CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-332

Chemistry Review(s)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-332 **Chemistry Review # 4** ***(Drug Product Section)*** **Date Reviewed:** 15-MAR-2005

Submission Type	**Document Date**	**CDER Rec. Date**	**Filing Date**
Original	07-DEC-2000	12-DEC-2000	06-FEB-2001
Amendment	17-SEP-2004 (AZ)		
Amendment	02-FEB-2005 (BL)		
Amendment	03-FEB-2005 (BL)		
Amendment	07-FEB-2005 (BL)		
Amendment	11-FEB-2005 (BL)		
Amendment	16-FEB-2005 (BC)		
Amendment	17-FEB-2005 (BL)		
Amendment	24-FEB-2005 (BL)		
Amendment	25-FEB-2005 (BC)		
Amendment	03-MAR-2005 (BL)		
Amendment	14-MAR-2005 (BL)		

Name & Address of the Applicant: Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
San Diego, CA 92121

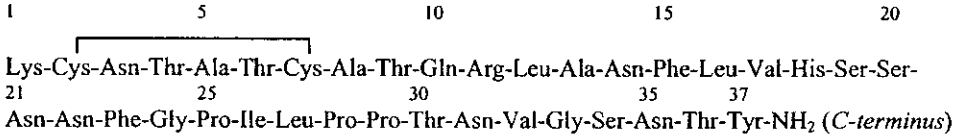
Drug Product Name

Proprietary:	Symlin™ Injection
Nonproprietary/Established/USAN:	Pramlintide acetate
Chem.Type/ Ther.Class:	**1 S**

Pharmacological Category/indication: Treatment of type 1 or type 2 diabetes as an adjunct to insulin
Dosage Form: Solution
Strength(s): 0.6 mg/mL in 5-mL Vials
Route of Administration: Parenteral Injection
Dispensed: Rx
SPOTS: No ✓

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Pramlintide / 25, 28, 29 Pro-h-amylin / AC-137
$C_{171}H_{267}N_{51}O_{53}S_2 \cdot (CH_3COOH)_x$ $3 \leq x \leq 8$ MW = 3949.45



Conclusions & Recommendations: Satisfactory CMC information has been provided to judge the quality of the drug substance, pramlintide acetate, and the drug product, Symlin™ (Pramlintide acetate) Injection. From the Chemistry viewpoint this application can be approved.

Xavier Ysern, PhD
Review Chemist

Stephen Moore. PhD
Chemist Team Leader

filename: /nda/21332_dp4.doc

AP

Supporting Documents:

DMF	*Subject*	*Holder*	*LOA* Date*	*Status*	*Rev. Date*
Type II					
	Pramlintide Acetate		27-NOV-2000	Adequate	See DS section
	Pramlintide Acetate		16-SEP-1999	Adequate	See DS section
	Pramlintide Acetate		07-NOV-2000	Adequate	See DS section
Type III					
			25-AUG-1999	Adequate[a]	Adequate[b]
			15-DEC-1998	Adequate[a]	Adequate[b]
			02-FEB-1999	Adequate[a]	Adequate[b]
			02-FEB-1999	Adequate[a]	Adequate[b]
			01-FEB-1999	Adequate[a]	Adequate[b]

* LOA (Letter of authorization) provided in volume 1.14, pages 3943 to 3949.
[a] See Container/Closure section for additional information and testing performed by NDA holder.
[b] Adequate information provided in the submission.

Related Documents: --

Consults: Sterilization Validation, Microbiology Division
Division of Drug Marketing, Advertising and Communications (DDMAC)
Trade name, Office of Post-Marketing Drug Risk Assessment (OPDRA)
Inspection of manufacturing facilities, Office of Compliance

Remarks/Comments: The **active ingredient pramlintide** acetate, a thirty-seven amino acid peptide shown in figure 1(A), **is an analog of human amylin**. Human amylin, a natural hormone secreted by the β-cells of the pancreas, plays an important physiological role in the regulation of glucose metabolism in conjunction with insulin and glucagon. Amylin, which is deficient in people with diabetes, is cosecreted with insulin and reduces nutrient-stimulated glucagon secretion after interaction with specific receptor in the brain (main site of action). Pramlintide differs from human amylin by the substitution of proline residues for alanine, serine, and serine residues at positions 25, 28, and 29 respectively as shown in Figure 1(B). Accordingly to the applicant these

The drug product, Symlin™ Injection, will be commercialized in strengths 0.6 mg/mL in 5-mL Vials.

