

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022200Orig1s000**

**CHEMISTRY REVIEW(S)**

**CMC Memo to File**

To:	NDA
Date	4 Jan 2012
Sponsor:	Amylin
Drug:	BYDUREON™ (exenatide LAR) injectable suspension
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “acceptable” recommendation given on 14-Nov-2011 for the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 22-200 be approved. All labeling changes have been communicated to the applicant through the clinical project manager. There are no pending CMC review deficiencies.

HFD-/Division File  
HFD-510  
HFD-510/P. Dharia

\_\_\_\_\_  
Olen Stephens, Ph.D.  
Chemistry Reviewer

\_\_\_\_\_  
Ali Al-Hakim, Ph.D.  
Branch VII Chief, ONDQA

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/s/  
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OLEN M STEPHENS

01/04/2012

CMC recommendation: approval

ALI H AL HAKIM

01/04/2012

# **NDA 22-200**

**Exenatide for injectable suspension**

**BYDUREON™**

**Olen M. Stephens**

**Office of New Drug Quality Assessment  
Pre-Marketing Division I, Branch II  
for the  
Division of Metabolism and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 22-200
2. REVIEW #: 4
3. REVIEW DATE: 20-Oct-2011
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous Documents

CMC Review #3

Document Date

23-Sep-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment (0047)

DocumentDate

4-Oct-2011

7. NAME & ADDRESS OF APPLICANT:

Name: Amylin Pharmaceuticals, Inc.  
Address: 9360 Towne Centre Drive  
San Diego, CA 92121-3030  
Representative: Dawn Viveash, MD  
Vice President, Regulatory Affairs and Safety  
Telephone: (858) 309-7658

8. DRUG PRODUCT NAME/CODE/TYPE:

## Chemistry Review Data Sheet

- a) Proprietary Name: BYDUREON™  
b) Non-Proprietary Name (USAN): Exenatide for injectable suspension  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Hormone

11. DOSAGE FORM: injection, powder, for suspension, extended release

12. STRENGTH/POTENCY: 2 mg

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Exenatide

Structural Formula:

<sup>1</sup>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<sup>39</sup>-NH<sub>2</sub>

Molecular Formula:

C<sub>184</sub>H<sub>282</sub>N<sub>50</sub>O<sub>60</sub>S

(b)

Molecular Weight: 4186.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	16-Dec-2009 8-Jul-2010 23-Dec-2010 14-Apr-2011	
				1	Adequate	18-Aug-2011	
				1	Adequate	28-Aug-2009	No changes (as of 15-Aug-2011) to this item since last review
				4	N/A		
17114	II	Mallinckrodt	Exenatide	1	Adequate	20-Sep-2011	
(b) (4)				4	Adequate	22-Jun-2011	
				(b) (4)			
(b) (4)				4	N/A		
				19646	II	Lonza	Exenatide
(b) (4)				3	Adequate	7-Jul-2009	

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,725	Exenatide injection
(b) (4)		

Chemistry Review Data Sheet

NDA	021-773	BYETTA® (exenatide) injection
NDA	021-919 (exenatide monotherapy)	BYETTA® (exenatide) injection

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	18-Aug-2011	
Biopharmaceutics	Acceptable	19-Oct-2011	Akm Khairuzzaman

**OGD: N/A**

19. ORDER OF REVIEW (OGD Only): N/A

# The Chemistry Review for NDA 22-200

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval. There are no CMC deficiencies and the Office of Compliance has rendered an "acceptable" recommendation".

A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Lonza and Mallinckrodt, when stored at -15°C. A 48 month expiration period is acceptable for the diluent component of the drug product, when stored between 2°C and 30°C. A bulk hold time (b) (4) is acceptable. A shelf life of 42 months is granted for the exenatide microspheres when stored at 2-8°C.

The expiration dating period grantable for the BYDUREON™ (exenatide) injectable suspension is 42 months or limited by the expiration of the exenatide microspheres or diluent. The kit may be stored at 25 °C for an additional 4 weeks for convenience of the patient.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- 1) In light of the failed BE and IVIVC, future changes to the manufacturing process, scale, and/or site may require clinical studies.

The following are CMC agreements (i.e., these are NOT post-marketing commitments or requirements and will NOT be posted on FDA's website as per FDAAA):



## Executive Summary Section

**A. Description of the Drug Product(s) and Drug Substance(s)**

Lonza Braine, S.A. Chaussée de Tubize 297 B – 1420 Braine-l'Alleud, Belgium	Mallinckrodt Tyco Health, Inc. 3600 North Second Street St. Louis, MO 63147, USA	Amylin Ohio, LLC 8814 Trade Port Drive, West Chester, OH 45071, USA
Drug Substance Manufacturer	Drug Substance Manufacturer	Drug Product Manufacturer

Exenatide (exendin, exendin-4, AC2993, LY2148568) is a 39-amino acid peptide manufactured by (b) (4)

Exenatide once weekly consists of exenatide encapsulated within biodegradable poly(D,L-lactide-co-glycolide) microspheres that are designed to release exenatide over an extended period of time. The exenatide once weekly drug product kit consists of microsphere powder in a (b) (4) vial, diluent in a (b) (4) syringe, injection needles, and a vial connector. The exenatide once weekly dose is prepared by mixing one vial of microspheres with one syringe of diluent. The resulting suspension is administered by subcutaneous injection using the diluent syringe. Two milligrams of exenatide from each single-dose kit are to be administered subcutaneously once per week.

