CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-773

CHEMISTRY REVIEW(S)

NDA 21-773

Byetta (exenantide) 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 (DMF). 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 .

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

Table of Contents

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:

Submission Type	Document Date
Original	29-JUN-2004
Amendment	12-AUG-2004 (BL)
Amendment	18-AUG-2004 (BC)
Amendment	28-OCT-2004 (BC)
Amendment	04-NOV-2004 (BL)
Amendment	17-DEC-2004 (BC)

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

Chemistry Review Data Sheet

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 [redacted]
- Submission Priority: **1 S**

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Hormone

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: [redacted]

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

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

Chemical Name: Exenatide

Structural Formula:

[1]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[39]-NH_2

Molecular Formula:

$C_{184}H_{282}N_{50}O_{60}S$

Molecular Weight: 4186.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Exenatide	1	Adequate	12-April -05	Review by Chien-Hua Niu for NDA #21-773
	II		Exenatide	1	Adequate	11-April-05	Reviewed by Chien-Hua Niu for NDA #21-773
	III		Glass cartridge	1	Adequate	14-September-01	Reviewed by Yvonne Yang
	III			1	Adequate	22-Auguust-02	Réviewed by Liang-Lii Huang

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,725	Exendin-4 for treatment of patients with type 2 diabetes mellitus
IND	[redacted]	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	18-MAR-05	Dr. Lee Ping Pian
EES	Acceptable	07-DEC-04	Office of Compliance
Pharm/Tox	Acceptable		Dr. John Colerangle
Biopharm	Acceptable		Dr. Xiao-Xiong Wei
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		Dr. Chien-Hua Niu
DMETS	Revision of the labels and labeling	14-FEB-05	Dr. Felicia Duffy
EA	Categorical exclusion	23-MAR-05	Dr. Chien-Hua Niu
Microbiology	Acceptable	22-MAR-05	Dr. Vinavak Pawar

REVIEW NOTE

The Chemistry Review for NDA [redacted]

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-Approvability Comments and Requests for Information)

II. Summary of Chemistry Assessments

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

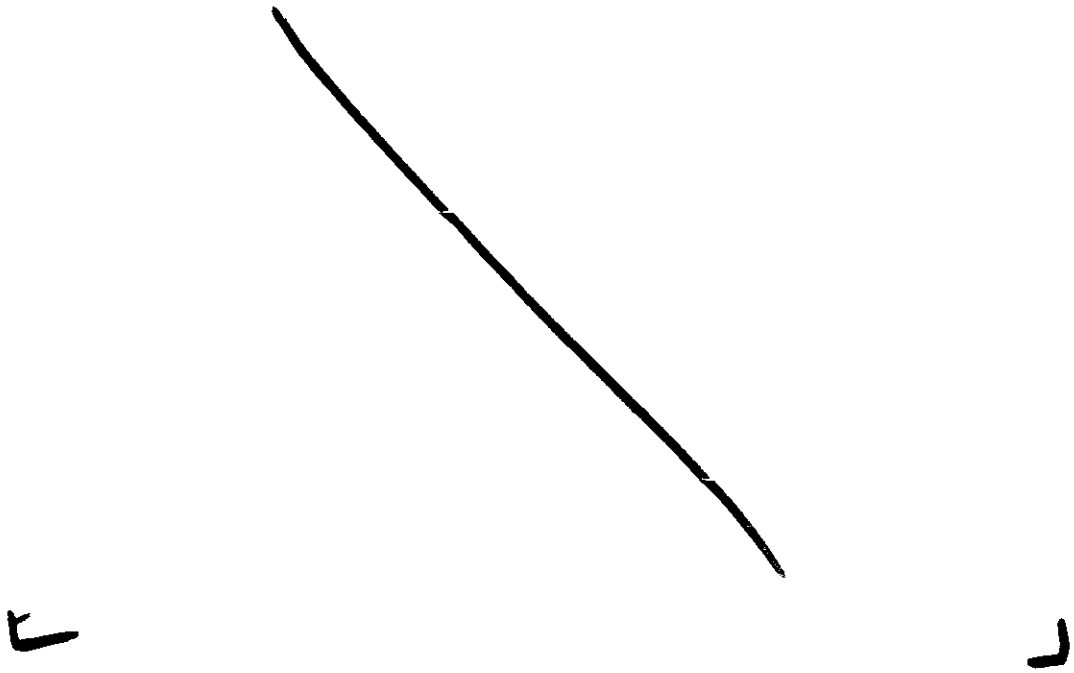
Byetta (exenatide injection) is utilized to improve glycemic control in people with type 2 diabetes mellitus. [redacted] enhances glucose-dependent insulin secretion, improves beta-cell function, suppresses inappropriately elevated glucagon secretion and slows gastric emptying.