(A) 1 5 10 15 20

Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-

21 25 30 35 37

Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH_2 (*C-terminus*)

Figure 1. Primary sequence[1] of human amylin and drug substance pramlintide (cysteines 2 and 7 are disulfide link).

[1] Standard amino acid one letter code: A=Ala, B=Asx = Asp or Asn, C=Cys, D=Asp, E=Glu, F=Phe, G=Gly, H=His, I=Ile, K=Lys, L=Leu, M=Met, N=Asn, P=Pro, Q=Gln, R=Arg, S=Ser, T=Thr, V=Val, W=Trp, Y=Tyr, and Z=Glx = Glu or Gln.

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_____ § 552(b)(5) Draft Labeling

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/s/

Xavier Ysern
3/15/05 01:38:21 PM
CHEMIST

Stephen Moore
3/15/05 03:44:41 PM
CHEMIST

3/14/05

NDA 21-332

SYMLIN (pramlintide acetate) Injection

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Amylin Pharmaceuticals, Inc.

Indication: Treatment of type 1 and 2 diabetes in pts failing to achieve adequate glycemic control with insulin and or a sulfonyl urea or metformin treatment

Presentation: multi-use 0.6 mg /mL in 5 mL vials

EER Status: Acceptable 08-DEC-2003

Consults: DMETS – Tradename: Symlin is acceptable
Statistics – none
EA – waiver granted
Micro – acceptable 12-JUL-2001

Phase IV Commitments/Agreements: none

The original NDA was received 07-DEC-2000

SYMLIN (pramlitide acetate) Injection was submitted 7-DEC-2000. The indication is as adjunctive to insulin therapy for improved glycemic control. The drug substance pramlintide acetate is a synthetic 37mer peptide with a single disulfide linkage.

The **drug substance** is manufactured by [redacted]. DMF [redacted] Note that the [redacted] methodology of the other two proposed manufacturers. Compliance found the manufacturing site to be acceptable based upon profile. The DMF is acceptable.

Drug Substance is also manufactured by [redacted] DMF [redacted] Compliance has found the facilities to be acceptable based upon profile class. The DMF is acceptable.

An additional manufacturer has been qualified, [redacted] DMF [redacted] was found acceptable. Compliance found the manufacturing site to be acceptable based upon profile class. The DMF is acceptable.

Discussion
The 3 drug substances have been demonstrated to be equivalent structurally, and equivalent in bioassay. Although the impurity profiles differ, [ ] and [ ] impurity profiles have been qualified from a safety perspective.

Conclusion
Drug substance is acceptable.

The **drug product** is a solution provided as multi-use 0.6 mg /mL in 5 mL vials. The manufacturer is [ ] The formulation is simply a solution with mannitol and metacresol as preservative and pH adjustment with acetic acid or sodium acetate. The manufacturing process is a [ ] Storage for 36 months at refrigerated temperature was found acceptable, and post dispensing the product is proposed to be stored at room temperature for 28 days .

All associated DMFs are acceptable.

All manufacturing facilities are acceptable

Manufacturing is acceptable from a sterility assurance perspective.

Labeling revisions are acceptable.

Conclusion
Drug product is acceptable.

Overall Conclusion From a CMC perspective the NDA should be approved.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
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/s/

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Stephen Moore
3/15/05 03:44:41 PM
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10/2/01

NDA 21-332

SYMLIN (pramlintide acetate) Injection

CHEMISTRY DIVISION DIRECTOR REVIEW

SYMLIN (pramlitide acetate) Injection was submitted 7-DEC-2000. The indication is as adjunctive to insulin therapy for improved glycemic control. The drug substance pramlintide acetate is a synthetic 37mer peptide with a single disulfide linkage.

