CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-332

Administrative/Correspondence Reviews

2/18/05 submission

14 PATENT CERTIFICATION WITH RESPECT TO ANY PATENT THAT CLAIMS THE DRUG

No certification is necessary because this application is for drug for which investigations described in 21 U.S.C. Section 355(b)(1)(A) and relied upon by the applicant for approval of this application were conducted by or for the applicant, and this application is not an abbreviated application for a new drug.

Lloyd Rowland
Vice President, Legal, Secretary
and General Counsel
AMYLIN PHARMACEUTICALS, INC.

2/18/05
Date

13 PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG

Pursuant to 21 CFR 314.53, Amylin hereby submits patent information for SYMLIN® (pramlintide acetate) Injection, NDA number 21-332 and claims 5-year market exclusivity under 21 CFR 314.50(j) under the provisions of 21 CFR 314.108(b)(2).

To the best of the applicant's knowledge and belief, no drug containing the active moiety in pramlintide acetate injection has previously been approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that patent numbers 5,175,145, 5,686,411, 5,814,600, 5,998,367, 6,114,304, 6,410,511, 6,608,029 and 6,610,824 cover the formulation, composition, and method of use of SYMLIN® (pramlintide acetate). This product, pramlintide acetate, is the subject of this application for which approval is being sought:

Lloyd Rowland
Vice President, Legal, Secretary and
General Counsel
AMYLIN PHARMACEUTICALS, INC.

2/18/05
Date

Owner	Patent No.	Expiration Date	Type
Amylin Pharmaceuticals, Inc.	5,175,145	December 29, 2009	Method of Use
Amylin Pharmaceuticals, Inc.	5,686,411	November 11, 2014	Drug Substance Drug Product Method of Use
Amylin Pharmaceuticals, Inc.	5,814,600	September 29, 2015	Method of Use
Amylin Pharmaceuticals, Inc.	5,998,367	March 8, 2011	Drug Substance Drug Product
Amylin Pharmaceuticals, Inc.	6,114,304	September 5, 2017	Method of Use
Amylin Pharmaceuticals, Inc.	6,410,511	January 9, 2018	Drug Product
Amylin Pharmaceuticals, Inc.	6,608,029	Sept 7, 2013	Method of Use
Amylin Pharmaceuticals, Inc.	6,610,824	March 8, 2011	Drug Substance

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,998,367	12/7/1999	3/8/2011

d. Name of Patent Owner	Address *(of Patent Owner)*	
Amylin Pharmaceuticals, Inc.	9360 Towne Centre Drive	
	City/State: San Diego / California	
	ZIP Code: 92121	FAX Number *(if available)*: 858.552.1936
	Telephone Number: 858.552.2200	E-Mail Address *(if available)*: mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method(s) of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

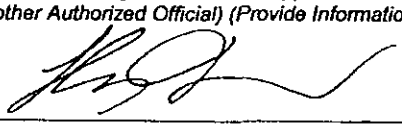
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Patent Information Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	2/18/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials), [illegible]

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,608,029	8/19/2003	9/7/2013

d. Name of Patent Owner
Amylin Pharmaceuticals, Inc.

Address *(of Patent Owner)*
9360 Towne Centre Drive

City/State
San Diego / California

ZIP Code	FAX Number *(if available)*
92121	858.552.1936
Telephone Number	**E-Mail Address *(if available)***
858.552.2200	mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1 - 22	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

SYMLIN is proposed for use as adjunctive therapy to established insulin regimens to improve glycemic control in patients with type 1 or type 2 diabetes mellitus who have failed to achieve adequate glycemic control despite appropriate, individualized insulin management with or without a concurrent sulfonylurea agent and/or metformin. See Indications and Usage. SYMLIN is proposed for use as a subcutaneous injection to replace the amylin effect and improve glycemic control through: 1) prevention of the abnormal postprandial rise in plasma glucagon; 2) modulation of gastric emptying (thus reducing the rate of glucose rise postprandially); and 3) a satiety effect. See Administration and Mechanism of Action.

Claims 1, 5, 6, 7, 11, 12, 13, 17, 18, 19, 21, and 22 relate to the use of an amylin agonist having particular receptor binding affinities, e.g., SYMLIN, to reduce gastric motility or delay gastric emptying, e.g., reducing the initial rate of glucose rise postprandially, a mechanism in the treatment of diabetes mellitus.

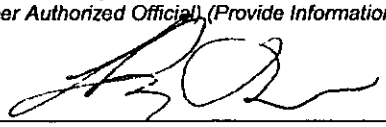
Claims 2, 3, 8, 9, 14, 15 describe physical features of the amylin agonist, e.g., SYMLIN;

Claims 4, 10, 16, and 20 are directed to parenteral administration of an amylin agonist including pramlintide.

6.0 Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	2/18/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,610,824	8/26/2003	3/8/2011

d. Name of Patent Owner
Amylin Pharmaceuticals, Inc.

Address *(of Patent Owner)*
9360 Towne Centre Drive

City/State
San Diego / California

ZIP Code	FAX Number *(if available)*
92121	858.552.1936
Telephone Number	**E-Mail Address *(if available)***
858.552.2200	mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	2/18/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

PSC Media Arts (301) 443-1090 EF

13 PATENT INFORMATION ON ANY PATENT THAT CLAIMS THE DRUG

Pursuant to 21 CFR 314.53, Amylin hereby submits patent information for SYMLIN® (pramlintide acetate) Injection, NDA number 21-332 and claims market exclusivity under 21 CFR 314.50(j) under the provisions of 21 CFR 314.108(b)(2).

The undersigned declares that patent numbers 5,175,145, 5,686,411, 5,814,600, 5,998,367, 6,114,304, 6,410,511, 6,608,029 and 6,610,824 cover the formulation, composition, and method of use of SYMLIN® (pramlintide acetate). This product, pramlintide acetate, is the subject of this application for which approval is being sought:

9/14/04

Lloyd Rowland
Vice President, Legal, Secretary
and General Counsel
AMYLIN PHARMACEUTICALS, INC.

Date

Owner	Patent No.	Expiration Date	Type
Amylin Pharmaceuticals, Inc.	5,175,145	December 29, 2009	Method of Use
Amylin Pharmaceuticals, Inc.	5,686,411	November 11, 2014	Drug Substance Drug Product Method of Use
Amylin Pharmaceuticals, Inc.	5,814,600	September 29, 2015	Method of Use
Amylin Pharmaceuticals, Inc.	5,998,367	November 11, 2014	Drug Substance Drug Product
Amylin Pharmaceuticals, Inc.	6,114,304	September 5, 2017	Method of Use
Amylin Pharmaceuticals, Inc.	6,410,511	January 9, 2018	Drug Product
Amylin Pharmaceuticals, Inc.	6,608,029	September 5, 2017	Method of Use
Amylin Pharmaceuticals, Inc.	6,610,824	November 11, 2014	Drug Substance

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

5. GENERAL

a. United States Patent Number 5,175,145	b. Issue Date of Patent 12/29/1992	c. Expiration Date of Patent 12/29/2009
d. Name of Patent Owner Amylin Pharmaceuticals, Inc.	Address *(of Patent Owner)* 9360 Towne Centre Drive	
	City/State San Diego / California	
	ZIP Code 92121	FAX Number *(if available)* 858.552.1936
	Telephone Number 858.552.2200	E-Mail Address *(if available)* mholman@amylin.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1, 4, 15, 20, 21	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a If the answer to **4.2** is	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

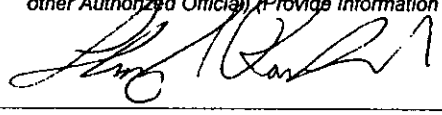
"Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	SYMLIN is proposed for use as adjunctive therapy to established insulin regimens to improve glycemic control in patients with type 1 or type 2 diabetes mellitus who have failed to achieve adequate glycemic control despite appropriate, individualized insulin management with or without a concurrent sulfonylurea agent and/or metformin. See Indications and Usage. SYMLIN is proposed for use as a subcutaneous injection to replace the amylin effect and improve glycemic control through: 1) prevention of the abnormal postprandial rise in plasma glucagon; 2) modulation of gastric emptying; and 3) a satiety effect. See Administration and Mechanisms of Action. Claim 1 relates to the treatment of diabetes mellitus with an amylin agonist, e.g., SYMLIN. Claim 4 relates to relates to the treatment of diabetes mellitus with a conservative variant of amylin, e.g., SYMLIN. Claim 15 relates to treatment of diabetes mellitus with an amylin agonist, e.g., SYMLIN, and insulin, e.g., adjunctive therapy. Claim 20 relates to the treatment of diabetes mellitus with a parenterally administered amylin agonist, e.g., SYMLIN. Claim 21 relates to the treatment of diabetes mellitus with an amylin agonist, e.g., SYMLIN, and parenterally administered insulin, e.g., adjunctive therapy.

No Relevant Patent

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

5. PATENT INFORMATION

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,686,411	11/11/1997	11/11/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Amylin Pharmaceuticals, Inc.	9360 Towne Centre Drive	
	City/State: San Diego / California	
	ZIP Code: 92121	FAX Number *(if available)*: 858.552.1936
	Telephone Number: 858.552.2200	E-Mail Address *(if available)*: mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (If patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
30, 31, 32, 33, 34, 35, 36, 37		☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

SYMLIN is proposed for use as adjunctive therapy to established insulin regimens to improve glycemic control in patients with type 1 or type 2 diabetes mellitus who have failed to achieve adequate glycemic control despite appropriate, individualized insulin management with or without a concurrent sulfonylurea agent and/or metformin. See Indications and Usage.

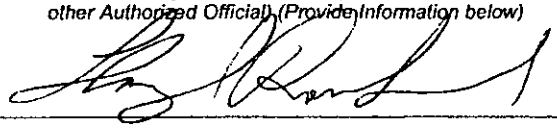
Claims 30, 31, 32, 33, 34, and 35 relate to the treatment of diabetes mellitus with an amylin agonist, e.g., SYMLIN or pramlintide itself.

Claims 36 and 37 relate to treatment of diabetes mellitus with an amylin agonist, e.g., SYMLIN, or pramlintide itself, and insulin, e.g., adjunctive therapy.

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,814,600	9/29/1998	9/29/2015

d. Name of Patent Owner	Address *(of Patent Owner)*	
Amylin Pharmaceuticals, Inc.	9360 Towne Centre Drive	
	City/State: San Diego / California	
	ZIP Code: 92121	FAX Number *(if available)*: 858.552.1936
	Telephone Number: 858.552.2200	E-Mail Address *(if available)*: mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method(s) of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*: 1-24 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

"Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	SYMLIN is proposed for use as adjunctive therapy to established insulin regimens to improve glycemic control in patients with type 1 or type 2 diabetes mellitus who have failed to achieve adequate glycemic control despite appropriate, individualized insulin management with or without a concurrent sulfonylurea agent and/or metformin. See Indications and Usage. SYMLIN is proposed for use as a subcutaneous injection to replace the amylin effect and improve glycemic control through: 1) prevention of the abnormal postprandial rise in plasma glucagon; 2) modulation of gastric emptying; and 3) a satiety effect. See Administration and Mechanisms of Action. Proposed doses are between 15-30 mg/dose (type 1 diabetes) or 60-120 mg/dose (type 2 diabetes) given with insulin prior to major meals. See Dosage and Administration. Claims 1, 2, 9, 10, and 11 relate to the treatment of a mammal having need of or reduced ability to produce insulin, e.g., one with diabetes mellitus, with an amylin, e.g., SYMLIN, and an insulin, e.g., adjunctive therapy, at a molar ratio between about 1:1 and about 67:1 Claims 3, 4, 5, 6, 7, 8, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 and 24 relate to the treatment of a mammal having need of or reduced ability to produce insulin, e.g., one with diabetes mellitus, with an amylin, e.g., SYMLIN, and an insulin, e.g., adjunctive therapy, at specific molar ratios, doses, and plasma concentrations.

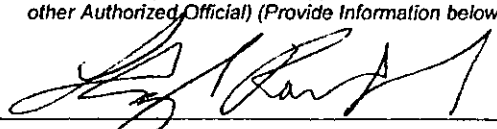
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Lloyd A. Rowland Vice President, Legal, Secretary and General Counsel	
Address AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	City/State San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,998,367	12/7/1999	11/11/2014

d. Name of Patent Owner
Amylin Pharmaceuticals, Inc.

Address *(of Patent Owner)*
9360 Towne Centre Drive

City/State
San Diego / California

ZIP Code	FAX Number *(if available)*
92121	858.552.1936

Telephone Number	E-Mail Address *(if available)*
858.552.2200	mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*

Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

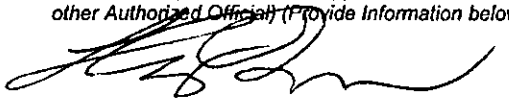
5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials): [illegible]

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,114,304	9/5/2000	9/5/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Amylin Pharmaceuticals, Inc.	9360 Towne Centre Drive	
	City/State: San Diego / California	
	ZIP Code: 92121	FAX Number *(if available)*: 858.552.1936
	Telephone Number: 858.552.2200	E-Mail Address *(if available)*: mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)*: 1-12, 19, 24, 29, 34, 35 — Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a	If the answer to 4.2 is ____ Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

"Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	SYMLIN is proposed for use as adjunctive therapy to established insulin regimens to improve glycemic control in patients with type 1 or type 2 diabetes mellitus who have failed to achieve adequate glycemic control despite appropriate, individualized insulin management with or without a concurrent sulfonylurea agent and/or metformin. See Indications and Usage. SYMLIN is proposed for use as a subcutaneous injection to replace the amylin effect and improve glycemic control through: 1) prevention of the abnormal postprandial rise in plasma glucagon; 2) modulation of gastric emptying (often disordered in diabetes patients; slowed gastric emptying thus reduces the rate of glucose rise postprandially); and 3) a satiety effect. See Administration and Mechanisms of Action Claims 1, 4, 7, 10, 19, and 24 relate to the use of an amylin agonist, e.g., SYMLIN or pramlintide, to reduce gastric motility or delay gastric emptying, e.g., modulation of gastric emptying to improve glycemic control by reducing the initial rate of glucose rise postprandially, a mechanism in the treatment of diabetes mellitus. Claims 2, 3, 5, 6, 8, 9,11, and 12 describe physical features of the amylin agonist, e.g., SYMLIN; Claim 29 relates to the use of an amylin agonist, e.g., SYMLIN, to reduce gastric motility or delay gastric emptying where the gastric motility is associated with gastrointestinal disorder, e.g., disordered gastric emptying in diabetes; Claims 34 and 35 relate to the use of an amylin agonist, e.g., SYMLIN or pramlintide, to treat postprandial hyperglycemia e.g., to improve glycemic control by controlling the rate of glucose rise postprandially, a mechanism in the treatment of diabetes mellitus.

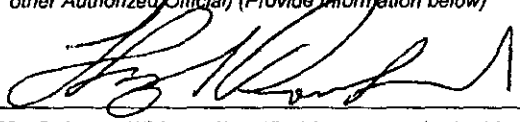
13. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6 Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)
Pramlintide (25, 28, 29Pro-human amylin)

STRENGTH(S)
0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

GENERAL

a. United States Patent Number
6,410,511

b. Issue Date of Patent
6/25/2002

c. Expiration Date of Patent
1/9/2018

d. Name of Patent Owner
Amylin Pharmaceuticals, Inc.

Address *(of Patent Owner)*
9360 Towne Centre Drive

City/State
San Diego / California

ZIP Code
92121

FAX Number *(if available)*
858.552.1936

Telephone Number
858.552.2200

E-Mail Address *(if available)*
mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3 Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5 Certification

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Lloyd A. Rowland Vice President, Legal, Secretary and General Counsel	
Address AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	City/State San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,608,029	8/19/2003	9/5/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
Amylin Pharmaceuticals, Inc.	9360 Towne Centre Drive	
	City/State: San Diego / California	
	ZIP Code: 92121	FAX Number *(if available)*: 858.552.1936
	Telephone Number: 858.552.2200	E-Mail Address *(if available)*: mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method(s)

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
1 - 22		☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

SYMLIN is proposed for use as adjunctive therapy to established insulin regimens to improve glycemic control in patients with type 1 or type 2 diabetes mellitus who have failed to achieve adequate glycemic control despite appropriate, individualized insulin management with or without a concurrent sulfonylurea agent and/or metformin. See Indications and Usage. SYMLIN is proposed for use as a subcutaneous injection to replace the amylin effect and improve glycemic control through: 1) prevention of the abnormal postprandial rise in plasma glucagon; 2) modulation of gastric emptying (thus reducing the rate of glucose rise postprandially); and 3) a satiety effect. See Administration and Mechanisms of Action and Mechanism of Action.

Claims 1, 5, 6, 7, 11, 12, 13, 17, 18, 19, 21, and 22 relate to the use of an amylin agonist having particular receptor binding affinities, e.g., SYMLIN, to reduce gastric motility or delay gastric emptying, e.g., reducing the initial rate of glucose rise postprandially, a mechanism in the treatment of diabetes mellitus.

Claims 2, 3, 8, 9, 14, 15 describe physical features of the amylin agonist, e.g., SYMLIN;

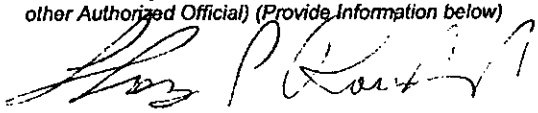
Claims 4, 10, 16, and 20 are directed to parenteral administration of an amylin agonist including pramlintide.