(b) (4)

Exenatide has an observed isoelectric point of (b) (4). The peptide is a white to off-white powder, (b) (4). It is (b) (4)

Exenatide QW bulk microspheres are manufactured as a white to off-white powder (b) (4)

(b) (4). The recommended storage temperature for the drug product in vials is 2-8°C and allows for four weeks of storage at up to 25°C for patient convenience. The proposed expiration period of (b) (4) months is based on data from the commercial site and scale and may be extended with additional stability data post-approval. However, the 36-months of long-term stability data currently submitted is only sufficient to support a 42 month expiration period (X + 6 months as per ICH Q1E). This 42 month expiration period is supported by statistical analysis of the data and is acceptable.

## Executive Summary Section

**B. Description of How the Drug Product is Intended to be Used**

BYDUREON (exenatide QW) is intended for patient self-administration. BYDUREON is provided in a single-dose kit containing: one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe and two needles (one provided as a spare). Exenatide QW is an extended release formulation in which the exenatide peptide is encapsulated within biodegradable polymer microspheres. The microspheres are suspended in an aqueous diluent prior to injection. The exenatide QW dose is prepared by adding diluent from the syringe to a vial of microspheres using the vial connector. The resulting suspension is then administered by subcutaneous injection using the diluent syringe. BYDUREON must be injected immediately after the powder is suspended in the diluent and transferred to the syringe. BYDUREON must not be administered intravenously or intramuscularly.

**C. Basis for Approvability or Not-Approval Recommendation**

This is the second cycle of review for NDA 22-200. In the first cycle, a complete response was rendered, but there were no pending CMC deficiencies at that time. In the current re-submission, the applicant has changed the in vitro complete release method for the drug product, which required review by the biopharmaceutics reviewer and a re-evaluation of the stability data. An information request sent 23-Sep-2011 was addressed with Amendment 0047 (4-Oct-2011), again leaving no pending CMC deficiencies.

The application is supported of 36 months long-term stability data for the exenatide microspheres and 42 months long-term stability data for the diluent. A 42-month shelf life is granted for the BYDUREON™ (exenatide suspension for injection) kits when stored at 2-8°C.

**III. Administrative****A. Reviewer's Signature**

Recorded electronically.

**B. Endorsement Block**

Chemist Name/Date: Same date as draft review  
Chemistry Branch Chief Name/Date

**C. CC Block**

Recorded electronically.

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/s/  
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OLEN M STEPHENS

10/20/2011

CMC Recommendation: Approval

ALI H AL HAKIM

10/20/2011

I concur.

**NDA 22-200**

**Exenatide for injectable suspension**

**BYDUREON<sup>TM</sup>**

**Olen M. Stephens**

**Office of New Drug Quality Assessment  
Pre-Marketing Division I, Branch II  
for the  
Division of Metabolism and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 22-200
2. REVIEW #: 3
3. REVIEW DATE: 23-Sep-2011
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment (0043)\* – Resubmission

27-Aug-201

\*Amendment numbering in the EDR is not sequential. In the EDR, this amendment appears as Amendment 0034.

7. NAME & ADDRESS OF APPLICANT:

Name:	Amylin Pharmaceuticals, Inc.
Address:	9360 Towne Centre Drive San Diego, CA 92121-3030
Representative:	Dawn Viveash, MD Vice President, Regulatory Affairs and Safety
Telephone:	(858) 309-7658

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: BYDUREON™  
b) Non-Proprietary Name (USAN): Exenatide for injectable suspension  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Hormone

## 11. DOSAGE FORM: injection, powder, for suspension, extended release

## 12. STRENGTH/POTENCY: 2 mg

## 13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Exenatide

Structural Formula:

<sup>1</sup>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<sup>39</sup>-NH<sub>2</sub>

Molecular Formula:

C<sub>184</sub>H<sub>282</sub>N<sub>50</sub>O<sub>60</sub>S

Chemistry Review Data Sheet

Molecular Weight: 4186.6

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	16-Dec-2009 8-Jul-2010 23-Dec-2010 14-Apr-2011	
				1	Adequate	18-Aug-2011	
				1	Adequate	28-Aug-2009	No changes (as of 15-Aug-2011) to this item since last review
				4	N/A		
17114	II	Mallinckrodt	Exenatide	1	Adequate	20-Sep-2011	
(b) (4)				4	Adequate	22-Jun-2011	
				(b) (4)			
(b) (4)				4	N/A		
19646	II	Lonza	Exenatide	1	Adequate	16-Aug-2011	
(b) (4)				3	Adequate	7-Jul-2009	

