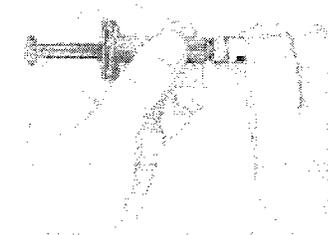
2e



**This is what the vial should now look like.**

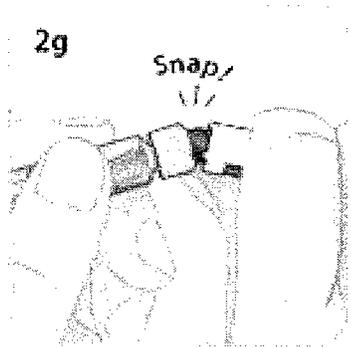
Put it aside for later.

2f



**Pick up the syringe.**

**With your other hand, firmly grasp the 2 gray squares on the white cap.**

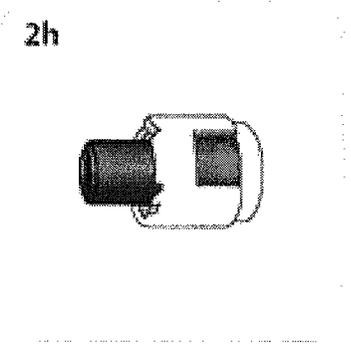


**Break off the cap.**

**Be careful not to push in the plunger.**

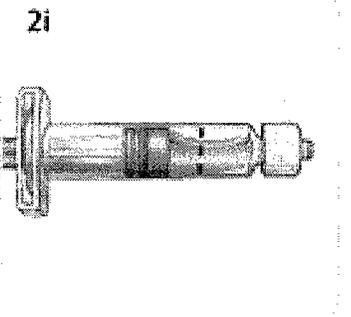


**Just like you might break a stick, you are breaking off the cap.**



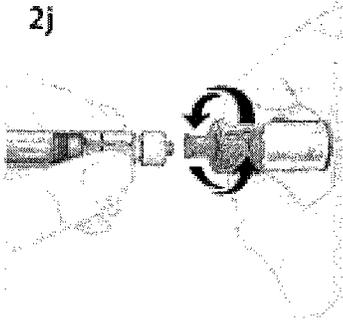
**This is what the broken-off cap looks like.**

You will not be using the cap and can throw it away.



**This is what the syringe should now look like.**

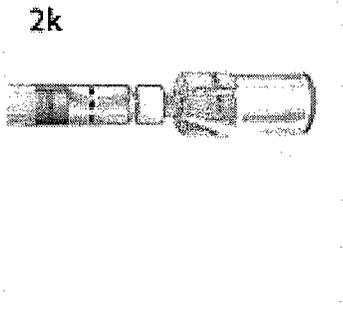
2j



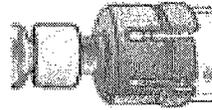
Now, pick up the vial with the orange connector attached.

**Twist the orange connector onto the syringe until snug.** While twisting, be sure to grasp the orange connector. Do not overtighten.

2k



**This is how the parts should now look when they are connected.**

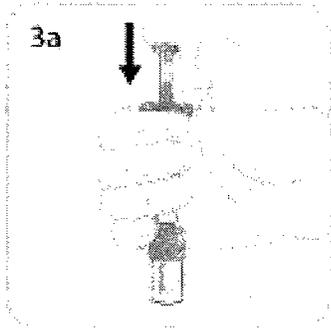


3.

### Mixing the Medicine and Filling the Syringe

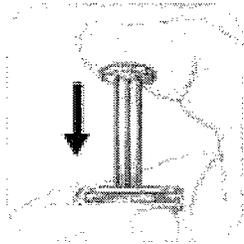
**IMPORTANT:**

During these next steps, you will be mixing the medicine and filling the syringe. Once you mix the medicine, you must inject it. You cannot save the mixed medicine to inject at a later time.

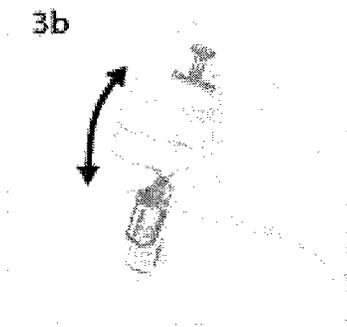


**With your thumb, push down the plunger until it stops.**

The plunger may feel like it is springing back a little.



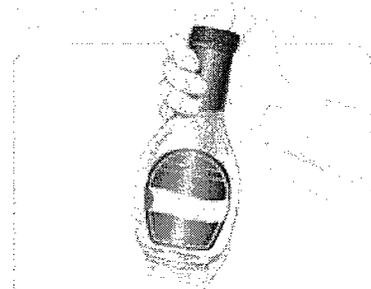
For steps 3a to 3f, keep pushing down on the plunger with your thumb.

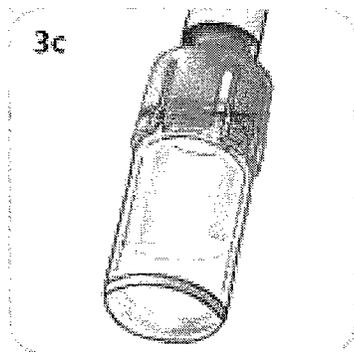


**Hold the plunger down and shake hard. Keep shaking until the liquid and powder are mixed well.**

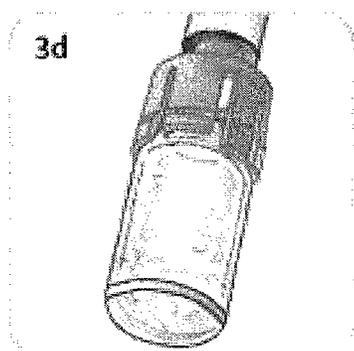
The vial will not come off. The orange connector will keep it attached to the syringe.

**Shake hard like you would shake a bottle of oil-and-vinegar salad dressing.**





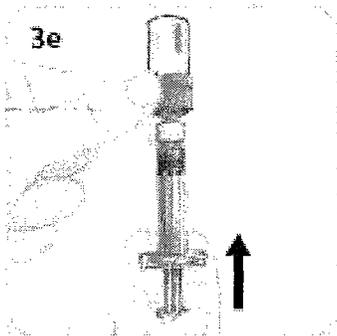
**When the medicine is mixed well, it should look cloudy.**



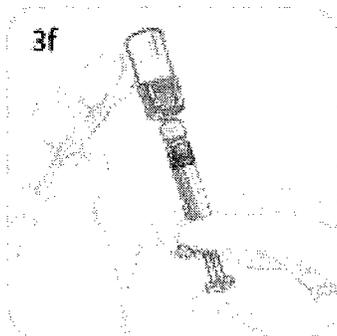
**If you see clumps of dry powder on the sides or bottom of the vial, the medicine is not mixed well.**

**Shake hard again until well mixed.**

**Keep pushing down on the plunger while shaking.**

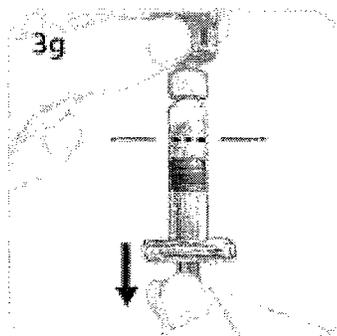


**Now, hold the vial upside down so the syringe is pointing up. Continue to hold the plunger in place with your thumb.**



**Gently tap the vial with the other hand. Continue to hold the plunger in place.**

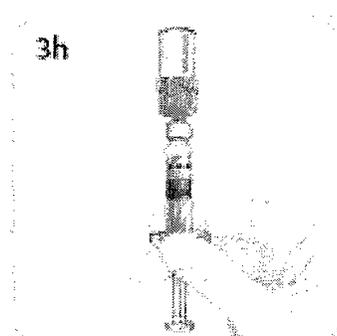
The tapping helps the medicine drip down. It is okay if there are bubbles.



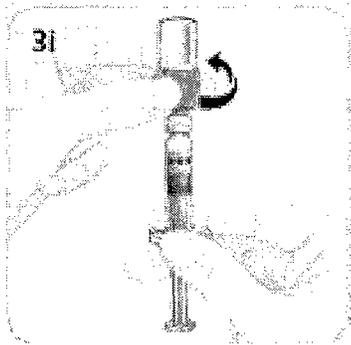
**Pull the plunger down beyond the black dashed Dose Line.**

This draws the medicine from the vial into the syringe. You may see air bubbles. This is normal.

A little bit of liquid may cling to the sides of the vial.

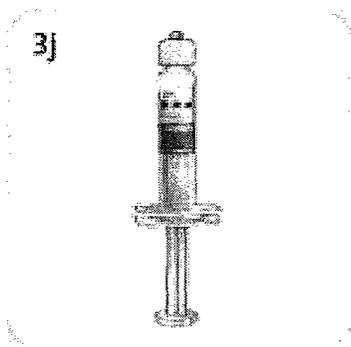


**With one hand, hold the plunger in place so it does not move.**



With the other hand, twist the orange connector to remove it from the syringe.

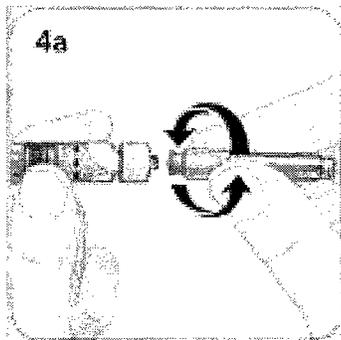
Be careful not to push in the plunger.



This is what the syringe should now look like.

4.

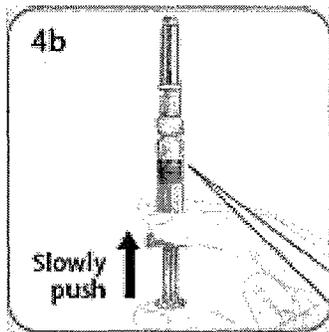
#### Injecting the Medicine



Pick up the needle. Twist the needle onto the syringe until snug. Do not remove the needle cover yet.

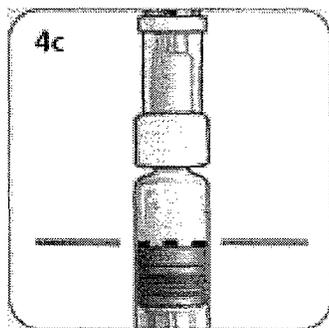
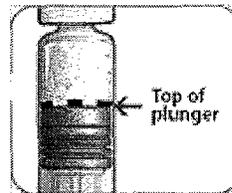
#### **IMPORTANT:**

Read the next steps carefully and look closely at the pictures. This helps you get the correct dose of medicine.



**Slowly push in the plunger so the top of the plunger lines up with the black dashed Dose Line.**

Then, take your thumb off the plunger.

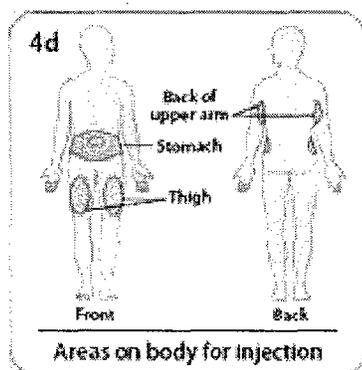


**The top of the plunger must stay lined up with the black dashed Dose Line as you go through the next steps. This will help you get the correct dose of medicine.**

Put aside the syringe with the needle attached.

**IMPORTANT:**

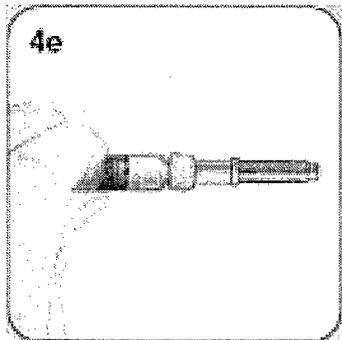
**It is normal to see a few bubbles in the mixture. The bubbles will not harm you or affect your dose.**



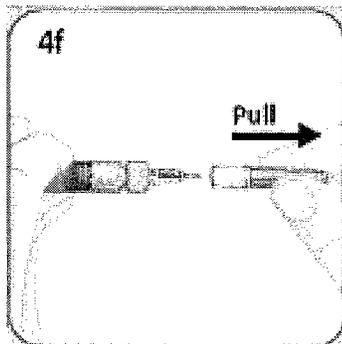
**You can inject the medicine in your stomach area (abdomen), your thigh, or the back of your upper arm.**

Each week you can use the same area of your body. But be sure to choose a different injection site in that area.

Clean the injection site prior to injecting the medicine (with soap and water or an alcohol swab).



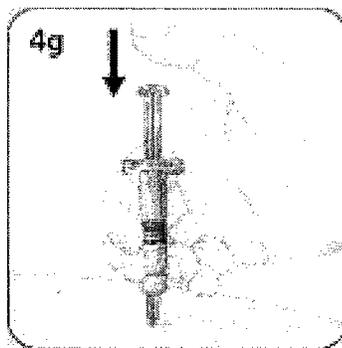
**Now, pick up the syringe and hold it near the black dashed Dose Line.**



**Pull the needle cover straight off. Do not twist.**

Be careful not to push in the plunger.

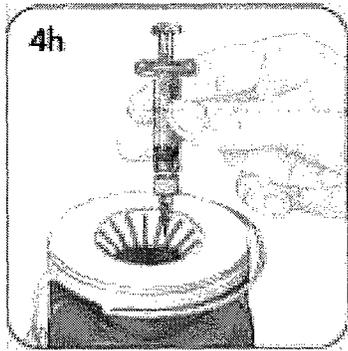
When you remove the cover, you may see 1 or 2 drops of liquid. This is normal.



**Insert the needle into your skin (subcutaneously). To inject your full dose, push down on the plunger with your thumb until it stops.**

Withdraw the needle.

Be sure to use the injection technique recommended by your healthcare provider.



**Use the puncture-resistant container to throw away the syringe with the needle still attached. To avoid a needlestick injury, do not put the cover back on the needle.**

Throw away all other parts in the trash. You do not have to save them. Each single-dose tray has a new supply of parts to use for your next dose of BYDUREON.

**Please keep this Instructions for Use for your next dose.**

## **Common Questions and Answers**

*If your question is about:*

*See question number:*

<b>How soon to inject after mixing</b>	<b>1</b>
<b>Mixing the medicine</b>	<b>2</b>
<b>Air bubbles in syringe</b>	<b>3</b>
<b>Attaching the needle</b>	<b>4</b>
<b>Removing the needle cover</b>	<b>5</b>
<b>Plunger not lining up with black dashed Dose Line</b>	<b>6</b>
<b>Being unable to push the plunger down when injecting</b>	<b>7</b>

### **1. After I mix the medicine, how long can I wait before taking the injection?**

You must take your injection of BYDUREON right after mixing it. If you do not inject BYDUREON right away, the medicine will start to form small clumps in the

syringe. These clumps can clog the needle when you take the injection (see question 7).

**2. How do I know that the medicine is mixed well?**

When the medicine is mixed well, it should look cloudy. There should not be any dry powder on the sides or bottom of the vial. **If you do see any dry powder, shake hard while continuing to push down on the plunger with your thumb.** (This question relates to the steps shown on pages 18 through 20.)

**3. I'm ready to take the injection. What should I do if I see air bubbles in the syringe?**

It is normal for air bubbles to be in the syringe. The air bubbles will not harm you or affect your dose. BYDUREON is injected into your skin (subcutaneously). Air bubbles are not a problem with this type of injection (This question relates to step 3f shown on page 21 and step 4c shown on page 27.).

**4. What should I do if I have trouble attaching the needle?**

First, be sure you have removed the blue cap. Then, **twist** the needle onto the syringe until snug. To prevent losing medicine, do not push in the plunger while attaching the needle. (This question relates to step 4a on page 25.)

**5. What should I do if I have trouble removing the needle cover?**

With one hand, hold the syringe near the black dashed Dose Line. With your other hand, hold the needle cover. **Pull the needle cover straight off.** Do not twist it. (This question relates to step 4f on page 29.)

**6. I am at step 4c. What should I do if the top of the plunger has been pushed past the black dashed Dose Line?**

The black dashed Dose Line shows the correct dose. If the top of the plunger has been pushed past the line, you should continue from step 4d and take the injection. Before your next injection in 1 week, carefully review the instructions on pages 17 through 31.

## **7. When I inject, what should I do if I cannot push the plunger all the way down?**

This means the needle has become clogged. Remove the needle from your skin and replace it with the spare needle from your tray. Then choose a different injection site and finish taking the injection.

To review how to:

- Remove the blue cap of the needle, see page 9
- Attach the needle, see page 25
- Remove the needle cover and give the injection, see pages 29 and 30

If you still cannot push the plunger all the way down, remove the needle from your skin. Use a puncture-resistant container to throw away the syringe with the needle still attached. It is important that you then call 1-877-700-7365.

To help prevent a clogged needle, always mix the medicine very well, and inject right after mixing.

### **Where to learn more about BYDUREON**

- **Talk with your healthcare provider**
- **Read the Medication Guide that came with your BYDUREON.** The Medication Guide can help answer your questions about BYDUREON, such as what it is used for, possible side effects, and when to take BYDUREON.
- Enroll in BYDUREON Support for FREE ongoing help managing your diabetes. **Visit [www.BYDUREON.com](http://www.BYDUREON.com) or call 1-877-700-7365.**

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

BYDUREON® is a registered trademark of Amylin Pharmaceuticals, LLC.

Manufactured by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543 USA

Marketed by:  
Bristol-Myers Squibb Company  
Princeton, NJ 08543  
and  
AstraZeneca Pharmaceuticals LP  
Wilmington, DE 19850

935001-03 / 735001-03

Rev February 2013

## Instructions for Use

### BYDUREON® (by-DUR-ee-on) Pen

(exenatide extended-release for injectable suspension)

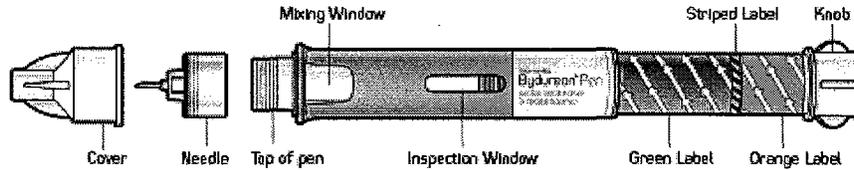


Figure A

Before using Bydureon Pen, your healthcare provider should show you how to use it the right way.

**Read the Instructions for Use before you start using Bydureon Pen and each time you get a refill.** There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

#### Getting ready

**Never share your Bydureon Pen or needles with anyone else. You may give an infection to them or get an infection from them.**

Bydureon Pen is not for self-injection by people who are blind or cannot see well.