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-332

NAME OF APPLICANT / NDA HOLDER
Amylin Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
SYMLIN

ACTIVE INGREDIENT(S)	STRENGTH(S)
Pramlintide (25, 28, 29Pro-human amylin)	0.6 mg/ml (vials)

DOSAGE FORM
Injection, solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

4. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,610,824	8/26/2003	11/11/2014

d. Name of Patent Owner
Amylin Pharmaceuticals, Inc.

Address *(of Patent Owner)*
9360 Towne Centre Drive

City/State
San Diego / California

ZIP Code	FAX Number *(if available)*
92121	858.552.1936
Telephone Number	**E-Mail Address *(if available)***
858.552.2200	mholman@amylin.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

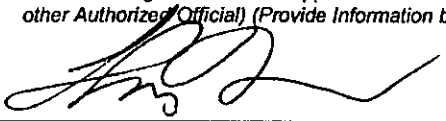
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	9/14/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Lloyd A. Rowland
Vice President, Legal, Secretary and General Counsel

Address	City/State
AMYLIN PHARMACEUTICALS, INC. 9360 Towne Centre Drive Suite 110	San Diego, CA
ZIP Code 92121	Telephone Number 858.552.2200
FAX Number *(if available)* 858.552.1936	E-Mail Address *(if available)* lrowland@amylin.com

EXCLUSIVITY SUMMARY FOR NDA # 20-563 SUPPL # N/A

Trade Name Symlin®

Generic Name Pramlintide acetate injection

Applicant Name Amylin Pharmaceuticals Inc.

HFD-510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x__/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / x / NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /_x__/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_x__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not

independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the

results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

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

/s/

Robert Meyer
3/16/05 03:59:08 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : *21-332* **Supplement Type (e.g. SE5):** *N/A* **Supplement Number:** *N/A*

Submission Date: *December 7, 2000* **Action Date:** March 18, 2005 **HFD-510**

Trade and generic names/dosage form: *Symlin®(pramlintide acetate injection)*

Applicant: *Amylin Pharmaceuticals, Inc.* **Therapeutic Class:** *1S*

Indication(s) previously approved: *None*

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: [illegible]

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: x Partial Waiver x Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.__1____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.__11 (inclusive)__	Tanner Stage____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- X **Other: Need for additional injections for children without clearly unique benefit of drug over intensive insulin**

therapy for this population

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min	**kg**	**mo.**	**yr. 12**	**Tanner Stage**
Max	**kg**	**mo.**	**yr. Less than or equal to 17**	**Tanner Stage**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- X **Other: Concern for Compliance**

Date studies are due (mm/dd/yy): 09/30/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min	**kg**	**mo.**	**yr.**	**Tanner Stage**
Max	**kg**	**mo.**	**yr.**	**Tanner Stage**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of metabolic and Endocrine Drug products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: **NDA 21-332**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: ***Type 2diabetes, as an adjunct to mealtime insulin in patients who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.***

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: _x_ Partial Waiver _x_ Deferred ____ Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg_____**	**mo._1___**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr. 11 (inclusive)**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- X **Other: Need for additional injections for children without clearly unique benefit of drug over intensive insulin therapy for this population**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 12	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** Less than or equal to 17	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- X **Other:** Concern for compliance

Date studies are due (mm/dd/yy): 09/30/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: NDA 21-332
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Robert Meyer
3/17/05 11:19:24 AM

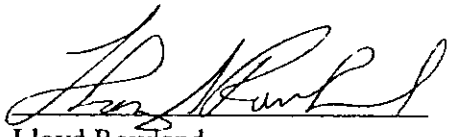
9/17/04 submission

16 DEBARMENT CERTIFICATION

NDA 21-332 – SYMLIN®

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Amylin Pharmaceuticals, Inc., states the following with respect to this new drug application:

Amylin Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



9/14/04

Lloyd Rowland
Vice President, Legal, Secretary
and General Counsel
AMYLIN PHARMACEUTICALS, INC.

Date

16 DEBARMENT CERTIFICATION

NDA 21-332 – SYMLIN®,

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, Amylin Pharmaceuticals, Inc., states the following with respect to this new drug application:

Amylin Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Lloyd Rowland
Vice President, Legal, Secretary
and General Counsel

6/6/03
Date

16 DEBARMENT CERTIFICATION

NDA 21-332 – SYMLIN

In compliance with the Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992, we, Amylin Pharmaceuticals, Inc., state the following with respect to this new drug application:

Amylin Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Nancy K. Dahl, Esq.
Vice President and General Counsel

11/7/00
Date

137-111, 112, 117, 123
139-150

from 2003 MOR

- it was conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations pertaining to informed consent; "at the first visit, prior to initiation of any study-related procedures, subjects gave their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits."

C. Financial Disclosure

Financial disclosure documents are provided for (1) studies cited in the Approvable Letter[38] and (2) studies conducted as a result of the Approvable Letter, and (3) "ongoing and other studies".

The applicant provided the following financial disclosure information:

- Form OMB No. 0910-0396. The applicant certifies that Amylin Pharmaceuticals "has not entered into any financial agreement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study".
- An extensive list of investigators who completed the financial disclosure forms is provided. None of these investigators (1) owned or entered into an agreement to own a proprietary interest in pramlintide, (2) received, or entered into an agreement to receive, payments, grants and/or equipment from Amylin Pharmaceuticals, Inc. having a monetary value exceeding $25,000, (3) owned or entered into an agreement to own, Amylin Pharmaceuticals stock and/or stock options that exceed $50,000.00 in value.
- A list of investigators who could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR 54.2(b) despite due diligence on

[38] The Approvabe Letter dated October 10, 2001 states that "financial disclosure information in accordance with 21 CFR Part 54 must be submitted for efficacy studies 137-111, 137-112, 137-117, and 137-123." All these were phase III studies in patients with either type 1 or type 2 diabetes.

9/17/04 submission

19 FINANCIAL INFORMATION

Amylin Pharmaceuticals, Inc. hereby provides financial disclosure information for clinical study 137-155 which is being submitted as part of this Complete Response in support of NDA 21-332 for SYMLIN® (pramlintide acetate) Injection. In addition, one-year post study financial information is provided for 137-153 and 137-154. Amylin is currently collecting one-year post study financial information for study 137-150. These same investigators from study 137-150 are participating in study 137-150E in which financial information was provided in the Resubmission dated June 16, 2003.

Financial disclosure information was provided in Amylin's original NDA 21-332 dated December 7, 2000 for covered clinical studies 137-121, 137-122, 137-140, 137-141, 137-142, 137-143 and 137-144.

As a result of the October 10, 2001 Approvable Letter, additional studies were conducted and financial disclosure information was provided for covered clinical studies 137-150, 137-151 (one-year post), 137-152 (one-year post), 137-153 and 137-154. Financial disclosure information was also provided in the Resubmission dated June 16, 2003 for on-going covered clinical studies 137-146, 137-147, 137-149 and 137-150E.

The Agency requested no additional financial disclosure information in its second Approvable Letter dated December 17, 2003.

Covered Clinical Studies:

Protocol No. 137-153:
One-Year Post
A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide when Injected Subcutaneously at Various Anatomical Sites in Non-Obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

Protocol No. 137-154:
One-Year Post
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide on the Pharmacokinetics of an Orally Administered Concomitant Medication When Given at Various Times in Relation to Pramlintide Dosing in Subjects With Type 2 Diabetes Mellitus (Phase 3B)

Protocol No. 137-155:
A Phase 3B, Multicenter, Open-Label Study Investigating the Clinical Utility and Safety of Pramlintide in Subjects With Type 1 and Type 2 Diabetes Mellitus Who Have Not Achieved Glycemic Targets With Insulin Therapy

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

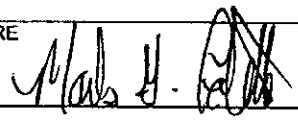
Please mark the applicable checkbox.

] (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE ATTACHED LISTS	

] (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mark G. Foletta	VP Finance, Chief Financial Officer
FIRM / ORGANIZATION: AMYLIN PHARMACEUTICALS, INC.	
SIGNATURE: 	DATE: 9/15/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Created by: PSC Media Arts Branch (301) 443-1090 EF

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

The attached lists of investigators and subinvestigators who appeared on a Form FDA 1572 for a site that enrolled patients in the above-named covered clinical studies 137-153, 137-154 and 137-155 (as defined in 21 CFR §54.2 (e)) could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR §54.2(b). I certify that I have acted with due diligence to obtain from the listed clinical investigators and subinvestigators this information, but it was not possible to do so. Due diligence effort taken and the reasons why this information could not be obtained are provided below.

Protocol No. 137-153:
A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide When Injected Subcutaneously at Various Anatomical Sites in Non-Obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin

One-Year Post Study

Investigator/ SubInvestigator Name	Due Diligence Effort Explanation/Comment Regarding Status of Form
Blevins, Thomas	In the process of obtaining from site – end of September 2004.
\	In the process of obtaining from site – end of September 2004.
\	In the process of obtaining from site – out-of-office until week of September 20, 2004.
\	In the process of obtaining from site – end of September 2004.
\	No Longer at institution.
\	Leave of absence, returning end of September 2004.

Protocol No. 137-154:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide on the Pharmacokinetics of an Orally Administered Concomitant Medication When Given at Various Times in Relation to Pramlintide Dosing in Subjects With Type 2 Diabetes Mellitus (Phase 3B)

One-Year Post Study

SubInvestigator Name	Due Diligence Effort Explanation/Comment Regarding Status of Form
——	No Longer at institution.
——	No Longer at institution.

Protocol No. 137-155:

A Phase 3B, Multicenter, Open-Label Study Investigating the Clinical Utility and Safety of Pramlintide in Subjects With Type 1 and Type 2 Diabetes Mellitus Who Have Not Achieved Glycemic Targets With Insulin Therapy

SubInvestigator Name	Due Diligence Effort Explanation/Comment Regarding Status of Form
—	Did not complete a financial disclosure form; removed from 1572 prior to drug shipment, did not participate in the study.
—	Did not complete a financial disclosure form; removed from 1572 prior to drug shipment, did not participate in the study.

From 2003 RS

19 FINANCIAL INFORMATION

In accordance with 21 CFR § 314.50 (k), this item contains financial certification by the applicant, Amylin Pharmaceuticals, Inc., as required under 21 CFR § 54, for all clinical investigators (as defined in 21 CFR § 54.2 (d)) who have enrolled patients into 1) those studies cited in the *Approvable Letter dated October 10, 2001*; 2) those studies conducted as a result of the *Approvable Letter*; and 3) ongoing and other studies, as identified below in support of NDA 21-332 for SYMLIN® (pramlintide acetate) Injection.

Amylin Pharmaceuticals, Inc. hereby provides financial disclosure information addressing Item No. 8, Financial Disclosure, Page 3 of *Approvable Letter* dated October 10, 2001, Amylin NDA 21-332:

"Financial disclosure information in accordance with 21 CFR Part 54 must be submitted for efficacy studies 137-111, 137-112, 137-117, and 137-123."

Amylin Pharmaceuticals, Inc. also hereby provides financial disclosure information for additional studies conducted as a result of *Approvable Letter* dated October 10, 2001, Amylin NDA 21-332 for studies 137-150, 137-151, 137-152, 137-153 and 137-154.

In addition, financial disclosure information is provided for clinical studies 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), and 137-150E (on-going study).

Covered Clinical Studies:

Protocol No. 137-111, entitled:
Fifty-Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled and AC137 Dose Ranging Study to Evaluate Glycated Hemoglobin in Patients With Type II Diabetes Mellitus (Phase 3)

Protocol No. 137-112, entitled:
Fifty Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Glycated Hemoglobin and Safety of Pramlintide (AC137) Versus Placebo in Patients With Type 1 Diabetes Mellitus (Phase 3)

Protocol No. 137-117, entitled:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC-137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type I Diabetes Mellitus (Phase 3)

Protocol No. 137-123, entitled:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC-137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type II Diabetes Mellitus. (Phase 3)

Protocol No. 137-140 (ongoing study), entitled:
An Open-Label Study of the Long Term Safety of Pramlintide Use in Study Subjects with Type 1 or 2 Diabetes Mellitus

Protocol No. 137-146, entitled:
A Placebo-Controlled, Single-Blind, Pilot Study to Examine the Effects of Adjunctive Pramlintide Therapy on Glucose Fluctuations in Subjects With Type 1 Diabetes Mellitus Utilizing Continuous Subcutaneous Insulin Infusion (CSII) (Phase 3B)

Protocol No. 137-147, entitled:
A Single-Arm, Open-Label, Dose-Escalation Study to Examine Dose Initiation in Subjects With Type 1 Diabetes Mellitus Given Pramlintide Subcutaneously (Phase 3B)

Protocol No. 137-149 (on-going), entitled:
A Single Center, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Cross-Over Study Evaluating the Acute Effect of Pramlintide on Satiety and Food Intake in Normal-Weight and Obese Non-Diabetic Subjects and in Insulin-Treated Subjects With Type 1 and Type 2 Diabetes Mellitus

Protocol No. 137-150, entitled:
A Randomized, Triple-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety of Pramlintide Treatment Employing Pramlintide Dose-Titration Followed by Insulin Dose Optimization in Subjects With Type 1 Diabetes Mellitus Who Have Not Achieved Glycemic Targets With Intensive Insulin Therapy

Protocol No. 137-150E (on-going), entitled:
A Multicenter, Open-Label, Extension Study of the Long-Term Safety of Pramlintide in Subjects With Type 1 Diabetes Mellitus Completing Protocol 137-150

Protocol 137-151, entitled:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide Dose Timing on Postprandial Plasma Glucose Profiles in Subjects With Type 1 Diabetes Mellitus and Subjects With Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

Protocol 137-152, entitled:
A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Volunteers to Assess the Effects of Pramlintide Upon the Recognition of Hypoglycemic Symptoms (Phase 3B)

Protocol 137-153, entitled:
A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide when Injected Subcutaneously at Various Anatomical Sites in Non-Obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

Protocol 137-154, entitled:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide on the Pharmacokinetics of an Orally Administered Concomitant Medication When

Given at Various Times in Relation to Pramlintide Dosing in Subjects With Type 2 Diabetes Mellitus (Phase 3B)

Certification Information:
Amylin Pharmaceuticals, Inc. certifies to the absence of financial interests and arrangements regarding *compensation affected by the outcome of clinical studies* (as defined in 21 CFR § 54.2 (a)), *proprietary interest in the tested product* (as defined in 21 CFR § 54.2 (c)), *significant equity interest in the sponsor of a covered study* (as defined in 21 CFR § 54.2 (b)), and *significant payments of other sorts* (as defined in 21 CFR § 54.2 (f)) for all clinical investigators who have enrolled patients into Protocol Numbers 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), 137-150, 137-150E (on-going study), 137-151, 137-152, 137-153 and 137-154 as listed in **Attachment A**. A completed FORM FDA 3454 for this certification, dated and signed by Mr. Mark Foletta, Vice President and Chief Financial Officer, Amylin Pharmaceuticals, Inc., is provided.

Amylin Pharmaceuticals, Inc. certifies that it acted with due diligence to obtain information regarding significant equity interest in the sponsor of a covered study from all clinical investigators who have enrolled patients into Protocol Numbers 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), 137-150, 137-150E (on-going study), 137-151, 137-152, 137-153 and 137-154. In the event that it was not possible to do so, Amylin Pharmaceuticals, Inc. provides the reasons why this information could not be obtained. This certification, FORM FDA 3454, dated and signed by Mr. Mark Foletta, Vice President and Chief Financial Officer, Amylin Pharmaceuticals, Inc., is provided in **Attachment B** for Protocol Numbers 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-151 and 137-153.

Disclosure Statements:
For those investigators who appeared on a Form FDA 1572 for a site that enrolled patients in the covered clinical studies in accordance with 21 CFR § 54, and disclosed financial interest, details of the investigator's disclosable financial arrangements and interests are provided, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests. This disclosure, FORM FDA 3455, dated and signed by Mr. Mark Foletta, Vice President and Chief Financial Officer, Amylin Pharmaceuticals, Inc., is provided in **Attachment C** for Protocol Numbers 137-146, 137-150 and 137-150E (on-going study).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please see Attachments A and B	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mark G. Foletta	Vice President and CFO
FIRM / ORGANIZATION: Amylin Pharmaceuticals, Inc.	
SIGNATURE: Mark G. Foletta	DATE: 5/30/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Please see Attachment C (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Please see Attachment C (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Mark G. Foletta	Vice President and CFO
FIRM/ORGANIZATION: Amylin Pharmaceuticals, Inc.	
SIGNATURE: Mark G. Foletta	DATE: 5/30/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

Attachment A

The following list of investigators who enrolled patients in the covered clinical studies: 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), 137-150, 137-150E (on-going study), 137-151, 137-152, 137-153 and 137-154 as defined in 21 CFR 54.2 (e), have certified that neither they, nor their spouses, nor dependent children have ever:

1) Owned or entered into an agreement to own a proprietary interest in the Amylin Pharmaceuticals, Inc. product which is the subject of the Clinical Trial (e.g., patent, trademark, copyright, licensing agreement and/or royalty arrangement, etc.).

2) Entered into any financial arrangement with Amylin Pharmaceuticals, Inc., whereby the value of your compensation for conducting the Clinical Trial could be influenced by the outcome of the Clinical Trial.

3) Received, or entered into an agreement to receive, payments, grants and/or equipment from Amylin Pharmaceuticals, Inc. (including payments to an institution to support your activities), having a monetary value exceeding $25,000 (exclusive of the costs of conducting the Clinical Trial or any other clinical study).