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,725	Exenatide injection
(b) (4)		
NDA	021-773	BYETTA® (exenatide) injection
NDA	021-919 (exenatide monotherapy)	BYETTA® (exenatide) injection

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	18-Aug-2011	
Biopharmaceutics	Pending		Akm Khairuzzaman

**OGD: N/A**

19. ORDER OF REVIEW (OGD Only): N/A

# The Chemistry Review for NDA 22-200

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC recommendation is pending resolution of issues dealing with the in vitro complete release method and post-approval stability commitment. The Office of Compliance has rendered an “acceptable” recommendation”.

A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Lonza and Mallinckrodt, when stored at -15°C. A 48 month expiration period is acceptable for the diluent component of the drug product, when stored between 2°C and 30°C. A bulk hold time for (b) (4) is acceptable.

The expiration dating period grantable for the BYDUREON™ (exenatide) injectable suspension will be determined when the in vitro complete release method has been deemed “acceptable” by the biopharmaceutics reviewer.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

- 1) In light of the failed BE and IVIVC, future changes to the manufacturing process, scale, and/or site may require clinical studies.

The following are CMC agreements (i.e., these are NOT post-marketing commitments or requirements and will NOT be posted on FDA’s website as per FDAAA):



## Executive Summary Section

**A. Description of the Drug Product(s) and Drug Substance(s)**

Lonza Braine, S.A. Chaussée de Tubize 297 B – 1420 Braine-l'Alleud, Belgium	Mallinckrodt Tyco Health, Inc. 3600 North Second Street St. Louis, MO 63147, USA	Amylin Ohio, LLC 8814 Trade Port Drive, West Chester, OH 45071, USA
Drug Substance Manufacturer	Drug Substance Manufacturer	Drug Product Manufacturer

Exenatide (exendin, exendin-4, AC2993, LY2148568) is a 39-amino acid peptide manufactured by (b) (4). Exenatide once weekly consists of exenatide encapsulated within biodegradable poly(D,L-lactide-co-glycolide) microspheres that are designed to release exenatide over an extended period of time. The exenatide once weekly drug product kit consists of microsphere powder in a (b) (4) vial, diluent in a (b) (4) syringe, injection needles, and a vial connector. The exenatide once weekly dose is prepared by mixing one vial of microspheres with one syringe of diluent. The resulting suspension is administered by subcutaneous injection using the diluent syringe. Two milligrams of exenatide from each single-dose kit are to be administered subcutaneously once per week.

(b) (4)

Exenatide has an observed isoelectric point of (b) (4). The peptide is a white to off-white powder, (b) (4).

Exenatide QW bulk microspheres are manufactured as a white to off-white powder (b) (4).

The recommended storage temperature for the drug product in vials is 2-8°C and allows for four weeks of storage at up to 25°C for patient convenience. An expiration period will be established upon resolution of the deficiencies listed above.

**B. Description of How the Drug Product is Intended to be Used**

BYDUREON is intended for patient self-administration. BYDUREON is provided in a single-dose kit 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. BYDUREON is administered as a subcutaneous (SC) injection. BYDUREON must not be administered intravenously or intramuscularly.

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

The CMC recommendation is pending resolution of issues pertaining to the in vitro complete release method and post-approval stability commitment. A list of questions to be sent to the applicant is appended at the end of this review. The Office of Compliance has rendered an “acceptable” recommendations pertaining to the manufacturing and testing sites.

**III. Administrative****A. Reviewer’s Signature**

Recorded electronically.

**B. Endorsement Block**

Chemist Name/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

**C. CC Block**

Recorded electronically.

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/s/  
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OLEN M STEPHENS

09/23/2011

Comments to be sent to the applicant in the appendix. CMC recommendation pending.

ALI H AL HAKIM

09/23/2011

**CMC Memo to File**

To:	NDA
Date	20 Sep 2010
Sponsor:	Amylin Pharmaceuticals, Inc.
Drug:	BYDUREON® (exenatide extended-release for injectable suspension)
Subject	Approval recommendation Applicant's submission follows Agency complete response letter
Reviewer	Dr. Olen Stephens

Pursuant the overall "acceptable" recommendation given on 20-Sep-2010 for the manufacturing facilities by the Office of Compliance and approval recommendation from the microbiology division (22-Jul-2010), CMC recommends that NDA application 22-200 be approved. All labeling changes have been communicated to the applicant through the clinical project manager and have been accepted by the applicant.