The **drug substance** is manufactured by [ ] DMF[ ] was reviewed on a consult basis by Dr. Chen Hua Niu/HFD-580. A request for additional information was sent to the firm 21-AUG-2001, however the information requested is not considered to be required for approval. Note that the synthesis process is a [ ] methodology in contrast to the [ ] methodology of the other two proposed manufacturers. Clinical trials, and pharm/tox studies have not been conducted using — drug substance to date, however the firm will be requested to conduct the new trial(s) using — drug substance. This study will serve to qualify the impurity profile as well as confirmation of absence of significant immunogenicity. Compliance found the manufacturing site to be acceptable based upon profile. The DMF is acceptable.

Drug Substance is also manufactured by [ ] DMF[ ] was reviewed on a consult basis. A request for additional information was sent to the firm 5-APR-2001. The issues are not considered to be approvability issues. The impurity profile, and immunogenicity has been assessed in the pharm/tox and clinical trials conducted with this material. Proposed specifications of impurities are roughly comparable to those qualified. Compliance has found the facilities to be acceptable based upon profile class. The DMF is acceptable.

An additional manufacturer has been qualified, [ ] DMF [ ] was review on a consult basis and was found acceptable. . The impurity profile, and immunogenicity has been assessed in the pharm/tox and clinical trials conducted with this material. Proposed specifications of impurities are roughly comparable to those qualified. Compliance found the manufacturing site to be acceptable based upon profile class. The DMF is acceptable.

Discussion

The 3 drug substances have been demonstrated to be equivalent structurally, and equivalent in bioassay. Although the impurity profiles differ, [ ] impurity profiles have been qualified from a safety perspective, the — drug substance will be qualified with respect to impurity profile and immunogenicity in the up-coming clinical trial(s). The specifications are composite and therefore cover material from all sources. Additionally, pharm/tox review (see review memorandum dated 10/9/2001) has concluded that there are no significant toxicity concerns with respect to the — impurity profile or proposed specification.

Conclusion
Pending analysis of the results of the up-coming clinical trial, no issues remain from a CMC perspective regarding comparability of the drug substance manufactured by the 3 proposed manufacturers. Outstanding DMF querries are not considered approvability issues.

The **drug product** is a solution provided as multi-use 0.6 mg /mL in 5 mL vial [ ] The formulation is simply a solution with mannitol and metacresol as preservative and pH adjustment with acetic acid or sodium acetate. The manufacturing process is a [ ]. Storage for 36 months at refrigerated temperature was found acceptable, and post dispensing the product is proposed to be stored at room temperature for 28 days . The insert labeling does not provide direction to the pharmacist to sticker the product with the in-use expiry.

> **Deficiency Comment**
> A system for labeling the product with in-use expiry post dispensing should be developed (e.g. stickering). The system should be designed such that there is no opportunity for the patient to confuse the shelf-life expiry with the in-use expiry. Please revise the insert labeling to provide instructions to the dispensing pharmacist to provide the in-use expiry, and/or revise the PPI to instruct the patient.

An additional labeling comment regarding the logo is included in the AE letter. The comment above should be incorporated into the AE letter. The OPDRA review of the trade-name finds it acceptable.

All associated DMFs are acceptable.

All manuafcturing facilities are acceptable with the exception of [ ]

> **Deficiency**
> Please note that an acceptable GMP finfnding for [ ] will be required for approval.

Manufacturing is acceptable from a sterility assurance perspective.

From a CMC perspective the application is reccomended for an approvable action.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
10/12/01 03:18:02 PM
CHEMIST
This is the correct version - previous version which was put into DFS was wrong and had to be removed by OIT.