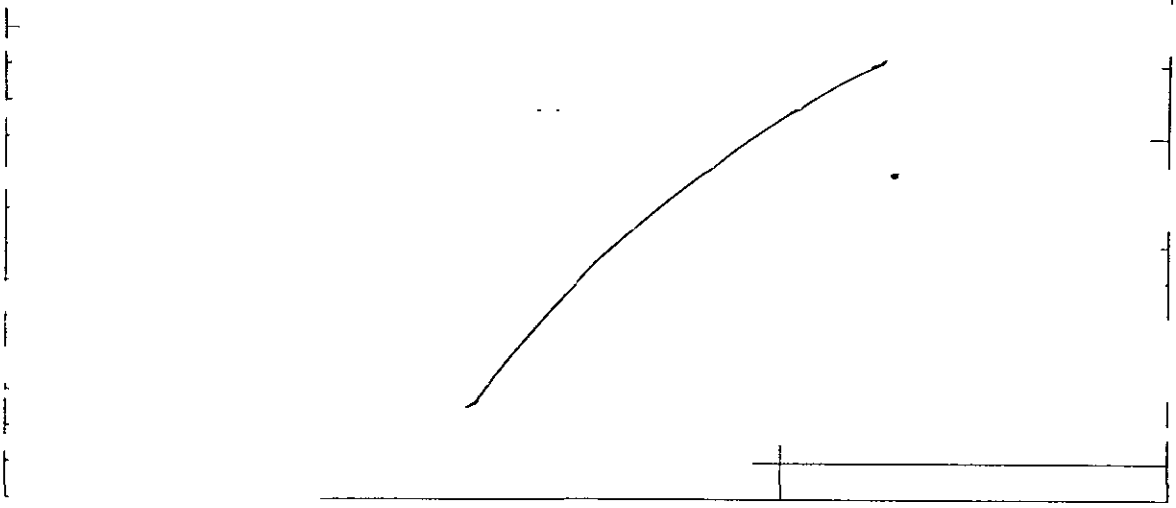
4) Owned or entered into an agreement to own, Amylin Pharmaceuticals stock and/or stock options that exceed $50,000.00 in value.

Protocol No.: 137-111

Protocol Title:
Fifty-Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled and AC137 Dose Ranging Study to Evaluate Glycated Hemoglobin in Patients With Type II Diabetes Mellitus (Phase 3)

Investigator	Investigator	Investigator

Investigator	Investigator	Investigator

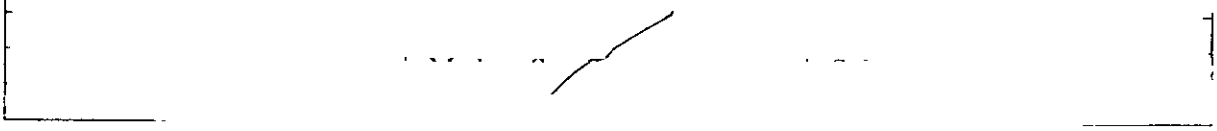


40

Protocol No.: 137-112

Protocol Title:
Fifty Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Glycated Hemoglobin and Safety of Pramlintide (AC137) Versus Placebo in Patients With Type 1 Diabetes Mellitus (Phase 3)

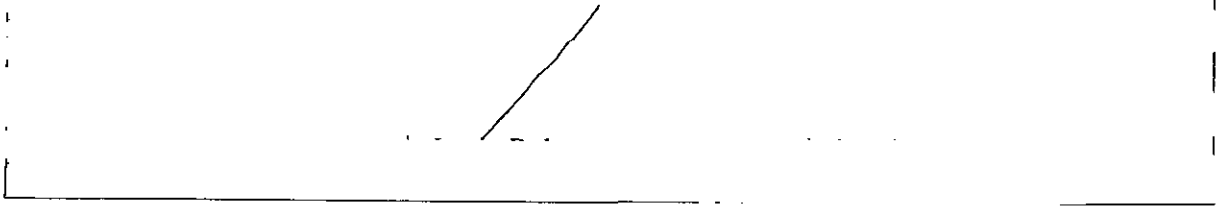
Investigator	Investigator	Investigator



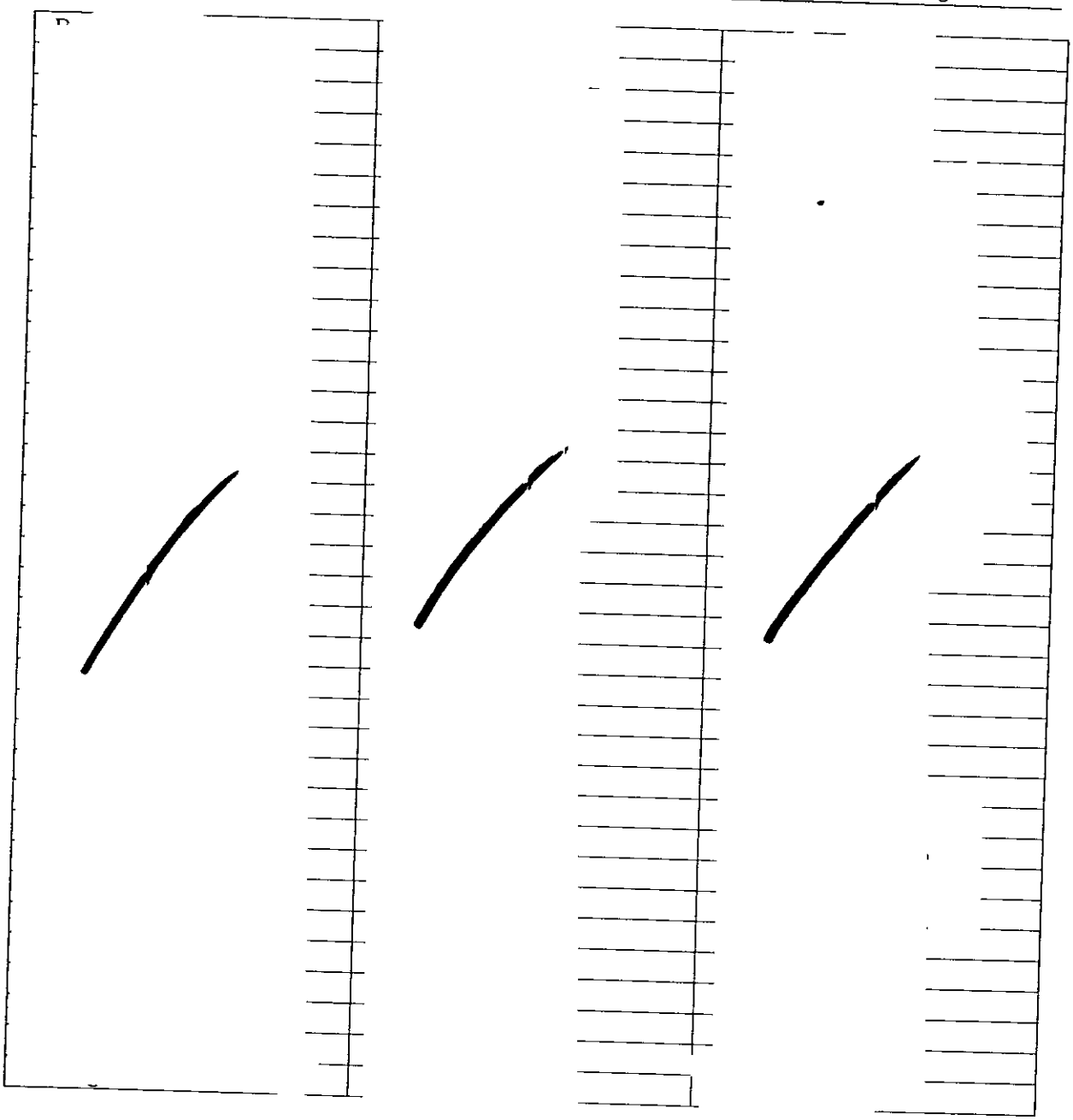
Protocol No.: 137-117

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type I Diabetes Mellitus (Phase 3)

Investigator	Investigator	Investigator

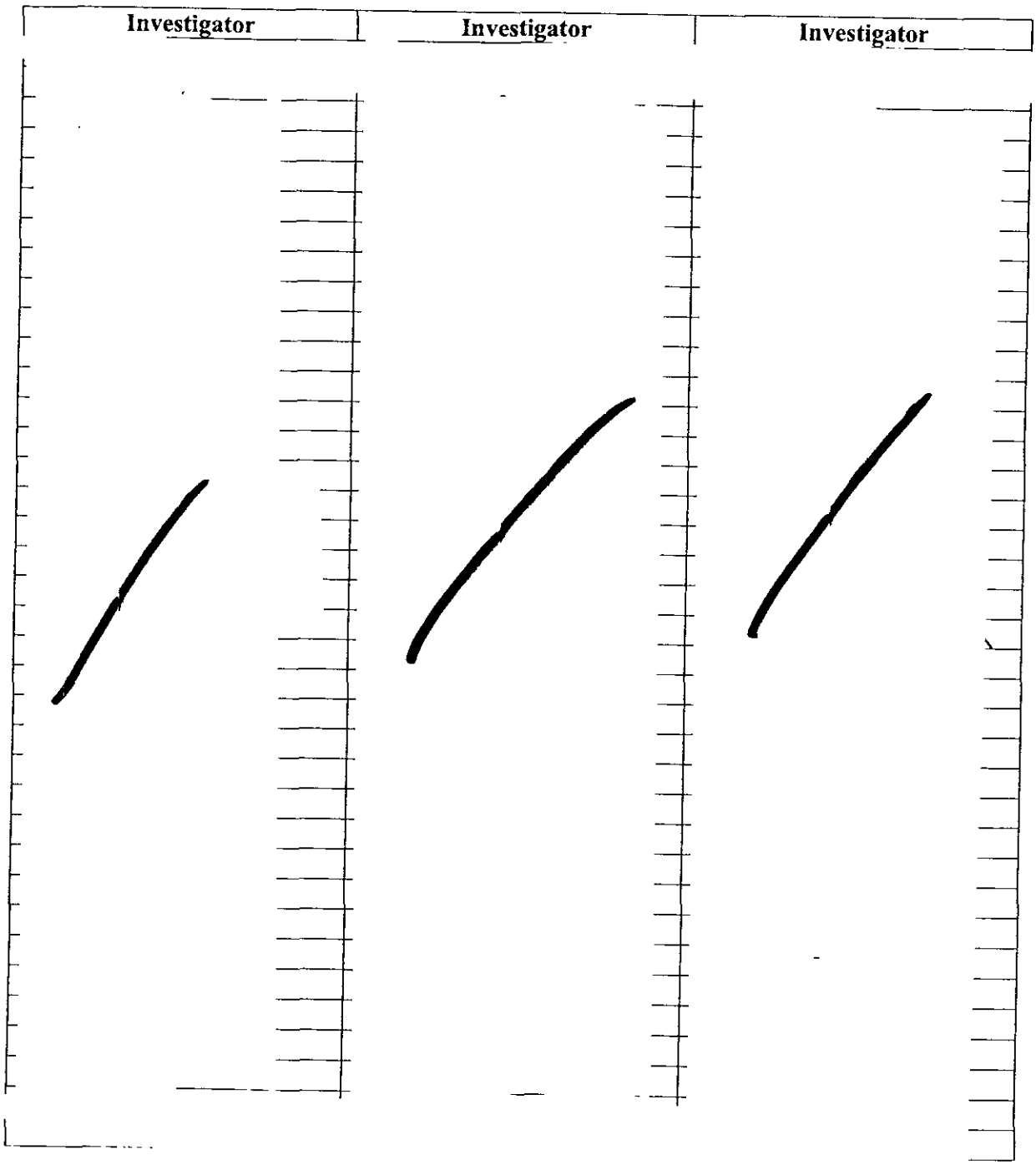


12



Protocol No.: 137-123

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type II Diabetes Mellitus (Phase 3)



Protocol No.: 137-140 (on-going)

Protocol Title:
An Open-Label Study of the Long Term Safety of Pramlintide Use in Study Subjects with Type 1 or 2 Diabetes Mellitus

Investigator	Investigator	Investigator

Protocol No.: 137-146

Protocol Title:
A Placebo-Controlled, Single-Blind, Pilot Study to Examine the Effects of Adjunctive Pramlintide Therapy on Glucose Fluctuations in Subjects With Type 1 Diabetes Mellitus Utilizing Continuous Subcutaneous Insulin Infusion (CSII) (Phase 3B)

Investigator	Investigator	Investigator

One-Year Post Study

Investigator	Investigator	Investigator

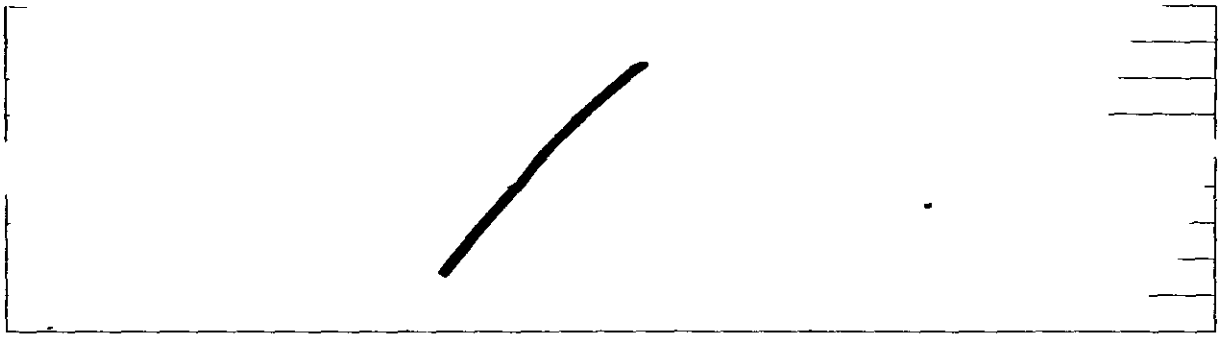
Protocol No.: 137-147

Protocol Title:
A Single-Arm, Open-Label, Dose-Escalation Study to Examine Dose Initiation in Subjects With Type 1 Diabetes Mellitus Given Pramlintide Subcutaneously (Phase 3B)

Investigator	Investigator	Investigator

One-Year Post Study

Investigator	Investigator	Investigator



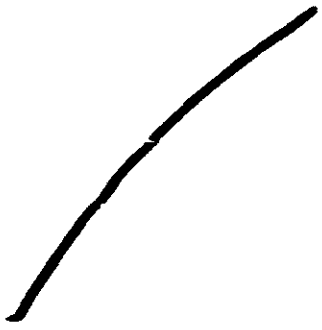
Protocol No.: 137-149 (on-going study)

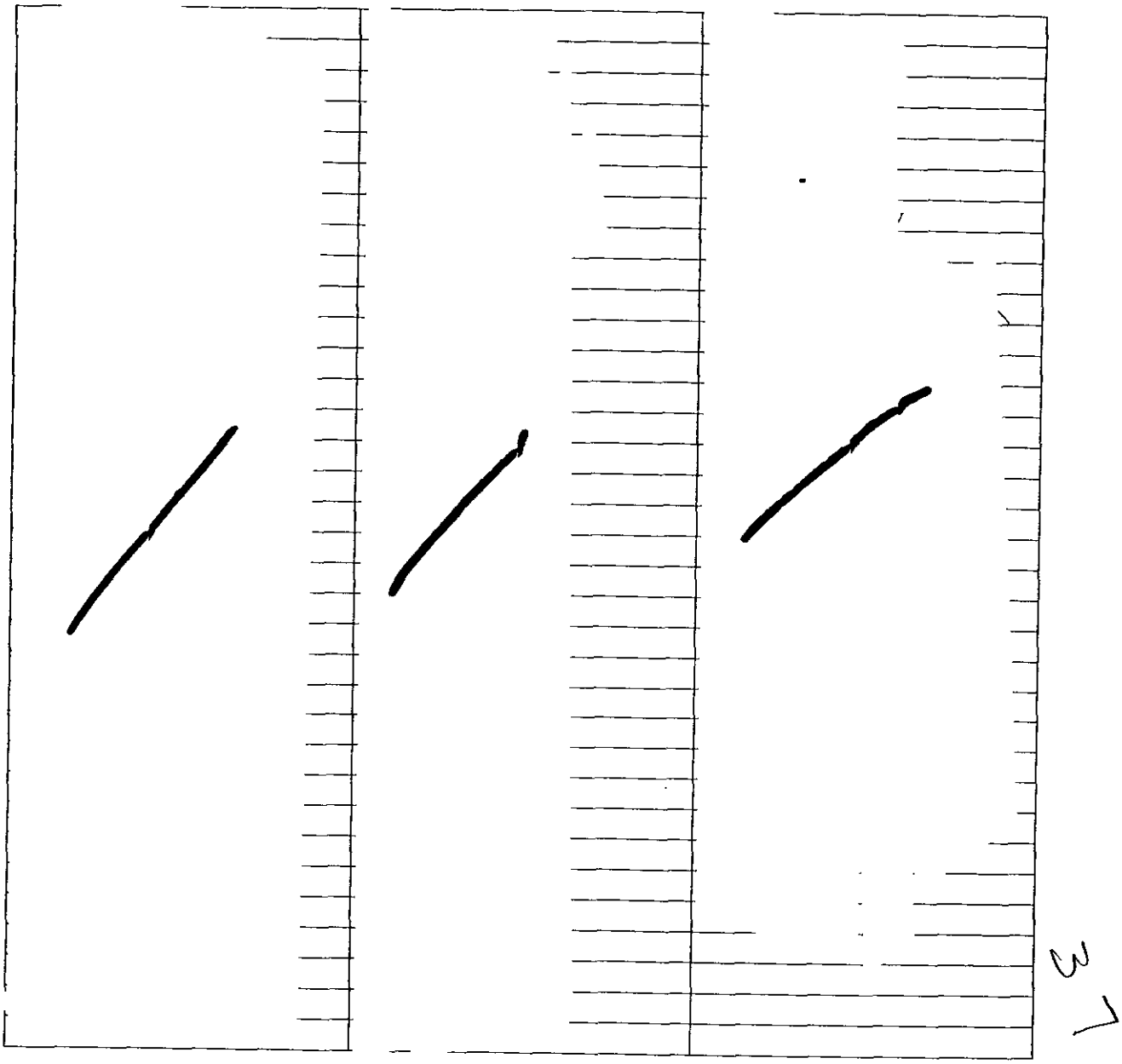
Protocol Title:
A Single Center, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Cross-Over Study Evaluating the Acute Effect of Pramlintide on Satiety and Food Intake in Normal-Weight and Obese Non-Diabetic Subjects and in Insulin-Treated Subjects With Type 1 and Type 2 Diabetes Mellitus