HFD-/Division File  
HFD-510  
HFD-510/J. Bishai

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Olen Stephens, Ph.D.  
Chemistry Reviewer

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Ali Al-Hakim, Ph.D.  
Branch Chief, ONDQA

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/s/

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OLEN M STEPHENS

09/22/2010

CMC recommendation for approval

ALI H AL HAKIM

09/22/2010

**CMC Memo to File**

To:	NDA
Date	22 JUL 2010
Sponsor:	Amylin Pharmaceuticals, Inc.
Drug:	BYDUREON® (exenatide extended-release for injectable suspension)
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “acceptable” recommendation given on 15-JUL-2009 for the manufacturing facilities by the Office of Compliance and approval recommendation from the microbiology division (22-Jul-2010), CMC recommends that NDA application 22-200 be approved. All labeling changes have been communicated to the applicant through the clinical project manager and have been accepted by the applicant.

HFD-/Division File  
HFD-510  
HFD-510/J. Bishai

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Olen Stephens, Ph.D.  
Chemistry Reviewer

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Ali Al-Hakim, Ph.D.  
Branch Chief, ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	Bydureon (exenatide LAR)

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/s/

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OLEN M STEPHENS  
07/22/2010

ALI H AL HAKIM  
07/22/2010



### CMC Memo to File

To:	NDA
Date	1 Mar 2010
Sponsor:	Amylin
Drug:	BYDUREON™ (exenatide LAR) injectable suspension
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Two outstanding items remained from CMC review #2, a recommendations from the Office of Compliance and the microbiology division:

1. The Office of Compliance has issued an overall “acceptable” recommendation on 1-Mar-2010 for the manufacturing facilities.
2. The microbiology division recommended a “complete response” on 1-Mar-2010 based on deficiencies that negatively impact (b) (4) of the drug product.

Pursuant the microbiology recommendation, the CMC recommendation is that NDA application 22-200 receive a complete response that enumerates deficiencies found in the microbiology review.

HFD-/Division File  
HFD-510  
HFD-510/J. Bishai

\_\_\_\_\_  
Olen Stephens, Ph.D.  
Chemistry Reviewer

\_\_\_\_\_  
Prasad Peri, Ph.D.  
Acting Branch II Chief, ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	Bydureon (exenatide LAR)

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/s/

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OLEN M STEPHENS

03/01/2010

CMC recommendation is to issue a complete response pursuant the microbiology recommendation

PRASAD PERI

03/02/2010

I concur

**Bydureon™ (Exanatide) for extended release  
injectable suspension**

**NDA 22-200**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Amylin Pharmaceuticals, Inc  
9360 Towne Centre Drive.  
San Diego, CA 92121-3030

**Representative:** Dawn Viveash, MD  
Vice President, Regulatory Affairs and Safety,  
Phone: (858) 309-7658

**Indication:** Treatment of type 2 diabetes

**Presentation:** BYDUREON is intended for patient self-administration. BYDUREON is provided in a single-dose kit 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. BYDUREON is administered as a subcutaneous (SC) injection. BYDUREON must not be administered intravenously or intramuscularly

**EER Status:** Recommendation pending 23-Jun-2009

**Consults:** EA – Categorical exclusion granted under 21 CFR §25.31(c)  
Methods Validation – Revalidation by Agency will not be requested since the methods listed are standard.  
Pharmacology/Toxicology –Acceptable

**Original Submission:** 29-May-2009

**Post-Approval CMC Commitments: None**

In light of the failed BE and IVIVC, future changes to the manufacturing process, scale, and/or site may require clinical studies.

**Drug Substance:**

Exenatide (exendin, exendin-4, AC2993, LY2148568) is a 39-amino acid peptide manufactured by (b) (4). The structural formula is shown below.

Structural Formula:

1His-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<sup>39</sup>-NH<sub>2</sub>

Molecular Formula: C<sub>184</sub>H<sub>282</sub>N<sub>50</sub>O<sub>60</sub>S

Molecular Weight: 4186.6

(b) (4)

Exenatide has an observed isoelectric point of (b) (4). The peptide is a white to off white powder, (b) (4)

The drug substance is manufactured by two companies: Lonza Braine S.A. and Mallinckrodt Inc, St. Louis, MO. Both manufacturers have DMFs associated with their manufacturing process, which were found adequate. Exenatide bulk microspheres are manufactured as a white to off-white powder (b) (4)

Amylin proposes a single, uniform specification for exenatide manufactured by Mallinckrodt and Lonza, with the exception of process-specific attributes including (b) (4) from each supplier differ because of different exenatide manufacturing processes employed at Lonza and Mallinckrodt.

A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Lonza, when stored at -15°C. A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Mallinckrodt, when stored at -15°C.

A 36 month expiration period is acceptable for the diluent component of the drug product, when stored between 2°C and 30°C. A bulk hold time for (b) (4) is acceptable.