3/10/05

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-332 **Chemistry Review # 3** (***Drug Product Section***) **Date Reviewed:** 04-MAR-2005

Submission Type	**Document Date**	**CDER Rec. Date**	**Filing Date**
Original	07-DEC-2000	12-DEC-2000	06-FEB-2001
Amendment	17-SEP-2004 (AZ)		
Amendment	02-FEB-2005 (BL)		
Amendment	03-FEB-2005 (BL)		
Amendment	07-FEB-2005 (BL)		
Amendment	11-FEB-2005 (BL)		
Amendment	16-FEB-2005 (BC)		
Amendment	17-FEB-2005 (BL)		
Amendment	24-FEB-2005 (BL)		
Amendment	25-FEB-2005 (BC)		
Amendment	03-MAR-2005 (BL)		

Name & Address of the Applicant: Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
San Diego, CA 92121

Drug Product Name
Proprietary: Symlin™ Injection
Nonproprietary/Established/USAN: Pramlintide acetate
Chem.Type/ Ther.Class: **1 S**

Pharmacological Category/indication: Treatment of type 1 or type 2 diabetes as an adjunct to insulin
Dosage Form: Solution
Strength(s): 0.6 mg/mL in 5-mL Vials
Route of Administration: Parenteral Injection
Dispensed: Rx
SPOTS: No ✓

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Pramlintide / 25, 28, 29 Pro-h-amylin / AC-137
$C_{171}H_{267}N_{51}O_{53}S_2$ $(CH_3COOH)_x$ $3 \leq x \leq 8$ MW = 3949.45

1 5 10 15 20
Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-
21 25 30 35 37
Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH_2 (*C-terminus*)

Conclusions & Recommendations: Satisfactory CMC information has been provided to judge the quality of the drug substance, pramlintide acetate, and the drug product, Symlin™ (Pramlintide acetate) Injection. From the Chemistry viewpoint this application can be approved. However, some minor revisions of the labeling are recommended (see list of Labeling Comments).

Xavier Ysern, PhD
Review Chemist

Stephen Moore. PhD
Chemist Team Leader

filename: /nda/21332_dp3.doc

AP

Supporting Documents:

DMF	Subject	Holder	LOA* Date	Status	Rev. Date
Type II					
	Pramlintide Acetate		27-NOV-2000	Adequate	See DS section
	Pramlintide Acetate		16-SEP-1999	Adequate	See DS section
	Pramlintide Acetate		07-NOV-2000	Adequate	See DS section
Type III					
			25-AUG-1999	Adequate[a]	Adequate[b]
			15-DEC-1998	Adequate[a]	Adequate[b]
			02-FEB-1999	Adequate[a]	Adequate[b]
			02-FEB-1999	Adequate[a]	Adequate[b]
			01-FEB-1999	Adequate[a]	Adequate[b]

* LOA (Letter of authorization) provided in volume 1.14, pages 3943 to 3949.

[a] See Container/Closure section for additional information and testing performed by NDA holder.

[b] Adequate information provided in the submission.

Related Documents: --

Consults: Sterilization Validation, Microbiology Division
Division of Drug Marketing, Advertising and Communications (DDMAC)
Trade name, Office of Post-Marketing Drug Risk Assessment (OPDRA)
Inspection of manufacturing facilities, Office of Compliance

Remarks/Comments: The **active ingredient pramlintide** acetate, a thirty-seven amino acid peptide shown in figure 1(A), **is an analog of human amylin**. Human amylin, a natural hormone secreted by the β-cells of the pancreas, plays an important physiological role in the regulation of glucose metabolism in conjunction with insulin and glucagon. Amylin, which is deficient in people with diabetes, is cosecreted with insulin and reduces nutrient-stimulated glucagon secretion after interaction with specific receptor in the brain (main site of action). Pramlintide differs from human amylin by the substitution of proline residues for alanine, serine, and serine residues at positions 25, 28, and 29 respectively as shown in Figure 1(B). Accordingly to the applicant these

The drug product, Symlin™ Injection, will be commercialized in strengths 0.6 mg/mL in 5-mL Vials

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Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-

21 25 30 35 37

Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH_2 (*C-terminus*)

Figure 1. Primary sequence[1] of human amylin and drug substance pramlintide (cysteines 2 and 7 are disulfide link).

[1] Standard amino acid one letter code. A=Ala, B= Asx = Asp or Asn, C=Cys, D=Asp, E=Glu, F=Phe, G=Gly, H=His, I=Ile, K=Lys, L=Leu, M= Met, N=Asn, P=Pro, Q= Gln, R=Arg, S=Ser, T=Thr, V=Val, W=Trp, Y=Tyr, and Z=Glx = Glu or Gln.