Investigator


Protocol No.: 137-150

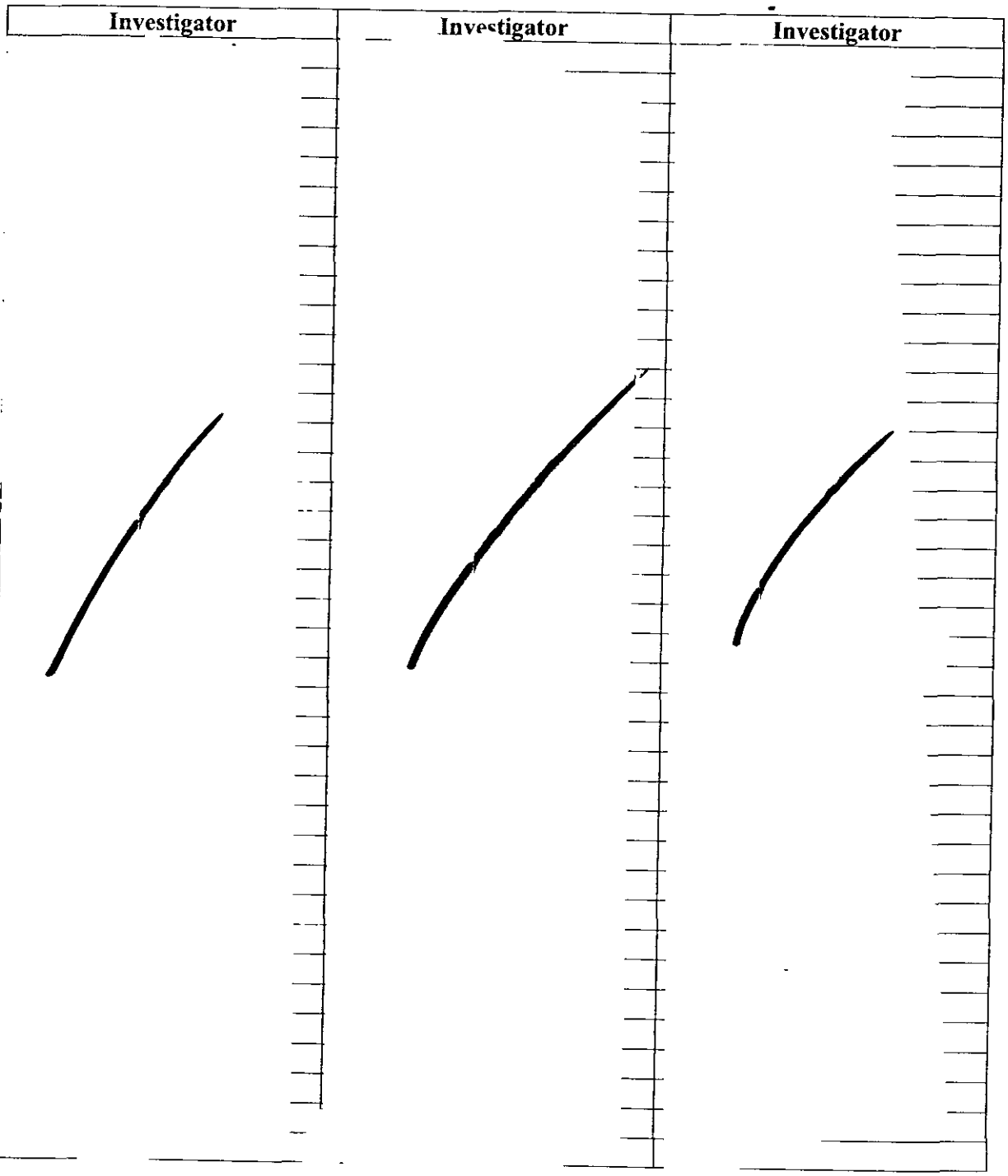
Protocol Title:
A Randomized, Triple-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety of Pramlintide Treatment Employing Pramlintide Dose-Titration Followed by Insulin Dose Optimization in Subjects With Type 1 Diabetes Mellitus Who Have Not Achieved Glycemic Targets With Intensive Insulin Therapy

Investigator	Investigator	Investigator
		



Protocol No.: 137-150E (on-going study)

Protocol Title:
A Multicenter, Open-Label, Extension Study of the Long-Term Safety of Pramlintide in Subjects With Type 1 Diabetes Mellitus Completing Protocol 137-150



Protocol No.: 137-151

Protocol Title:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide Dose Timing on Postprandial Plasma Glucose Profiles in Subjects With Type 1 Diabetes Mellitus and Subjects With Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

Investigator	Investigator	Investigator

One-Year Post Study

Investigator	Investigator	Investigator

Protocol No.: 137-152

Protocol Title:
A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Volunteers to Assess the Effects of Pramlintide Upon the Recognition of Hypoglycemic Symptoms (Phase 3B)

Investigator	Investigator

One-Year Post Study

Investigator

Protocol No.: 137-153

Protocol Title:
A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide When Injected Subcutaneously at Various Anatomical Sites in Non-Obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin

Investigator	Investigator	Investigator

Protocol No.: 137-154

Protocol Title:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide on the Pharmacokinetics of an Orally Administered Concomitant Medication When Given at Various Times in Relation to Pramlintide Dosing in Subjects With Type 2 Diabetes Mellitus (Phase 3B)

Investigator	Investigator

Attachment B

Certification: **Financial Interests and Arrangements of Clinical Investigators**
Significant Equity Interest Certification
Due Diligence: Information Not Obtained

The attached list of investigators who appeared on a Form FDA 1572 for a site that enrolled patients in the covered clinical studies 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), 137-150, 137-150E (on-going study), 137-151, 137-152, 137-153 and 137-154, (as defined in 21 CFR 54.2 (e)) could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR 54.2(b). I certify that I have acted with due diligence to obtain from the listed clinical investigators this information, but it was not possible to do so. Due diligence effort taken and the reasons why this information could not be obtained are provided below.

Protocol No.: 137-111, entitled:
Fifty-Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled and AC137 Dose Ranging Study to Evaluate Glycated Hemoglobin in Patients With Type II Diabetes Mellitus (Phase 3)

Protocol 137-112, entitled:
Fifty Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Glycated Hemoglobin and Safety of Pramlintide (AC137) Versus Placebo In Patients With Type 1 Diabetes Mellitus (Phase 3)

Protocol 137-117, entitled:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type I Diabetes Mellitus (Phase 3)

Protocol 137-123, entitled:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type II Diabetes Mellitus (Phase 3)

Protocol No. 137-140 (ongoing study), entitled:
An Open-Label Study of the Long Term Safety of Pramlintide Use in Study Subjects with Type 1 or 2 Diabetes Mellitus

Protocol No. 137-146, entitled:
A Placebo-Controlled, Single-Blind, Pilot Study to Examine the Effects of Adjunctive Pramlintide Therapy on Glucose Fluctuations in Subjects With Type 1 Diabetes Mellitus Utilizing Continuous Subcutaneous Insulin Infusion (CSII) (Phase 3B)

Protocol No. 137-147, entitled:

A Single-Arm, Open-Label, Dose-Escalation Study to Examine Dose Initiation in Subjects With Type 1 Diabetes Mellitus Given Pramlintide Subcutaneously (Phase 3B)

Protocol No. 137-149 (on-going), entitled:
A Single Center, Randomized, Double-Blind, Placebo-Controlled, Two-Period, Cross-Over Study Evaluating the Acute Effect of Pramlintide on Satiety and Food Intake in Normal-Weight and Obese Non-Diabetic Subjects and in Insulin-Treated Subjects With Type 1 and Type 2 Diabetes Mellitus

Protocol No. 137-150, entitled:
A Randomized, Triple-Blind, Placebo-Controlled, Multicenter Study to Investigate the Safety of Pramlintide Treatment Employing Pramlintide Dose-Titration Followed by Insulin Dose Optimization in Subjects With Type 1 Diabetes Mellitus Who Have Not Achieved Glycemic Targets With Intensive Insulin Therapy

Protocol No. 137-150E (on-going), entitled:
A Multicenter, Open-Label, Extension Study of the Long-Term Safety of Pramlintide in Subjects With Type 1 Diabetes Mellitus Completing Protocol 137-150

Protocol 137-151, entitled:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide Dose Timing on Postprandial Plasma Glucose Profiles in Subjects With Type 1 Diabetes Mellitus and Subjects With Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

Protocol 137-152, entitled:
A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Volunteers to Assess the Effects of Pramlintide Upon the Recognition of Hypoglycemic Symptoms (Phase 3B)

Protocol 137-153, entitled:
A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide when Injected Subcutaneously at Various Anatomical Sites in Non-Obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

Due diligence was shown by Amylin Pharmaceuticals, Inc., by sending each Principal Investigator and Subinvestigator who entered patients in Protocols 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), 137-150, 137-150E (on-going study), 137-151, 137-152, 137-153 and 137-154 an explanatory letter and a Financial Disclosure Form. For all sites in which no response was received from an Investigator or Subinvestigator, or there was receipt of an incomplete response, or there was indication of where an Investigator may have relocated, multiple follow-up attempts were made by both facsimile and telephone communications to obtain the disclosure information.

Listed are the Investigators and/or Subinvestigators who participated in Protocols 137-111, 137-112, 137-117, 137-123, 137-140 (on-going study), 137-146, 137-147, 137-149 (on-going study), 137-150, 137-150E (on-going study), 137-151, 137-152 and 137-153 from whom

complete Financial Disclosure Forms were not obtained. The reasons for information not being obtained are shown in four categories:

1) No response by the Investigator or site to initial and follow-up inquires

2) Incomplete response where a reply was received, but the information requested was only partially completed

3) No longer at institution/No further contact information

4) Investigator did not participate in the Amylin Study/No. patient enrollment.

Following each name is a designation of person type: (1) for "Principal Investigator" or a (4) for "Subinvestigator."

Mark Foletta
Vice President and Chief Financial Officer

6/6/03
Date

Due Diligence - Information Not Obtained

Protocol No.: 137-111

Protocol Title:
Fifty Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Glycated Hemoglobin and Safety of Pramlintide (AC137) Versus Placebo in Patients With Type 1 Diabetes Mellitus (Phase 3)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response
	4	No longer at institution
Baker, Michael	1	No response
	4	No response
	4	No response
	4	No response
Bell, David	1	No response
		No response
		No response
		No response
		No response
		No longer at institution
		No response
		No response
		No longer at institution
		Incomplete Response
		No longer at institution
		No response
		No response
		No longer at institution
		No response
		No response
		No response
		No longer at institution
		No response
		No longer at institution
		No longer at institution
Free, Richard	1	No response
		No response
	4	No longer at institution
	4	Incomplete response
	4	No longer at institution
	4	No response

34

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
Kaplan, Roy	1	Incomplete response
	4	No response
	4	No longer at institution
Krosnick, Arthur	1	Incomplete response
	4	Incomplete response
	4	No response
Levy, Benjamin	1	No response
	4	No longer at institution
Lucas, Charles	1	No longer at institution
	4	No longer at institution
Madan, Khorshed	1	No response
	4	No response
	4	No longer at institution
McGill, Janet	1	No response
	4	No response
	4	Incomplete response
	4	No longer at institution
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
Schimel, David	1	No longer at institution
	4	No response
	4	No response
	4	No longer at institution
Spiler, Ira	1	No response
	4	No longer at institution
	4	No longer at institution
Sussman, Allen	1	No response
	4	No longer at institution
Taylor, Marilynn	1	No longer at institution
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution

Protocol No.: 137-112

Protocol Title:
Fifty Two Week, Multicenter, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate Glycated Hemoglobin and Safety of Pramlintide (AC137) Versus Placebo In Patients With Type 1 Diabetes Mellitus (Phase 3)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No longer at institution
	4	No response
Berelowitz, Michael	1	No longer at institution
Bone, Henry	1	No response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
Clinkingbeard, Cynthia	1	No response
	4	No longer at institution
	4	No response

	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
Henriquez, Fidel	1	No longer at institution
	4	No longer at institution
	4	No response
	4	No longer at institution
Lahvis, Fredrick	1	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
Nadeau, Daniel	1	No response
	4	No response
	4	No response
Powell, Walter	1	No response
	4	No response
	4	No response
Schimel, David	1	No response
	4	No longer at institution
	4	No response
	4	No response

34

Protocol No.: 137-117

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type I Diabetes Mellitus (Phase 3)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No longer at institution
Andrews, William	1	No response
	4	Incomplete response
Bandurska, Elzbieba	1	No longer at institution
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
DeBaere, Herman	1	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Flynn, Michael	1	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No longer at institution
Halle, Jean-Pierre	1	No response
	4	No longer at institution
	4	No response
	4	No response
	4	Did not participate
Hramiak, Irene	1	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
Kerenyi, Zauzsa	1	No response

	4	Incomplete response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No longer at institution
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No longer at institution
Nadeau, Andre	1	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Rahnau, Klaus-Jurgen	1	No response
	4	No response
	4	No longer at institution
	4	Incomplete response
Scholtz, Gerhard	1	No response
	4	No response
Slama, Gerard	1	No response
	4	No response
	4	No longer at institution
St-Pierre, Bruno	1	No response
Tamas, Gyula	1	No response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No longer at institution
	4	No response

	4	No response
	4	No response
Verhagen, Ann	1	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
Woo, Vincent	1	No response
Yale, Jean-Francois	1	No response
	4	No longer at institution
	4	No response
	4	No longer at institution

Protocol No.: 137-123

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients with Type II Diabetes Mellitus (Phase 3)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
Anders, Martin	1	No response
	4	No longer at institution
Belanger, Andre	1	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
Czekalski, Stanislaw	1	No response
	4	No response
DeBaere, Herman	1	No response
	4	No response
DePaepe, Lutgarde	1	No response
	4	No response
	4	No response
Drupa-Wojciechowska, Barbara	1	No response
	4	No response

	4	No response
Dumas, Richard	1	No response
	4	No longer at institution
Flynn, Michael	1	No response
	4	No response
Freedman, Peter	1	No response
	4	No response
	4	No response
	4	No response
Halle, Jean-Pierre	1	No response
	4	No response
Harvey, John	1	No response
	4	No longer at institution
	4	No response
	4	No response
Holzinger, Gabor	1	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
Kerenyi, Zsuzsa	1	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
LeFloch, Jean-Pierre	1	No response
Levy, J.C	1	No response
	4	No response
	4	No response
	4	No response
Lopatynski, Prof. Jerzy	1	No response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response

Masood, Kahaja	1	No response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
Nadeau, Andre	1	No response
	4	No longer at institution
	4	No response
	4	No response
Orgiazzi, Prof. Jacques	1	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
Rath, Ulrich	1	No longer at institution
	4	No response
	4	No response
Ruhnau, Klaus-Juren	1	No response
	4	No response
	4	No response
Rybka, Jaroslav	1	No response
	4	No response
	4	No response
Simpson, Hugh	1	Incomplete response
	4	No response
	4	No response
	4	No longer at institution
	4	No longer at institution
St-Pierre, Bruno	1	No response
Tamas, Gyula	1	No response
Taylor, Adrian	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
	4	Incomplete response
	4	No longer at institution
	4	No response
	4	No response
	4	No longer at institution

Wheatley, Trevor	1	No response
	4	No longer at institution
Yale, Jean-Francois	1	No response
	4	No response
	4	No response

Protocol No.: 137-140 (ongoing study)

Protocol Title:
An Open-Label Study of the Long Term Safety of Pramlintide Use in Patients with Type 1 or 2 Diabetes Mellitus

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response

Protocol No.: 137-146

Protocol Title:
A Placebo-Controlled, Single-Blind, Pilot Study to Examine the Effects of Adjunctive Pramlintide Therapy on Glucose Fluctuations in Subjects With Type 1 Diabetes Mellitus Utilizing Continuous Subcutaneous Insulin Infusion (CSII) (Phase 3B)

One-Year Post Study

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response
	4	No response

Protocol No.: 137-147

Protocol Title:
A Single-Arm, Open-Label, Dose-Escalation Study to Examine Dose Initiation in Subjects With Type 1 Diabetes Mellitus Given Pramlintide Subcutaneously (Phase 3B)

One-Year Post Study

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No longer at institution
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
Kaplan, Roy	1	No response
	4	No response
Klaff, Leslie	1	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No response
	4	No longer at institution
	4	No response
	4	No response

Protocol No.:

Protocol Title:
A Randomized, Single-Blind, Placebo-Controlled, Crossover Study to Examine the Effect of Pramlintide Dose Timing on Postprandial Plasma Glucose Profiles in Subjects With Type 1 Diabetes Mellitus and Subjects With Type 2 Diabetes Mellitus Using Insulin (Phase 3B)

One-Year Post Study

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response

Protocol No.:

Protocol Title:
A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Study in Healthy Volunteers to Assess the Effects of Pramlintide Upon the Recognition of Hypoglycemic Symptoms (Phase 3B)

One-Year Post Study

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response

Protocol No.: 137-153

Protocol Title:
A Randomized, Open-Label, Crossover Study to Examine the Absolute Bioavailability of Pramlintide when Injected Subcutaneously at Various Anatomical Sites in Non-Obese and Obese Subjects With Type 1 and Type 2 Diabetes Mellitus Using Insulin

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No response
	4	No response

Attachment C

Disclosure: Financial Interests and Arrangements of Clinical Investigators

The attached list of investigators who appeared on a Form FDA 1572 for a site that enrolled patients in the covered clinical studies 137-146, 137-150 and 137-150E (on-going), is submitted in accordance with 21 CFR § 54. These investigators have participated in financial arrangements or hold financial interest that is required to be disclosed as outlined below. Details of the investigator's disclosable financial arrangements and interests are provided below, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

1) Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study.