**Conclusion:** The drug substance is satisfactory.

### **Drug Product:**

The drug product consists of 2 mg of exenatide encapsulated within biodegradable poly(D,L-lactide-co-glycolide) microspheres stored in (b) (4) vials with (b) (4) stoppers, (b) (4) mL diluent stored in a (b) (4) syringe, injection needles, and a vial connector. When mixed with (b) (4) mL of the diluent and injected subcutaneously, the formulation is designed to release exenatide over an extended period of time (one week). Exenatide formulation is composed of exenatide (drug load of (b) (4) w/w) and sucrose (b) (4) w/w) encapsulated within biodegradable polymer (poly(D,L lactide-co-glycolide; (b) (4) w/w) (PLG) microspheres. Exenatide bulk microspheres are manufactured as a white to off-white powder (b) (4) Each vial contains 2 mg of exenatide, 0.8 mg sucrose and 37.2 mg poly(D,L lactide-co-glycolide). The recommended storage temperature for the drug product in vials is 2-8°C. The bulk dry powder is made by Amylin Ohio, LLC.

The diluent per syringe consists of carboxymethylcellulose sodium (23 mg), sodium chloride (5 mg), polysorbate (b) (4) (0.77 mg), Monobasic Sodium Phosphate Monohydrate (0.74 mg), Dibasic Sodium Phosphate Heptahydrate (0.62 mg) and water sufficient for (b) (4) It is a sterile,

The dose is prepared by mixing one vial of microspheres with the contents of the syringe of diluent. The resulting suspension is administered by subcutaneous injection using the diluent syringe. Two milligrams of exenatide from each single-dose kit are to be administered subcutaneously once per week.

Note that the manufacturing process was scaled up during the clinical trials and the site was changed for the commercial manufacturing. Bridging between the two drug product manufacturing sites was conducted via a clinical study (with PK and clinical endpoints) because the sponsor previously failed to show a successful IVIVC; the biowaiver request for the commercial product was denied.

The Clinical Division commented at the 03-NOV-2009 Mid-Cycle Review Meeting that, in light of the failed BE and IVIVC, future changes to the manufacturing process, scale, and/or site may require clinical studies.

The recommended storage temperature for the drug product in vials is 2-8°C and allows for four weeks of storage at up to 25°C for patient convenience. The proposed expiration period of (b) (4) months is based on data from the commercial site and scale and may be extended with additional stability data post-approval. However, the (b) (4) - months of long-term stability data currently submitted is only sufficient to support a (b) (4) month expiration period. This (b) (4) month expiration period is supported by statistical analysis of the data and is acceptable.

**Outstanding issues: An evaluation of the sterility assurance by the micro group is not complete and their review is pending. A final recommendation from the OC is pending.**

**Conclusion:** The drug product is acceptable. However if the micro group finds any issues with the sterility assurance, the CMC recommendation may change.

**Additional Items:**

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Method validation will not be requested since all methods are standard.

Acceptable compliance status and microbiology review of the sterility assurance have not been provided yet.

**Overall Conclusion:** CMC recommends approval pending final recommendation from Office of Compliance on the establishments and from the New Drug Microbiology review team on the Sterility Assurance.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22200

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ORIG-1

-----  
AMYLIN  
PHARMACEUTICA  
LS INC

-----  
EXENATIDE LAR

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/s/  
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PRASAD PERI

02/08/2010

**NDA 22-200**

**Exenatide for injectable suspension**

**BYDUREON<sup>TM</sup>**

**Olen M. Stephens**

**Office of New Drug Quality Assessment  
Pre-Marketing Division I, Branch II  
for the  
Division of Metabolism and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 22-200
2. REVIEW #: 2
3. REVIEW DATE: 20-Jan-2010
4. REVIEWER: Olen M. Stephens

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

5-MAY-2009

Amendment (0005) – Response to 74-day letter

1-SEP-2009

Amendment (0007) – Updated Stability Data

2-OCT-2009

Amendment (0012) – Updated Stability Data

20-NOV-2009

Amendment (0015) – Response to Information request

11-DEC-2009

Amendment (0016) – Response to Information request

31-DEC-2009

Amendment (0017) – Response to Information request

13-JAN-2010

7. NAME & ADDRESS OF APPLICANT:

Name:

Amylin Pharmaceuticals, Inc.