#### Supplies needed to give your Bydureon Pen injection (not all supplies are included):

- 1 Bydureon single-use "Pen" tray that contains:
  - 1 Bydureon Pen
  - 1 custom needle
- a clean flat surface
- alcohol swab
- sharps container for throwing away used needles and Pens. See "**Disposing of used needles and Pens**" at the end of these instructions.



## How should I store Bydureon?

- Store your Bydureon Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Protect pens from light until you are ready to prepare and use your dose.
- **DO NOT** use pens past the expiration date printed on the paper cover of each Bydureon Pen tray.
- **DO NOT** freeze Bydureon. **DO NOT** use Bydureon if it has been frozen.
- Keep Bydureon in its sealed tray until ready for use.

**Keep Bydureon Pen, and all medicines, out of the reach of children.**

## Step 1: Prepare your Bydureon Pen

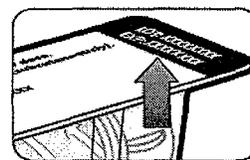
### Let your Pen warm up.

- Remove 1 Pen from the refrigerator and let it stand at room temperature for at least 15 minutes.



### Check the expiration date printed on your Pen tray.

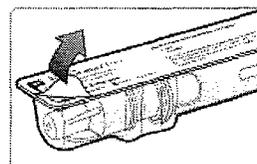
- **Do not** use a Pen past the expiration date printed on your Pen tray.



### Wash your hands.

### Open the tray.

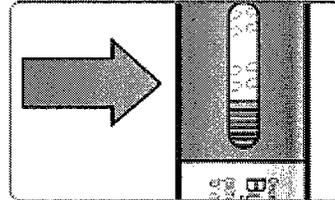
- Pull up on the corner tab.
- Remove the Pen and needle.
  - **Do not** use your Pen or needle if any parts are broken or



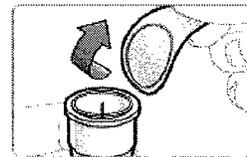
missing.

### Check the liquid in your Pen.

- **Check the liquid** inside the inspection window. It should be clear and free of particles. **Do not** use the Pen if the liquid is colored, has particles, or is not clear. Throw it away and get a new one.
  - You may see bubbles in the liquid, this is normal.

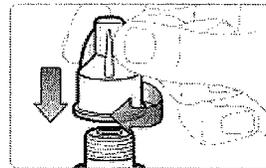


### Peel off the paper tab from the needle cover.



### Attach the needle to the Pen.

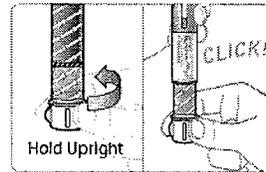
- Screw the needle onto the Pen by pushing and twisting clockwise until it is tight. **Do not** remove the needle cover yet.



## Step 2: Mix your dose

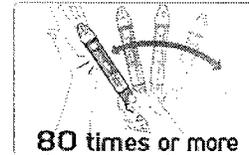
### Combine the medicine.

- While holding the pen straight up, **slowly** turn the knob. **Stop** when you hear the click and the green label disappears.



### Firmly tap your Pen to mix.

- Hold your Pen by the end with the orange label and **tap the Pen firmly against the palm of your hand**.
  - **DO NOT** twist the white knob.
  - **ROTATE** your Pen every 10 taps.
  - **You may need to tap your Pen 80 times or more.**



### Check the Bydureon mix.

- **Hold your Pen up to the light and look through both sides of the mixing window.** The solution should have **NO CLUMPS** and be uniformly cloudy (**see Figure B**).

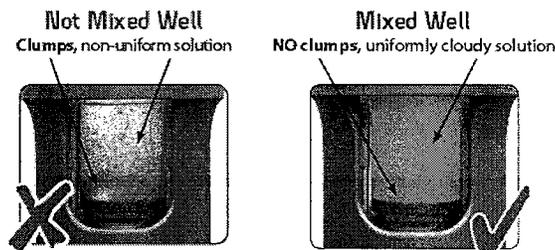


Figure B

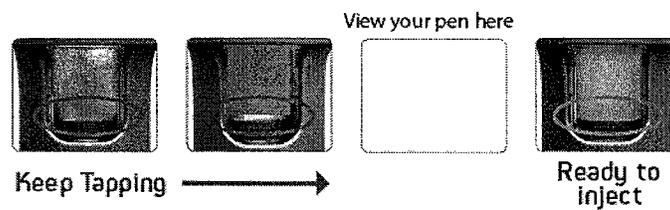
- **To get your full dose, Bydureon must be mixed well.**
- **If Bydureon is not mixed well, keep tapping your Pen longer and more firmly until it is mixed well.**
- **Do not give your Bydureon injection unless your Bydureon is mixed well.**

**STOP. Do Not proceed unless your medicine is mixed well.**

To get your full dose the medicine must be mixed well. If it's not mixed well, tap longer and more firmly.

**Check the Bydureon mix again.**

- **Compare both sides of the mixing window to the photos below** by holding your Pen against the page. Pay attention to the **bottom surface**. If you **do not see clumps** you are ready to inject (see **Figure C**).



**Figure C**

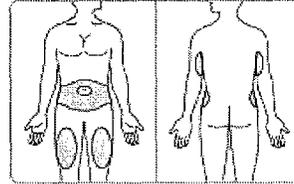
**If you have any questions or are not sure if your Bydureon is mixed well, call 1-877-700-7365 for help.**

### Step 3: Inject your dose

**IMPORTANT: After the medicine is mixed well, you must inject your dose right away.** You cannot save it for later use.

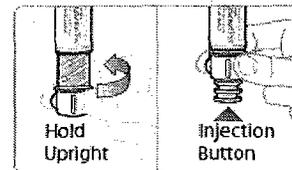
#### Choose your injection site.

- The recommended injection sites for Bydureon are your stomach (abdomen), thigh, or back of the arm.
- Each week you can use the same area of your body but choose a different injection site in that area.
- Gently wipe the site you choose with an alcohol swab (not included).



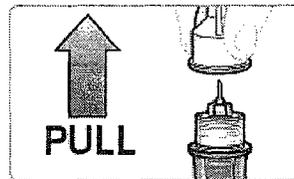
#### Twist knob to release injection button.

- Hold your **Pen with the needle pointing straight up** and turn the white knob until the orange label disappears and the injection button is released. **DO NOT** push the injection button yet.



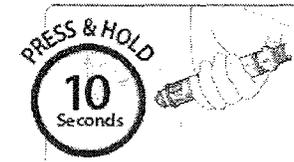
#### Remove the needle cover.

- Pull the needle cover straight off. **DO NOT** twist the needle cover.
  - You may see a few drops of liquid on the needle or in the cover.



#### Inject your Bydureon.

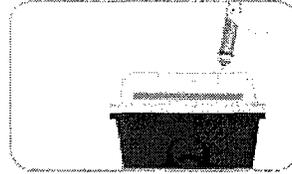
- Insert the needle into your skin.
- Press the injection button with your thumb until you hear a "click." Keep holding **the button down and slowly count to 10**



**to get your full dose.**

**Properly dispose of your Pen.**

- Put your used needles and Pens in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and Pens in your household trash. See **Common Questions and Answers** for additional disposal information.



**Common Questions and Answers:**

**1. How do I know that the Bydureon is mixed well?**

The Bydureon is mixed well when the liquid looks cloudy from both sides of the window. You should not see any clumps in the liquid. It may help to hold your Pen up to the light to see in the window. If you see clumps of any size keep tapping your Pen firmly against the palm of your hand until mixed.

**2. I am having trouble mixing my dose. What should I do?**

Remember, before preparing your dose, leave your Pen out of the refrigerator for at least 15 minutes. This will let your Pen warm up to room temperature. It will be easier to mix Bydureon if your Pen is at room temperature.

Be sure you are holding your Pen at the end with the knob and the orange label. This will help you grip your Pen better and tap it more firmly against your palm.

It may also help to tap the mixing window on both sides against your palm. If you see any clumps, keep tapping.

**3. After I mix Bydureon, how long can I wait before taking the injection?**

You must inject your dose of Bydureon right after mixing it. If you do not inject your Bydureon right away, small clumps of medicine may form in your Pen and you may not get your full dose.

**4. I am ready to inject my dose. What should I do if I see air bubbles in the Pen?**

It is normal for air bubbles to be in your Pen. Bydureon is injected into your skin (subcutaneously). Air bubbles will not harm you or affect your dose with this type of injection.

**5. What should I do if I cannot push the injection button all the way in when trying to inject my dose?**

Check that you have fully screwed on the pen needle. Also be sure you twisted the knob until it stopped, the orange label disappeared, and the injection button appears.

If you still cannot push the button in, this may mean that the needle is clogged. Remove the needle from your skin and replace it with the spare needle from the carton. Review how to attach the needle. Then choose a different injection site and finish taking the injection.

If you still cannot push the button all the way in, remove the needle from your skin. Use a puncture-resistant container to throw away the pen with the needle still attached.

If you have problems giving your Bydureon Pen injection or have any questions call 1-877-700-7365 for more instructions.

**6. How do I know if I injected my full dose?**

To be sure you get your full dose, press the injection button with your thumb until you hear a "click." After the "click," continue to hold the needle in your skin for 10 seconds. This will allow enough time for you to get your full dose.

**7. What if I do not have an FDA-cleared sharps disposal container?**

**Do not** throw away (dispose of) loose needles and Pens in your household trash.

- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and



Manufactured for:  
AstraZeneca Pharmaceuticals LP  
Wilmington, DE 19850

By:  
Amylin Ohio LLC  
West Chester, OH 45071

Approved: February 2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**MEDICAL REVIEW(S)**

**Medical Officer Safety Review  
Division of Metabolism and Endocrinology Products**

**NDA 22-200 SDN 282 Prior Approval Supplement (PAS) 8 Pen Presentation**

**Name of drug:** Exenatide for extended-release injectable suspension (Bydureon)

**Sponsor:** Amylin (a subsidiary of Bristol-Myers Squibb)

**Relevant IND:** 67,092

**Indication:** Type 2 diabetes mellitus (T2DM)

**Date of Submission:** August 30, 2013

**Medical Reviewer:** Valerie Pratt, M.D.

**Medical Team Leader:** Karen Mahoney, M.D.

**BACKGROUND**

On January 27, 2012, Bydureon was approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings. It is provided in a single-dose tray (SDT) containing: one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe, and two needles (one provided as a spare).

Bydureon must be injected immediately after the powder is suspended in the diluent and transferred to the syringe. It is administered as a subcutaneous (SC) injection in the abdomen, thigh or upper arm region once weekly.

The sponsor now submits a supplemental application for approval of a manually operated, single-use, pen presentation.

The sponsor submitted briefing documents related to this submission on March 26, 2012 and February 6, 2013. Key information conveyed in the written responses to these submissions was as follows:

- June 4, 2012 Written Response:
  - Although control strategy is a review issue, the proposed microbiological specifications and associated acceptance criteria appear adequate.
  - The proposal to establish equivalency of the Bydureon Pen to the approved product without clinical trial data appears to be acceptable. However, the final decision will be based on the review of the chemical and physical data to be submitted for the drug product in the new presentation.
  - Performance of anti-needle stick mechanism should be tested per Center for Devices and Radiological Health (CDRH) guidance.
  - Data should demonstrate that the drug delivery device is able to deliver precise dose accuracy without leakage, medication error, device malfunction/failure, or injury to the patient or caregiver.
  - Comments were conveyed on the human factors validation study, need for stability data, and the Instructions for Use (IFU).

- March 4, 2013 Written Response:
  - Advice was given on the new Human Factors Validation Study (study 5)
  - Recommended IFU be revised to increase likelihood of achieving uniform solution (e.g., state “tap 80 or more times”)
  - Recommended the sponsor maintain the 10-second hold time for the definition of a successful complete dose and that the definition of use-error for holding the device remain at  $\pm 45^\circ$ .
  - The sponsor should provide adequate stability data and any extractable/leachable information for the proposed container closure system.

The sponsor also submitted a proprietary name application for “Bydureon Pen (exenatide extended-release for injectable suspension)” on July 16, 2013. The Division of Medication Error Prevention and Analysis (DMEPA) concluded the proprietary name was acceptable.

#### **SUBMISSION**

Bydureon Pen is a prefilled, single-use pen injector. The pen device contains exenatide microspheres and diluent prefilled into separate chambers on the glass dual-chamber cartridge. The microspheres and diluent have the same composition as for the SDT and comply with the approved specifications for Bydureon. The dual-chamber pen needle is the same gauge and length as that in the SDT.

The dose is prepared by affixing the covered needle to the pen, twisting the knob to transfer the diluent via a bypass channel to the microsphere chamber, and then agitating the mixture to suspend the microspheres. After removing the needle cover, the patient inserts the needle at the injection site and depresses the plunger to administer the dose. This system eliminates the need for the patient to transfer the product between a vial and syringe, reducing the number of steps required and simplifying the self-injection process.

The final product, Bydureon Pen, is supplied in cartons that contain four single-dose pens and one spare needle (NDC 66780-222-04). Each single-dose pen contains:

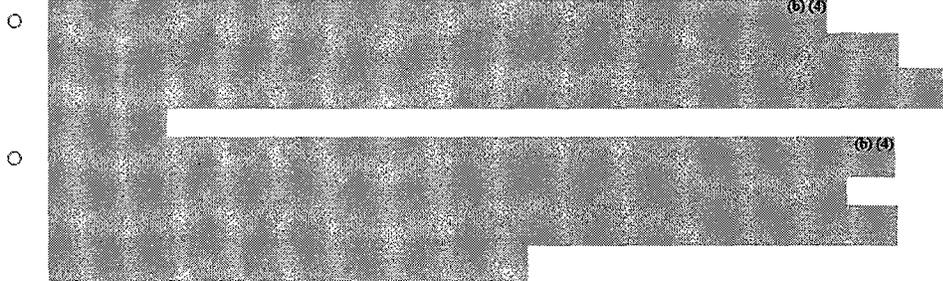
- One pen containing 2 mg exenatide (as a white to off-white powder) and delivering 0.65 ml diluent
- One custom needle (23 G, 9/32”) specific to this delivery system

Bydureon and Bydureon Pen are identical in the following ways:

- Formulation of exenatide microspheres and diluent
- Drug substance
- Manufacturing site of the exenatide microspheres and drug product (Amylin Ohio)
- Method of manufacture of the bulk exenatide microspheres
- Concentration of the suspended exenatide microspheres in diluent
- Volume of suspension to be injected
- Target delivered dose of exenatide microspheres
- Needle length and gauge

Bydureon and Bydureon Pen differ as follows:

- Change in primary container closure and addition of the pen device
- Modifications to the manufacture of the diluent
  - Diluent is manufactured and tested at Amylin Ohio, which is where bulk microspheres are produced and cartridges are filled.



The sponsor submitted the following information in support of this PAS:

- Module 1 Labeling
  - Prescribing Information (PI) and Medication Guide (MG)
  - IFU
  - Carton (trade and sample)
  - [Redacted] (b) (4)
  - Pen label (trade and sample)
  - [Redacted] (b) (4)
- Module 2 Quality documents
- Module 3 Information specific to the dual-chamber pen
  - Development of the cartridge
  - Manufacture of the bulk diluent
  - Filing of microspheres and diluent into cartridges
  - Assembly of cartridges into pen injectors
  - Analytical controls
  - Stability data
  - Analytical characterization demonstrating comparability of the dual-chamber pen to the SDT
  - Regional information: Description of injector device design, development, and validation, including human factor considerations
  - Reference to previously submitted drug substance quality modules
  - Manufacturing facility information
- Sample Bydureon Pens
- Draft instructional video demonstration in DVD format

On December 11, 2013, the sponsor responded to the following information request: *Human factor validation study results submitted on August 30, 2013 for the new single pen presentation of your product showed that most patients are likely to receive the formulation as mix C (Table 14 in your submission). As shown from your HPLC analysis, with mix C, the delivered dose could be up to 10% lower than the intended dose of 2 mg. Please provide a detailed justification for why a chronic reduction in dose*

by up to 10% would not be clinically relevant. This response was discussed at the December 16, 2013 internal meeting and determined by the reviewers present to be acceptable.

#### **INTERNAL DISCUSSION**

On February 3, 2014, multiple disciplines discussed relevant issues at an internal meeting.

- CDRH's QuynhNhu Nguyen expressed her concern that failure to deliver the full dose of Bydureon could result in patient harm.
- Clinical pharmacology's Johnny Lau stated that a 10% reduction in dose would not result in a clinically significant effect on glycemic control.
- CDER's Sarah Vee commented that subjects who were trained to use Bydureon performed better than those who were not trained. In the Human Factors Study, one subject disregarded the training and was an outlier, in that respect. She believes the risk of delivering an incomplete dose can be mitigated with labeling and training.
- Clinical's Valerie Pratt concurred with Johnny Lau and stated, therefore, that a slight reduction in delivered dose will not result in "harm". She pointed out that Bydureon is already on the market in a vial presentation. The pen presentation represents an improvement in drug delivery for the patient as it is inherently more user-friendly when compared to the currently available vial.
- The group recommended approval of the pen supplement with changes to the PI, MG, and IFU to maximize dose delivery.

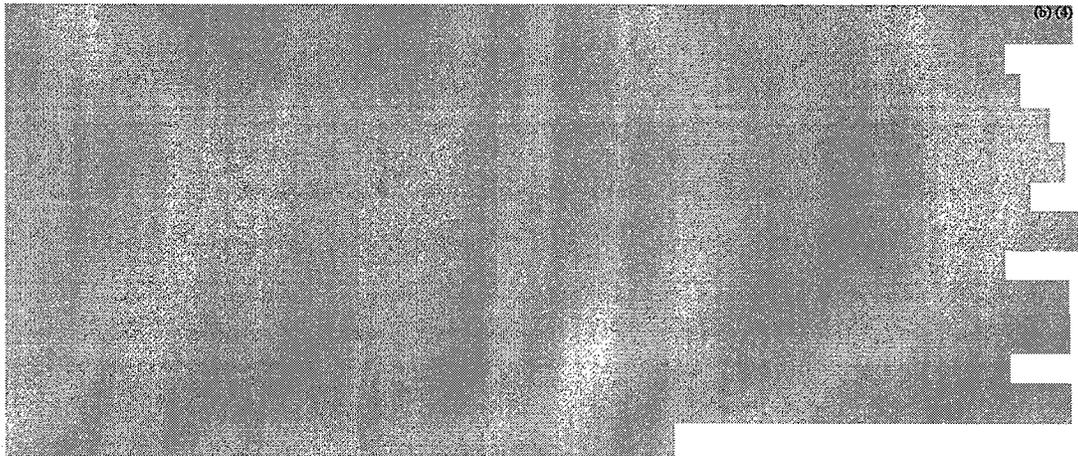
#### **RELATED REVIEWS/CONSULTS**

*Internal Comment: See also the original documents.*

#### Chemistry, Manufacturing, and Controls (ONDQA)

Reviewer: Erika Englund

On February 23, 2014, CMC concluded that the supplement was adequate.