2) Any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

3) Any proprietary interest in the product tested in the covered study held by the clinical investigator.

4) Any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Following each name is a designation of person type: (1) for "Principal Investigator" or a (4) for "Subinvestigator."

Studies 137-146, 137-150 and 137-150E are multicenter studies; therefore, the impact of a single investigator is minimized.

Mark M. Foletta

Mark Foletta
Vice President and Chief Financial Officer

6/6/03
Date

Protocol No.: —

Protocol Title:

[ ]

Dr. [ ], participated as a *subinvestigator* in Amylin study — Dr. [ ] entered into a Collaborative Research and Assignment Agreement from October 15, 1996 through October 15, 1998 to establish a collaborative relationship to perform clinical research on another diabetes drug candidate, not pramlintide. The monetary amount per year was $275,000 — Subsequent to this Collaborative Research and Assignment Agreement, on May 4, 1999, there was an extension for a third year of research in the amount of $130,000 — Dr. [ ] has performed [ ]
These grant monies were partially for payment for these clinical studies.

Protocol No.: —

Protocol Title:

[ ]

Dr. [ ] between July 1999 and June 30, 2001, and during this time was a *subinvestigator* for Amylin clinical study — Although Dr. — was listed on the 1572 as a subinvestigator, he did not see any patients during the — study duration.

From May 2001 to June 30, 2001, Dr. — was working for Amylin one half day per week as a consultant while working for [ ] On July 1, 2001, Dr. — terminated his employment with [ ] to become a full time employee at Amylin Pharmaceuticals, Inc. on July 10, 2001. On August 23, 2001, Dr. — was removed from FDA FORM 1572 for clinical study —

At the time of financial disclosure dated 4/16/01 for Amylin study — , Dr. — had Amylin stock worth $20,000, which he purchased prior to joining Amylin in July 2001. At the one-year post study, Dr. — had purchased 10,000 shares of Amylin stock valued at $159,900 at the time of financial disclosure dated 2/21/03.

Dr. [ ] current role at Amylin Pharmaceuticals is [ ]

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
\	4	Purchase 3,500 shares of Amylin stock in 1998. Stock is worth $57,000 at the time of financial disclosure dated 2/20/03.

One-Year Post Study

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
\	4	Purchase 3,500 shares of Amylin stock in 1998. Stock is worth $57,000 at the time of financial disclosure dated 2/20/03.

Protocol No.: —

Protocol Title:

[ ]

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
\	1	Purchased ~10,000 shares of Amylin stock in June 1997. Stock is worth $149,500 at the time of financial disclosure dated 10/7/02.

Protocol No. —

Protocol Title:

[ ]

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
\	1	Purchased ~10,000 shares of Amylin stock in June 1997. Stock is worth $149,500 at the time of financial disclosure dated 10/7/02.
	4	Purchased 3,750 shares of Amylin

		stock in November/December 2001. Stock is worth $62, 213 at the time of financial disclosure dated 11/19/02.

19 FINANCIAL INFORMATION

In accordance with 21 CFR § 314.50 (k), this item contains financial certification by the applicant, Amylin Pharmaceuticals, as required under 21 CFR § 54, for all clinical investigators (as defined in 21 CFR § 54.2 (d)) who have enrolled patients into the covered clinical studies identified below (as defined in 21 CFR § 54.2 (e)) in support of NDA Number 21-332 for SYMLIN™ Injection (pramlintide acetate). No clinical investigator identified in this certification is a full-time or part time employee of Amylin Pharmaceuticals, the sponsor of each covered clinical study.

Covered Clinical Studies:

Protocol No. 137-121, entitled:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 1 Diabetes Mellitus. (12 Month Type 1 U.S.)

Protocol No. 137-122, entitled:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in patients With Type 2 Diabetes Mellitus. (12 Month Type 2 U.S.)

Protocol No. 137-140, entitled:
An Open-Label Study of the Long-Term Safety of Pramlintide Use in Patients With Type 1 or 2 Diabetes Mellitus

Protocol No. 137-141, entitled:
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137).

Protocol No. 137-142, entitled:
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137).

Protocol No. 137-143, entitled:
An Open-Label Assessment of the Single Dose and Multiple Dose Pharmacokinetic Profiles of Pramlintide in Subjects with Type 1 Diabetes Mellitus.

Protocol No. 137-144, entitled:
An Open-Label Assessment of the Single Dose and Multiple Dose Pharmacokinetic Profiles of Pramlintide in Subjects with Type 2 Diabetes Mellitus.
Certification Information:

Amylin Pharmaceuticals certifies to the absence of financial interests and arrangements regarding *compensation affected by the outcome of clinical studies* (as defined in 21 CFR § 54.2 (a)), *proprietary interest in the tested product* (as defined in 21 CFR § 54.2 (c)), and *significant payments of other sorts* (as defined in 21 CFR § 54.2 (f)) for all clinical investigators who have enrolled patients into Protocol Nos. 137-121, 137-122, 137-140, 137-141, 137-142, 137-143 and 137-144. A completed FORM FDA 3454 for this certification (dated and signed by the Vice President, Finance and Chief Financial Officer, Mark Foletta) is provided.

Amylin Pharmaceuticals certifies to the absence of financial interests and arrangements regarding *significant equity interest in the sponsor of a covered study* (as defined in 21 CFR § 54.2 (b)) for all clinical investigators who have enrolled patients into Protocol Numbers 137-121, 137-122, 137-140, 137-141, 137-142, 137-143 and 137-144 as listed in Attachment A. If an investigator participated in more than one study and only provided certification documentation for one study, they are considered certified for all studies in which they participated.

Amylin Pharmaceuticals certifies that it acted with due diligence to obtain information regarding significant equity interest in the sponsor of a covered study from all clinical investigators who have enrolled patients into Protocol Nos. 137-121, 137-122, 137-140, 137-141, 137-142, 137-143 and 137-144. In the event that it was not possible to do so, Amylin Pharmaceuticals provides the reasons why this information could not be obtained. This certification (dated and signed by the Vice President, Finance and Chief Financial Officer at Amylin Pharmaceuticals is provided in Attachment B for Protocol No. 137-121, Protocol No. 137-122, Protocol No. 137-140, Protocol No. 137-141, Protocol No. 137-142, Protocol No. 137-143 and Protocol No. 137-144.

Disclosure Statements:

Disclosure statements are not applicable to this NDA. As the applicant, Amylin Pharmaceuticals certifies to the absence of financial interests and arrangements for all clinical investigators who have enrolled patients into Protocol Nos. 137-121, 137-122, 137-140, 137-141, 137-142, 137-143 and 137-144 or certifies that it acted with due diligence to obtain the information required under 21 CFR § 54 from all clinical investigators who have enrolled patients into Protocol Nos. 137-121, 137-122, 137-140,

137-141, 137-142, 137-143 and 137-144. In the event that it was not possible to do so, Amylin Pharmaceuticals provides the reasons why this information could not be obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

[(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
Please see Attachments A and B	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mark G. Foletta	Vice President and CFO
FIRM/ORGANIZATION	
Amylin Pharmaceuticals Inc.	
SIGNATURE	**DATE**
Mark G. Foletta	6/1/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Attachment A

The following list of Investigators who enrolled patients in the covered clinical studies: 137-121, 137-122, 137-140, 137-141, 137-142, 137-143 and 137-144, as defined in 21 CFR 54.2 (e), have certified that neither they, nor their spouses, nor dependent children have ever:

1) Owned or entered into an agreement to own a proprietary interest in the Amylin Pharmaceuticals product which is the subject of the Clinical Trial (e.g., patent, trademark, copyright, licensing agreement and/or royalty arrangement, etc.).

2) Entered into any financial arrangement with Amylin Pharmaceuticals, whereby the value of your compensation for conducting the Clinical Trail could be influenced by the outcome of the Clinical Trial.

3) Received, or entered into an agreement to receive, payments, grants and/or equipment from Amylin Pharmaceuticals (including payments to an institution to support your activities), having a monetary value exceeding $25,000 (exclusive of the costs of conducting the Clinical Trial or any other clinical study).

4) Owned or entered into an agreement to own, Amylin Pharmaceuticals stock and/or stock options that exceed $50,000.00 in value.

Protocol No.: 137-121

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 1 Diabetes Mellitus. (12 Month Type 1 U.S.)

Investigator	Investigator	Investigator

3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

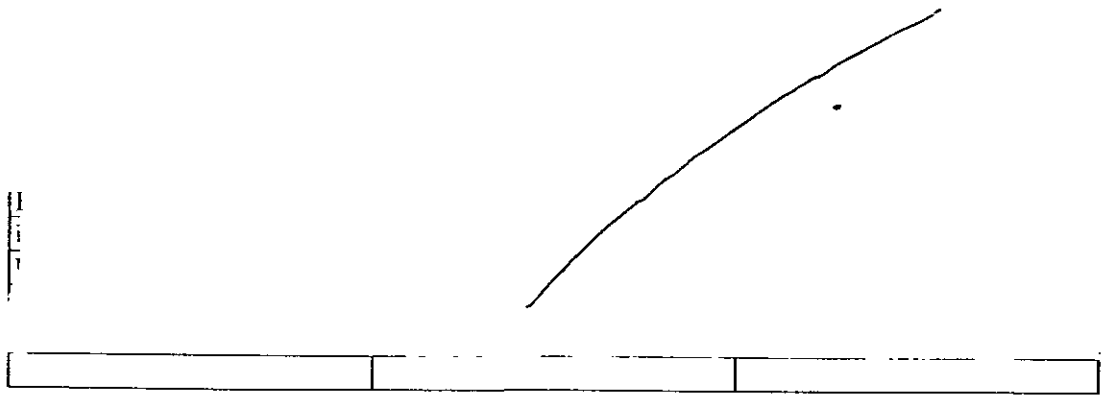
_____ § 552(b)(5) Draft Labeling

Protocol No.: 137-122

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 2 Diabetes Mellitus. (12 Month Type 2 U.S.)

Investigator	Investigator	Investigator

Investigator	Investigator	Investigator



Protocol No.: 137-140

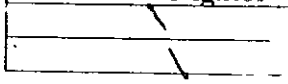
Protocol Title:
An Open-Label Study of the Long Term Safety of Pramlintide Use in Patients with Type 1 or 2 Diabetes Mellitus

Investigator	Investigator	Investigator

Protocol No.: 137-141

Protocol Title:
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137)

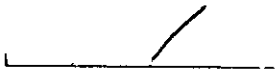
Investigator



Protocol No.: 137-142

Protocol Title:
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137)

Investigator



Protocol No.: 137-143

Protocol Title:
An Open-Label Assessment of the Single Dose and Multiple Dose Pharmacokinetic Profiles of Pramlintide in Subjects with Type 1 Diabetes Mellitus

Investigator

Protocol No.: 137-144

Protocol Title:
An Open-Label Assessment of the Single Dose and Multiple Dose Pharmacokinetic Profiles of Pramlintide in Subjects with Type 2 Diabetes Mellitus

Investigator

Electronic Mail Message

Date: 9/20/01 1:03:19 PM
From: Julie Rhee (RHEEJ)
To: Leah Ripper (RIPPER)
Subject: Symlin studies

Lee,

The following a list of the study initiation date:

1. Protocol 137-121: 2/19/96
2. Protocol 137-122: 11/26/96
3. Protocol 137-141: 10/1/99
4. Protocol 137-142: 11/24/99

Julie

Attachment B

Certification: Financial Interests and Arrangements of Clinical Investigators
Significant Equity Interest Certification
Due Diligence: Information Not Obtained

The attached list of investigators who appeared on a Form FDA 1572 for a site that enrolled patients in the covered clinical studies 137-121, 137-122, 137-141, and 137-142 (as defined in 21 CFR 54.2 (e)) could not be certified with regard to the lack of a significant equity interest as defined in 21 CFR 54.2(b). I certify that I have acted with due diligence to obtain from the listed clinical Investigators this information, but it was not possible to do so. Due diligence efforts taken and the reasons why this information could not be obtained are provided below.

Protocol No. 137-121, entitled: 3/19/96
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 1 Diabetes Mellitus. (12 Month Type 1 U.S.)

Protocol No. 137-122, entitled: 11/26/96
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 2 Diabetes Mellitus. (12 Month Type 2 U.S.)

Protocol No. 137-141, entitled: 10/1/99
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137).

Protocol No. 137-142, entitled: 11/24/99
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137).

Due diligence was shown by Amylin Pharmaceuticals by sending each Principal Investigator and Subinvestigator who entered patients in Protocols 137-121, 137-122, 137-141, 137-142, 137-143, and 137-144 an explanatory letter and Financial Disclosure Form. For all sites in which no response was received from an Investigator or Subinvestigator, or there was receipt of an incomplete response, or there was indication of where an Investigator may have relocated, multiple follow-up attempts were made by both facsimile and telephone communications to obtain the disclosure information.

Listed are the Investigators and/or Subinvestigators who participated in Protocols 137-121, 137-122, 137-141, and 137-142, from whom complete Financial Disclosure Forms

were not obtained. The reasons for information not being obtained are shown in four categories:

1) **No response** by the Investigator or site to initial and follow-up inquiries

2) **Incomplete response** where a reply was received, but the information requested was only partially completed

3) **No longer at institution**/No further contact information

4) Investigator **did not participate** in the Amylin Study/No. patient enrollment.

Following each name is a designation of person type: (1) for "Principal Investigator" or a (4) for "Subinvestigator."

Mark Foletta
Vice President, Finance and Chief Financial Officer

12/1/00
Date

Title: Due Diligence, Information Not Obtained

Protocol No.: 137-121

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 1 Diabetes Mellitus. (12 Month Type 1 U.S.)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
Levy, Carol	1	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
Stine, Sandra	1	No Response
	4	No Response
Thompson, Daniel	1	No Response
	4	No Response
	4	No Response
Winikoff, Janet	1	No Response

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No Response
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Dills, Diana	1	No longer at institution
Duick, M.D., Daniel	1	No longer at institution
	4	No longer at institution
		No longer at institution
		No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Kessler, Daniel	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Levai, Julia	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
Raff, Sandra	1	No longer at institution
	4	No longer at institution
Rhie, Francis	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Springgate, Clark	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Anderson, M.D., James W.	1	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
Fisher, Lynda	1	Did not participate in study
Levine, M.D., Jon	1	Did not participate in study
Marcus, M.D., Alan	1	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study

Appears This Way
On Original

Protocol No.: 137-122

Protocol Title:
A Double-Blind, Placebo-Controlled, Multicenter, Phase III Study to Evaluate the Effects of Pramlintide (AC137) on Glycemic Control as Determined by Glycated Hemoglobin in Patients With Type 2 Diabetes Mellitus. (12 Month Type 2 U.S.)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
	4	No Response
Stine, Sandra	1	No Response
	4	No Response
	4	No Response
Thompson, Daniel	1	No Response
	4	No Response
	4	No Response
	4	Incomplete response
	4	No longer at institution

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Chavez, M.D., Denise	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Garber, M.D., Jason	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
Glatte, Hayden	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
Kessler. M.D., Daniel	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Mikolich. Dennis	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Terrell M Dale	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
Wilson, Addison	1	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	No longer at institution
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study
	4	Did not participate in study

Protocol No.: 137-141

Protocol Title:
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
	4	No longer at institution

Protocol No.: 137-142

Protocol Title:
An Open-Label, Randomized, Two-Period Cross-Over Study in Healthy Volunteers of the Bioequivalence of Two Different Formulations and Dosage Forms of Pramlintide (AC137)

Name of Investigator	Person Type	Explanation/Comment Regarding Status of Form
/	4	No longer at institution

Rhee, H Julie

From: Zimmer, Donna [Donna.Zimmer@amylin.com]

Sent: Wednesday, March 16, 2005 4:23 PM

To: Rhee, H Julie

Subject: RE: Symlin AP letter

Hi Julie,
35 pounds and 1 second after close of market!! This is to confirm that we received the AP letter. Thanks for all your efforts as you have worked with Amylin to bring us to this moment. We look forward to working with you as we move SYMLIN into the commercial arena.

I'll call you in a few minutes.

Donna

-----Original Message-----
From: Rhee, H Julie [mailto:RHEEJ@cder.fda.gov]
Sent: Wednesday, March 16, 2005 1:09 PM
To: Zimmer, Donna
Cc: Data, Joann; Kolterman, Orville; Kim, Michael
Subject: Symlin AP letter

Hi Donna,

Congratulations!!!!!

Here is the approval letter for Symlin. Could you please send me an e-mail letting me know that you have received the letter?

Our document room will be sending you a hard copy of the letter.

It's been a pleasure to work with all of you.

