APPLICATION NUMBER:

21-773

CHEMISTRY REVIEW(S)
NDA 21-773

Byetta (exenatide) Injection, 250 mcg/mL

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Amylin Pharmaceuticals, Inc.

Indication: NDA 21-773: Treatment to improve glycemic control in pts with type 2 diabetes who have not achieved adequate glycemic control on metformin, a sulfonyl urea or a combination of metformin, and a sulfonyl urea.

Presentations: NDA 21-773: Prefilled pen-injector device, 60 doses of 5 mcg per dose

EER Status: acceptable 7-DEC-2004

Consults: DMETS – comments 14-FEB-2005
Statistics – comments 18-MAR-2005
Micro – approval recommendation 22-MAR-2005
EA – none – waiver granted

The Byetta NDA was submitted 29-JUN-2004

The drug substance is a 39mer peptide manufactured by (DMF and DF). Both of the DMFs are acceptable. Adequate controls are in place. The drug substance is adequately characterized, however it remains unclear whether the peptide is the from the manufacturing process. Amylin has agreed to study this issue post approval and if the peptide is indeed a salt they will revise the USAN name accordingly. Impurity profiles from each manufacturer differ slightly, however they have been safety qualified in comparative toxicity studies. The specification is found acceptable. Submitted stability data support a re-test of when stored at

Conclusion
Drug substance is acceptable.
The drug product is a buffered solution formulated with mannitol and metacresol antimicrobial preservative in glass cartridges for use in a pen injector device. Cartridge sizes are 1.2 mL and 2.4 mL for the 2 dosing regimens (combination). The established process controls are considered adequate. The product is manufactured by [Redacted].

The pen injectors are assembled at Eli Lilly and Company, Indianapolis, IN. The specification is acceptable and includes 2 in vitro bioassays – one functional and the other a receptor binding assay. Controls for impurities are also adequate.

Based upon the submitted 24 months of stability data an expiry of 24 months at 5° C is granted. The stability protocol is acceptable.

All associated DMFs are acceptable.

Labeling is acceptable.

Conclusion
Drug product and device are acceptable – an agreements have been made to determine whether the peptide is an acetate salt and to revise the USAN name accordingly is appropriate.

Overall Conclusion
From a CMC perspective the applications are recommended for approval actions.

Eric P. Duffy, PhD
Director, DNDC II/ONDC
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Duffy
4/27/05 04:32:34 PM
CHEMIST
NDA 21-773

BYETTA
(exenatide injection)

Amylin Pharmaceutical, Inc.

Chien-Hua Niu, Ph.D.,
ONDC/DNDC-II/HFD-510
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   I. DRUG SUBSTANCE
   II. DRUG PRODUCT
   III. LABELING & PACKAGE INSERT
   IV. Claim Of Categorical Exclusion
   V. List Of Deficiencies To Be Communicated
Chemistry Review Data Sheet

1. NDA 21-773

2. REVIEW #: 1

3. REVIEW DATE: March 23, 2005

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

   Name: Amylin Pharmaceuticals, Inc.
   Address: 9360 Towne Centre Drive
             San Diego, California 92121
   Representative: David C. Furlano, Ph.D.
   Telephone: (858)642-7248
8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: BYETTA
   b) Non-Proprietary Name (USAN): Exenatide
   c) Code Name/# (ONDC only): 141732-76-5 (CAS registry number)
      AC2993 (Amylin Pharmaceuticals, Inc.)
      LY2148568 (Eli Lilly and Co)
   d) Type/Submission Priority (ONDC only):
      - Chem. Type: 1
      - Submission Priority: 1 S

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Hormone

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: ________

13. ROUTE OF ADMINISTRATION: Injection

14. Rx/OTC DISPENSED: X Rx  ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

   ____ SPOTS product – Form Completed

   X Not a SPOTS product
CHEMISTRY REVIEW
Chemistry Review Data Sheet

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

Chemical Name: Exenatide

Structural Formula:

\[ \text{His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser}^{39}\text{-NH}_2 \]

Molecular Formula:

\[ C_{184}H_{252}N_{50}O_{66}S \]

Molecular Weight: 4186.6

17. RELATED/SUPPORTING DOCUMENTS:

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1 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")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
**B. Other Documents:**

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The Chemistry Review for NDA

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   The application can be approved from chemistry point of view.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
   A Phase 4 commitment regarding the proper established name for the drug is being requested (see List of Non-Aprovability Comments and Requests for Information)

II. Summary of Chemistry Assessments

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

Byetta (exenatide injection) is utilized to improve glycemic control in people with type 2 diabetes mellitus. Enhances glucose-dependent insulin secretion, improves beta-cell function, suppresses inappropriately elevated glucagon secretion and slows gastric emptying.