Address:

9360 Towne Centre Drive  
San Diego, CA 92121-3030

## Chemistry Review Data Sheet

Representative: Dawn Viveash, MD  
Vice President, Regulatory Affairs and Safety  
Telephone: (858) 309-7658

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: BYDUREON™
- b) Non-Proprietary Name (USAN): Exenatide for injectable suspension
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Hormone

## 11. DOSAGE FORM: injection, powder, for suspension, extended release

## 12. STRENGTH/POTENCY: 2 mg

## 13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

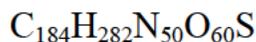
Chemical Name: Exenatide

Structural Formula:

<sup>1</sup>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<sup>39</sup>-NH<sub>2</sub>

Chemistry Review Data Sheet

Molecular Formula:



Molecular Weight: 4186.6

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS		
(b) (4)				3	Adequate	7-Feb-2006 20-May-2005 13-Dec-2001 21-Jan-2009			
				1	Adequate	22-Oct-2009			
				1	Adequate	28-Aug-2009			
				4	N/A				
17114	II	Mallinckrodt	Exenatide	1	Adequate	7-Dec-2009			
(b) (4)				4	N/A				
								(b) (4)	No direct contact to drug product – not reviewed.
				4	N/A				
19646	II	Lonza	Exenatide	1	Adequate	21-Oct-2009			
(b) (4)				3	Adequate	7-Jul-2009			

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,725	Exenatide injection
(b) (4)		
NDA	021-773	BYETTA® (exenatide) injection
NDA	021-919 (exenatide monotherapy)	BYETTA® (exenatide) injection

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	This review may not impact CMC recommendation		Brian T. Hummer
Clin/Pharm	This review may not impact CMC recommendation		Jayabharathi Vaidyanathan
Microbiology	Pending Review of sterility assurance		Robert Mello

**OGD: N/A**

19. ORDER OF REVIEW (OGD Only): N/A

# The Chemistry Review for NDA 22-200

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending adequate microbiology response and an Acceptable recommendation from Office of Compliance.

Note: A recommendation from the Office of Compliance is pending. The final CMC recommendation does not incorporate any potential GMP facility inspection issues.

A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Lonza, when stored at -15°C. A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Mallinckrodt, when stored at -15°C. A 36 month expiration period is acceptable for the diluent component of the drug product, when stored between 2°C and 30°C. A bulk hold time for (b) (4) is acceptable.

The expiration dating period grantable for the BYDUREON™ (exenatide) injectable suspension is (b) (4) months or limited by the expiration of the exenatide microspheres or diluent.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- 1) In light of the failed BE and IVIVC, future changes to the manufacturing process, scale, and/or site may require clinical studies.

The following are CMC agreements (i.e., these are NOT post-marketing commitments or requirements and will NOT be posted on FDA's website as per FDAAA):



## Executive Summary Section

(b) (4)



## Executive Summary Section

**A. Description of the Drug Product(s) and Drug Substance(s)**

Lonza Braine, S.A. Chaussée de Tubize 297 B – 1420 Braine-l'Alleud, Belgium	Mallinckrodt Tyco Health, Inc. 3600 North Second Street St. Louis, MO 63147, USA	Amylin Ohio, LLC 8814 Trade Port Drive, West Chester, OH 45071, USA
Drug Substance Manufacturer	Drug Substance Manufacturer	Drug Product Manufacturer

Exenatide (exendin, exendin-4, AC2993, LY2148568) is a 39-amino acid peptide manufactured by (b) (4). Exenatide once weekly consists of exenatide encapsulated within biodegradable poly(D,L-lactide-co-glycolide) microspheres that are designed to release exenatide over an extended period of time. The exenatide once weekly drug product kit consists of microsphere powder in a (b) (4) vial, diluent in a (b) (4) syringe, injection needles, and a vial connector. The exenatide once weekly dose is prepared by mixing one vial of microspheres with one syringe of diluent. The resulting suspension is administered by subcutaneous injection using the diluent syringe. Two milligrams of exenatide from each single-dose kit are to be administered subcutaneously once per week.

(b) (4)

Exenatide has an observed isoelectric point of (b) (4). The peptide is a white to off-white powder, (b) (4)

Exenatide QW bulk microspheres are manufactured as a white to off-white powder (b) (4)

The recommended storage temperature for the drug product in vials is 2-8°C and allows for four weeks of storage at up to 25°C for patient convenience. The proposed expiration period of (b) (4) months is based on data from the commercial site and scale and may be extended with additional stability data post-approval. However, the (b) (4) months of long-term stability data currently submitted is only sufficient to support a (b) (4) month expiration period (X + 6 months as per ICH Q1E). This (b) (4) month expiration period is supported by statistical analysis of the data and is acceptable.

**B. Description of How the Drug Product is Intended to be Used**

BYDUREON is intended for patient self-administration. BYDUREON is provided in a single-dose kit 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

## Executive Summary Section

transferred to the syringe. BYDUREON is administered as a subcutaneous (SC) injection. BYDUREON must not be administered intravenously or intramuscularly.

**C. Basis for Approvability or Not-Approval Recommendation**

This is the first cycle of review for NDA 22-200. Two main deficiencies were identified in CMC Review #1 that have since been resolved. The drug product specification for individual product-related impurities was unacceptable as first proposed only the (b) (4)

[REDACTED]

Additionally, by recommendation of the non-clinical reviewer, the applicant shall institute a specification for the total amount of (b) (4) of no more than (b) (4) ppm for each. This attribute should be included as part of the release testing, but does not need to be monitored on stability because the degradants are formed upon (b) (4).