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/s/

Xavier Ysern
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CHEMIST

Stephen Moore
3/10/05 05:21:26 PM
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Drug product 9/4/01

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-332 **Chemistry Review # 2** (***Drug Product Section***) **Date Reviewed:** 23-AUG-2001

Submission Type	**Document Date**	**CDER Rec. Date**	**Filing Date**
Original	07-DEC-2000	12-DEC-2000	06-FEB-2001
Amendment	10-AUG-2001	13-AUG-2001	

Name & Address of the Applicant: Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
San Diego, CA 92121

Drug Product Name
Proprietary: Symlin™ Injection
Nonproprietary/Established/USAN: Pramlintide acetate
Chem.Type/ Ther.Class: **1 S**

Pharmacological Category/indication: Treatment of type 1 or type 2 diabetes as an adjunct to insulin

Dosage Form: Solution

Strength(s): 0.6 mg/mL in 5-mL Vials

Route of Administration: Parenteral Injection

Dispensed: R

SPOTS: No ✓

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:

Pramlintide / 25, 28, 29 Pro-h-amylin / AC-137
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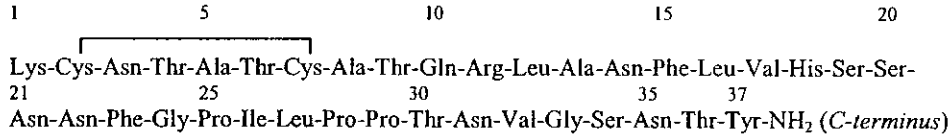

Conclusions & Recommendations: Satisfactory CMC information has been provided to judge the quality of the drug substance, pramlintide acetate, and the drug product, Symlin™ (Pramlintide acetate) Injection. From the Chemistry viewpoint this application can be approved pending adequate response to the minor deficiency listed in the draft letter, and satisfactory evaluation of the manufacturing sites. See Draft Letter.

Xavier Ysern, PhD
Review Chemist

Orig. NDA 21-332
cc: HFD-510/ Division File/ MooreS/ RheeJ / YsernX HFD-820/ DuffyE

R/D Init by:
Stephen Moore. PhD
Chemist Team Leader

AE

filename: /nda/21332_dp2.doc

Supporting Documents:

DMF	Subject	Holder	LOA* Date	Status	Rev. Date
Type II					
	Pramlintide Acetate		27-NOV-2000	Adequate	See DS section
	Pramlintide Acetate		16-SEP-1999	Adequate	See DS section
	Pramlintide Acetate		07-NOV-2000	Adequate	See DS section
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			02-FEB-1999	Adequate[a]	Adequate[b]
			02-FEB-1999	Adequate[a]	Adequate[b]
			01-FEB-1999	Adequate[a]	Adequate[b]

* LOA (Letter of authorization) provided in volume 1.14, pages 3943 to 3949.
[a] See Container/Closure section for additional information and testing performed by NDA holder.
[b] Adequate information provided in the submission.

Related Documents: --

Consults: Sterilization Validation, Microbiology Division
Division of Drug Marketing, Advertising and Communications (DDMAC)
Trade name, Office of Post-Marketing Drug Risk Assessment (OPDRA)
Inspection of manufacturing facilities, Office of Compliance

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/s/

Xavier Ysern
8/28/01 12:19:48 PM
CHEMIST

Labeling deficiency AE

Stephen Moore
9/4/01 11:54:07 AM
CHEMIST

Comments faxed to the sponsor on 8/1/01

Drug Product

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-332 **Chemistry Review # 1** (***Drug Product Section***) **Date Reviewed:** 31-JUL-2001

Submission Type	**Document Date**	**CDER Rec. Date**	**Filing Date**
Original	07-DEC-2000	12-DEC-2000	06-FEB-2001

Name & Address of the Applicant: Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
San Diego, CA 92121

Drug Product Name		
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	Nonproprietary/Established/USAN:	Pramlintide acetate
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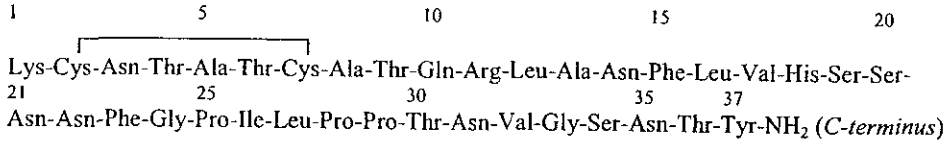
Pramlintide / 25, 28, 29 Pro-h-amylin / AC-137