Take care,
Julie

Office Director's Sign-Off Memorandum

Date:	Wednesday, March 16, 2005
NDA:	21-332
Sponsor:	Amylin Pharmaceuticals
Proprietary Name:	Symlin (pramlintide acetate) injection
Date of submission:	Resubmission date: Sept 17th, 2004
	Original submission: Dec. 8, 2000

Introduction: This is the third cycle for this drug product, which is an analogue of a naturally occurring hormone, amylin, that is co-secreted from the pancreas along with insulin. It's intended physiologic results is a lowering of glucose, at least in part mediated by a suppression of glucagon release postprandially and through delayed GI transit/gastric emptying.

I am in substantial agreement with Dr. Orloff's excellent Division Director's memo of 03/10/05, which I co-signed to document my agreement. Dr. Orloff's memorandum will stand as the decisional memo of record and this memorandum will briefly highlight some key points.

As requested, the sponsor has provided further data (albeit from uncontrolled studies) that establish a method of use for this drug that will allow labeling and marketing. Given its effects in reducing post-prandial glucose excursions and in aiding in controlling weight gain, it does have benefits for certain individuals that justify its marketing for the treatment of type 1 and type 2 diabetics as an adjunct to mealtime insulin therapy. We have in place an agreement on a risk management plan or RMP (with Office of Drug Safety's input), to include a Medguide to warn about proper use (especially not mixing with insulin) and hypoglycemic risk. There will be a surveillance program to assess for the latter, as well. One important note – the October 10th 2001, approval letter had raised the issue of whether Symlin might be associated with accelerated retinopathy, based on the results from trials to that point and raised the issue of a phase 4 study to delineate any such effect. On review of the original and additional information, there is no clear signal of such with many subsequent studies showing lower rates of retinopathic changes with active drug compared to placebo. At this point, there are two phase 4 commitments being made by the company. The first is to report, by Sept. 2008, the results of a multicenter, open-label, observational study to prospectively collect data that characterize the use of SYMLIN following introduction into the marketplace. This study will include non-targeted prescribers in the same approximate proportion as those targeted by Symlin for detailing and promotion of the product (the intent of marketing is to target skilled diabetologists and endocrinologists). The second is a study under PREA to perform a PK study of SYMLIN in adolescents aged 12 to [redacted] years with type 1 and type 2 diabetes to evaluate the pharmacokinetics and relevant pharmacodynamic effects of different subcutaneous doses of the drug.

Though not formal phase 4 commitments, the sponsor also agreed to a number of measures as a part of their RMP. These following agreements are also summarized in the action letter:

- No direct-to-consumer advertisement,
- No journal advertisement for one year after SYMLIN is launched,
- Promotion limited primarily to physicians that specialize in diabetes management and are supported by certified diabetes educators,
- Gradual introduction of SYMLIN to the marketplace with concomitant evaluation of patterns of Symlin use by "targeted" and "non-targeted" health care providers; to this end also assess available databases for information regarding Symlin prescription practices and submit the results of these assessments on a semiannual basis
- Education and outreach programs for health care providers and patients,
- Surveillance Plan: report severe hypoglycemic events in an expedited manner for 2 years or as long as the Phase 4 observational study remains ongoing, whichever is longer,
- Postmarketing Observational Study to assess the potential hypoglycemic risk for SYMLIN in the actual use setting (an effort will be made to enroll also "non-targeted" health care providers")
- A 24/7 nationwide call-center to assist patients and physicians with the use of SYMLIN.

With the new data reviewed and considered and the agreements to this RMP and phase 4 commitments, I will approve Symlin with the following indications:

Symlin is given at mealtimes and is indicated for:

- Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

- Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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

/s/

Robert Meyer
3/16/05 10:22:54 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 10, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-332
Symlin (pramlintide) injection
Amylin Pharmaceuticals
Adjunct to insulin for the treatment of type 1 and type 2 diabetes mellitus

SUBJECT: NDA review issues and recommended action

Background
This is the third division director memorandum for pramlintide injection, a 37 amino acid synthetic analogue of human amylin, a peptide co-secreted from the beta cell with insulin and deficient in type 1 and type 2 diabetes. The original NDA was submitted to the Agency on December 8, 2000. The other memoranda and one addendum are dated October 1, 2001, October 9, 2001, and December 2, 2003. All recommended "approvable" actions based on deficiencies to be summarized below.

While the physiologic role of amylin is not known, pramlintide when administered in pharmacologic doses has multiple effects, including inhibition of gastric emptying, modulation of post-prandial nutrient absorption, inhibition of glucagon secretion, nausea, and early satiety. It has been developed as mealtime adjunct to prandial insulin in types 1 and 2 diabetes with demonstrated effects to improve glycemic control and to promote weight loss. Additionally, use of pramlintide is associated with reduced insulin requirements. If approved, it would be the first adjunct to insulin for use in type 1 diabetes and the first new therapy for the treatment of type 1 diabetes since the advent of insulin. It is critical to understand that pramlintide itself has no direct hypoglycemic actions. Its anti-hyperglycemic effect in the treatment of diabetes relies completely on the glucose-lowering effect of insulin. As such, and as discussed further below, the insulin (particularly prandial bolus insulin) regimen must be modified for safe and effective use of pramlintide.

The clinical development of the drug has progressed through three separate periods with regard to goals of investigation. The first set of pivotal clinical studies, submitted in the original NDA filing, were placebo-controlled, double-blind investigations of the safety and efficacy of a pramlintide/insulin regimen versus a regimen of insulin alone in patients with DM1 and DM2. The studies demonstrated that the pharmacologic effect of pramlintide could translate into improved glycemic control relative to insulin alone. This was based on differences in mean change from baseline between treatment groups (on average about 0.3 HbA1c percentage units)

and, significantly, on analyses showing superiority of the combination regimen with regard to percent of patients achieving glycemic targets according to ADA guidelines. These original trials were, additionally, designed specifically not to include routine adjustments in insulin dose toward optimization of glycemic control, rather only for persistent hypoglycemia, thus permitting the *demonstration* of superior efficacy of the combination regimen. But this method of use could not reasonably be translated to recommendations in labeling as it also engendered a substantial increased risk of severe hypoglycemia with pramlintide/insulin, disproportionate both to the difference from insulin monotherapy in glycemic control and to the absolute level of glycemic control achieved. As expected based on the kinetics of pramlintide, hypoglycemic risk was restricted to the post-prandial period, and attributed to the action of prandial bolus insulin on the markedly attenuated post-prandial glucose absorption from the gut, the specific effect of pramlintide. As such, the sponsor was charged with developing a method of use whereby the pharmacologic activity of pramlintide could be used to advantage while mitigating or at least minimizing hypoglycemic risk. This, then, would potentially permit labeling for safe and effective use.

In response to the first "approvable" action, which required further studies of safe methods of initiation and maintenance therapy with pramlintide, the sponsor, after discussion with FDA, conducted a study (trial 137-150), restricted to DM1, like the phase 3 trials double-blind and placebo-controlled, and in which a new method of initiation of therapy with pramlintide was implemented. This involved significant downward adjustment of insulin dose and gradual titration of pramlintide dose, largely against nausea. In addition, in contrast to previous trials, once at target dose of pramlintide, adjustments of insulin dose to achieve optimum glycemic control were directed per protocol such that an effect of pramlintide/insulin non-inferior to insulin monotherapy could be achieved. As such, rates of hypoglycemia could be compared between treatment groups in the absence of confounding by differences in glycemic control. The trial was successfully implemented with regard to efficacy (and thus interpretable with regard to comparative rates of hypoglycemia between treatment groups). As a result of the modification in initiation of therapy with pramlintide, the overall incidence of severe hypoglycemia was markedly reduced from previous studies (and notably comparable to the historical experience in the intensive therapy arm of the DCCT). Serious adverse events attributable to hypoglycemia were mitigated, though the rate of severe hypoglycemia per patient years among pramlintide-treated patients was still somewhat increased relative to insulin alone.

As a consequence of the persistent increased risk of hypoglycemia demonstrated in this trial, the Agency again took another "approvable" action. This rested on the conclusion that the achievement of essentially equivalent glycemic control with insulin monotherapy and pramlintide/insulin was evidence that pramlintide offered no particular generalizable advantages with regard to glycemic control as an adjunct to insulin and proposing therefore that any difference in hypoglycemic risk was unacceptable. Specifically, the letter stated:

"To be approved, you must identify, through clinical trials, a patient population and a method of use for pramlintide where there is an acceptable risk-benefit profile (i.e. either without an increased risk of significant hypoglycemia or where there is an added benefit that clearly counterbalances any potential for increases in episodes of hypoglycemia)."

In effect, the Agency had concluded that, for all intents and purposes, evidence was lacking that pramlintide, while clearly pharmacologically active, conferred clinical advantages over insulin alone. Furthermore, it appeared that by its pharmacology, pramlintide merely served to complicate the use of insulin by contributing to the risk of hypoglycemia in the period shortly following pramlintide and prandial (short-acting) insulin co-administration.

The sponsor has now responded adequately to these concerns.

Pramlintide, by delaying gastric emptying (and perhaps by variably reducing appetite and thus meal size), does complicate the use of mealtime insulin, in the same manner as do any variations in meal size and nutritional composition, exercise, and alcohol intake. As such, and since for insulin, perhaps uniquely in the pharmacopeia, benefit is intimately tied to risk (i.e., hypoglycemia benefit versus hypoglycemia risk; any increase in dose to better control blood sugar carries a proportional increased risk of hypoglycemia), blinding to therapy sets up a situation in which it is extremely difficult, if not impossible, to address, patient by patient in a clinical trial, both efficacy and safety objectives in clinical management.

In short, the blinded trials conducted to date need to be interpreted carefully and with an understanding that neither specific design employed (fixed insulin dosing or insulin dose adjusted to goal) is fully amenable to informing simultaneously both the safe and the effective use of the drug. By extension, neither design translates readily to real-world clinical use. That is, the hypoglycemia risks in the blinded trials are unlikely to be quantitatively reflective of "actual use" risks, and logically would overestimate risks relative to glucose lowering benefits. Likewise, given the blinding of experimental therapy studied in a condition in which dose adjustments of an interacting and inherently dangerous drug (insulin) are critical to efficacy in achieving glycemic goals, neither the superiority of pramlintide/insulin in the original trials nor the "equivalence" of the pramlintide/insulin regimen to the insulin monotherapy regimen in the later study can be extrapolated directly to quantitative expectations with regard to benefit in glucose lowering. Suffice it to say that, as demonstrated in the overall clinical package and discussed in further detail below, it is apparent that the drug at the recommended doses is pharmacologically active, lowers glycemic exposure by modulating substrate availability for insulin-mediated glucose disposal, and can be used safely if mechanistic factors are integrated into prudent therapeutic application.

After discussion of these issues and reconsideration of the data package submitted through the second review cycle, it was decided that further blinded trials of pramlintide were, even if ethical based on the risks of insulin-induced hypoglycemia in the blinded setting (which indeed is arguable), not apt to yield further useful results. Discussion, post-action, with the sponsor ensued, and it was eventually agreed that additional data from open-label studies of pramlintide in DM1 and DM2 would be adequate for review. Furthermore, it was agreed that proposals with regard to a restricted patient population of those unable to meet glycemic goals and use only under the care of experienced diabetes practitioners implemented in the context of a concerted risk management program were, in principle, potentially acceptable as a path forward for this drug.

Clinical Safety and Efficacy Data in the latest submission

Dr. Roman has conducted and written a thorough review of the information submitted in response to the last action letter. He has as well as made an overall assessment of the risk versus benefit of this drug for the proposed indications based on the totality of the information in the application. He recommends approval of pramlintide injection as an adjunct to prandial insulin in type 1 and type 2 diabetes, with risk management to include a restriction of the indication in DM1 to those who have failed to achieve glycemic goals on insulin alone and who are in the care of a diabetes specialist. I concur with his overall recommendation.

In this latest submission, the sponsor has submitted efficacy and safety information, as well as insulin dose data, quality of life questionnaire results, and weight change data from a series of investigations. These include the following:

- Study 137-155, an open-label, uncontrolled clinical practice experience in patients enrolled by their physicians on the basis of not having achieved adequate glycemic control on an intensive insulin regimen. There were 265 patients with DM1 and 176 patients with DM2 who contributed data to the analyses in Dr. Roman's review.
- Study 137-150E, an open-label extension of study 137-150 in which all patients were treated with a pramlintide/insulin regimen. The original study was blinded and placebo-controlled and examined the efficacy and safety of pramlintide as an adjunct to insulin in DM1 when used according to a regimen involving gradual upward titration to tolerance of pramlintide with initial reduction in insulin dose to mitigate hypoglycemic risk. The extension study enrolled patients who had completed trial 150, and data from 205 patients with DM1 contributed to the analyses in Dr. Roman's review.
- Study 137-140, an open-label study in which patients enrolled in the original phase 3 trials were treated with a regimen of pramlintide/insulin. In this safety update of an ongoing clinical observational study, data from 87 patients with DM1 and 52 patients with DM2 were presented.

Study 137-155

In study 137-155, over 6-12 months of treatment, among patients with DM1, the mean reduction in HbA1c was minimal, at 0.2% percentage units (range -2.1 to +3.4). On the other hand, mean weight loss was 2-4 kg with a range from approximately -18 kg to +4 kg. In addition, there was a substantial mean reduction in total insulin dose, driven virtually completely by a mean reduction in prandial (short-acting) insulin of 22%. As shown in Dr. Roman's table 1 (page 12), the number of severe hypoglycemic events per patients years of exposure during the titration phase (months 0-3) was dramatically reduced compared to the pramlintide groups in previous blinded trials and essentially equivalent to the rate in the placebo group in trial 150. Compared to the original phase 3 trials, the rate of patient-reported severe hypoglycemia among pramlintide-treated patients was reduced from 1.55 events per patient year to 0.29 events. A similar relative reduction (~80%) compared to the original phase 3 trials was observed for medically-assisted severe hypoglycemia. Likewise, during the maintenance phase of treatment (months 4-6), the rate of severe hypoglycemia (table 3, page 14) among patients in study 155 was markedly reduced relative to both the pramlintide and placebo groups in the blinded portion of trial 150.

Among patients with DM2 in study 137-155, the mean reduction in HbA1c was 0.6 percentage units (range -3.9 to +2.2), mean weight loss was 2-3 kg (range -18 to +4.5), and total insulin dose was reduced by a mean of 7%, divided between short-acting and basal. With regard to severe hypoglycemia, much less of an issue for patients with DM2 treated with pramlintide in previous trials, the rates during the titration and maintenance phases were nevertheless reduced relative to those observed in the original phase 3 blinded trials (note that trial 150 did not enroll patients with DM2, so the only comparison is to the original blinded trials).

Study 150E

In study 150E, there were 108 patients with DM1 who had been in the insulin-only arm of trial 150 for whom the insulin-pramlintide regimen was therefore new (thus pramlintide-naïve). Over 6-12 months of follow up, the mean change in HbA1c in this group was +0.1 percentage units; mean weight change was approximately -3 kg, and there was a substantial (22-26%) reduction in total daily dose of short-acting insulin with a minimal reduction in basal insulin. Among the 97 patients who had received pramlintide in trial 150, mean HbA1c increased slightly (0.2 and 0.3 percentage units at 6 and 12 months, respectively). Weight increased by a mean of 0.1 and 0.2 kg at the two time points, and there was no change in mean dose of either short-acting or basal insulin.

The rates of severe hypoglycemia (patient-reported and medically-assisted categories) during the pramlintide titration phase in the patients who were naïve to pramlintide at entry into trial 150E were in the range of those observed in association with blinded pramlintide use during the titration phase of trial 150, in effect reconfirming the relative safety of the titration method of pramintide/insulin use first applied in that trial (see table 1 of Dr. Roman's review). The rates in patients previously treated with pramlintide were similar to placebo rates during the blinded trial (150) titration phase and thus lower than with blinded pramlintide therapy. Dr. Roman points out that patients in 150E had lower HbA1c at the start of the open-label treatment period (mean 7.6%) than did patients in any other trials to date, including the open-label 137-155 (baseline HbA1c 8.1%). This conceivably contributed to the difference in rates of hypoglycemia during the titration phase between 150E (pramlintide-naïve patients) and the DM1 patients treated in the 137-155. Of note, the rates of hypoglycemia in 150E pramlintide-naïve patients during titration were still markedly reduced compared to the phase 3 pramlintide groups, and indeed comparable to phase 3 placebo rates.

In trial 150E, Dr. Roman notes 10 motor vehicle accidents of which perhaps 5 appeared related to hypoglycemia. The timing of the 5 events relative to pramlintide administration is not well-documented, and, of course, there is no comparator arm in this study. Thus, it is not clear whether these are truly related to pramlintide therapy or not. There were no motor vehicle accidents reported in trial 155. Regardless of assessments of causality in any particular case, the overall increased risk of hypoglycemia with pramlintide, albeit apparently small in absolute terms, while not offsetting the benefits in terms of improved or maintained glycemic control with reduced insulin use and consequent weight loss or moderation of weight gain, nevertheless dictates caution in the operation of automobiles (or "heavy"machinery) in the immediate post-prandial period, during which the risk is greatest. This should be a precaution in use, at the very least during the titration phase of pramlintide therapy, or until it can be established that combination therapy is well-tolerated with regard to fluctuations in glycemia.