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, $C_{184}H_{282}N_{50}O_{60}S$; 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-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2

[redacted]

REVIEW NOTE



DRUG PRODUCT: Exenatide injection is a parenteral drug product for subcutaneous administration. It is supplied in multipe-dose, pre-filled, 1.2 and 2.4 mL pen-injections assembled with cartridges containing a sterile, preserved [redacted] exenatide solution, intended for self-injection by the patient The formulation consists of exenatide in [redacted] 4.5 acetate buffer containing [redacted] metacresol (m-cresol) as an antimicrobial preservative and [redacted] 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 [redacted] 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.

REVIEW NOTE

The drug product is currently manufactured by [redacted] Later, a second commercial manufacturer, [redacted], has been qualified to manufacture exenatide injection.

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

The proposed regulatory methods have been validated.

The drug product is packaged in a glass cartridge [redacted] Two cartridge sizes are used. The nominal "1.2 mL cartridge" uses a [redacted] USP Type I glass cartridge. The nominal "2.4-mL cartridge" uses a [redacted] USP Type 1 glass cartridge that is filling to deliver a minimum volume of 2.4 mL.

Based on data from the [redacted] primary stability batches from [redacted] the following drug product attributes do not change as function of storage temperatures (5°C, [redacted] or time (up [redacted] an expiration dating period of 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 [redacted] as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea. [redacted] 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 [redacted] and DMF [redacted] 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) [redacted] primary stability batches have been manufactured by [redacted] and [redacted] primary batches have been manufactured by [redacted] All these batches were produced with the drug substance manufactured by [redacted] (4) Stability data indicate that no significant changes were observed in terms of appearance, m-cresol content, pH, particulates, [redacted] 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 [redacted] (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./ONDC/DNDC-II/HFD-510
Chemistry Team Leader Name/Date: Stephen Moore, Ph.D., /ONDC/DNDC-II/HFD-510
Project Manager Name/Date: Lina AlJuburi , OND/HFD-510

C. CC Block

HFD-820: Dr. Eric Duffy/ Dr. Blair Fraser

55 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-1

CHEMISTRY REVIEW

REVIEW NOTE

□(s0P□&k4S□&17.27c66F 21-MAR-2005 FDA CDER EES
1 of 2

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21773/000
Org Code : 510
Priority : 1S

Sponsor: AMYLIN
9360 TOWNE CENTRE DR STE 110
SAN DIEGO, CA 921213030

Stamp Date : 30-JUN-2004
PDUFA Date : 30-APR-2005
Action Goal :
District Goal: 01-MAR-2005

Brand Name : [redacted] (EXENATIDE) INJ SOL 0.25MG/ML
Estab. Name:
Generic Name: EXENATIDE INJECTION
Dosage Form: (SOLUTION)
Strength : [redacted]

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-2004by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : [redacted] FEI [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-DEC-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

REVIEW NOTE

Establishment : [redacted]

Responsibilities: [redacted]

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-AUG-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-AUG-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1819470 FEI : 1819470

LILLY, ELI & CO.

LILLY CORPORATE CENTER

INDIANAPOLIS, IN 46285

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-AUG-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

REVIEW NOTE

Establishment : [redacted]

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-AUG-04		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

Establishment : [redacted]

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-AUG-04		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

---

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 2

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

8 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry-3

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 4

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 5