Microbiology 1-7-14

Reviewer: Erika Pfeiler

Recommendation: Approval.

Nonclinical

Reviewer: Tim Hummer

ONDQA/DivIII's Priyanka Kumar consulted nonclinical for leachables and extractables. However, Erika Englund exchanged several e mails with Tim Hummer in November concerning the need to reevaluate the leachables data for this product. Most of the potential leachables were below the limit of detection. (b) (4)

There were no specific safety concerns identified. At that time, Erika requested to include his statement in her review that no safety concerns were identified in lieu of a full review; Tim agreed.

Clinical Pharmacology 1-31-14

By Johnny Lau

The sponsor's justification for a chronic reduction in dose by up to 10% of Bydureon would not be clinically relevant and appears acceptable.

Division of Medication Error Prevention and Analysis (DMEPA) Human Factors, Labeling, and Packaging Review 1-10-14

Reviewers: Sarah Vee and Yelena Maslov

“Comments to the Division:

Human Factors Validation Study results demonstrated that some patients encountered difficulties during mixing and injecting the Bydureon Pen. As a result, we recommend the following revisions regarding training and counseling be added to the appropriate sections of the physician insert to further mitigate potential medication errors.

A. Section 2.2 of the Full Prescribing Information: Administration

1. Second paragraph after the first sentence: For Bydureon Pen, Human Factors Validation Study results demonstrated that errors occurred during tasks involving mixing and holding the needle in the skin for 10 seconds after injecting. These errors can result in under doses. In order to ensure that the product is fully mixed and the full dose is delivered, patients should be trained on how to properly use Bydureon prior to self-administration and counseled regarding how to properly mix, check the mix level, and to hold the pen in the skin for 10 seconds according to the instructions for use.

B. Section 17.7 of the Full Prescribing Information: Instructions

1. First paragraph: Patients should be trained on how to properly use Bydureon prior to self-administration. Bydureon must be properly mixed and the pen injector held in the skin for 10 seconds in order for the full 2 mg dose to be delivered. Instruct the patient on how to properly mix, check the

mix level, and to hold the pen in the skin for 10 seconds according to the instructions for use.

Comments to the Sponsor:

A. Instructions for Use (IFU)

1. Step 2: Mix Your Dose

- a. Label the diagrams “Not Mixed Well” and “Mixed Well” using numbers or letters so that it is easily referred to in the IFU (e.g. Figure X).
- b. Revise the “check the mix” statement to state “Check the mix. Your mix should look like “Figure X” (refer to the “Mixed Well” picture).
- c. In the third section: Highlight the phrase “both sides” by using a different color or font since participants in the human factors study missed this step.

B. Carton, Pen, and Blister Labeling

1. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.”

CDRH/ODE/DAGRID Biomedical engineer/Human Factors 2-25-14

Reviewer: QuynhNhu Nguyen

“The Division of Metabolism and Endocrinology Products requested a consultative review from CDRH Human Factors team to review the human factors validation study report contained in the NDA 22200. The device is a single-use peninjector containing exenatide microspheres and diluent prefilled into separate chambers of the glass dual-chamber cartridge. The final product is supplied in cartons that contain four single-dose pens and one spare needle.

In March 2012, the Sponsor submitted a Type C meeting briefing package regarding the BYDUREON dual-chamber pen (Serial 0060, 26 March 2012). Following a subsequent request from FDA, the Sponsor provided samples of the Pen and Instructions for Use (IFU) and the final results of the Human Factors Validation Study 4a (Serial 0064, 23 April 2012). FDA provided a written response to this briefing document and the questions therein in a letter dated 04 June 2012. The Agency also provided a number of specific comments focused on the device and its use, especially the design, results, and interpretation of the human factors validation study. The Sponsor has taken FDA’s comments into consideration in subsequent development of the IFU and human factors validation, and this information was submitted in Module 3.2.R, Regional Information, Device Design and Development (Exenatide, Dual-Chamber Pen)(Amylin).

The review of the human factors validation study identified the following deficiency that should be communicated to the Sponsor:

The results of your recent human factors validation study showed use errors were observed with high priority task of mixing the drug powder and diluent, and in ensuring that the mix level was acceptable prior to injection since acceptable mixing must be achieved in order to deliver a full dose. The results also showed that two users can make multiple use errors in the use sequence that could lead to the drug not being delivered. These results indicate that further optimization of the user interface are needed to further reduce or eliminate the use errors seen with this product. We note that you have proposed additional changes to the instructions for use (IFU) for the mixing step. We recommend that you make those changes, and further optimize the device user interface, and perform human factors validation testing with 15 representative users (healthcare providers and patients combined) to demonstrate that the mitigations are effective in reducing or eliminating use error that could cause harm and that the mitigations do not introduce new use-related hazards into the design.

However, this deficiency was not sent to the Sponsor, and an internal meeting was held on 2/3/2014 to discuss a path forward with this deficiency. At this meeting, CDRH HF clarified that the Sponsor considered mixing the drug and diluent a high priority i.e. critical task in the simulated use. Because that was considered as critical task, we interpreted any performance failures associated with that task to mean that those failures can result in patient harm in actual use. The Sponsor stated that they intend to modify the IFU to address observed failures with that task; however, we do not have any evidence demonstrating those modifications are effective and that they do not introduce new issues. At this meeting, the team noted that the same type of errors noted with the vial/syringe configuration, and injecting an unmixed product would have likely resulted in an underdose of 10%, which was thought to be clinically insignificant.

Review of the Sponsor's latest labeling showed that edits have been made to the tasks of mixing, priming, and injecting to increase clarity and emphasis on proper technique. In addition, the revised labeling also includes specific number for patient helpline. This consultant found these changes to be acceptable.

Since additional changes have been made to address the mixing steps, and other critical steps, and the clinical significance associated with injecting an unmixed drug product is low, the consultant does not believe that additional human factors study is needed."

Office of Prescription Drug Promotion (OPDP) 12-20-13

Reviewer: Kendra Jones

Provided comments on proposed draft PI. Will provide comments on draft MG and IFU under separate cover.

Division of Medical Policy Programs (DMPP) 1-13-14

Reviewers: Robin Duer, Kendra Jones, and Melissa Hulett

The IFU is acceptable with the recommended changes. Send comments to the sponsor.

**SUMMARY**

At this time, all disciplines recommend approval of the proposed Bydureon pen supplement.

**CLINICAL RECOMMENDATION**

Approval with PI, MG, and IFU labeling revisions to mitigate potential medication errors, including the risk of improper mixing

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VALERIE S PRATT  
02/27/2014

KAREN M MAHONEY  
02/27/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**CHEMISTRY REVIEW(S)**

Memorandum:

Date: February 27, 2014

From: Erika E. Englund, CMC Reviewer, ONDQA

To: NDA 22-200 S008

Subject: CMC review conclusion following evaluation of NDA 22-200 S008 by CDRH

The CMC review of NDA 22-200 S008 was signed on February 23, 2014. NDA 22-200 S008 was recommended for approval from CMC perspective pending final evaluation of this supplement by CDRH. The CDRH review by Mary Brooks was submitted as a consult review by Pooja Dharia on February 27, 2014. This review covered the materials of construction, components, dimensions, stability, and mechanism of action of the Bydureon dual chamber pen presentation from Amylin. No safety concerns were identified by CDRH. This supplement is now recommended for approval from CMC perspective.

The CDRH review evaluated risk management for the pen presentation. The design of the pen was based on FDA regulations and guidances for Design Controls, Risk Management, and Human Factors Engineering (HFE). The review found that residual risks were within acceptable levels.

The performance of the dual-chamber pen presentation was also evaluated. The dual-chamber pen was designed and tested in accordance with the following design controls and performance standards:

 (b) (4) Refer to the review by Mary Brooks for a full discussion of these referenced documents. The needle selection was also evaluated. The required compatibility testing of the needle with the injector was provided. The application was also found to provide adequate testing to determine the risk of leakage of diluent into the microsphere chamber.

In summary, no concerns were identified with the device component of the dual-chamber pen presentation. This supplement is now recommended for approval from CMC perspective.

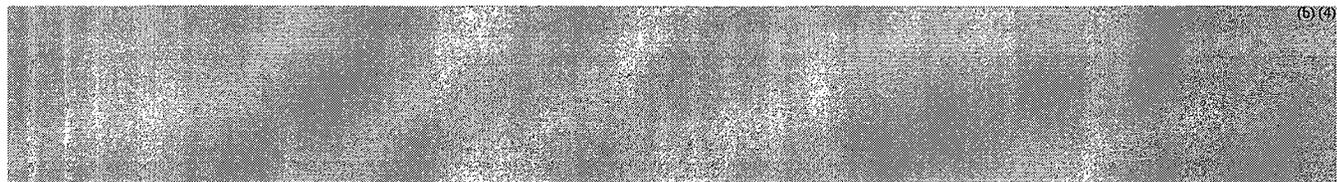
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/s/  
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ERIKA E ENGLUND  
02/27/2014

RAMESH RAGHAVACHARI  
02/27/2014

<b><u>Chemistry Review:# 1</u></b>	<b>1. Division:</b> ONDQA-DMEP	<b>2. NDA Number:</b> 22-200
<b>3. Name and Address of Applicant:</b> Amylin Pharmaceuticals LLC Rt. 206 and Province Line Rd Princeton NJ USA, 08543		<b>4. Supplement(s):</b> PAS-labeling <b>Number:</b> 008 <b>Date(s):</b> 08/29/2013
<b>5. Name of Drug:</b> Bydureon®		<b>6. Nonproprietary name:</b> Exenatide extended-release for injectable suspension
<b>7. Supplement Provides for:</b> new, dual-chamber pen presentation and associated labeling		<b>8. Amendment(s):</b> None
<b>9. Pharmacological Category:</b> Glucagon-like peptide-1 (GLP-1) receptor agonist	<b>10. How Dispensed:</b> Rx	<b>11. Related Documents:</b>
<b>12. Dosage Form:</b> injection, powder for suspension, extended release	<b>13. Potency:</b> 2 mg	
<b>14. Chemical Name and Structure:</b> Exenatide is a 39- amino acid synthetic peptide. MW = 4186.6; C <sub>184</sub> H <sub>282</sub> N <sub>50</sub> O <sub>60</sub> S  H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH <sub>2</sub>		
<b>15. Comments:</b> <ul style="list-style-type: none"> <li>▪ The supplement provides for a manually operated, single-use, dual-chamber pen presentation of Bydureon.</li> <li>▪ The dual-chamber pen contains the same exenatide microspheres and diluent as the Bydureon single dose tray. The delivered dose is also the same</li> <li>▪ The microbiology review by Erika Pfeiler, Ph.D. found this supplement adequate on 1/07/2014.</li> <li>▪ CDRH was consulted for review of the device and associated labeling and the reviews are pending at this time. A memo to this review will be submitted to discuss the impact of the CDRH evaluation once the CDRH reviews are finalized.</li> <li>▪ The statistical review by Meiyu Shen, Ph.D. found the [REDACTED] (b)(4) [REDACTED] A 24 month shelf life is supported by the data. [REDACTED] (b)(4) [REDACTED]</li> </ul>		
<b>16. Conclusion:</b> This supplement is recommended for approval from CMC perspective pending the final evaluation from the CDRH review.		
<b>17. Name:</b> Erika Englund, Ph.D., Chemist	<b>Signature:</b>	<b>Date:</b>
<b>18. Concurrence:</b> Ramesh Raghavachari, Ph.D., Branch Chief, Br., IX, ONDQA	<b>Signature:</b>	<b>Date:</b>



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ERIKA E ENGLUND  
02/21/2014

RAMESH RAGHAVACHARI  
02/23/2014  
Concur. CDRH conclusions on the device is pending.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**STATISTICAL REVIEW(S)**



## STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

<b>NDA No.:</b>	22200
<b>SERIAL NO.:</b>	S008
<b>DATE RECEIVED BY THE CENTER:</b>	August 30, 2013
<b>DRUG NAME:</b>	Bydureon® (exenatide extended release) Suspension
<b>DOSAGE FORM:</b>	Suspension
<b>INDICATION:</b>	
<b>SPONSOR:</b>	AMYLIN PHARMACEUTICALS LLC
<b>REVIEW FINISHED:</b>	February 19, 2014
<b>NAME OF STATISTICAL REVIEWER:</b>	Meiyu Shen, Ph.D.
<b>NAME OF PROJECT MANAGER:</b>	Priyanka Kumar

---

Meiyu Shen, PhD, Mathematical Statistician

Concur:

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Yi Tsong, Ph.D.  
Acting Division Director, DBVI

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## 1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 1.1 Introduction and Background

On December 20, 2013, Office of New Drug Quality Assessment requested the CMC statistical team in Office of Biostatistics to evaluate the sponsor's stability analysis for the new dual chamber pen injector submitted on August 30, 2013.

The sponsor's primary stability studies of the new dual chamber pen injector include full 12-month data under the normal storage condition at 2<sup>o</sup>C to 8<sup>o</sup>C for 4 registration lots from the commercial production site. An additional "in-use" study was conducted on 1 lot stored for 1 month outside the recommended storage condition to support patient convenience.

The sponsor used 12-month data of the new dual chamber pen injector under the normal storage condition at 2<sup>o</sup>C to 8<sup>o</sup>C and ambient relative humidity (RH) for 4 registration lots (b) (4)

### 1.2 Data Analyzed and Sources

Four lots used in long term stability studies for the new dual chamber pen injector are Lot 72761, Lot 72765, Lot 72899, and Lot 73006. The sponsor used 12-month data of the new dual chamber pen injector under the normal storage condition at 2<sup>o</sup>C to 8<sup>o</sup>C and ambient relative humidity (RH) from 4 registration lots (b) (4)

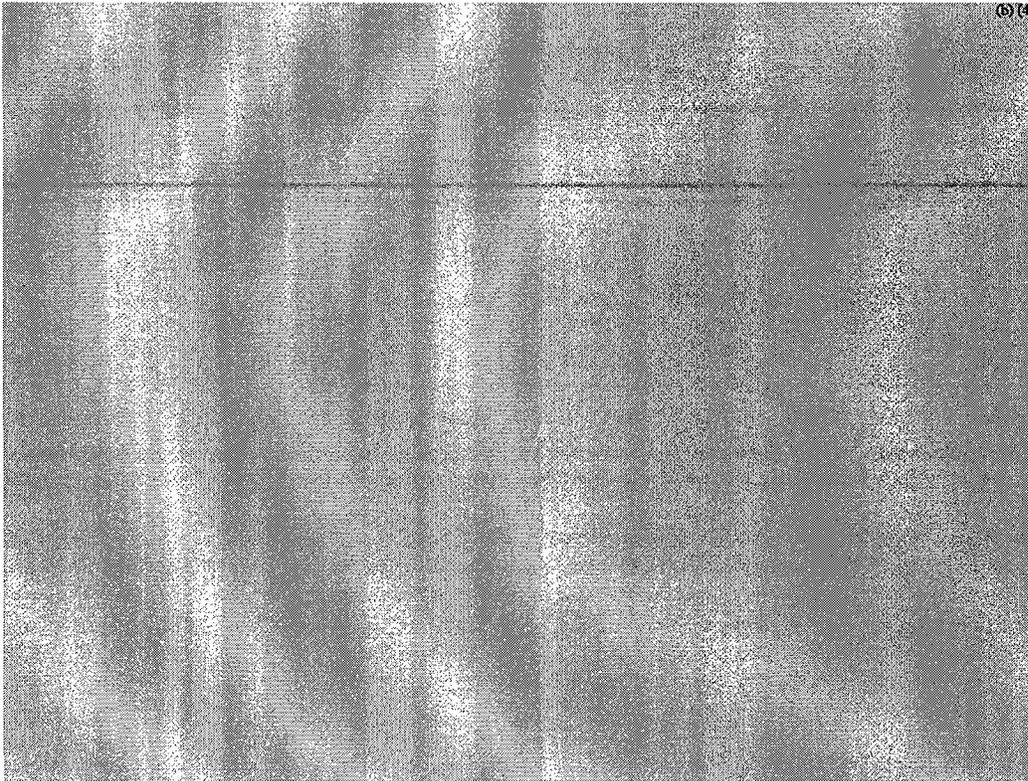
### 1.3 Sponsor's statistical analysis

The sponsor tabulated the 12-month data of the new dual chamber pen injector under the normal storage condition at 2<sup>o</sup>C to 8<sup>o</sup>C show that all results remain within the approved specification limits at the 5 ± 3<sup>o</sup>C condition, and that the stability characteristics of microspheres and diluent are consistent with BYDUREON vial and syringe presentation.

The sponsor performed statistical analyses of covariance for SCX-HPLC purity and impurity content, in vitro initial release, in vitro complete release at 37<sup>o</sup>C, polymer weight, and viscosity using 12-month data of the new dual chamber pen injector under the normal storage condition at 2<sup>o</sup>C to 8<sup>o</sup>C (b) (4)

### 1.4 Acceptance criteria

The acceptance criteria for SCX-HPLC purity and impurity content, in vitro initial release, in vitro complete release at 37<sup>o</sup>C, polymer weight, and viscosity are listed in Table 1.



### 1.5 Statistical reviewer's comments on the sponsor's statistical analysis

(b) (4)

(b) (4) Based on FDA Guidance for Industry Q1E Evaluation of Stability Data, June 2004, the maximum extrapolation of 12-month stability data is 12 months assuming that the statistical analyses of 12-month stability support the extrapolation. In other words, the maximum shelf life is 24 months assuming that the statistical analyses of 12-month stability support the extrapolation. (b) (4)

We analyzed the 12-month stability data for the new dual chamber pen injector and found that the statistical analyses of 12-month stability support 12-month extrapolation. Worst case for viscosity shown in Figure 1 shows that 90% confidence limit is just below the upper limit, 85, at 24 months.