DRUG SUBSTANCE: Exenatide is originally isolated from the venom of Gila monster (Heloderma suspectum). Exenatide shares 53% of amino acid sequence with glucagon-like peptide-1 (GLP-1) and binds and activates the human GLP-1 receptor in vitro. Thus it leads to an increase in both glucose-dependent synthesis and secretion of insulin from pancreatic beta cells by mechanism involving cyclic AMP and/or other intracellular signaling pathways. Exenatide is an acetate salt of a synthetic 39 amino acid polypeptide (elemental composition, C_{184}H_{332}N_{96}O_{46}S; molecular weight, 4186.6 Daltons). The amino acid sequence for exenatide is presented below:

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-Gly-Asp-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂
**DRUG PRODUCT:** Exenatide injection is a parenteral drug product for subcutaneous administration. It is supplied in multi-pie-dose, pre-filled, 1.2 and 2.4 mL pen-injections assembled with cartridges containing a sterile, preserved exenatide solution, intended for self-injection by the patient. The formulation consists of exenatide in 4.5 acetate buffer containing metacresol (m-cresol) as an antimicrobial preservative and mannitol as a tonicity-modifying agent. Cartridges are assembled into the disposable pen-injector. Two prefilled pens are available to deliver unit doses of 5 micrograms (mcg) or 10 mcg.

Drug substance supplied by is used for formulation of the drug product. While each of the exenatide suppliers meets the uniform specifications for purity and total related substance, the percentage and distribution of the individual related substances is supplier specific. All impurities from both suppliers have been fully qualified and used in the toxicology studies and clinical trials.

Formulation development included investigation of the effects of pH, buffer, mannitol and m-cresol on exenatide stability. Process development for the drug product included investigation of process parameters and exenatide from multiple suppliers. Bioactivity of exenatide during processing was confirmed by a validated bioassay.
The drug product is currently manufactured by Later, a second commercial manufacturer, has been qualified to manufacture exenatide injection.

The manufacturing and processing controls at are similar. However, a major difference in the filling process between is noted. In the manufacturing process, the bulk solution

The proposed regulatory methods have been validated.

The drug product is packaged in a glass cartridge Two cartridge sizes are used. The nominal "1.2 mL cartridge" uses a USP Type I glass cartridge. The nominal "2.4-mL cartridge" uses a USP Type I glass cartridge that is filling to deliver a minimum volume of 2.4 mL.

Based on data from the primary stability batches from the following drug product attributes do not change as function of storage temperatures (5°C, ) or time (up

24 months is recommended for exenatide injection.

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.
B. Description of How the Drug Product is Intended to be Used

Byetta is intended to improve glycemic control in patients with type 2 diabetes mellitus as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. Therapy should be initiated at 5 mcg per dose administered twice daily (BID) at any time within the 60-minute period before the morning and evening meals.

Each dose should be administrated as a SC injection in the thigh, abdomen, or upper arm.

C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC viewpoint pending satisfactory responses from DMF holders and NDA applicant. This recommendation is based upon several issues identified during the review. (1) General procedures for the synthesis of exenatide are outlined in DMF and DMF. All chemistry deficiencies have been addressed by the DMF holders and found satisfactory. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Primary stability batches have been manufactured by and primary batches have been manufactured by. All these batches were produced with the drug substance manufactured by. (4) Stability data indicate that no significant changes were observed in terms of appearance, m-cresol content, pH, particulates, a period of up to 24 months. However, total product-related impurities increase with storage temperatures and time, but remained within the proposed specification when stored at. (5) CGMP inspection of the manufacturing sites for the drug substance, the drug product as well as testing site has been completed and found to be acceptable by the Office of Compliance.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDCCDNDC-II/HFD-510
Chemistry Team Leader Name/Date: Stephen Moore, Ph.D., ONDCCDNDC-II/HFD-510
Project Manager Name/Date: Lina AlJuburi, OND/HFD-510

C. CC Block

HFD-820: Dr. Eric Duffy/ Dr. Blair Fraser
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☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
**CHEMISTRY REVIEW**

**REVIEW NOTE**

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**ESTABLISHMENT EVALUATION REQUEST**

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| Stamp Date | 30-JUN-2004 |
| Fрма Date  | 30-APR-2005 |
| Action Goal|              |
| District Goal | 01-MAR-2005 |

| Brand Name | (EXENATIDE) INJ SOL |
| Dosage Form | (SOLUTION) |

| Generic Name | EXENATIDE INJECTION |
| Strength     |                    |

| FDA Contacts | C. NIU Review Chemist (HFD-510) 301-827-6420 |
|             | S. MOORE Team Leader (HFD-510) 301-827-6401 |

---

**Overall Recommendation:** ACCEPTABLE on 07-DEC-2004 by J. D ANBROGIO(HFD-322) 301-827-5049

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**Establishment:** FEI

**DIN No:** AADA:

**Responsibilities:**

**Profile:** CSN

**CAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 07-DEC-04

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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## CHEMISTRY REVIEW

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Responsibilities: 

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Reason: BASED ON PROFILE 

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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Chien-Hua Niu
4/12/05 03:21:08 PM
CHEMIST

Stephen Moore
4/12/05 06:31:22 PM
CHEMIST
Page(s) Withheld

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