$C_{171}H_{267}N_{51}O_{53}S_2 \cdot (CH_3COOH)_x$ x = 1.6 to 3.2 MW = 3949.45



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Xavier Ysern, PhD
Review Chemist

Orig. NDA 21-332
cc: HFD-510/ Division File/ MooreS/ RheeJ / YsernX HFD-820/ DuffyE

R/D Init by:
Stephen Moore. PhD
Chemist Team Leader

AE

filename: /nda/21332_dp.doc

Supporting Documents:

DMF	Subject	Holder	LOA* Date	Status	Rev. Date
Type II					
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[b] Adequate information provided in the submission.

Related Documents: --

Consults: Sterilization Validation, Microbiology Division
Division of Drug Marketing, Advertising and Communications (DDMAC)
Trade name, Office of Post-Marketing Drug Risk Assessment (OPDRA)
Inspection of manufacturing facilities, Office of Compliance

Remarks/Comments: The **active ingredient pramlintide** acetate, a thirty-seven amino acid peptide shown in figure 1(A), **is an analog of human amylin**. Human amylin, a natural hormone secreted by the β-cells of the pancreas, plays an important physiological role in the regulation of glucose metabolism in conjunction with insulin and glucagon. Amylin, which is deficient in people with diabetes, is cosecreted with insulin and reduces nutrient-stimulated glucagon secretion after interaction with specific receptor in the brain (main site of action). Pramlintide differs from human amylin by the substitution of proline residues for alanine, serine, and serine residues at positions 25, 28, and 29 respectively as shown in Figure 1(B). Accordingly to the applicant

The drug product, Simlin™ Injection, will be commercialized in strengths 0.6 mg/mL in 5-mL Vials

(A) 1 5 10 15 20

Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-

21 25 30 35 37

Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH_2 (*C-terminus*)

Figure 1. Primary sequence[1] of human amylin and drug substance pramlintide (cysteines 2 and 7 are disulfide link).

[1] Standard amino acid one letter code: A=Ala, B=Asx = Asp or Asn, C=Cys, D=Asp, E=Glu, F=Phe, G=Gly, H=His, I=Ile, K=Lys, L=Leu, M=Met, N=Asn, P=Pro, Q=Gln, R=Arg, S=Ser, T=Thr, V=Val, W=Trp, Y=Tyr, and Z=Glx = Glu or Gln.

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_____ § 552(b)(5) Draft Labeling

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/s/

Xavier Ysern
8/1/01 11:30:06 AM
CHEMIST

AE List od [minor] deficiencies to be send

Stephen Moore
8/1/01 01:33:48 PM
CHEMIST

2/22/05

MEMORANDUM

Date: February 22, 2005

From: Chien-Hua Niu, Ph.D. Chemistry Reviewer, ONDC/DNDCII/DMEDP (HFD-510)

Subject: CMC Recommendation for NDA 21-332

To: NDA 21-332 File [Symlin (pramlintide acetate) Injection]

Through Dr. Stephen Moore, Chemistry Team Leader, ONDC/DNDCII/DMEDP (HFD-510)

Since the firm has properly responded all chemistry deficiencies regarding the drug substance (see the 9/5/01 Chemistry Review #2 from the reviewer) and drug product (see the 11/18/03 Memorandum from Dr, Xavier Ysern), the application can be approved from CMC viewpoint

cc: Org. NDA #21-332
HFD-510/Division File
HFD-510/SMoore/JRhee/KJohnson

File Name: NDA21332MEM4

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/s/

Chien-Hua Niu
2/22/05 04:19:17 PM
CHEMIST

Stephen Moore
2/22/05 05:44:06 PM
CHEMIST

2/1/05

MEMORANDUM

DATE: February 1, 2005

SUBJECT: Labeling Revisions for Symlin (The 9/17/04 amendment of NDA # 21-332)