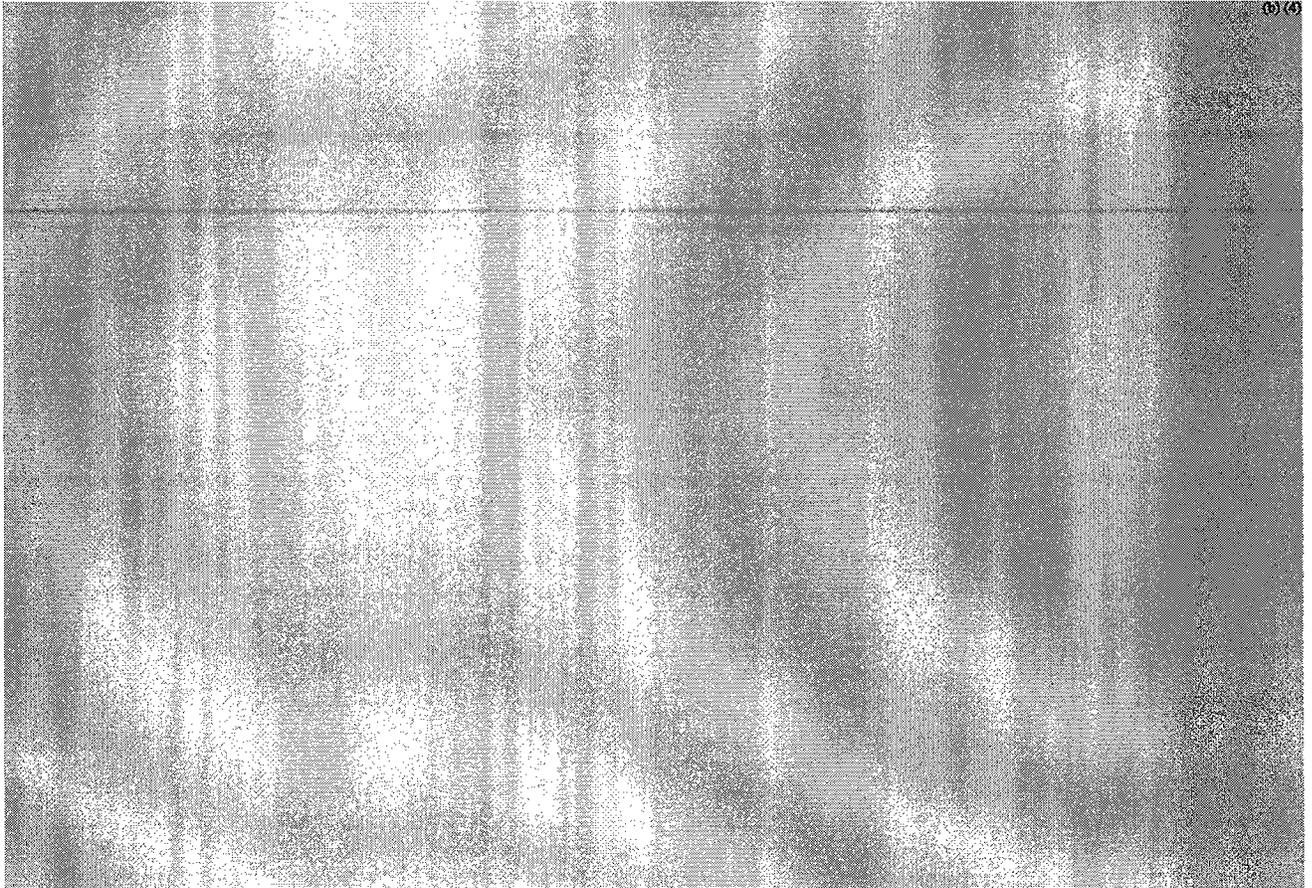


Figure 1 Viscosity versus time

### 1.6 Conclusions and Recommendation

Based on the FDA Guidance for Industry Q1E Evaluation of Stability Data, June 2004, the maximum extrapolation of 12-month stability data is 12 months assuming that the statistical analyses of 12-month stability under the normal storage condition at 2<sup>0</sup>C to 8<sup>0</sup>C support the 12-month extrapolation. In other words, the maximum shelf life is 24 months under the normal storage condition at 2<sup>0</sup>C to 8<sup>0</sup>C since the statistical analyses of 12-month stability support the 12-month extrapolation.

[Redacted text block]

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/s/  
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MEIYU SHEN  
02/19/2014

YI TSONG  
02/19/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

07 January 2014

**NDA: 22200/S008**

**Drug Product Name**

**Proprietary: BYDUREON®**

**Non-proprietary: exendin-4**

**Review Number: 1**

**Dates of Submission(s) Covered by this Review**

<b>Submit</b>	<b>Received</b>	<b>Review Request</b>	<b>Assigned to Reviewer</b>
29 AUG 2013	30 AUG 2013	3 SEP 2013	5 SEP 2013
17 OCT 2013	17 OCT 2013	N/A	N/A
14 NOV 2013	14 NOV 2013	N/A	N/A
23 DEC 2013	23 DEC 2013	N/A	N/A

**Applicant/Sponsor**

**Name: Amylin Pharmaceuticals, LLC**

**Address: Rt. 206 & Province Line Road**

**Representative: Gerald C. DiDonato, Ph.D.**

**Telephone: 609-818-6043**

**Name of Reviewer: Erika Pfeiler, Ph.D.**

**Conclusion: Recommended for Approval**

---

## Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** PAS
  2. **SUBMISSION PROVIDES FOR:** Addition of a dual chamber pen dosing format, change in sterilization method for diluent
  3. **MANUFACTURING SITE:** Amylin Ohio, LLC  
8814 Trade Port Drive  
West Chester, OH 45071
  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**  
Dual-chambered single use pen injector  
Exenatide microspheres, 2 mg/Diluent, 0.65 mL  
Subcutaneous injection
  5. **METHOD(S) OF STERILIZATION:** (b) (4)
  6. **PHARMACOLOGICAL CATEGORY:** Used as a treatment adjunct to improve glycemic control in adults with Type 2 diabetes.
- B. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:**

The proposed drug product consists of microspheres containing the active pharmaceutical ingredient, and a diluent which are mixed immediately prior to administration via subcutaneous injection. This supplemental application describes the introduction of a dual chamber single-use pen injector format. A single-dose tray system was previously approved. Manufacturing changes resulting from the proposed format include a change in (b) (4), a change in primary container closure system, and a change in filling equipment.

**filename:** N22200S008.doc

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**Executive Summary**

**I. Recommendations**

**A. Recommendation on Approvability - Recommended for Approval**

**B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

**II. Summary of Microbiology Assessments**

**A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** [REDACTED] <sup>(b) (4)</sup>

**B. Brief Description of Microbiology Deficiencies – N/A**

**C. Assessment of Risk Due to Microbiology Deficiencies – N/A**

**D. Contains Potential Precedent Decision(s)-  Yes  No**

**III. Administrative**

**A. Reviewer's Signature** \_\_\_\_\_  
Erika Pfeiler, Ph.D.  
Microbiologist

**B. Endorsement Block** \_\_\_\_\_  
John Metcalfe, Ph.D.  
Senior Review Microbiologist

**C. CC Block**  
N/A

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ERIKA A PFEILER  
01/07/2014

JOHN W METCALFE  
01/07/2014  
I concur.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**CLINICAL PHARMACOLOGY AND**  
**BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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<b>NDA</b>	22-200/S0103 (282); /S0115 (334)
<b>Submission Dates</b>	August 30, 2013; December 9, 2013
<b>Brand Name</b>	BYDUREON®
<b>Generic Name</b>	Exenatide extended-release for injectable suspension
<b>Reviewer</b>	S.W. Johnny Lau, R.Ph., Ph.D.
<b>Team Leader</b>	Lokesh Jain, Ph.D.
<b>OCP Division</b>	Clinical Pharmacology-2
<b>OND Division</b>	Metabolism and Endocrinology Products
<b>Sponsor</b>	Amylin (Bristol-Myers Squibb and AstraZeneca)
<b>Formulation; Strength</b>	Exenatide extended release; 2 mg
<b>Relevant IND</b>	67,092
<b>Submission Type</b>	Labeling supplement
<b>Indication</b>	Adjunct therapy to diet and exercise to treat Type 2 Diabetes

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### Background

The sponsor submitted this supplemental application for the approval of a manually operated, single-use, pen presentation of BYDUREON® as a Labeling Prior Approval Supplement. This review concerns the change to this pen presentation for BYDUREON®.

### Review of current submission

In this submission, the sponsor did not propose any change to the Clinical Pharmacology related language in the BYDUREON® label.

The sponsor developed 2 presentations of BYDUREON®, namely the single-dose tray and dual-chamber pen presentations. The dual-chamber pen contains the same formulations of exenatide microspheres and diluent as the approved BYDUREON® single-dose tray. BYDUREON® consists of exenatide-containing biodegradable polymeric microspheres for suspension in an aqueous diluent. BYDUREON® microspheres are suspended in diluent by the user immediately prior to subcutaneous injection. The recommended dose is 2 mg BYDUREON® once weekly via subcutaneous injection.

The originally approved single-dose tray presentation consists of exenatide microsphere powder in a glass vial, the aqueous diluent in a prefilled syringe, the syringe needles, and a vial connector for ease of diluent transfer. The exenatide once weekly dose is prepared via mixing 1 vial of microspheres with the diluent, and the resulting suspension is administered via the syringe.

This supplement describes the new BYDUREON® dual-chamber pen presentation. The dual-chamber pen is a manually operated, prefilled single-use pen injector. This presentation is supplied as a pen device containing exenatide microspheres and diluent prefilled into separate chambers of the glass dual-chamber cartridge. The dual-chamber pen is supplied with a needle of the same gauge and length as that for the single-dose tray. The dose is prepared thru affixing the covered needle to the pen, twisting the knob to transfer the diluent via a bypass channel to the microsphere chamber, and then agitating the mixture to suspend the microspheres. After removing the needle cover, the patient inserts the needle at the injection site and depresses the plunger to administer the dose. This system eliminates the need for

the patient to transfer the product between a vial and syringe, reducing the number of steps required and simplifying the self-injection process.

The Safety Evaluator, Dr. Sarah Vee, found that the participants in the Human Factor Validation Study (3.2.R) had difficulty mixing the exenatide and then verifying the proper mixing. If the participants were to inject exenatide in that state, participants would receive an underdose (the amount would depend on the state of the mixture). However, the sponsor claimed that (Page 38/194):

Also, slight underdoses are only a potential hazard to the patient when the drug is short acting and has a lifesaving indication (e.g., epinephrine for anaphylactic shock). As the drug delivered with this device (BYDUREON) is a long-acting, weekly injection and not an acute, lifesaving intervention (e.g., EpiPen), and the dose delivered is a relatively large volume of a drug, a small under-dose of this magnitude is a minor concern.

This reviewer cannot find any justification apart from a few tables on Pages 129 – 132 of 194, which are not helpful without explanations.

Per the original Clinical Pharmacology review for BYDUREON<sup>®</sup>, the exenatide pharmacokinetic (PK) variability with the single-dose tray presentation was relatively high. The horizontal purple dash line in Figure 1 below shows the range of steady-state exenatide concentrations for the 2 mg dose from pivotal efficacy and safety trials, which ranged about 150 – 750 pg/mL. Age, gender, and race cannot explain this variability in PK. Moreover, no data exist to evaluate whether the external mixing step might contribute to this variability.

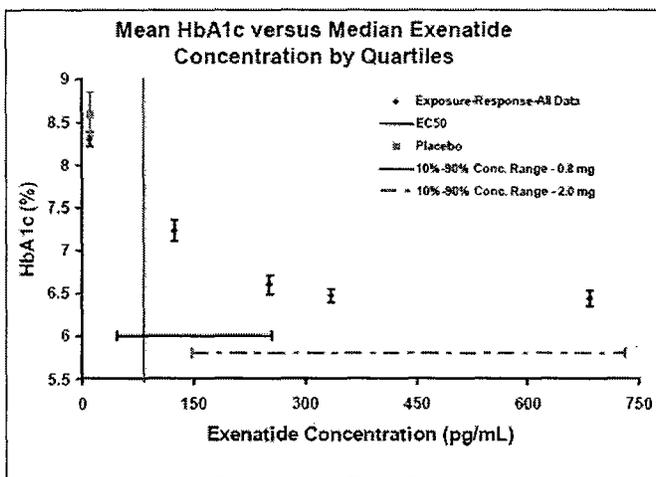


Figure 1: The 2 mg dose produces exposure related to maximal response. Mean HbA1c ( $\pm$  SEM) for each quartile of average steady-state concentrations of patients treated with exenatide LAR. The placebo and treated responses are shown in black and red. The 10<sup>th</sup> - 90<sup>th</sup> percentile of the concentration range following 0.8 mg (blue) and 2 mg (pink) dose in each quartile is shown by the horizontal line at the bottom of the graph. EC<sub>50</sub> (83.5 pg/mL) is shown as the vertical line in the graph.

(Clinical Pharmacology review of NDA 22-200's Page 58 of 127

[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/022200Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf))

At steady-state exenatide concentrations > 300 pg/mL, the reduction in HbA1c plateaus (Figure 1). Given this relationship and knowing that most patients will receive the Mix Level C (dose delivered at least  $\geq$  90%) with the new presentation, it is expected that efficacy will not be compromised in the majority of patients. However, some patients may be under-dosed on a chronic basis due to the difficulty of mixing which might result in compromised efficacy. The review team concerns that patients chronically underdose themselves with exenatide due to the difficulty of mixing with the new presentation. Thus, the Division of Metabolism and Endocrinology Products (DMEP) sent the following information request to the sponsor on November 13, 2013:

*Human factor validation study results submitted on August 30, 2013 for the new single pen presentation of your product showed that most patients are likely to receive the formulation as mix C (Table 14 in your submission). As shown from your HPLC analysis, with mix C, the delivered dose could be up to 10% lower than the intended dose of 2 mg.*

*Please provide a detailed justification for why a chronic reduction in dose by up to 10% would not be clinically relevant.*

The sponsor responded to DMEP's information request on December 6, 2013 (see Attachment for details). Briefly, the sponsor responded via the population PK/pharmacodynamics (PD) analyses as the following:

- Simulate the steady-state concentration of exenatide at Week 28 for a patient receiving a 1.8 mg (90% dose) or 2 mg (100% dose) weekly dose of the extended-release exenatide via a previously developed PK model.
- With the prior step's simulated exenatide steady-state concentrations, predict the steady-state glycemc (HbA1c) response at Week 28 for the 2 doses (1.8 and 2.0 mg) via a previously developed PK/PD model.

The sponsor assumes that the baseline HbA1C value is 8.2% and no antibody titers to exenatide. The sponsor claims that 8.2% is the median baseline HbA1C value, whereas the clinical pharmacology review states that 8.2 is the mean baseline value ([http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/022200Orig1s000ClinPharmR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf) Page 58 of 127). Assumption of no exenatide antibody titers may be acceptable since antibody formation was associated with an attenuated glycemc response (< 0.7% reduction in HbA1c) in 6% of BYDUREON<sup>®</sup>-treated patients for 5 comparator-controlled 24- to 30-week studies (BYDUREON<sup>®</sup> label).

In the sponsor's population PK/PD analysis (IND 107815 Serial 0011 November 14, 2011), baseline renal function and baseline body weight were significant predictors of steady state exenatide concentrations. The sponsor simulated 3 patients for change in HbA1C at Week 28 (< median values, mean values, and > mean values; see Table 1 below).

**Table 1. Predicted Steady-State Exenatide Exposure and HbA1c Response for Subjects Receiving a 1.8 or 2 mg Dose of BYDUREON At 28 Weeks**

Dose (mg)	Baseline eGFR (mL/min/1.73 m <sup>2</sup> )	Baseline IBW (kg)	Predicted Steady-State Concentration (pg/mL)	Predicted %HbA1c at Steady-State ( $\Delta\%$ HbA1c) <sup>a</sup>
2.0	50	50	371	6.45 (-1.75)
1.8			334	6.47 (-1.73)
2.0	81.6 <sup>b</sup>	64.1 <sup>b</sup>	243	6.56 (-1.64)
1.8			218	6.60 (-1.60)
2.0	100	100	145	6.75 (-1.45)
1.8			131	6.79 (-1.41)

<sup>a</sup>Assume a baseline HbA1c level of 8.2% and no antibody titers to exenatide.

<sup>b</sup>Median value of the dataset used for the population PK analysis of BYDUREON.

The sponsor claims that a 10% reduction in the overall dose of BYDUREON<sup>®</sup> (2 mg) over 28 weeks would have no clinically meaningful effect on glycemc response because:

- All 3 patients had similar responses in glycemc control (-1.41 – -1.75%), as all the predicted steady state exenatide concentrations were above the EC<sub>50</sub> of 52.8 pg/mL for glycemc response.

- The differences in glyceimic response for the 1.8 mg or 2 mg dose across the 3 patients were 0.02 – 0.04% in HbA1c reduction.
- All 3 patients (baseline HbA1c 8.2%) achieved the American Diabetes Association recommended HbA1c goal of < 7%.
- These results are consistent with the observations that the predicted steady-state concentrations for 1.8 mg and 2 mg dose of BYDUREON<sup>®</sup> were on the plateau of the exposure-response curve for exenatide.

This reviewer notices that the extended-release exenatide EC<sub>50</sub> for glyceimic control is 83.5 pg/mL per NDA 22-200's original clinical pharmacology review. The sponsor used the extended-release exenatide EC<sub>50</sub> for glyceimic control is 52.8 pg/mL in this submission and published the extended-release exenatide EC<sub>50</sub> for glyceimic control is 56.8 pg/mL (Fineman et al. *Clin Pharmacokinetics* 2011;50:66-74). Nevertheless, the predicted steady state exenatide concentrations for the 3 simulated patients (Table 1) are above the EC<sub>50</sub> of 83.5 pg/mL for glyceimic control.

#### **Recommendation**

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) reviewed NDA 22-200/S0103 (282) and /S0115 (334). The sponsor's justification for a chronic reduction in dose by up to 10% of BYDUREON would not be clinically relevant appears acceptable.