The application is supported of 18 months long-term stability data for the exenatide microspheres and 36 months long-term stability data for the diluent.

As described in the initial quality assessment and minutes for the pre-NDA meeting, comparability between clinical and proposed commercial drug product manufacturing sites was determined by a clinical trial because BE studies and IVIVC biowaivers were denied. The clinical pharmacology team has determined that the two sites are equivalent. However, it should be noted that future manufacturing changes may require clinical trials to establish bioequivalency in the future.

There are no other CMC deficiencies were identified. The pre-approval inspections are pending review by the Office of Compliance.

**III. Administrative****A. Reviewer's Signature**

Recorded electronically.

**B. Endorsement Block**

Chemist Name/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

**C. CC Block**

Recorded electronically.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	EXENATIDE LAR

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OLEN M STEPHENS

01/20/2010

CMC Recommendation: Approval pending an adequate response from microbiology consult and the recommendation of OC regarding facilities inspections.

PRASAD PERI

01/20/2010

I Concur

**NDA 22-200**

**Exenatide for injectable suspension**

**BYDUREON™**

**Olen M. Stephens**

**Office of New Drug Quality Assessment  
Pre-Marketing Division I, Branch II  
for the  
Division of Metabolism and Endocrinology Products**

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# Chemistry Review Data Sheet

1. NDA 22-200
2. REVIEW #: 1
3. REVIEW DATE: 12-Oct-2009
4. REVIEWER: Olen M. Stephens

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

5-MAY-2009

Amendment (0005) – Response to 74-day letter

1-SEP-2009

Amendment (0007) – Updated Stability Data

2-Oct-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Amylin Pharmaceuticals, Inc.
Address:	9360 Towne Centre Drive San Diego, CA 92121-3030
Representative:	Dawn Viveash, MD Vice President, Regulatory Affairs and Safety
Telephone:	(858) 309-7658

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: BYDUREON™  
b) Non-Proprietary Name (USAN): Exenatide for injectable suspension  
c) Code Name/# (ONDC only):  
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

## 10. PHARMACOL. CATEGORY: Hormone

## 11. DOSAGE FORM: injection, powder, for suspension, extended release

## 12. STRENGTH/POTENCY: 2 mg

## 13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Exenatide

Structural Formula:

<sup>1</sup>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<sup>39</sup>-NH<sub>2</sub>

Molecular Formula:

C<sub>184</sub>H<sub>282</sub>N<sub>50</sub>O<sub>60</sub>S

Chemistry Review Data Sheet

Molecular Weight: 4186.6

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS			
(b) (4)				3	Adequate	7-Feb-2006 20-May-2005 13-Dec-2001 21-Jan-2009				
				1	Adequate	31-Aug-2009				
				1	Adequate	28-Aug-2009				
				4	N/A					
17114	II	Mallinckrodt	Exenatide	1	Adequate	14-Sep-2009				
(b) (4)				4	N/A					
				(b) (4)					No direct contact to drug product – not reviewed.	
				4	N/A					
19646	II	Lonza	Exenatide	7	Pending		Pending Review			
(b) (4)				3	Adequate	7-Jul-2009				
				(b) (4)						

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,725	Exenatide injection
(b) (4)		
NDA	021-773	BYETTA® (exenatide) injection
NDA	021-919 (exenatide monotherapy)	BYETTA® (exenatide) injection

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending Review of limits on specific impurities and (b) (4)		Brian T. Hummer
Biopharm			
LNC			
Methods Validation			
OPDRA			
Microbiology	Pending Review of sterility assurance		Robert Mello

**OGD: N/A**

19. ORDER OF REVIEW (OGD Only): N/A

# The Chemistry Review for NDA 22-200

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is approvable, pending resolution of the deficiencies regarding specifications for the total impurities and specified impurities as monitored by SCX-HPLC and an Acceptable recommendation from Office of Compliance.

A (b) (4) month retest date is acceptable for the exenatide drug substance manufactured by Lonza, when stored at -15°C. A (b) (4) month shelf life is acceptable for the diluent component of the drug product, when stored between 2°C and 30°C.

The expiration dating period grantable for the BYDUREON™ (exenatide) injectable suspension is pending review of CMC deficiencies regarding specifications for the total impurities and specified impurities as monitored by SCX-HPLC.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following are CMC agreements (i.e., these are NOT post-marketing commitments or requirements and will NOT be posted on FDA's website as per FDAAA):



## Executive Summary Section

(b) (4)

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Exenatide (exendin, exendin-4, AC2993, LY2148568) is a 39-amino acid peptide manufactured by (b) (4). Exenatide once weekly consists of exenatide encapsulated within biodegradable poly(D,L-lactide-co-glycolide) microspheres that are designed to release exenatide over an extended period of time. The exenatide once weekly drug product kit consists of microsphere powder in a (b) (4) vial, diluent in a (b) (4) syringe, injection needles, and a vial connector. The exenatide once weekly dose is prepared by mixing one vial of microspheres with one syringe of diluent. The resulting suspension is administered by subcutaneous injection using the diluent syringe. Two milligrams of exenatide from each single-dose kit are to be administered subcutaneously once per week.