Patient satisfaction
Dr. Roman has reviewed in brief the information submitted related to patient satisfaction as assessed through a 14-item questionnaire (not formally validated). In the blinded, placebo-controlled trial 137-150, significantly higher percentages of pramlintide-treated than placebo-treated patients reported improvements in glucose control, greater "predictability" of glucose levels, improved weight and greater ease of weight control, and enhanced appetite control. Perhaps lending some validity to these findings, pramlintide-treated patients also reported more side effects of therapy than did placebo patients, clearly evident in the overall assessment of safety in the trial. Patients in the open label studies 137-150E and 137-155 gave similar answers to the pramlintide-treated patients in study 137-150.

Overall assessment of Safety and Efficacy
As discussed in "Background" above, and by Dr. Roman, the extensive development program for pramlintide has elucidated the clinical pharmacology of the drug. In addition, it has characterized the benefits and risks through blinded trials designed to demonstrate its glycemic-exposure (i.e., HbA1c) -lowering efficacy (the original phase 3 program), as well as through a blinded trial to establish a method of use that mitigates to a large extent the risk of post-prandial hypoglycemia associated with pramlintide/short-acting insulin combination therapy. Finally, risk and benefit have been explored through open-label treatment protocols in patients previously treated with pramlintide, and in those naïve to the drug, in particular those who in the estimation of their physicians have exhausted the possibilities for metabolic control with insulin alone (study 137-155).

The risks associated with pramlintide/insulin therapy are greatest in patients with DM1, for reasons that, as a group compared to patients with DM2, they have greater insulin sensitivity, and can more readily achieve daily glycemic excursions in the ranges where hypoglycemia becomes limiting to further control of blood glucose. Indeed, in DM2, the risk of hypoglycemia in pramlintide-treated patients, while increased relative to placebo, was never deemed an overriding issue in the decision regarding approval. By contrast, the division's risk-benefit assessment of pramlintide in DM1 has, all along, been impacted by the increased risk of hypoglycemia relative to insulin alone.

That said, there is a population of patients with DM1 who, despite the best efforts by them and their physicians, cannot achieve desired control of blood sugar with insulin alone. In many instances, glycemic control in these patients is limited by hypoglycemia and weight gain, itself an undesirable, if often inevitable consequence of the increasing doses of insulin used, engendering increased caloric intake, and initiating a vicious cycle toward frank obesity and its sequelae. As an aside, metabolic syndrome is increasingly recognized as a part of the natural history of type 1 diabetes, given our current methods of disease management.

Given the preceding, and taking into consideration the aggregate clinical investigational experience with pramlintide, the following conclusions are offered:

1. Within the population of DM1 patients unable to achieve desired control of glucose, the population studied specifically in 137-155, evidence suggests that a number will likely benefit with the addition of pramlintide to their regimens, some with substantial

reductions in HbA1c, marked reductions in weight, reductions and thus simplification of their prandial insulin requirements, and potentially improvements in quality of life.

2. By implementing a method of use of pramlintide, specifically under the direction of an experienced diabetes medical practice, that involves gradual titration to tolerance of pramlintide with an initial marked reduction in insulin dose, the risk of hypoglycemia with pramlintide/insulin is reduced to a level similar to that with insulin alone.

Pediatric investigations

Amylin has committed to conduct a pharmacokinetic study of Symlin in adolescent patients with DM2. Approximately 12 patients aged 12 to — years will be enrolled in a study to evaluate the pharmacokinetics and relevant pharmacodynamic effects of different subcutaneous doses of Symlin. The sponsor has committed to the submission of a final study report by 30 September 2007.

Risk Management

Risk management for pramlintide, specifically related to the risk of hypoglycemia, by and large an issue in DM1, as discussed above, will include (among other specific measures proposed by the sponsor) the following:

- Placing pramlintide management in the hands of experienced diabetes teams with appropriate patient support. This will be effected by the exclusion of DTC advertising of pramlintide, by limiting detailing to diabetes-focused endocrinology practices, with certified diabetes educators and nurses on staff, and by a health care professional educational program, with on-line accessibility.
- Labeling
  - Warnings regarding the potential for hypoglycemia; Warnings regarding the operation of heavy machinery or engaging in dangerous activities in the immediate post-prandial period, at least during the titration phase
  - Method of use: when Symlin therapy is initiated in DM1 or DM2, the dose of pre-prandial insulin should be reduced by 50%; Symlin should be titrated slowly and dose increased only when there has been no significant nausea for 3-7 days.
  - All insulin and Symlin dose adjustments should be made only as directed by the health care professional
- restricting the indication to patients who cannot achieve desired glycemic goals despite optimal insulin therapy

The sponsor also intends to maintain active surveillance for safety issues arising in post-market use. The central aspect of this program will be a multicenter, controlled, open-label observational study to collect data that characterize the use of symlin following introduction into the marketplace. This will be a formal phase 4 commitment. ⊏

Additionally, the pharmacovigilance program will include a nationwide Call Center.

The details of the risk management plan have been commented on by the Office of Drug Safety. Discussions between ODS and the division have resulted in comments and discussion with the sponsor. A Medication Guide for Symlin has been drafted. Labeling negotiations continue at this time.

Finally, in the approvable letter of October 10, 2001, a potential association between pramlintide treatment an progression of retinopathy was raised, and subsequently the possibility of a phase 4 study to address this was preliminarily discussed with the sponsor. In his original review, Dr. Roman concluded that the data were not supportive of a role of pramlintide in progression of retinopathy. Dr. Roman has re-reviewed this issue and addressed it in a brief memorandum to the NDA dated February 28, 2005 that reaches the same conclusion, with which I fully concur. Briefly, in Dr. Roman's review dated September 6, 2001, table 24 summarized the data on "retinal disorders" by treatment group in trials 111, 122, and 123, in patients with DM2. These were placebo-controlled trials each with three pramlintide-treated groups. The lowest dose studied was 30 mcg TID and the highest dose studied was 150 mcg TID. In one of the nine pramlintide arms (150 TID) across the three studies, retinal disorders were noted in 15 (~10%) patients, and this was twice the number and percent of patients so diagnosed in the placebo group of that trial. In no other pramlintide arm of any of the three trials was there an notable excess of retinal events relative to placebo arm in the respective study. Indeed, in five out of the nine total pramlintide arms in the three studies, the percent of patients experiencing a retinal event on treatment was lower than in the placebo group for the same trial. Of note also is an analysis of "retinal disorder" adverse events in the DM1 patients in the placebo-controlled trials in the pramlintide clinical program showing no difference from placebo. In sum, there is no compelling basis for concern of an effect of pramlintide on the risk for retinopathy in patients with either DM1 or DM2, and no phase 4 study of this issue is therefore indicated.

Recommendation
Pending final labeling, pramlintide injection should be approved to improve glycemic control as an adjunct to mealtime insulin in patients with DM1 who have not achieved desired glucose control despite optimal insulin therapy and as an adjunct to mealtime insulin in patients with DM2 who have failed to achieve desired glucose control despite optimum therapy with insulin with or without sulfonylurea or metformin.

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

/s/

David Orloff
3/10/05 01:21:08 PM
MEDICAL OFFICER

Robert Meyer
3/15/05 05:15:41 PM
MEDICAL OFFICER
I am in substantial agreement with this memo by
Dr. Orloff and plan to approve this drug
per the division's recommendation.

Rhee, H Julie

From: Data, Joann [Joann.Data@amylin.com]

Sent: Tuesday, March 01, 2005 9:18 AM

To: RHEEJ@cder.fda.gov; Zimmer, Donna

Cc: Data, Joann; Kolterman, Orville; Kim, Michael; Wood, John

Subject: Re: Amylin Pharmaceuticals - SYMLIN Medication Guide - Amylin Com ments 28Feb2005 and Updated Phase 4 Commitment Letter

Yes Julie--we agree to the "by" dates unlss something unforeseen were to occur but we would let the Agency know well in advance if something like this were to happen. We plan to keep our commitments.
Joann Data

Sent from my BlackBerry Wireless Handheld

-----Original Message-----
From: Rhee, H Julie <RHEEJ@cder.fda.gov>
To: Zimmer, Donna <Donna.Zimmer@amylin.com>
CC: Data, Joann <Joann.Data@amylin.com>; Kolterman, Orville <Orville.Kolterman@amylin.com>; Kim, Michael <Michael.Kim@amylin.com>; Wood, John <John.Wood@amylin.com>
Sent: Tue Mar 01 06:03:19 2005
Subject: RE: Amylin Pharmaceuticals - SYMLIN Medication Guide - Amylin Com ments 28Feb2005 and Updated Phase 4 Commitment Letter

Hi Donna,

Thanks for your rapid turn around with the Medication Guide. I'll try to let you know sometime today whether or not we have any other revisions.

As for the Phase 4 commitment letter, it does not have the word "by" by the dates. Please let me know whether or not you agree with the following timelines:

Protocol Submission: By April/2005
Study Start: By September/2005
Final Report Submission: By September/2008

Thank you,
Julie

-----Original Message-----
From: Zimmer, Donna [mailto:Donna.Zimmer@amylin.com]
Sent: Monday, February 28, 2005 8:38 PM
To: Rhee, H Julie
Cc: Data, Joann; Kolterman, Orville; Kim, Michael; Wood, John
Subject: Amylin Pharmaceuticals - SYMLIN Medication Guide - Amylin Comments 28Feb2005 and Updated Phase 4 Commitment Letter
Sensitivity: Confidential

Hi Julie,

Attached is a copy and the official cover letter and submission for Amylin's Medication Guide comments to the FDA's
Revision 2(2/25/05). Please note that at the end of the Medication Guide document there is a summary table documenting each change with the corresponding rationale. The reference lines in the summary table correspond with the track change lines in the Medication Guide.

As requested, also attached is a copy of the official updated Phase 4 Commitment Letter for the SYMLIN Observational Study.

Both of these submissions have been sent via Fed-ex today for early morning delivery tomorrow, March 1.

Should you have any questions, please do not hesitate to call.

Donna Zimmer
Regulatory Operations Manager
Amylin Pharmaceuticals, Inc.
9360 Towne Centre Drive, Suite 110
San Diego, California 92121-3030
(858) 642-7268 (Direct)
(858) 334-1268
dzimmer@amylin.com

<<cover.pdf>> <<Amylin_Pharmaceuticals,_dated_28Feb2005_300_pm_PT.doc>>
<<cover.pdf>>

18 USER FEE COVER SHEET (FORM FDA 3397)

Amylin Pharmaceuticals, Inc. has received a small business waiver of the application fee for NDA #21-332 for Symlin™ Injection (pramlintide acetate).

Immediately following are the User Fee Cover Sheet, Form FDA 3397, and the official FDA notification that the waiver has been granted.

Appears This Way
On Original

Review of Action Package for NDA 21-332 Symlin (pramlintide acetate injection)

Matching IND: 39,897

Reviewer: Julie Rhee, HFD-510 Review Date: February 14, 2005
UF_6 due date: March 20, 2005 Drug Class: 1S
Action type: AP 505(b)(1) application
Original NDA submission date: December 7, 2000
Indication:

- Type 1 diabetes, as an adjunct to mealtime insulin in patients who have failed to achieve desired glucose control despite optimal insulin therapy.

- Type 2diabetes, as an adjunct to mealtime insulin in patients who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

Debarment Certification: dated 9/17/04 acceptable
Patent information: Included form FDA 3542a in the 9/17/04 submission, acceptable
Financial Disclosure: 9/17/04 acceptable
Tradename Review: In DMETS review dated 12/21/04, DMETS did not have any objection to the proposed tradename "Symlin". Review comments were forwarded to the sponsor.
Presentation: Originally, the sponsor [redacted]

[redacted] only 5 mL vial presentation is going to be marketed when the NDA is approved. [redacted]

[redacted]

Medication Guide: Because of concern for hypoglycemia and complexity of its usage, it was decided to have Medication Guide replace patient package insert. Proposed draft (dated 2/3/05) is being reviewed by ODS/DSRCS.

ADRA Rev #1 of Action Package for NDA 21-332, Symlin (pramlintide acetate) Inj

Reviewer: Lee Ripper, HFD-102 Date: *December 5, 2003*
Date received in HFD-102: December 1, 2003 UF GOAL : December 17, 2003
Indication: L

Action type: AE RPM: Julie Rhee, 7-6424/Kati Johnson, 7-6380
Drug Classification: 1S Date original NDA received: Dec 8, 2000
505(b)(1) application

Patent Info: Dated 12/1/00, AC. *Dated 6/6/03, appears to include one new patent (511) for drug product, AC*
EER: *AC 11/18/03*
Clinical Inspection Summary: 7/13/01, studies acceptable. *12/03: No new audit reports*
OPDRA review of tradename: Acceptable 3/21/01; *AC 10/28/03 - contains comments on labels and labeling*
DDMAC review of PI: *No review in pkg; OPDRA 10/03 review states that DDMAC finds proprietary name AC from a promotional perspective.*
Debarment statement: 11/7/00 statement AC. *6/6/03 statement AC*
EA: Categorical exclusion
Financial disclosure information/review: *See comment #1 below.*

1. Financial Disclosure: *A significant (greater than 50%) percent of investigators in the covered clinical studies did not provide financial information. I have asked Dr. Roman to look at whether any enrolled sufficient patients to affect the results of the study or had study results that were outside the norm. 12/17/03: Dr. Roman asked the applicant for additional analyses - see his December 12, 2003 review. Financial disclosure information AC.*

2. *The 2001 action letter contained comments on revising the pregnancy category from — to C. The new draft labeling retains the —category. Dr. Alavi is going to wirte a brief review addressing this point. Deficiency needs to be added to letter. 12/17/03: Done*

C:\Data\Wpfiles\N21332AE#2.doc

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

/s/

Leah Ripper
12/18/03 04:44:25 PM
CSO

AMYLIN PHARMACEUTICALS, INC.
9360 Towne Centre Drive
San Diego, California 92121 USA
www.amylin.com
(858) 552-2200 FAX: (858) 552-2212

28 February 2005

David G. Orloff, MD, Director
CDER/FDA
Division of Metabolic and Endocrine Drug Products
c/o Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705

Re: NDA 21-332 SYMLIN® (pramlintide acetate) Injection
Updated Phase 4 Commitment – SYMLIN Observational Study

Dear Dr. Orloff:

Reference is made to an email from Ms. Julie Rhee (Regulatory Project Manager, CDER/FDA), dated 28 February 2005, and previous Phase 4 Commitment submitted to the Agency on 25 February 2005 to Amylin's New Drug Application. In the email from Ms. Rhee, it was requested that Amylin re-submit the commitment letter to conduct a Phase 4 Post-Marketing Observational Study for SYMLIN in a format that states each submission date with month and year only. Amylin has provided the most reasonable dates below, and will do its best to exceed these dates.

The FDA requested information on the SYMLIN Observational Study is provided below:

DESCRIPTION:	SYMLIN Observational Study
Protocol Submission:	April/2005
Study Start:	September/2005
Final Report Submission:	September/2008

Should you have any questions concerning this submission, please contact Michael Kim, Associate Director, Regulatory Affairs, at (858) 458-8499, or Donna Zimmer, Regulatory Operations Manager at (858) 642-7268 or me, either by phone at (858) 642-7324 or by facsimile at (858) 625-0737.

Sincerely,

Joann L. Data, MD
by Donna Zimmer

Joann L. Data, MD, PhD
Senior Vice President
Regulatory Affairs and QA

JLD/dz

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 8, 2005

To: Joann L. Data, M.D., Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** 301-443-9282
Phone number: 858-642-7324	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin (pramlintide acetate) injection

Total no. of pages including cover: 3

Comments:

We have completed our review of your Risk MAP response dated February 24, 2005, which was in response to our February 16, 2005, communication. I have attached our review comments/recommendations (italicized) on your February 24, 2005, submission.

The item numbers correspond to our February 16, 2005, submission. Please let us know whether or not you agree with the recommendations. Thank you.

Document to be mailed: YES ☑ NO

NDA 21-332 Symlin (pramlintide acetate) injection

Date of submission: February 24, 2005

Risk Management plan review comments

Item 3: Regarding the Surveillance Plan: Recommend that adverse event reports of hypoglycemia requiring medical intervention from any source (spontaneous or study reports) be submitted to the Agency in an expedited manner (as 15-day report) for one year and be followed up for pertinent clinical circumstances.

Continue to submit the agreed upon events in an expedited manner for 2 years or as long as the Observational Study remains ongoing unless the Agency notifies the sponsor otherwise (e.g., the Agency determines that they do not add value).

Item 4: The Sponsor's plan to evaluate the SYMLIN RiskMAP should include a plan to evaluate the following 2 components: The extent of off-label use

Submit information on a semiannual basis, even just to give incomplete descriptive data. We also suggest that Amylin look for information regarding indication for use in available databases, in addition to determining prescribing practices through the use of surveys.

Regarding the proposed Observational Study:

Try to include non-targeted physicians in the same approximate proportion as they are of all prescribers. We will be able to offer further comment on the survey after receipt and review of a protocol.

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

/s/

Julie Rhee
3/8/05 02:35:49 PM

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 7, 2005

TO: David Orloff, M.D., Director
Division of Endocrine and Metabolic Drug Products (DMEDP), HFD-510

THROUGH: Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety
(ODS), HFD-400

FROM: Symlin RiskMAP Review Team
Division of Surveillance, Research and Communication Support
(DSRCS), HFD-410
Division of Medication Errors and Technical Support
(DMETS), HFD-420
Division of Drug Risk Evaluation (DDRE), HFD-430

DRUG: Symlin® (pramlintide acetate) Injection

NDA #: 21-332

SPONSOR: Amylin Pharmaceuticals, Inc.

SUBJECT: Amylin's response to the Risk Minimization Action Plan (RMAP) comments received from the Agency; submitted February 24, 2005

PID #: **D050137**

During a teleconference held on February 22, 2005, the FDA and the sponsor discussed modifications to the proposed Risk Minimization Action Plan (RiskMAP). Initial comments Agency were shared with the Sponsor on February 16, 2005.