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01/31/2014

LOKESH JAIN  
01/31/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**OTHER REVIEW(S)**

**REGULATORY PROJECT MANAGER LABELING REVIEW**  
**Division of Metabolism and Endocrinology Products**

**Application Number:** NDA 022200/S-008 Bydureon (exenatide extended-release) for injectable suspension  
**Applicant:** Amylin LLC

**Material Reviewed:**

**Submission Date:** August 29, 2013 (original submission) and February 24, 2014 (final draft labeling)

**Type of Labeling Reviewed:** Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU)

**Last approved labeling:** January 27, 2012 (initial NDA approval)

**Background and Summary**

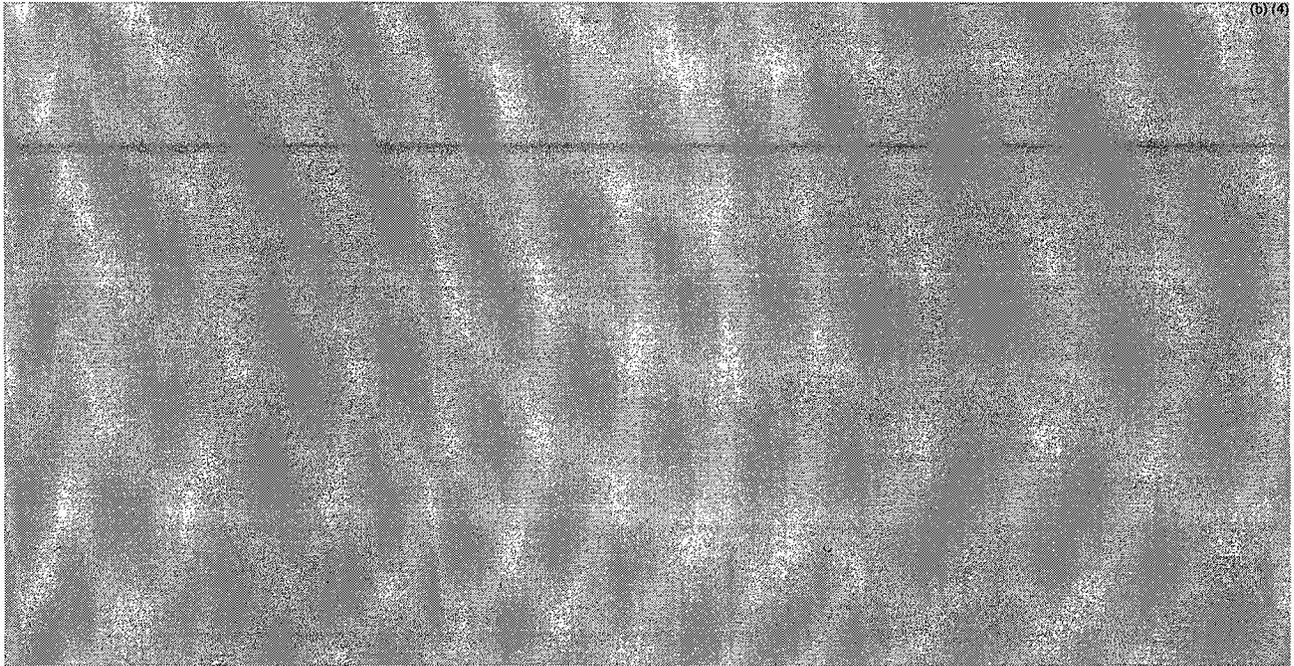
Bydureon (exenatide extended-release for injectable suspension) is a glucagon-like peptide-1 (GLP-1) receptor agonist approved on January 27, 2012 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This “Prior Approval” labeling supplement proposes a manually operated, single-use, dual-chamber pen presentation of Bydureon (exenatide extended release for injectable suspension).

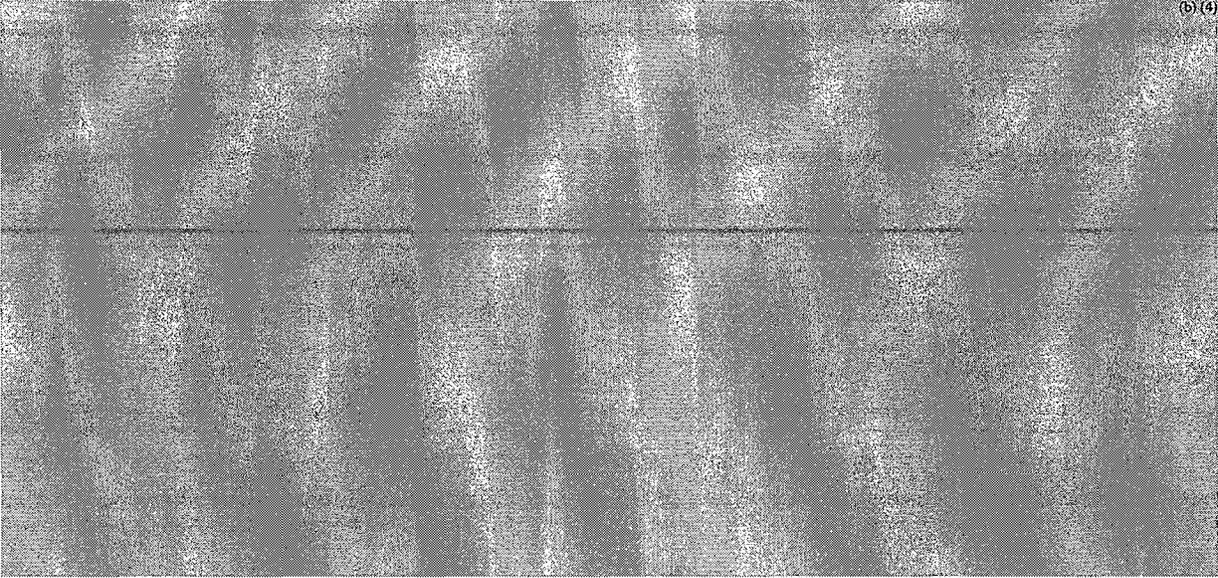
**Review**

The Prescribing Information (PI) and Medication Guide (MG) submitted on February 24, 2014 was compared to the last approved PI and MG dated January 27, 2012. A new Instructions for Use (IFU) was created for the pen presentation of Bydureon.

The following revisions were made. Additions are noted in underline and deletions are noted as ~~strikethrough~~.



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**C. Instructions for Use**

A new Instructions for Use (IFU) was created for this supplement for the Bydureon Pen presentation. This IFU will be issued when Bydureon Pen is dispensed; a separate IFU is approved for the single-dose tray presentation.

**D. Carton and Container Labels**

New carton and container labels were created for this supplement for the Bydureon Pen presentation.

**Recommendations**

A supplement approval letter will be issued. Concurrence by Clinical, CMC, DMEPA, CDRH, and Human Factors.

\_\_\_\_\_  
Pooja Dharia, Pharm.D.  
Regulatory Project Manager

Supervisory Comment/Concurrence:

\_\_\_\_\_  
Julie Van der Waag, MPH  
Chief, Project Management Staff

Drafted: PD/2.25.14  
Revised/Initialed: J.Van der Waag/2.27.14  
**Finalized: PD/2.27.14**

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POOJA DHARIA  
02/27/2014



Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** February 27, 2014

**From:** Mary Brooks, CDR USPHS, MS, BSN, RN, Nurse Consultant, WO66, RM 2524  
CDRH/ODE/DAGRID/General Hospital Devices Branch (GHDB)

**To:** Pooja, Dharia

**Subject:** CDRH Consult, NDA 022200, Amylin LLC  
Pen injector to deliver Bydureon (exenatide)

#### 1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding NDA 022200. The device constituent of this combination product consists of a dual-chamber pen injector that contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.

Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.

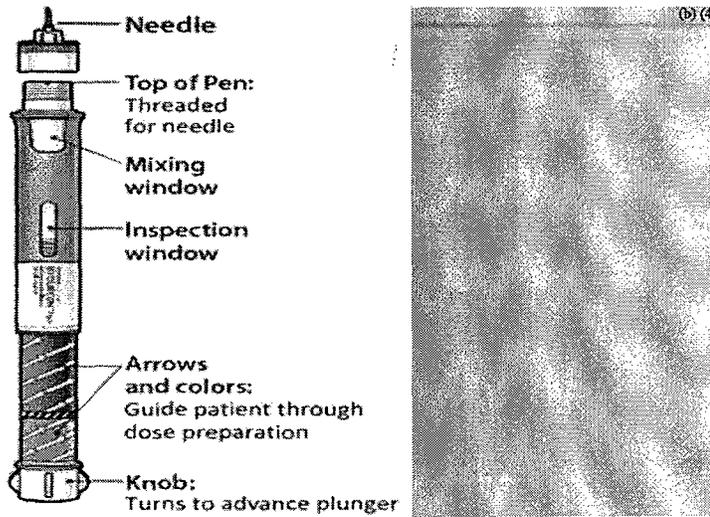
#### 2. Device Description

The dual-chamber pen is a prefilled single-use delivery system consisting of 3 major elements: pen-injector, prefilled dual-chamber cartridge, and a needle specific to the dual-chamber pen. The dual-chamber cartridge is (b) (4) and maintains the separation of the exenatide microspheres and diluent until time of use. The pen-injector provides the mechanism for combining the diluent and microspheres into a single chamber for mixing prior to dose delivery. The mixing step involves tapping the device against the palm of the hand to create a uniform suspension. After mixing, a priming step is required to remove the air needed for mixing prior to delivering the dose.

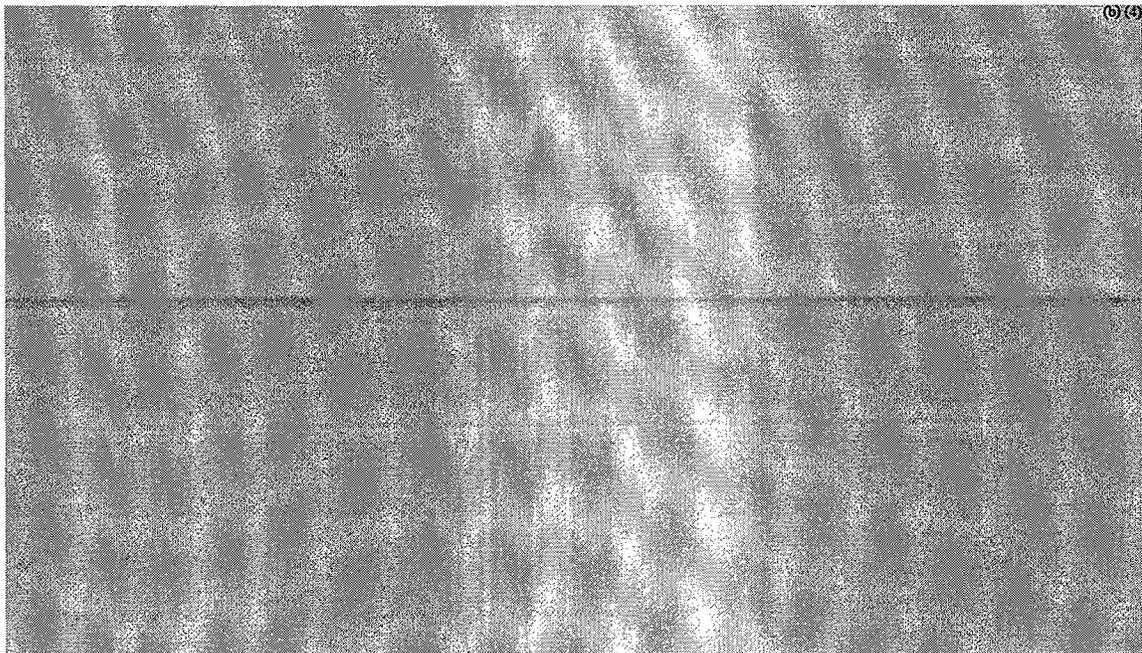
The resulting design shown in Figure 1 consists of an injection device with an integrated dual-chamber cartridge containing microsphere powder in 1 chamber and diluent in the other chamber. (b) (4) needle is provided to enable a subcutaneous route of dose delivery (b) (4) The needle is beveled with a sharp point, to allow ease of skin penetration. The dual-chamber pen needle assembly was developed by BD to meet the Sponsor's specific requirements for delivering the exenatide suspension. The dual-

chamber pen is designed to enable the transfer of the diluent into the microsphere chamber to form a suspension prior to administration.

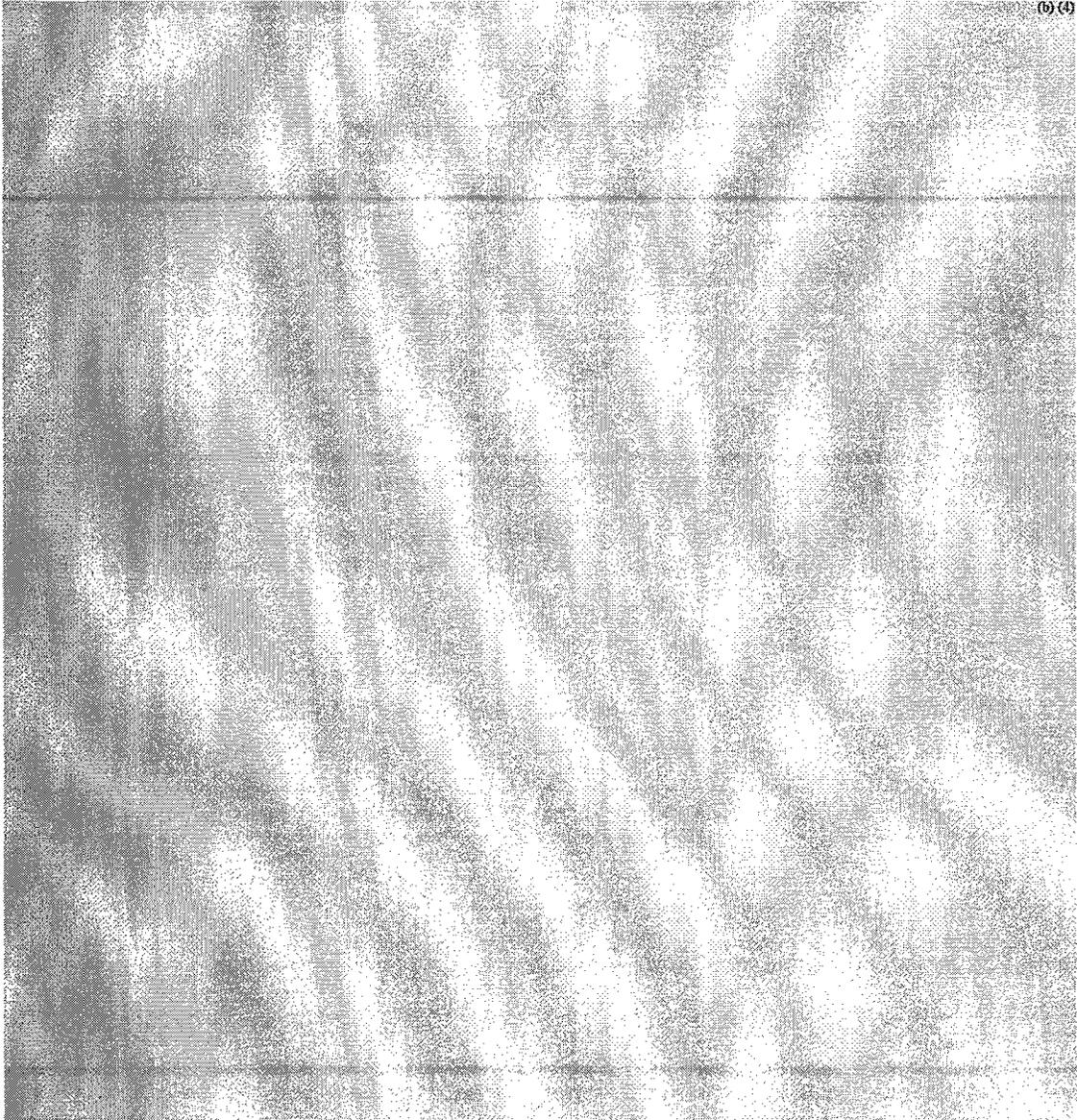
**Figure 1: Assembled Pen-Injector and Cut-Away View of Cartridge**



The dual-chamber pen's theory of operation for each of these fundamental use steps is summarized in Table 1.



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**3. Documents Reviewed**

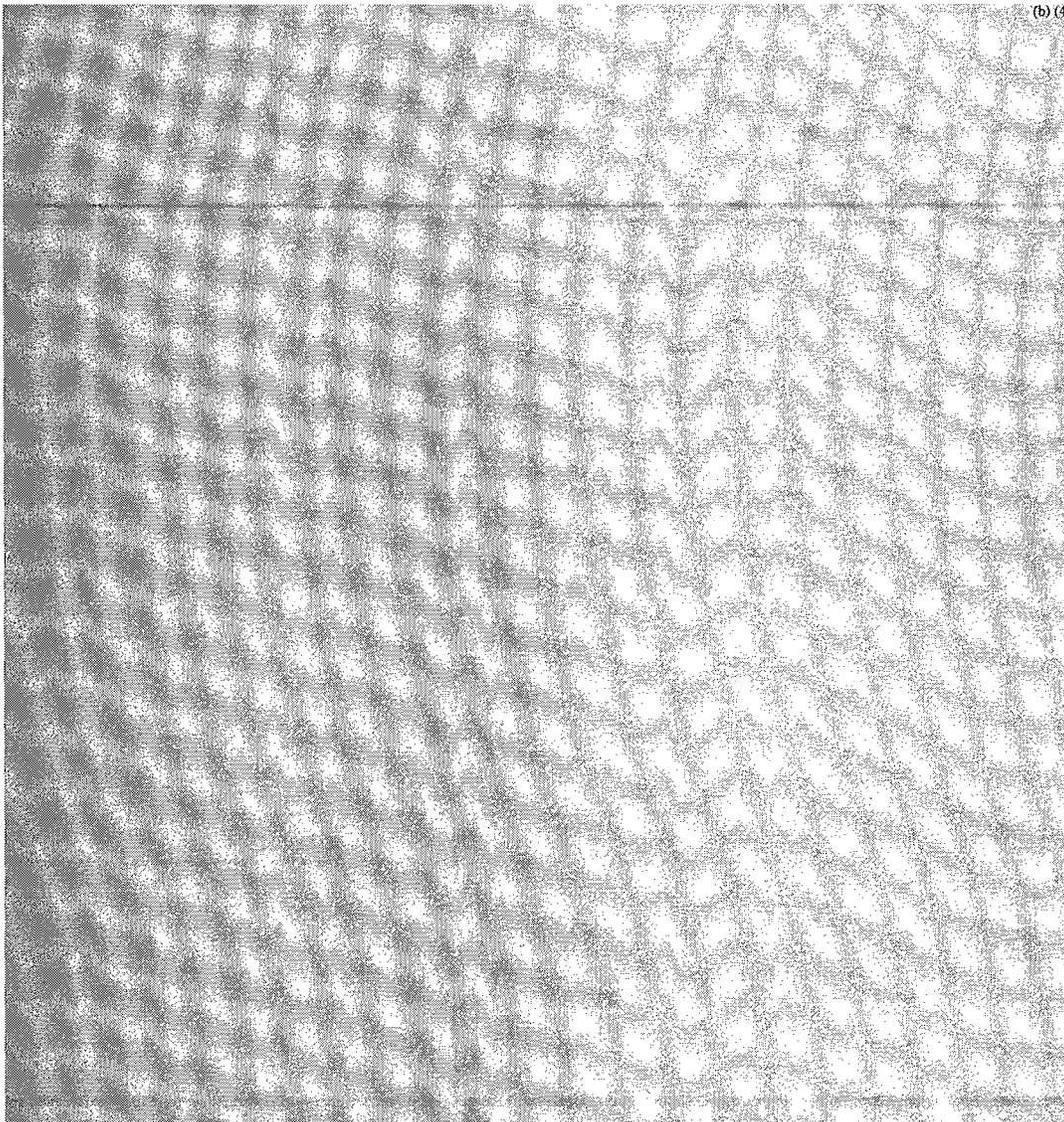
NDA Section- 3.2.R Regional Information, Device Description and Development

(b) (4)  
(b) (4)

**4. CDRH Review and Comments**

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of device performance and device biocompatibility. The sponsor is claiming conformity to (b) (4)

(b) (4) The Agency currently recognizes the updated 2012



**5. CDRH Recommendation**

Based on our review, CDRH does not have any concerns regarding the device constituent of this Combination Product.