TO: File of NDA #21-332

FROM: Chien-Hua Niu, Ph.D., Chemistry Reviewer, ONDC/DNDC2/HFD-510

THROUGH: Dr. Stephen Moore, Chemistry Team Leader, ONDC/DNDC2/HFD-510

1. Package Insert:

The submitted draft package insert for Symlin (NDA #21-332) should be revised to read as follows:

DESCRIPTION:

SYMLIN (pramlintide acetate) Injection is antihyperglycemic drug for use in patients with diabetes treated with insulin. Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic beta cell that contributes to glucose control during the postprandial period. [ ] Pramlintide is an acetate salt of synthetic, 37-amino acid polypeptide, which differs in amino acid sequence from human amylin by replacement with proline at position 25 (alanine), 28 (serine), and 29 (serine).

The structural formula of pramlintide acetate is a shown:

<Structure>

Pramlintide acetate is a white powder that has a molecular formula of $C_{171}H_{267}N_{51}O_{53}S_2 \cdot xC_2H_4O_2$ ($3 \leq x \leq 8$); the molecular weight of pramlintide is 3949.4. Pramlintide acetate is soluble in water.

SYMLIN [ ] Injection is formulated as a clear, isotonic, sterile solution of subcutaneous (SC) administration. [ ] SYMLIN vials contains 0.6 mg/mL of pramlintide (as acetate), 2.25 mg/mL of metacresol as a preservative, D-mannitol as a tonicity modifier, and acetic acid and sodium acetate as pH modifiers. SYMLIN has a pH of approximately 4.0.

HOW SUPPLIED:

SYMLIN is supplied as [ ] a sterile injection in 5 mL vials containing 0.6 mg/mL pramlintide (as acetate), for use with a syringe. To administer SYMLIN from vials, use : [ ] If using a syringe calibrated for use with U-100 insulin, use the chart below) to measure the microgram dosage in unit increments. **Do not mix SYMLIN with insulin** .

[ ]

STORAGE

Unopened (not in-use) Vials: Before use, SYMLIN vials should be refrigerated, 36°F to 46°F (2°C to 8°C), and protected from light. Do not freeze. If a vial has been frozen or overheated, throw it away.

Open (In-use) Vials: Open vials in use (punctured) can be kept either refrigerated or at room temperature for up to 28 days as long as the temperature is not greater than 77°F (25°C). Open vials, whether or not refrigerated, must be used within 28 days. s. Discard after 28 days.

These storage conditions are summarized in the following table:

	Unopened (not in-use)	Opened (in-use)
	Refrigerated	Refrigerated or Room Temperature
5 mL vials	Until expiration date	Use within 28 days

Vials are manufactured for:
Amylin Pharmaceuticals, Inc.
San Diego, CA 92121 USA

Rx only

*** Insertions are denoted by underlining. Deletions are denoted by strike out.**

Comments:

2. Vial Label:

(A). To increase the prominence of the product strength and concentration, the following changes should be made:

Symlin
(Pramlintide acetate) Injection
0.6 mg/mL

(B). The route of administration should be spelled out such as "Subcutaneous Use Only" instead of "SC Use Only".

(C). The phase "Usual Dosage" should be inserted before the statement "See enclosed package insert".

3. Carton Label:

(A). See the general comments (A) and (C) in section of "**Vial Label**".

(B). Revise the sentence to read contains: 0.6 mg pramlintide (as acetate), 2.25 mg metacresol, D-mannitol, acetic acid and sodium acetate"

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/s/

Chien-Hua Niu
2/1/05 05:07:05 PM
CHEMIST

Stephen Moore
2/1/05 05:12:44 PM
CHEMIST

8/20/03

MEMORANDUM

Date: August 6, 2003

From: Chien-Hua Niu, Ph.D. Chemistry Reviewer, ONDC/DNDCII/DMEDP (HFD-510)

Subject: Name and Mailing Address Changes for the Testing Laboratory
(S#000BC 01/31/03 CMC Amendment)

To: NDA 21-332 File (Symlin)

Through Dr. Stephen Moore, Chemistry Team Leader, ONDC/DNDCII/DMEDP (HFD-510)