(b) (4)

Exenatide has an observed isoelectric point of (b) (4). The peptide is a white to off-white powder, (b) (4).

### B. Description of How the Drug Product is Intended to be Used

Exenatide QW bulk microspheres are manufactured as a white to off-white powder (b) (4). The recommended storage temperature for the drug product in vials is 2-8°C and allows for four weeks of storage at up to 25°C for patient convenience. The proposed shelf life of (b) (4) months is based on data from the commercial site and scale and may be extended with additional stability data post-approval. The (b) (4)-months of long-term stability data currently submitted is only sufficient to support a (b) (4) month shelf life (X + 6 months as per ICH Q1E). This shelf-life may be extended pending additional stability data.

### C. Basis for Approvability or Not-Approval Recommendation

The drug product specifications for purity, total impurities, and specified impurities are unacceptable at this time. Because the drug product is a large

## Executive Summary Section

peptide formulated within a biodegradable polymer,  (b) (4)



Additionally,  (b) (4)

There are no other CMC deficiencies identified at this point of the review. Specifications that might concern the clinical or non-clinical reviewer have been flagged and communicated to the appropriate reviewer. The pre-approval inspections are pending review by the Office of Compliance.

### III. Administrative

#### A. Reviewer's Signature

Recorded electronically.

#### B. Endorsement Block

Chemist Name/Date: Same date as draft review

Chemistry Team Leader Name/Date

Project Manager Name/Date

#### C. CC Block

Recorded electronically.

126 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22200	ORIG-1	AMYLIN PHARMACEUTICA LS INC	EXENATIDE LAR

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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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OLEN M STEPHENS

10/13/2009

CMC Recommendation: approvable pending resolution of deficiencies regarding total drug product impurities and individual drug product impurities

PRASAD PERI

10/17/2009

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Division of Metabolism and Endocrinology Products**

**NDA:** 22-200

**Applicant:** Amylin Pharmaceuticals, Inc.

**Stamp Date:** 05-MAY-2009

**PDUFA Date:** 05-MAR-2010

**Proposed Proprietary Name:** BYDUREON

**Established Name:** Exenatide for injectable suspension

**Dosage form and strength:** Injection, powder, for suspension, extended release  
2 mg

**Route of Administration:** injection

**Indications:** Treatment of type 2 diabetes

**CMC Lead:** Su (Suong) Tran, Branch II/DPA I/ONDQA

**ONDQA Fileability:** Yes

**Comments for 74-Day Letter:** Yes, on the last page.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	Not Applicable
CDRH or CBER	Not Applicable
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	EER was sent to Office of Compliance on 12-MAY-2009.
OSE	Labeling consult request will be sent as part of DMEP's request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Review of 1) microbiology controls proposed for the drug substance, exenatide drug product and diluent, and 2) sterilization and aseptic processing validation for the exenatide drug product and diluent.
Pharm/Tox	To be determined by the primary reviewer. A consult review may be needed for the safety evaluation of leachables and impurities.

**Summary: [See the discussion in Critical Issues later in this review.]**

This is an electronic NDA, filed as a 505(b)(1) application. Reference is made to the approved NDA 21-773 and pending NDA 21-919 for the same drug substance, all NDAs having the same applicant.

The drug product is an extended-release formulation of exenatide for once weekly dosing. The drug powder is reconstituted with the co-packaged diluent prior to use. The current approved Byetta of NDA 21-773 (same applicant, same drug substance) is for twice daily dosing.

The new drug product is 2 mg of exenatide (b) (4) w/w) and sucrose ( (b) (4) ) encapsulated in biodegradable (b) (4) polymer (poly-D,L-lactide-co-glycolide, 50:50) (b) (4) microspheres. The polymer degrades in vivo over time to lactic and glycolic acids and releases the active ingredient by a combination of diffusion and polymer erosion. The product is a powder in a stoppered (b) (4) vial, co-packaged in a kit that includes the diluent in a syringe, injection needles, and a vial connector. The diluent is composed of carboxymethylcellulose sodium, polysorbate 20, monobasic sodium phosphate monohydrate, dibasic sodium phosphate heptahydrate, sodium chloride, and water for injection. Immediately after reconstitution, the suspension is administered subcutaneously.

**Maximum weekly dose is 2 mg exenatide.**

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/s/

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Suong Tran  
6/16/2009 11:13:45 AM  
CHEMIST

Ali Al-Hakim  
6/16/2009 11:32:04 AM  
CHEMIST