If you have any questions, please contact CDR Mary Brooks at (301) 796 - 6078.

Sincerely,

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CDR Mary E. Brooks, RN, BSN, MS  
Nurse Consultant

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/s/  
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POOJA DHARIA  
02/27/2014



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**MEMORANDUM**

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**CDRH Human Factors Consult Review**

DATE: February 24, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID  
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID  
TO: Pooja Dharia, Regulatory Project Manager, CDER/OND/ODEII/DMEP

SUBJECT: **NDA 22200**  
Applicant: Amylin  
Device Constituent: Pen injector  
Drug Constituent: Bydureon (exenatide extended-release for injectable suspension)  
Intended Treatment: Diabetes  
CDRH CTS Tracking No.: ICC 1300466

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QuynhNhu Nguyen, Combination Products Human Factors Specialist

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Ron Kaye, Human Factors and Device Use-Safety Team Leader

## CDRH Human Factors Review

### *Combination Product Device Information*

Submission No.: NDA 22200

Applicant: Amylin

Device Constituent: Pen injector

Drug Constituent: Bydureon (exenatide extended-release for injectable suspension)

### *Intended Treatment: Diabetes CDRH Human Factors Involvement History*

- 9/9/2013 – CDRH HF was requested to review the human factors validation study report included in the NDA. Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose. We would like CDRH and human factors reviewer QuynhNhu Nguyen to review the device and associated labeling (PI, MG, IFU, container).
  - Review Materials:
    - EDR Location: <\\CDSESUB1\evsprod\NDA022200\022200.enx>
    - Cover Letter: <\\CDSESUB1\evsprod\NDA022200\0103\m1\us\cover.pdf>
- 12/23/2013 – CDRH HF identified a deficiency regarding the study failures on critical tasks, and the need to improve product user interface, and additional human factors testing. This deficiency was not sent to the Sponsor.
- 2/3/2014 – CDRH HF participated in an internal meeting to discuss the deficiency identified.
- 2/18/2014 – CDRH HF received Amylin's revised labeling from the project manager

### *Overview and Recommendation*

The Division of Metabolism and Endocrinology Products requested a consultative review from CDRH Human Factors team to review the human factors validation study report contained in the NDA 22200. The device is a single-use peninjector containing exenatide microspheres and diluent prefilled into separate chambers of the glass dual-chamber cartridge. The final product is supplied in cartons that contain four single-dose pens and one spare needle.

In March 2012, the Sponsor submitted a Type C meeting briefing package regarding the BYDUREON dual-chamber pen (Serial 0060, 26 March 2012). Following a subsequent request from FDA, the Sponsor provided samples of the Pen and Instructions for Use (IFU) and the final results of the Human Factors Validation Study 4a (Serial 0064, 23 April 2012). FDA provided a written response to this briefing document and the questions therein in a letter dated 04 June 2012. The Agency also provided a number of specific comments focused on the device and its use, especially the design, results, and interpretation of the human factors validation study. The Sponsor has taken FDA's comments into consideration in subsequent development of the IFU and human factors validation, and this information was submitted in Module 3.2.R, Regional Information, Device Design and Development (Exenatide, Dual-Chamber Pen) (Amylin).

The review of the human factors validation study identified the following deficiency that should be communicated to the Sponsor:

The results of your recent human factors validation study showed use errors were observed with high priority task of mixing the drug powder and diluent, and in ensuring that the mix level was acceptable prior to injection since acceptable mixing must be achieved in order to deliver a full dose. The results also showed that two users can make multiple use errors in the use sequence that could lead to the drug not being delivered. These results indicate that further optimization of the user interface are needed to further reduce or eliminate the use errors seen with this product. We note that you have proposed additional changes to the instructions for use (IFU) for the mixing step. We recommend that you make those changes, and further optimize the device user interface, and perform human factors validation testing with 15 representative users (healthcare providers and patients combined) to demonstrate that the mitigations are effective in reducing or eliminating use error that could cause harm and that the mitigations do not introduce new use-related hazards into the design.

However, this deficiency was not sent to the Sponsor, and an internal meeting was held on 2/3/2014 to discuss a path forward with this deficiency. At this meeting, CDRH HF clarified that the Sponsor considered mixing the drug and diluent a high priority i.e. critical task in the simulated use. Because that was considered as critical task, we interpreted any performance failures associated with that task to mean that those failures can result in patient harm in actual use. The Sponsor stated that they intend to modify the IFU to address observed failures with that task; however, we do not have any evidence demonstrating those modifications are effective and that they do not introduce new issues. At this meeting, the team noted that the same type of errors noted with the vial/syringe configuration, and injecting an unmixed product would have likely resulted in an underdose of 10%, which was thought to be clinically insignificant.

Review of the Sponsor's latest labeling showed that edits have been made to the tasks of mixing, priming, and injecting to increase clarity and emphasis on proper technique. In addition, the revised labeling also includes specific number for patient helpline. This consultant found these changes to be acceptable.

Since additional changes have been made to address the mixing steps, and other critical steps, and the clinical significance associated with injecting an unmixed drug product is low, the consultant does not believe that additional human factors study is needed.

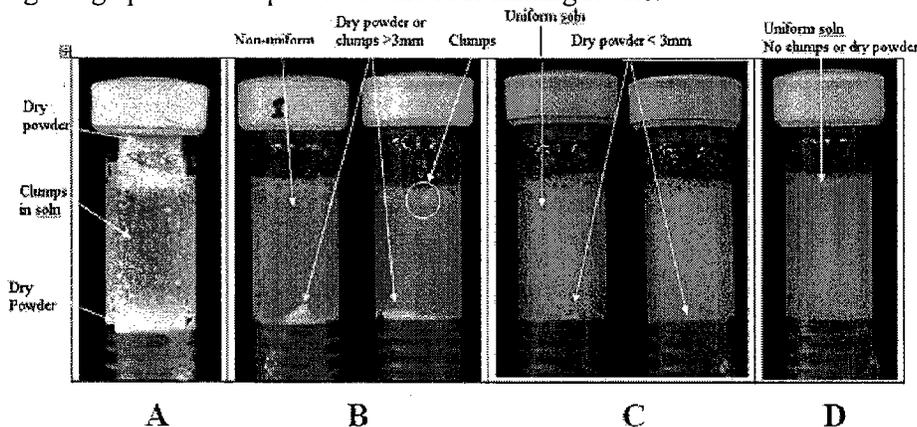
## CDRH Human Factors Review

The human factors validation study was conducted with 63 participants. Of those, there were 16 healthcare providers, and 47 patients with Type 2 diabetes with varying levels of self-injection experience, and varying level of disease-related physical impairments such as diabetic retinopathy or color blindness, and peripheral neuropathy. All of the healthcare providers and 30 patients did not receive training. The remaining 17 patients received training representative of actual training. Observational data were obtained to determine whether the study participants were able to perform tasks associated with the product use. Additional interviewed data were obtained from discussion with study participants who experienced use errors and operational difficulties.

The study results showed use errors and difficulties, and of most concern to the consultant are those that were reported when participants mixed the diluent with the drug powder and when participants did not achieve acceptable mix levels. Acceptable mixing must be performed in order to deliver a full dose. There are four levels of mixing that can result:

- Mix Level A represented the status of the mixing chamber just after the transfer of the diluent.
- Mix Level B is where the suspension is still nonuniform, with clumps (aggregates) of unsuspended powder visible in the suspension and only a significant amount of unsuspended powder visible ( $\geq 3$  mm) in an air pocket or around the plunger.
- Mix Level C is essentially a complete mix with uniform suspension, with only a small amount of unsuspended powder visible (characterized by a thin film or powder  $\leq 3$  mm in length) in an air pocket or across the plunger surface.
- Mix Level D is a complete mix with uniform suspension, with no visible unsuspended powder

The following image provides depiction of the four mixing levels:



An A or B level mix represented a use error. And there were six use errors observed in one healthcare provider, four untrained patients, and one trained patient. The single healthcare provider achieved a B level mix and this was a result only checking 1 side of the window, where the suspension appeared to be a good mix but there were still clumps visible on the other side of

the viewing window. The same observation was also reported for the one train patient. The four untrained patients were reported (1) not checking the bottom surface for clumps, (2) was confused about the term “clumps”, (3) proceeded to the next step even when he noticed that the suspension was not mixed, and (4) did not check the other side of the viewing window. There were also 6 use difficulties observed where three untrained users instead of turning the entire pen while mixing the powder and the diluent, they twisted the knobs at the end of the device which resulted in inadvertent release of the dose button.

There were two untrained patients, due to a series of use errors, did not successfully complete the injection during the study. One untrained participant did not prime the device, and subsequently failed to push the button to inject the dose and failed to hold for 10 seconds. As a result, the drug was not administered. The other untrained participant skipped the priming step, which resulted in the injection button not being released. This participant inserted the needle, pressed the top of the pen and waited for 10 seconds. This participant did not realize that the injection button was not released, and therefore no drug would have been delivered.

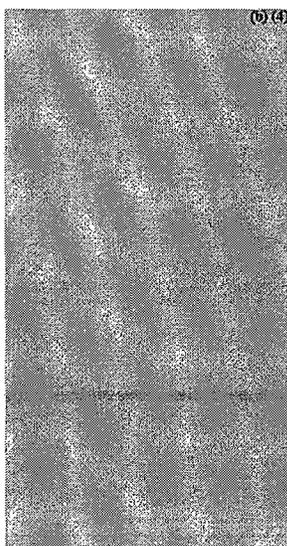
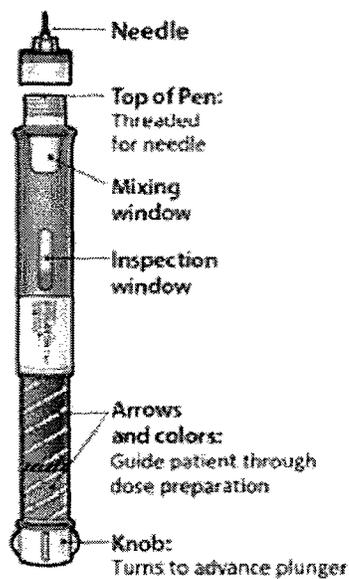
## Appendix 1: Device Description

This pen injector presentation (also referred to as BYDUREON Pen below) is designed to be used for the preparation and administration of BYDUREON®, providing the patient with a more simplified and convenient method of dose administration as compared to the BYDUREON vial and syringe Single Dose Tray (SDT) presentation.

The BYDUREON Pen is a prefilled single-use pen injector. This presentation is supplied as a pen device containing exenatide microspheres and diluent prefilled into separate chambers of the glass dual-chamber cartridge. The microspheres and diluent have the same composition as for the SDT and comply with the approved specifications for BYDUREON.

The dual-chamber pen is supplied with a needle of the same gauge and length as that supplied for the SDT. The final product, BYDUREON Pen, supplied in cartons that contain four single-dose pens and one spare needle (NDC 66780-222-04). Each single-dose pen contains:

- One pen containing 2 mg of exenatide (as a white to off-white powder) and delivering 0.65 mL diluent.
- One custom needle (23G, 9/32") specific to this delivery system.



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/s/  
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POOJA DHARIA

02/25/2014

On behalf of QuynhNhu Nguyen

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

**PATIENT LABELING REVIEW**

Date: January 13, 2014

To: Jean-Marc Guettier, MD  
Director (acting)  
**Division of Metabolism and Endocrinology Products (DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Kendra Y. Jones  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Instructions for Use (IFU),  
single-dose tray

Drug Name (established name): BYDUREON (exenatide extended-release for injectable suspension)

Dosage Form and Route: For injectable suspension, for subcutaneous use

Application Type/Number: NDA 22-200

Supplement Number: 008

Applicant: Bristol-Myers Squibb

## 1 INTRODUCTION

On August 30, 2013, Bristol-Myers Squibb submitted for the Agency's review a Prior Approval Supplement (PAS-008) to the New Drug Application (NDA-22200) for BYDUREON (exenatide extended-release for injectable suspension). The purpose of the submission was to seek approval of a manually operated, single-use Pen presentation. BYDUREON (exenatide extended-release for injectable suspension) was originally approved on January 27, 2012, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) provided a comprehensive review of the BYDUREON (exenatide extended-release for injectable suspension) MG and Pen IFU on December 30, 2013.

This collaborative review is written by DMPP and OPDP in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on January 7, 2014, and January 7, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for the BYDUREON (exenatide extended-release for injectable suspension) single-dose tray.

## 2 MATERIAL REVIEWED

- Draft BYDUREON (exenatide extended-release for injectable suspension) single-dose tray IFU received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 7, 2014
- Draft BYDUREON (exenatide extended-release for injectable suspension) single-dose tray IFU received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on January 7, 2014
- Draft BYDUREON (exenatide extended-release for injectable suspension) Prescribing Information (PI) received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 24, 2013
- Draft BYDUREON (exenatide extended-release for injectable suspension) Prescribing Information (PI) received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 24, 2013
- DMPP and OPDP review of the BYDUREON (exenatide extended-release for injectable suspension) MG and Pen IFU dated December 30, 2013
- DMPP and Division of Medication Error Prevention and Analysis (DMEPA) review of the BYDUREON (exenatide extended-release for injectable suspension) single-dose tray IFU dated December 21, 2011

### **3 REVIEW METHODS**

In our collaborative review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

### **4 CONCLUSIONS**

The IFU is acceptable with our recommended changes.

### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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ROBIN E DUER  
01/13/2014

KENDRA Y JONES  
01/13/2014

MELISSA I HULETT  
01/13/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Human Factors, Label, Labeling and Packaging Review**

Date: January 9, 2014

Reviewer: Sarah K. Vee, Pharm.D.  
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, Pharm.D.  
Division of Medication Error Prevention and Analysis

Division Director: Kellie Taylor, PharmD, MPH  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Budureon Pen (exenatide) suspension for injection  
2 mg/pen

Application Type/Number: NDA 22200/S-008

Applicant: Amylin

OSE RCM #: 2013-2043

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## **1 INTRODUCTION**

This review evaluates the Human Factors/Usability Study results, proposed container label, carton and insert labeling, and instructions for use (IFU) for Bydureon Pen, NDA 22200/S-008, for areas of vulnerability that could lead to medication errors.

### **1.1 BACKGROUND**

Bydureon was approved on January 27, 2012 under NDA 22200 as a single dose tray (SDT) containing 2 mg vial. On August 30, 2013 the Applicant submitted a prior approval supplement that proposes a manually operated, single-use, dual-chamber pen presentation of Bydureon. The supplement contained results from the Human Factors Validation Study.

### **1.2 PRODUCT INFORMATION**

The following product information is provided in the August 30, 2013 prior approval labeling supplement submission.

- Active Ingredient: Exenatide extended-release
- Indication: Indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- Route: Subcutaneous
- Dosage Form: Extended-release injectable suspension
- Strengths: 2 mg (1 pen)
- Dose and Frequency: Inject once weekly
- How supplied: a carton containing four single dose pens and 1 spare needle
- Storage: Refrigerate at 2°C to 8°C (36° to 46°F)
- Applicant: Amylin Pharmaceuticals Inc.
- Container Closure System: Pen injector containing a glass dual-chamber cartridge with a bypass channel Microsphere powder filled into the front chamber of the glass cartridge Diluent filled in the rear chamber of the glass cartridge Injection needle (sterile, single use, in a sealed package) of the same gauge and length as that supplied for BYDUREON

## **2 LABELS AND LABELING REVIEWED**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Container Labels submitted August 30, 2013 (Appendix A)
- (b) (4)
- Carton Labeling submitted August 30, 2013 (Appendix C)
- Insert Labeling submitted August 30, 2013
- Instructions for Use submitted August 30, 2013
- Response to FDA Information Request (IR) submitted December 4, 2013

### **3 HUMAN FACTORS VALIDATION USABILITY STUDY RESULTS AND EVALUATION**

#### **3.1 USABILITY STUDY OBJECTIVE**

The Applicant states that, “This study was designed to demonstrate that the dual-chamber pen conforms to user needs and intended uses, as well as to assess the ability of users to follow the instructions for use for self-administration of the dual-chamber pen.”

#### **3.2 STUDY POPULATION**

To represent the intended user population, the study included 3 groups: untrained HCPs, untrained patients, and trained patients.

Study size:

- Untrained patients (PU): n = 30
- Trained patients (PT): n = 17
- Health Care Professionals (HCPs): n = 16

Respondent demographics:

- Participants met all mandatory criteria:
  - Patients: diagnosed with Type 2 diabetes, adult, over 21 years old
  - HCPs: licensed and responsible for the care, training, or education of patients with diabetes. Minimum of 2 years’ experience in their current position with responsibility training patients with Type 2 diabetes on the use of injection devices.

The trained patients were given the type/level of training that patients might receive prior to starting this treatment by a CDE (instructor was trained on the use of the dual-chamber pen by the Applicant prior to the study). The instructor demonstrated the use of the pen according to the patient instructional proposed IFU booklet, then the participant had an opportunity to try the pen themselves, and ask questions. The subject returned after 1 day (training decay) to simulate the use of the pen.

#### **3.3 RESULTS AND ANALYSIS OF THE USABILITY STUDY**

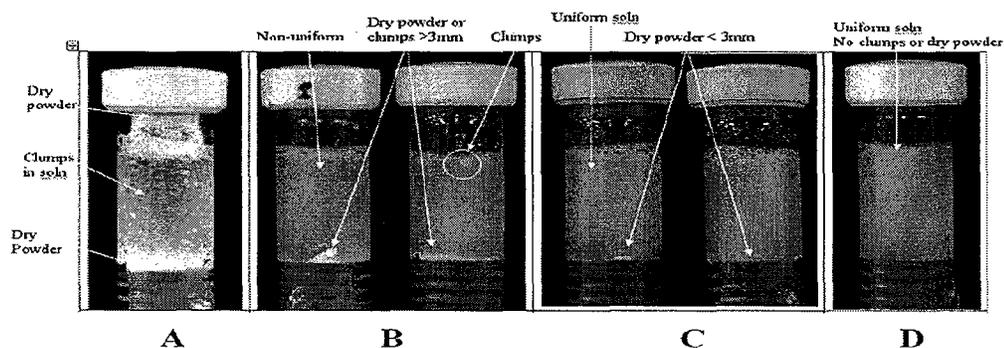
Table A identifies high priority tasks that were identified by the Applicant and the FDA. The table also summarizes use errors, difficulties, and percentage of completion observed for each group.