On 31/1/03, Amylin Pharmaceuticals submitted an amendment to inform the Agency that the testing laboratory, [ ] was purchased by [ ] Thus the official mailing address of [ ] has been changed as follows:

[ ]

However, the location of the testing activities is unaffected.

cc: Org. NDA #21-332
HFD-510/Division File
HFD-510/SMoore/JRhee
NDA21332MEM2

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/s/

Chien-Hua Niu
8/18/03 09:52:43 AM
CHEMIST

Stephen Moore
8/20/03 02:14:30 PM
CHEMIST

Drug substance
9/6/01

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS

Review of Chemistry, Manuacturing and Controls

NDA #: 21-332 **DATE REVIEWED**: September 5, 2001

CHEMISTRY REVIEW #: 2 **REVIEWER**: Chien-Hua Niu, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12/07/00	12/12/00	12/14/00
Amendment	07/16/01	07/17/01	07/17/01

NAME & ADDRESS OF APPLICATION: Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary:	Symlin Injection
Established:	Pramlintide acetate
Code Name:	None
Chem. Type/Ther. Class:	1 S

CONCLUSION AND RECOMMENDATION:
The sponsor has properly responded to chemistry deficiencies. No action is indicated.

/S/

Chien-Hua Niu, Ph.D.
Review Chemist

cc: Org. NDA
HFD-510/Division File
HFD-510/CHNiu
HFD-510/JRhee/SMoore
R/D init. by: S. Moore

File Name: NDA21332N002

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/s/

Chien-Hua Niu
9/6/01 01:04:06 PM
CHEMIST

Stephen Moore
9/6/01 01:31:21 PM
CHEMIST

Drug Substance

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS

Review of Chemistry, Manuacturing and Controls

NDA #: 21-332

DATE REVIEWED: June 12, 2001

CHEMISTRY REVIEW #: 1

REVIEWER: Chien-Hua Niu, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	12/7/00	12/12/00	12/14/00

NAME & ADDRESS OF APPLICATION: Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
San Diego, CA 92121

DRUG PRODUCT NAME:

Proprietary:	Symlin Injection
Established:	Pramlintide acetate
Code Name:	None
Chem. Type/Ther. Class:	1 S

CONCLUSION AND RECOMMENDATION:
This review only deals with chemistry, manufacturing and controls of the drug substance. From chemistry viewpoint, sufficient information on CMC of the drug substance has been submitted for the NDA. The sponsor needs to address only a few of minor CMC issues of the drug substance prior to the approval of the application (see List of Chemistry Deficiencies):

/S/

Chien-Hua Niu, Ph.D.
Review Chemist

cc: Org. NDA
HFD-510/Division File
HFD-510/CHNiu
HFD-510/JRhee/SMoore
R/D init. by: S. Moore

File Name: NDA21332N001

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/s/

Chien-Hua Niu
7/3/01 10:39:01 AM
CHEMIST

Stephen Moore
7/3/01 02:02:02 PM
CHEMIST

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21332/000
Org Code : 510
Priority : 1S

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

Stamp Date : 08-DEC-2000
PDUFA Date : 20-MAR-2005
Action Goal :
District Goal: 18-OCT-2003

Brand Name : SYMLIN (PRAMLINTIDE ACETATE)
Estab. Name:
Generic Name: PRAMLINTIDE ACETATE
Dosage Form: (INJECTION)
Strength : 0.6 MG/ML [ ]

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

Overall Recommendation: ACCEPTABLE on 08-DEC-2003by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 18-NOV-2003by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 03-DEC-2002by B. MERRITT(HFD-323) 301-827-9007

WITHHOLD on 05-OCT-2001by HARTMANB

Establishment : CFN : [ ] FEI : [ ]
[ ]
[ ]
[ ]

DMF No: AADA:

Responsibilities: [ ]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
lestone Date: 09-SEP 03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

IF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-NOV-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-SEP-03

ecision : ACCEPTABLE

eason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

rofile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-NOV-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

ilestone Date: 06-DEC-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI :

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-SEP-03

cision : ACCEPTABLE

eason : DISTRICT RECOMMENDATION

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