**Table A High Priority Tasks: Errors/Difficulties (% successful completion)**

HIGH PRIORITY TASK	POTENTIAL CLINICAL IMPACT IF AN ERROR OCCURS	HCPs (N=16)	UNTRAINED PATIENTS (N = 30)	TRAINED PATIENTS (N=17)
A. TAKE PEN OUT OF REFRIGERATOR FOR AT LEAST 15 MINUTES PRIOR TO USE	Make the mixing more difficult resulting in suboptimal dose	1/0 (94%)	1/0 (97%)	0/0 (100%)
B. ATTACH THE COVERED NEEDLE TO THE PEN	Missed dose	0/0 (100%)	0/0 (100%)	0/2 (100%)
C. HOLD PEN UPRIGHT, TWIST HANDLE TO TRANSFER DILUENT INTO MICROSPHERE CHAMBER	Small amount of drug/diluent could be expelled resulting in suboptimal dose	0/2 (100%)	1/1 (97%)	0/1 (100%)
D. TAP PEN FIRMLY AGAINST PALM OF HAND TO MIX THE DILUENT AND MICROSPHERES	Solutions that are unmixed or under mixed may result in suboptimal dose	0/2 (100%)	0/4 (100%)	0/0 (100%)
E. LOOK INSIDE THE MIXING WINDOW TO DETERMINE IF THE SOLUTION IS WELL MIXED	Solutions that are unmixed or under mixed may result in suboptimal dose	0/0 (100%)	0/0 (100%)	0/0 (100%)
F. CHECK THE MIX (SUBOPTIMAL MIX GRADE A OR B)	Solutions that are unmixed or under mixed may result in suboptimal dose	1/2 (94%)	4/1 (87%)	1/0 (94%)
G. CHOOSE YOUR INJECTION SITE	Suboptimal dose	0/0 (100%)	0/1 (100%)	0/0 (100%)
H. HOLD PEN UPRIGHT, WITH COVERED NEEDLE POINTING UP AND TWIST HANDLE TO PRIME THE PEN	Small amount of drug could be expelled resulting in suboptimal dose	0/1 (100%)	3/2 (90%)	0/0 (100%)
I. PULL THE NEEDLE COVER STRAIGHT OFF	Missed dose	0/0 (100%)	0/3 (100%)	1/0 (94%)
J. INSERT NEEDLE AND PUSH THE BUTTON TO INJECT THE DOSE	Missed dose	0/0 (100%)	1/0 (97%)	0/0 (100%)
K. HOLD AFTER INJECTION FOR 10 SECONDS	Suboptimal dose	0/1 (100%)	1/2 (97%)	0/0 (100%)

High priority task use errors are detailed below.

1. Take Pen Out of Refrigerator for at Least 15 Minutes Prior to Use (Use Error = 2)
  - Two participants (1 HCP and 1 PU) stated that they did not see the instructions.
2. Hold pen upright, twist handle to transfer diluent into microsphere chamber and to prime the pen (User Error = 4)
  - PU17 held the pen horizontally, indicated skipped over the instructions, was trying to pay attention.
  - PU19 skipped the instructions and primed while the needle was in the injection pad and stated that the instructions were written well but was doing what they usually do.
  - PU43 skipped the step and suggested adding step numbers. Stated would have been more careful if it was a real injection.
  - PU33 primed the pen while holding the pen horizontally due to habit (to see the dial).
3. Check the mix (An A or B level mix represents a use error due to large clumps of the product that would result in underdose over 25%). Use Error (n = 6).
  - H28 used an alternate tapping method, did not rotate, and did not check both sides. Missed the instructions to check both sides.
  - PT63 did not rotate nor check both sides.
  - PU18 rotated the knob during mixing, used soft to medium tap, and did not check the bottom surface for clumps.
  - PU22 confused by concept of clumps and believed he achieved a well-mixed liquid.
  - PU42 rotated the knob during mixing, stated had a hard time seeing and proceeded since he knew that stakes weren't that high (wasn't injecting self). If injecting at home, he would have been more precise and wear glasses (brought wrong pair of glasses to trial).
  - PU55 did not realize the mix can be seen on two sides.



Mix levels C and D resulted in acceptable doses (mean delivered doses greater than 90% or 1.8 mg)

Mix Level	Trained Patients	Untrained Patients	HCPs
	n = 17	n = 30	n = 16
A	0%	0%	0%
B	6%	13%	6%
C	94%	77%	69%
D	0%	10%	25%
Overall % good mix	94%	87%	94%

HCP = health care professionals.

4. Hold after injection for 10 seconds (n = 1)
  - PU19 inserted needle, primed in the pad, then removed needle. Indicated hold it for 10 seconds is a new step (injection experienced).

#### 4 DISCUSSION OF HUMAN FACTORS RESULTS

The Human Factors Study demonstrated that some users encountered difficulties while administering this product. Some difficulties occurred with tasks that are common to many of injection pen devices and other protein-containing products (i.e., Taking pen/product out of refrigerator for at least 15 minutes prior to use, reconstituting the product and ensuring the product is well mixed, and holding the pen in the skin for 10 seconds) and are not unique to the proposed product. However, some tasks are unique to the proposed pen (i.e., holding the pen upright and twisting to transfer the diluent and to prime the pen).

1. Taking the pen out of refrigerator for at least 15 minutes prior to use was not identified as high priority by the Applicant, but we concluded that it should be a high priority task because according to the Applicant skipping this step may make the mixing step more difficult, which may potentially result in the underdose if the product is not mixed well. However, skipping this step does not affect the overall usability of the pen.
2. Tasks involving holding the pen upright and twisting to transfer the diluent and to prime the pen are considered high priority since holding the pen horizontally while performing these two steps may expel a small amount of the drug and/or diluent. Failure to either transfer the diluent or prime the pen would prevent the patient from moving onto the next step, thus the design of the pen requires these steps to be performed. The Applicant states that based on laboratory testing, the pen could be held up to 75° from vertical before the dose could be potentially affected. It is unlikely that the pen would be held completely horizontal in actual use setting. Thus, the potential loss of small amount of drug does not affect the overall usability or the clinical effectiveness of the pen or the drug. As a result, we find these results acceptable.

3. The majority of errors occurred during the “check the mix” task where the participants were tasked to check the mix for visible clumps (Mix levels A and B were considered errors because these errors would result in underdoses of 25% or more). Use errors resulted from participants not rotating and not checking both sides of the viewing window as well as the bottom to ensure that there were no visible clumps. The Applicant also identified achieving the correct mix to be a residual risk that is specific to the proposed product.

To further assess whether failure of this task represents an issue, the Agency sent the following information request on November 11, 2013:

***Human factor validation study results submitted on August 30, 2013 for the new single pen presentation of your product showed that most patients are likely to receive the formulation as mix C (Table 14 in your submission). As shown from your HPLC analysis, with mix C, the delivered dose could be up to 10% lower than the intended dose of 2 mg.***

***Please provide a detailed justification for why a chronic reduction in dose by up to 10% would not be clinically relevant.***

On December 4, 2013 the Applicant sent the following response:

*In order to assess the clinical significance of a 10% chronic reduction in the delivered dose of the Dual chamber Pen (2 mg), the following steps were used for the modeling and simulation.*

*1) Simulate the steady-state concentration of exenatide at week 28 for a subject receiving a 1.8 mg (90% dose) or 2 mg (100% dose) weekly dose of the extended release formulation of exenatide using a previously developed PK model.*

*2) Using the simulated exenatide steady-state concentrations from Step 1, predict the steady-state glycemic (HbA1c) response at week 28 for the two doses (1.8 and 2.0 mg) using a previously developed PK/PD model.*

*The differences in the glycemic response for subjects receiving the 1.8 mg or 2 mg dose across the 3 subject profiles were small and not clinically meaningful (0.02% to 0.04% HbA1c reduction) and that all profiles (baseline HbA1c 8.2%) achieved the American Diabetes Association recommended HbA1c goal of <7%.*

*The results presented in this response, which utilize the previously developed exenatide PK and PK/PD models, indicate that a potential chronic dosing reduction of 10% from the target 2 mg dose of BYDUREON over 28 weeks does not have a clinically meaningful effect on glycemic response. This analysis further supports the conclusion that a C level mix will provide the glycemic response expected for BYDUREON.*

Based on the Applicant’s response, the Division of Metabolic and Endocrinology Products agree that a 10% reduction in dose of Bydureon is not clinically significant. Thus, DMEPA considers level C (or D) mix acceptable.

We note that six participants achieved mix B, which would result in underdoses of 25% or more. However, difficulties mixing the Bydureon (Appendix D) microspheres have been reported with the vial presentation of the product as well. Thus, the pen design does not introduce new errors related to the mixing step. Due to the results of this study and the potential for underdoses of more than the 25% (with Mix A or B), we will be adding additional information in the PI to ensure that patients are properly trained and counseled regarding the correct mix levels.

4. One error occurred with one patient who did not hold the pen in for 10 seconds. The patient indicated that she was on “auto-pilot”, did not review the instructions, and holding for 10 seconds was a new step (injection-experienced user). The Applicant states that the full dose is delivered within 3 seconds, thus the hold time of 10 seconds would ensure that the full dose is delivered even when the pen is pulled out before the full 10 seconds have elapsed. This is not unique to the proposed pen and according to the clinical team and CDRH, will not result in an underdose.

The results of the Human Factors Validation Study demonstrated that trained patients could use the pen acceptably well. Untrained patients had the most use errors, where most of the errors were caused by skipping over or not paying attention to the provided instructions. Several of the untrained patients indicated that they would pay more attention and be more careful if it was a real injection for them. Therefore, with proper training, we expect that patients will be able to use the Bydureon pen safely and effectively.

## **5 CONCLUSIONS**

The Human Factors Study demonstrated that untrained users may encounter difficulties while administering this product. As a result, DMEPA concludes that proper education and training prior to first injection of Bydureon Pen is needed in order for the product to be used safely and effectively.

We also conclude that the proposed instructions for use, container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

## **6 RECOMMENDATIONS**

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

### **6.1 COMMENTS TO THE DIVISION**

Human Factors Validation Study results demonstrated that some patients encountered difficulties during mixing and injecting the Bydureon Pen. As a result, we recommend the following revisions regarding training and counseling be added to the appropriate sections of the physician insert to further mitigate potential medication errors.

- A. Section 2.2 of the Full Prescribing Information: Administration
  - 1. Second paragraph after the first sentence: For Bydureon Pen, Human Factors Validation Study results demonstrated that errors occurred during tasks involving mixing and holding the needle in the skin for 10 seconds after injecting. These errors can result in under doses. In order to ensure that the product is fully mixed and the full dose is delivered, patients should be trained on how to properly use Bydureon prior to self-administration and counseled regarding how to properly mix, check the mix level, and to hold the pen in the skin for 10 seconds according to the instructions for use.
- B. Section 17.7 of the Full Prescribing Information: Instructions
  - 1. First paragraph: Patients should be trained on how to properly use Bydureon prior to self-administration. Bydureon must be properly mixed and the pen injector held in the skin for 10 seconds in order for the full 2 mg dose to be delivered. Instruct the patient on how to properly mix, check the mix level, and to hold the pen in the skin for 10 seconds according to the instructions for use.

## 6.2 COMMENTS TO THE APPLICANT

- A. Instructions for Use (IFU)
  - 1. Step 2: Mix Your Dose
    - a. Label the diagrams “Not Mixed Well” and “Mixed Well” using numbers or letters so that it is easily referred to in the IFU (e.g. Figure X).
    - b. Revise the “check the mix” statement to state “Check the mix. Your mix should look like “Figure X” (refer to the “Mixed Well” picture).
    - c. In the third section: Highlight the phrase “both sides” by using a different color or font since participants in the human factors study missed this step.
- B. Carton, Pen, (b) (4)
  - 1. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

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KELLIE A TAYLOR  
01/10/2014

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

**PATIENT LABELING REVIEW**

Date: December 30, 2013

To: Jean-Marc Guettier, MD  
Director (acting)  
**Division of Metabolism and Endocrinology Products (DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Kendra Y. Jones  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): BYDUREON (exenatide extended-release for injectable suspension)

Dosage Form and Route: For injectable suspension, for subcutaneous use

Application Type/Number: NDA 22-200

Supplement Number: S-008

Applicant: Bristol-Myers Squibb

## **1 INTRODUCTION**

On August 30, 2013, Bristol-Myers Squibb submitted for the Agency's review a Prior Approval Supplement (PAS-008) to the New Drug Application (NDA-22200) for BYDUREON (exenatide extended-release for injectable suspension). The purpose of the submission was to seek approval of a manually operated, single-use pen presentation. BYDUREON (exenatide extended-release for injectable suspension) was originally approved on January 27, 2012, and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Metabolism and Endocrinology Products (DMEP) on September 09, 2013 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BYDUREON (exenatide extended-release for injectable suspension).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

## **2 MATERIAL REVIEWED**

- Draft BYDUREON (exenatide extended-release for injectable suspension) MG and IFU received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on September 09, 2013.
- Draft BYDUREON (exenatide extended-release for injectable suspension) MG and IFU received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 23, 2013.
- Draft BYDUREON (exenatide extended-release for injectable suspension) Prescribing Information (PI) received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on December 24, 2013.
- Draft BYDUREON (exenatide extended-release for injectable suspension) Prescribing Information (PI) received on August 30, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on December 23, 2013.

## **3 REVIEW METHODS**

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

31 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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SHAWNA L HUTCHINS  
12/30/2013

KENDRA Y JONES  
12/30/2013

MELISSA I HULETT  
12/30/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** December 20, 2013

**To:** Pooja Dharia, Regulatory Project Manager  
Division of Metabolism and Endocrinology Products (DMEP)

**From:** Kendra Y. Jones, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 022200/S-008  
OPDP labeling comments for BYDUREON® (exenatide extended-release for injectable suspension)

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OPDP has reviewed the proposed draft prescribing information (PI) and carton container labeling for BYDUREON® (exenatide extended-release for injectable suspension) submitted for consult on September 9, 2013.

We note that S-008 includes changes to the Highlights of the PI (Dosage and Administration), Dosage and Administration, and How Supplied/Storage and Handling and the Patient Counseling Information sections of the PI. As such, OPDP's review focuses on the changes to these sections only. OPDP's comments on the proposed draft PI are based on the version located in the eRoom entitled, "Physician Insert.doc" (last modified December 20, 2013) provided directly below.

OPDP has no comments on the proposed draft carton and container labeling or the proposed draft PI at this time.

OPDP's comments regarding the draft medication guide and instructions for use (IFU) will be provided under separate cover.

Thank you for the opportunity to comment on the proposed draft PI.

If you have any questions, please contact Kendra Jones at 301.796.3917 or [Kendra.jones@fda.hhs.gov](mailto:Kendra.jones@fda.hhs.gov).

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/s/  
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KENDRA Y JONES  
12/20/2013

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 022200/S-008**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**		
TO: <b>CDER-DMPP-PatientLabelingTeam</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Pooja Dharia, Pharm.D. Regulatory Project Manager Division of Metabolism and Endocrinology Products Center for Drug Evaluation and Research pooja.dharia@fda.hhs.gov (301) 796-5332		
REQUEST DATE 1/7/14	IND NO. 67092	NDA/BLA NO. 22200	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)	
NAME OF DRUG T2DM	PRIORITY CONSIDERATION] Standard – 6 month timeline	CLASSIFICATION OF DRUG T2DM	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)  1/21/14	
NAME OF FIRM: Amylin LLC		PDUFA Date: 2/28/14		
TYPE OF LABEL TO REVIEW				
<b>TYPE OF LABELING:</b> (Check all that apply) X PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING X MEDICATION GUIDE X INSTRUCTIONS FOR USE (IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT X LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
<b>EDR link to submission:</b> EDR Location: \\CDSESUB1\evsprod\NDA022200\022200.enx Cover Letter: \\CDSESUB1\evsprod\NDA022200\0103\m1\us\cover.pdf				
<b>Please Note:</b> There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.  We would like to consult DMPP to review the device and associated labeling (PI, MG, IFU). OPDP, DMEPA, and CDRH/human factors are also being consulted. Please make sure the syringe/vial labeling aligns with the new presentation labeling (the pen presentation has already been reviewed).  This is a labeling supplement with a 6-month timeline. PDUFA goal date = 2/28/14.				
SIGNATURE OF REQUESTER Pooja Dharia				
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> eMAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND		

06/18/2013

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/s/  
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POOJA DHARIA  
01/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Office/Division): <b>Office of Biostatistics</b>			FROM (Name, Office/Division, and Phone Number of Requestor): <b>Priyanka Kumar, ONDQA, Division of Metabolic and Endocrine, Post Marketing, 240-402-3722</b>	
DATE 12/20/2013	IND NO.	NDA NO. 22200	TYPE OF DOCUMENT S-008	DATE OF DOCUMENT 8/30/2013
NAME OF DRUG <b>Bydureon® (exenatide extended release) Suspension</b>		PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 1/28/2014
NAME OF FIRM: <b>AMYLIN PHARMACEUTICALS LLC</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): <input checked="" type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST				
<b>IV. DRUG SAFETY</b>				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS				
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> A new dual chamber pen injector, primary container/closure system, and manufacturing process (sterilization steps) Comparing the approved packaging system and the new system.statistical analysis of the stability data to establish shelf life in 3.2.P.8.1.				
SIGNATURE OF REQUESTOR <b>Priyanka Kumar</b>			METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

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PRIYANKA KUMAR  
12/20/2013



NDA 22200/S-008

INFORMATION REQUEST

Amylin Pharmaceuticals, LLC  
Attention: Cindy Cao, Ph.D.  
Associate Director, CV & Metabolics  
Global Regulatory & Safety Sciences – US  
P.O. Box 4000 (Mail Stop: D22-06)  
Princeton, NJ 08543-4000

Dear Dr. Cao:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bydureon Pen (exenatide extended release for injectable suspension).

We also refer to your submission dated August 29, 2013

We are reviewing the Chemistry Manufacturing and Control sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application by December 13, 2013.

In your November 14, 2013 response, you provide a rationale for a (b) (4) [redacted] that the (b) (4) [redacted] are identical and utilize the same (b) (4) [redacted] cycle parameters. We do not agree with this rationale, or your approach to qualification, for three reasons:

- The identical construction of equipment does not necessarily ensure identical performance, and qualifying studies should be performed for each piece of equipment to establish that each is capable of robust and repeatable performance.

- Although (b) (4) [redacted]

- Your (b) (4) [redacted]

In order to continue review of your application, we request that you submit additional data from qualifying runs from each (b) (4) [redacted] for both the (b) (4) [redacted]

(b) (4), to total three runs. We acknowledge the data that you have already submitted, and are only requesting that you submit data to total three runs for each (b) (4)

The other aspects of your study design (b) (4) are adequate to support the qualification of this equipment.

If you have questions, call Priyanka Kumar, Regulatory Project Manager, at (240) 402-3722.

Sincerely,

*{See appended electronic signature page}*

Ramesh Raghavachari, Ph.D.  
Branch Chief, Branch IX  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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RAMESH RAGHAVACHARI  
11/26/2013

**From:** Dharia, Pooja  
**To:** [Cao, Cindy \(Yang\) \(Cindy.Cao@bms.com\)](mailto:Cindy.Cao@bms.com)  
**Subject:** Bydureon Pen S-008 information request 11/13/13  
**Date:** Wednesday, November 13, 2013 8:44:00 AM

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Hi Cindy,

We have the following request regarding the Bydureon Pen supplement 8:

**Human factor validation study results submitted on August 30, 2013 for the new single pen presentation of your product showed that most patients are likely to receive the formulation as mix C (Table 14 in your submission). As shown from your [REDACTED] (b) (4)**

**Please provide a detailed justification for why a chronic reduction in dose by up to 10% would not be clinically relevant.**

Thanks,

Pooja

Pooja Dharia, Pharm.D.  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
[pooja.dharia@fda.hhs.gov](mailto:pooja.dharia@fda.hhs.gov)  
(301) 796-5332

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POOJA DHARIA  
11/13/2013



NDA 22200/S-008

INFORMATION REQUEST

Amylin Pharmaceuticals, LLC  
Attention: Cindy Cao, Ph.D.  
Associate Director, CV & Metabolics  
Global Regulatory & Safety Sciences – US  
P.O. Box 4000 (Mail Stop: D22-06)  
Princeton, NJ 08543-4000

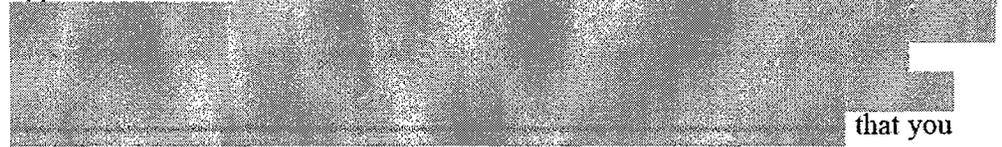
Dear Dr. Cao:

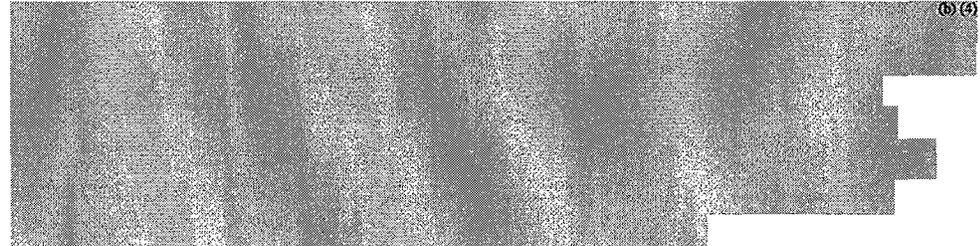
Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bydureon Pen (exenatide extended release for injectable suspension).

We also refer to your submission dated August 29, 2013

We are reviewing the Chemistry Manufacturing and Control sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application by November 12, 2013

1. Your application describes [REDACTED] (b) (4) in validation studies.
2. Your 17 October information request response states that [REDACTED] (b) (4) following this testing?
3. At what point in the manufacturing process does [REDACTED] (b) (4) occur? Provide a justification for not including [REDACTED] (b) (4) as an in-process control.
4. Your application describes [REDACTED] (b) (4). State your production parameters for the [REDACTED] (b) (4). How do parameters used for [REDACTED] (b) (4) in validation studies compare to those in production?
5. Your application describes qualification studies for [REDACTED] (b) (4). Address the following points:
  - a. [REDACTED] (b) (4) Your

approach involves  (b) (4)  
 that you  
have selected for your qualification studies.

b.  (b) (4)

If you have questions, call Priyanka Kumar, Regulatory Project Manager, at (240) 402-3722.

Sincerely,

*{See appended electronic signature page}*

Ramesh Raghavachari, Ph.D.  
Acting Branch Chief, Branch IX  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH RAGHAVACHARI  
10/30/2013



NDA 22200/S-008

**INFORMATION REQUEST**

Amylin Pharmaceuticals, LLC  
Attention: Cindy Cao, Ph.D.  
Associate Director, CV & Metabolics  
Global Regulatory & Safety Sciences – US  
P.O. Box 4000 (Mail Stop: D22-06)  
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We also refer to your submission dated August 29, 2013.

We are reviewing the Chemistry Manufacturing and Control sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application by October 17, 2013.

1. Your application describes container closure integrity studies for the proposed cartridge format. The positive controls for these studies consisted of (b) (4)  
Typical positive controls for container closure integrity studies utilize an intentionally breached container closure unit to ensure that non-integral units can be detected by the testing method. (b) (4)
2. You describe a container closure system that includes a separately packaged sterile needle for assembly by the end user. More information on the sterilization of the needle is needed. Fully describe the sterilization method and corresponding validation studies for the needle. Alternatively, you may provide a letter of authorization for a drug master file that contains this information, or provide reference to a 510(k) clearance for this needle.
3. Your application describes (b) (4) sterilization of the (b) (4). More information is needed. Address the following points:
  - a. State the production parameters for this (b) (4). How do these parameters compare to those used in validation?

- b. You describe two (b) (4) validation studies, (b) (4). The reason for using these two different validation testing methods is unclear. Provide a rationale for this testing. Does the use of two testing methods reflect differences in the way that the (b) (4) is used in production?
  - c. You do not provide the results of the (b) (4) validation test. Provide these results.
  - d. Provide a justification for (b) (4).
  - e. Provide a justification for the locations of (b) (4) and biological indicators used in validation studies.
  - f. Describe the culturing and handling methods for the biological indicators used in (b) (4) validation studies. State the growth medium used as well as the time and temperature of BI incubation.
4. Your application describes the use of component (b) (4). Provide a description of this equipment and its production parameters.
5. Your application describes (b) (4). More information is needed. Address the following points:
- a. Were validation studies performed using (b) (4)?
  - b. What is the formulation of the fluid in which (b) (4)?
  - c. How long was the (b) (4)?
  - d. Were (b) (4)?
  - e. Were (b) (4) tested for integrity? How do the integrity testing values compare to integrity testing values used for production filters?
6. Your application describes validation studies for the (b) (4) of the drug product cartridges. The data you provide from these studies are presented in tables which are alternately titled (b) (4). Provide a clarification for these descriptions.
7. State which autoclaves in your facility are used for sterilization of the (b) (4).
8. Describe the culturing and handling methods for the biological indicators used in autoclave sterilization validation studies. State the growth medium used as well as the time and temperature of BI incubation. Were these indicators (b) (4)?
9. For the (b) (4), provide a justification for the locations of thermocouples

and biological indicators in validation studies.

10. Your media fill simulations involve [REDACTED] (b) (4). Do media fill simulations utilize the same filling equipment as used in production?

11. Your application states that the [REDACTED] (b) (4) [REDACTED] ?

12. The stability testing protocol that you have provided states that [REDACTED] (b) (4) [REDACTED], you should plan to document this switch in the applicable annual report for the drug product.

If you have questions, call Priyanka Kumar, Regulatory Project Manager, at (240) 402-3722.

Sincerely,

*{See appended electronic signature page}*

Ramesh Raghavachari, Ph.D.  
Acting Branch Chief, Branch IX  
Division of New Drug Quality Assessment III  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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RAMESH RAGHAVACHARI  
09/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION <b>**Please send immediately following the Filing/Planning meeting**</b>	
TO: <b>CDER-DMPP-PatientLabelingTeam</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) Pooja Dharia, Pharm.D. Regulatory Project Manager Division of Metabolism and Endocrinology Products Center for Drug Evaluation and Research pooja.dharia@fda.hhs.gov (301) 796-5332	
REQUEST DATE 9/9/13	IND NO. 67092	NDA/BLA NO. 22200	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG T2DM	PRIORITY CONSIDERATION] Standard – 6 month timeline	CLASSIFICATION OF DRUG T2DM	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)  12/13/13
NAME OF FIRM: Amylin LLC		PDUFA Date: 2/28/14	
<b>TYPE OF LABEL TO REVIEW</b>			
<b>TYPE OF LABELING:</b> (Check all that apply) X PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) X CARTON/CONTAINER LABELING X MEDICATION GUIDE X INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT X LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> EDR Location: \\CDSESUB1\evsprod\NDA022200\022200.enx Cover Letter: \\CDSESUB1\evsprod\NDA022200\0103\m1\us\cover.pdf			
<b>Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.</b>			
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.  We would like to consult DMPP to review the device and associated labeling (PI, MG, IFU, carton&container). OPDP, DMEPA, and CDRH/human factors are also being consulted.  This is a labeling supplement with a 6-month timeline. PDUFA goal date = 2/28/14. Please send reviewer assignments so they can be invited to labeling meetings.			
SIGNATURE OF REQUESTER Pooja Dharia			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> eMAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND	

06/18/2013

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/s/

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POOJA DHARIA  
09/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION <b>**Please send immediately following the Filing/Planning meeting**</b>		
TO:  CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Pooja Dharia, Pharm.D. Regulatory Project Manager Division of Metabolism and Endocrinology Products Center for Drug Evaluation and Research pooja.dharia@fda.hhs.gov (301) 796-5332		
REQUEST DATE 9/9/13	IND NO. 67092	NDA/BLA NO. 22200	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)	
NAME OF DRUG T2DM	PRIORITY CONSIDERATION] Standard – 6 month timeline	CLASSIFICATION OF DRUG T2DM	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)  12/13/13	
NAME OF FIRM: Amylin LLC		PDUFA Date: 2/28/14		
<b>TYPE OF LABEL TO REVIEW</b>				
<b>TYPE OF LABELING:</b> <b>(Check all that apply)</b> X PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) X CARTON/CONTAINER LABELING X MEDICATION GUIDE X INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT X LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
<b>EDR link to submission:</b> EDR Location: \\CDSESUB1\evsprod\NDA022200\022200.enx Cover Letter: \\CDSESUB1\evsprod\NDA022200\0103\m1\us\cover.pdf				
<b>Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.</b>				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.  We would like to consult OPDP to review the device and associated labeling (PI, MG, IFU, carton&container). DMPP, DMEPA, and CDRH/human factors are also being consulted.  This is a labeling supplement with a 6-month timeline. PDUFA goal date = 2/28/14. Please send reviewer assignments so they can be invited to labeling meetings.				
SIGNATURE OF REQUESTER Pooja Dharia				
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> eMAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND		

06/18/2013

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/s/  
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POOJA DHARIA  
09/09/2013

**MANDATORY:** Send a copy of the consult request form to the Office of Combination Products as follows:  
--Originating Center: When the consult request is initiated.  
--Consulting Center: When the consult is completed.  
Email: combination@fda.gov or FAX: 301-427-1935

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_  
Assigned to: \_\_\_\_\_  
Date Assigned: \_\_\_\_\_  
Assigned by: \_\_\_\_\_  
  
Completed date: \_\_\_\_\_  
Reviewer Initials: \_\_\_\_\_  
Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center: CDRH  
Division:  
Mail Code: HF  
Consulting Reviewer Name:  
Building/Room #:  
Phone #:  
Fax #:  
Email Address:  
RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER  
Division: Division of Metabolism and Endocrin  
Mail Code: HF 510  
Requesting Reviewer Name: Pooja Dharia  
Building/Room #: Bldg 22/3373  
Phone#: 301-796-5332  
Fax #:  
Email Address: pooja.dharia@fda.hhs.gov  
RPM/CSO Name and Mail Code: Pooja Dharia  
Requesting Reviewer's Concurring  
Supervisor's Name:

**Receiving Division:** If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 9/9/13

**Requested Completion Date:** 12/13/13

Submission/Application Number: NDA 022200  
(Not Barcode Number)

Submission Type: Labeling supplement 008  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: 8/30/13

Official Submission Due Date: 2/28/14

Name of Product: Bydureon Pen

Name of Firm: Amylin LLC

Intended Use: Type 2 Diabetes Mellitus

**Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):**

EDR Location: \\CDSESUB1\evsprod\NDA022200\022200.enx  
Cover Letter: \\CDSESUB1\evsprod\NDA022200\0103\m1\us\cover.pdf

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues. (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.

We would like CDRH and human factors reviewer QuynhNhu Nguyen to review the device and associated labeling (PI, MG, IFU, container). DMEPA is also being consulted.

This is a labeling supplement with a 6-month timeline. PDUFA goal date = 2/28/14. Please send reviewer assignments so they can be invited to labeling meetings.

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/s/  
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POOJA DHARIA  
09/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Pooja Dharia, Pharm.D. Regulatory Project Manager Division of Metabolism and Endocrinology Products Center for Drug Evaluation and Research pooja.dharia@fda.hhs.gov (301) 796-5332		
DATE 9/9/13	IND NO. 67092	NDA NO. 22200	TYPE OF DOCUMENT Labeling supplement S-008	DATE OF DOCUMENT 8/30/13
NAME OF DRUG Bydureon Pen		PRIORITY CONSIDERATION Standard – 6 month clock	CLASSIFICATION OF DRUG T2DM	DESIRED COMPLETION DATE 12/13/13
NAME OF FIRM: Amylin LLC				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<p><b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Bydureon was approved on January 27, 2012 for the treatment of Type 2 Diabetes Mellitus, as a vial and syringe Single Dose Tray (SDT) presentation. Amylin has submitted a labeling supplement for a manually operated, single-use, pen presentation of Bydureon. The dual-chamber pen contains exenatide microspheres and diluent with the same composition as the Bydureon SDT and delivers the same dose.</p> <p>We would like to consult DMEPA to review the device and associated labeling (PI, MG, IFU, carton&amp;container). CDRH/human factors are also being consulted.</p> <p>This is a labeling supplement with a 6-month timeline. PDUFA goal date = 2/28/14. Please send reviewer assignments so they can be invited to labeling meetings.</p> <p>EDR Location: <a href="#">\\CDSESUB1\evsprod\NDA022200\022200.enx</a>          Cover Letter: <a href="#">\\CDSESUB1\evsprod\NDA022200\0103\m1\us\cover.pdf</a></p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input type="checkbox"/> DARRTS <input type="checkbox"/> HAND		

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/s/

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POOJA DHARIA  
09/09/2013



NDA 022200/S-008

**ACKNOWLEDGEMENT --  
PRIOR APPROVAL SUPPLEMENT**

Amylin Pharmaceuticals, LLC  
Attention: Cindy Cao, Ph.D.  
Associate Director, CV & Metabolics  
Global Regulatory & Safety Sciences – US  
P.O. Box 4000 (Mail Stop: D22-06)  
Princeton, NJ 08543-4000

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBER:** 022200  
**SUPPLEMENT NUMBER:** 8  
**PRODUCT NAME:** Bydureon Pen (exenatide extended release for injectable suspension)  
**DATE OF SUBMISSION:** August 29, 2013  
**DATE OF RECEIPT:** August 30, 2013

This supplemental application proposes a manually operated, single-use, dual-chamber pen presentation of Bydureon (exenatide extended release for injectable suspension).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **October 29, 2013**, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be **February 28, 2014**.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

If you have questions, please call me at (301) 796-5332.

Sincerely,

*{See appended electronic signature page}*

Pooja Dharia, Pharm.D.,  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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POOJA DHARIA  
09/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**CMC MICRO & STERILITY ASSURANCE  
REVIEW REQUEST**

TO (Division/Office): **New Drug Microbiology Staff**  
  
**E-mail to: CDER OPS IO MICRO**  
**Paper mail to: WO Bldg 51, Room 4193**

FROM: **Priyanka Kumar Regulatory Project Manager (240)  
402-3722.**

PROJECT MANAGER (if other than sender):

REQUEST DATE  
**9/3/2013**

IND NO.  
**N/A**

NDA NO.  
**22200/S-008**

TYPE OF DOCUMENT  
**Electronic**

DATE OF DOCUMENT  
**8/30/2013**

NAMES OF DRUG  
**Bydureon (exenatide LAR)  
microcapsules for Injection  
Suspension Sterile**

PRIORITY CONSIDERATION  
**N/A**

PDUFA DATE  
**2/28/14**

DESIRED COMPLETION DATE  
**1/28/14**

NAME OF APPLICANT OR SPONSOR: **Bristol Myers-Squibb**

**GENERAL PROVISIONS IN APPLICATION**

- |   |   |
|---|---|
| <input type="checkbox"/> 30-DAY SAFETY REVIEW NEEDED        | <input checked="" type="checkbox"/> PAS                       |
| <input type="checkbox"/> NDA FILING REVIEW NEEDED BY: _____ | <input type="checkbox"/> CBE-30 SUPPLEMENT                    |
| <input type="checkbox"/> BUNDLED                            | <input type="checkbox"/> CHANGE IN DOSAGE, STRENGTH / POTENCY |
| <input type="checkbox"/> DOCUMENT IN EDR                    |   |

**COMMENTS / SPECIAL INSTRUCTIONS:**

The supplement is for a new dual-chamber pen injector, primary container/closure system, and manufacturing process (sterilization steps). Comparing the approved packaging system and the new system:

The original single-dose tray presentation consists of exenatide microsphere powder in a glass vial, the aqueous diluent in a prefilled syringe, the syringe needles, and a vial connector for ease of diluent transfer. The exenatide once weekly dose is prepared by mixing one vial of microspheres with the diluent, and the resulting suspension is administered using the syringe.

This supplement describes the BYDUREON dual-chamber pen presentation. The dual-chamber pen is a manually operated, prefilled single-use pen injector. This presentation is supplied as a pen device containing exenatide microspheres and diluent prefilled into separate chambers of the glass dual-chamber cartridge. The dual-chamber pen is supplied with a needle of the same gauge and length as that for the single-dose tray. The dose is prepared by affixing the covered needle to the pen, twisting the knob to transfer the diluent via a bypass channel to the microsphere chamber, and then agitating the mixture to suspend the microspheres. After removing the needle cover, the patient inserts the needle at the injection site and depresses the plunger to administer the dose. This system eliminates the need for the patient to transfer the product between a vial and syringe, reducing the number of steps required and simplifying the self-injection process.

Please Assign Reviewer

SIGNATURE OF REQUESTER

**Priyanka Kumar**  
Reference ID: 3367204

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS  EDR  E-MAIL  MAIL  HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR  E-MAIL  MAIL  HAND

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PRIYANKA KUMAR  
09/03/2013