ODS has reviewed Amylin's responses submitted on February 24, 2005 and have the following comments for each of their responses (*ODS comments in italics*).

Item 1: Agency Comment Regarding Limited Promotion

"The Sponsor should clarify how they will identify appropriate prescriber specialties to which this product will be targeted with specific outreach."

Sponsor's Response
Since SYMLIN will be indicated for use by patients treated with insulin, health care professionals (HCPs) who frequently prescribe insulin will be "targeted". [redacted]

As a second step, Amylin's initial contacts and educational efforts will be directed toward the subset of those [redacted] high insulin prescribers who are in endocrinology and diabetes specialty practices or otherwise evidence good clinical practices related to diabetes care (e.g., practices that utilize certified diabetes educators). [redacted]

[redacted], Amylin does not plan to utilize journal advertisements during its first year of marketing and has no plans for direct to consumer advertising at this time. We will have information available to physicians and other healthcare providers upon request via our medical affairs and medical information groups, as well as via Amylin's website.

ODS comment: This response is acceptable. We support the Sponsor's plan/commitment not to pursue DTC advertising for Symlin at this time.

Item 2: Agency Comment Regarding Education and Outreach

"The strategy that will be utilized to identify the targeted group of physicians for more in-depth medical education should be specified."

Sponsor's Response
The strategy to identify the target group of physicians for medical education is outlined in the response to **Item 1**.

"The two proposed medical education objectives mainly address the incorporation

of SYMLIN into therapy. We recommend the sponsor add a specific objective relating to the safety issues of intolerance (nausea) and hypoglycemia."

Sponsor's Response
Based on the Agency's comments and feedback during the February 22 teleconference, four additional objectives will be added to the proposed medical education objectives:

- Understand the role of SYMLIN dose-titration in limiting tolerability issues (i.e., nausea).
- Understand the role of proper patient selection, patient education, insulin dose-reduction, and appropriate self-blood glucose monitoring in reducing the risk for severe hypoglycemia during SYMLIN therapy.
- Understand that SYMLIN and insulin should not be mixed.
- Understand that syringes should not be reused. Most importantly, syringes that have been used to inject SYMLIN should not be used to inject insulin (or vice versa).

ODS comment: Response is acceptable.

Item 3: Agency Comment Regarding the Surveillance Plan

"Recommend that adverse event reports of hypoglycemia requiring medical intervention from any source (spontaneous or study reports) be submitted to the Agency in an expedited manner (as 15-day report) for one year and be followed up for pertinent clinical circumstances."

Sponsor's Response
Pertinent clinical circumstances surrounding episodes of severe hypoglycemia requiring medical assistance (i.e., episodes requiring glucagon, IV glucose, hospitalization, paramedic assistance, or emergency room admission) will be pursued and reported. As the Agency initially requested, Amylin will report these episodes in an expedited manner (15-day report) for 1 year. During the teleconference, the Agency modified this request to extend expedited reporting to 2 years, or as long as the Observational Study remains ongoing. It was agreed that the utility of the expedited reports would be reviewed 1 year after the launch of SYMLIN to consider appropriate adjustments to the reporting process. If it is concluded that the expedited reports add value, Amylin will continue these reports for an additional year. This timing would be most relevant if the Observational Study is continuing into the second year, so there is a basis for comparison of study-related events vs. the spontaneous event reporting. In addition to these expedited reports, the data regarding medically-assisted hypoglycemia will also be summarized in the mandated, quarterly, periodic safety updates.

Amylin's sales force, medical science liaisons (MSLs), and diabetes clinical liaisons (DCLs who are certified diabetes educators) will be educated regarding the importance of reporting spontaneous events of medically assisted severe hypoglycemia.

ODS comment: The Sponsor should continue to submit the agreed upon events in an expedited manner for 2 years or as long as the Observational Study remains ongoing unless the Agency notifies the sponsor otherwise (e.g., the Agency determines that they do not add value).

Item 4:

"The Sponsor's plan to evaluate the SYMLIN RiskMAP should include a plan to evaluate the following 2 components:

The extent of off-label use

Sponsor's Response
Amylin will specifically train its sales force not to provide any information on off-label use.

As indicated in the response to Item 1, Amylin agrees to use available prescribing databases to identify non-contacted HCPs who prescribe SYMLIN. Amylin will try to capture descriptive information regarding the identity and prescribing practices of "non-targeted" prescribers

However, privacy protection measures restrict the patient information that can legitimately be obtained in this setting. These limitations may preclude precise quantitation. These data will be submitted to the Agency no less frequently than annually during the first 2 years following approval.
Amylin will work to understand off-label use in the market place and to implement the appropriate modifications to the educational process to address this issue. In accordance with the Agency's compliance guidelines, this information will be obtained indirectly from insights gained during educational activities and the activities of the Medical Affairs field force, which includes MSLs and DCLs (certified diabetes educators). Relevant insights will be shared with the Agency as appropriate. Additionally, Amylin will seek to Comments 24 February 2005 enroll "non-targeted" physicians into the planned Observational Study to further evaluate this group's approach to SYMLIN use (see Item 1).

ODS comment: We prefer the Sponsor submit information on a semiannual basis, even just to give incomplete descriptive data. We also suggest that Amylin look for information regarding indication for use in available databases, in addition to determining prescribing practices through the use of surveys.

"Prescribing to physicians outside of those that are targeted by the sponsor as being able to titrate patients carefully to avoid hypoglycemia."

Sponsor's response
Amylin will try to quantify and identify prescribing HCPs from

prescription records. We will work to understand the characteristics of "non-targeted" HCPs who prescribe SYMLIN. In addition to including some of these "non-targeted" HCPs in the Observational Study (see Item 1), Amylin will survey the occurrence of spontaneously reported, medically assisted severe hypoglycemia occurring in the practices of "targeted" versus "non-targeted" prescribing HCPs.

ODS Comment: This response is acceptable.

Regarding the proposed Observational Study

The cover letter stipulates that Amylin commits to conducting a prospective Observational Study. Based on discussion at the teleconference, they plan to identify "non-targeted prescribers

The Sponsor plans to submit a draft protocol within the next few weeks.

ODS Comments: We suggest Amylin try to include non-targeted physicians in the same approximate proportion as they are of all prescribers. We will be able to offer further comment after receipt and review of a protocol.

Symlin RMP Review Team:

Mark Avigan, MD, C.M., Director, DDRE /s/ 03-07-05
Allen Brinker, M.D., M.P.H., Epidemiology Team Leader, DDRE /s/ 03-04-05
Gerald Dal Pan, MD, MHS, Director, DSRCS /s/ 03-03-05
Mary Dempsey, Project Management Officer, ODS IO /s/ 03-07-05
Lanh Green, Pharm.D., M.P.H., SE Team Leader, DDRE
Carol Holquist, RPh, Director, DMETS /s/ 03-03-05
Claudia B. Karwoski, Pharm.D., Scientific Coordinator (Detail) ODS IO /s/ 03-07-05
Toni Piazza-Hepp, Pharm.D., Deputy Director, DSCRS /s/ 03-03-03
Josyln Swann, Pharm.D., Safety Evaluator, DDRE
Kristina Arnwine, Safety Evaluator, DMETS
Denise Toyer, Pharm.D., Deputy Director, DMETS /s/03-03-05

/s/

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400

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

/s/

Mary Dempsey
3/7/05 03:27:20 PM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
3/7/05 03:41:55 PM
DRUG SAFETY OFFICE REVIEWER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: ODS (Room 15B-08, PKLN Bldg.)			Julie Rhee, DMEDP, HFD-510	
DATE February 25, 2005	IND NO.	NDA NO. 21-332	TYPE OF DOCUMENT Response to RMP request	DATE OF DOCUMENT February 24, 2005
NAME OF DRUG Symlin (pramlintide acetate) injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 4, 2005

NAME OF FIRM: Amylin Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW)

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the sponsor's response to your requests/recommendations in your review dated February 11, 2005, and see whether or not they have addressed your concerns adequately. The February 24, 2005, submission is available in EDR. Thank you.

UF_6 due date: March 18, 2005

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 11, 2005

TO: David Orloff, M.D., Director
Division of Endocrine and Metabolic Drug Products (DMEDP), HFD-510

THROUGH: Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety
(ODS), HFD-400

FROM: Symlin RiskMAP Review Team
Division of Surveillance, Research and Communication Support
(DSRCS), HFD-410
Division of Medication Errors and Technical Support
(DMETS), HFD-420
Division of Drug Risk Evaluation (DDRE), HFD-430

DRUG: Symlin® (pramlintide acetate) Injection

NDA #: 21-332

SPONSOR: Amylin Pharmaceuticals, Inc.

SUBJECT: Review of Revised Risk Minimization Action Plan, submitted September 17, 2004

PID #: D040662

1 EXECUTIVE SUMMARY

At the request of the Division of Endocrine and Metabolic Drug Products (DMEDP), the Office of Drug Safety (ODS) reviewed the most recent revised Risk Minimization Action Plan (RiskMAP) for Symlin (pramlintide acetate) injection submitted by Amylin Pharmaceuticals as part of its new drug application (NDA 21-332). Symlin® is a synthetic analogue of human amylin and was developed as a glucose lowering drug to be used in combination with insulin in patients with type 1 and type 2 diabetes.

There are three major safety issues of concern to the ODS and/or DMEDP: the risk of hypoglycemia particularly in patients with type 1 diabetes or patients with a history of gastroparesis, the potential for medication errors, and the potential for off-label use in patients where the benefit/risk profile has not been characterized or demonstrated.

The Symlin RiskMAP as proposed by the Sponsor was intended to address the risk of hypoglycemia and utilizes healthcare professional and patient education, limited promotion, planned surveillance, as well as a plan to evaluate the RiskMAP. ODS has recommendations regarding each of the Sponsor's proposed tools, as well as issues around the formulation that should be addressed in the completed RiskMAP prior to approval/marketing of the product. Specific recommendations to the Sponsor and DMEDP are provided in bulleted format on pages 11-12 of this review.

Labeling and Packaging

The Sponsor proposes to contraindicate use of pramlintide in "patients with a confirmed diagnosis of gastroparesis [ ] and/or hypoglycemia unawareness". We recommend that the contraindication not be limited to patients that are diagnosed by [ ] as the method for diagnosis should be determined by the prescribing physician and/or consulting gastroenterologist. We also recommend [ ] 'should NOT be considered for Symlin therapy as these patients are probably poor candidates for Symlin therapy. The label should include information for patients describing the incompatibility which occurs upon mixing Symlin with other types of insulin.

The Sponsor is [ ]

[ ]

[ ]

Limited Promotion

DMEDP has indicated that the Sponsor plans to detail only a limited number of physicians that specialize in diabetes management. However, the strategy that will be utilized to identify such a targeted group has not been specified. There is also not a clear monitoring or evaluation plan to ascertain the degree and appropriateness of prescribing that may occur outside of these targeted specialties.

Education and Outreach

The Sponsor plans to provide an educational program healthcare professionals and to patients. The strategy that will be utilized to identify the targeted group for more in-depth medical education has not been specified. The two proposed medical education objectives mainly address the incorporation of Symlin into therapy. We recommend the

sponsor add a specific objective relating to the safety issues of tolerance (nausea) and hypoglycemia.

We additionally recommend that a medication guide (MG) serve as a primary educational tool for patients and more detailed educational offerings, [redacted], should be nonpromotional and consistent with the MG. The Patient Information Subcommittee (PISC) has agreed that the product met the regulatory requirements for a Medication Guide and the sponsor has submitted a draft MG to the Agency in December 2004. A separate review of the recently submitted MG will be sent to HFD-510 from DSRCS.

Surveillance Program

The Sponsor should clearly define different manifestations of hypoglycemia and apply such definitions consistently across all proposed studies. The proposed surveillance program will entail a postmarketing observational study (PMOS) and standard pharmacovigilance. The PMOS as proposed will only provide insight into utilization within participating clinical practices and will not reflect the "real world" as the sponsor has suggested. We recommend that the Sponsor recruit a diverse or random sample of clinical practices which would afford a more representative estimate for the clinical outcomes the PMOS study seeks to quantify. We also recommend that adverse event reports of hypoglycemia requiring medical intervention from any source (spontaneous or study) be submitted to the Agency in an expedited manner (as 15-day report) and be followed-up for pertinent clinical circumstances.

Evaluation Plan

The Sponsor proposes to assess process metrics and outcome metrics. However their plan does not present measures of process conformance or process deviation. The quality of their evaluation plan thus cannot be assessed. We recommend the sponsor's evaluation plan include measures to assess prescribing outside of the targeted healthcare professionals as well as prescribing to off-label indications [redacted]

[redacted] The sponsor should also propose a targeted rate of severe hypoglycemia that they consider acceptable in the postmarketing setting. This will aid them and FDA in determining whether pramlintide risk management is acceptably minimizing the risk of hypoglycemia.

2 BACKGROUND

Symlin® (pramlintide acetate) is a synthetic analogue of human amylin. Injectable pramlintide acetate was developed as a glucose lowering drug to be used in combination with insulin in patients with type 1 and type 2 diabetes. Symlin, as adjunctive therapy to insulin, regulates glucose by restoring the physiologic effects of amylin. Thus, Symlin works together with insulin. It does this through three mechanisms: 1) prevention of the

postprandial rise in plasma glucagon; 2) modulation of gastric emptying; and 3) satiety leading to weight loss in patients who are overweight.[1]

The NDA for Symlin was initially submitted to the Agency on December 8, 2000. Following an Advisory Committee in July 2001 and an extensive efficacy and safety review, the application was deemed approvable. The October 10, 2001 Action Letter issued by the Agency listed four clinical deficiencies (truncated below)[2].

- There is an increased risk of severe hypoglycemia relative to insulin alone, particularly in the first month of therapy, in trials of Type 1 and Type 2 diabetes, as well as an increased risk of serious adverse events including motor vehicle accidents and other injuries seen in the patients with Type 1 diabetes. Of particular concern is the potential role of Symlin in the deaths of several patients in the trials in patients with Type 1 diabetes.
- Investigations to date have not excluded a role for Symlin in altering (lowering) the threshold for hypoglycemia awareness or in otherwise impairing patient response to hypoglycemia, a specific concern in light of the hypoglycemia safety issues discussed above.
- An apparent dose-dependent incidence of progression of diabetic retinopathy associated with Symlin therapy relative to insulin alone was observed in study 137-111 in patients with Type 2 diabetes.
- The antibody response to Symlin, produced by using drug substance manufactured by — , has not been adequately characterized.

A supplemental NDA (sNDA) was submitted on June 17, 2003 and according to the medical officer review addressed satisfactorily three of the four clinical deficiencies. It failed to reduce the risk of severe hypoglycemia associated with pramlintide/insulin coadministration relative to insulin treatment alone particularly in patients with type 1 diabetes, and therefore received another approvable action on December 17, 2003. In September, 2003 the sponsor submitted their risk management strategy to address the concerns of severe hypoglycemia. The divisions within the Office of Drug Safety reviewed this material and provided comments regarding the risk management strategy as well as other potential concerns regarding with this product.[3,4]

The sponsor subsequently submitted a complete response on September 17, 2004, including some revisions to the RiskMAP.

3 RISK ASSESSMENT/SAFETY CONCERNS

3.1 Hypoglycemia Risk

[1] See Proposed label, NDA 21-332, submitted September 17, 2004.
[2] See Approvable Letter, NDA 21-332, October 1, 2001.
[3] Toyer, D. Division of Medication Errors and Technical Support, Proprietary Name Review, October 9, 2003.
[4] DDRE & DSRCS, Feedback on RMP for Symlin, October 31, 2003.

Pramlintide acetate treatment as adjunctive therapy to insulin includes an increased risk for episodes of clinically significant nausea and/or vomiting and hypoglycemia. Of particular concern is the likely occurrence of insulin-induced hypoglycemic reactions in patients with nausea/vomiting or slowed gastric emptying (both potential side-effects of pramlintide acetate). In addition, patients with underlying diabetic gastroparesis may be particularly vulnerable to exaggerated slowing of gastric emptying by the agent and thus be at increased risk to develop episodes of nausea and vomiting or hypoglycemia. It is important that with Symlin treatment, the ability to rapidly reverse hypoglycemia by oral intake of glucose containing solutions (e.g. orange juice) be preserved especially in patients with slow gastric emptying.

3.2 Labeling- and Packaging-Related Safety Concerns

The Divisions in the Office of Drug Safety have the following major concerns with Symlin which may lead to confusion and error in dosing:

- We are concerned with the sponsor's proposal [redacted]

- The sponsor proposes to market [redacted] concentrations of Symlin (0.6 mg/mL (vial) [redacted] of

Finally when using the 0.6 mg/mL vial, we note doses such as 15 mcg will be difficult to measure in an insulin syringe since this dose would require administering 0.025 mL. Insulin syringes are not calibrated to deliver such a volume. Conversations with DMEDP have reassured ODS that dosing accuracy within 0.005 mL is acceptable in terms of the efficacy and safety of this product,

but that they will also encourage use of the smaller insulin syringe for administration.

- We are concerned with the proposed units of measure for Symlin. Since Symlin is an injectable product that will be used in conjunction with insulin most patients and health care providers will be familiar with the units of measure provided on insulin syringes. Insulin syringes are calibrated in units; however, Symlin's unit of measure is described as micrograms per milliliter. In order to convert mcg per mL to units that can be measured using an insulin syringe, the sponsor proposes [ ] Even with the use of a conversion table the potential for calculation errors increases since patients and health care providers will have to use three different units of measure (mcg, mL, and units) to calculate the correct dosage.
- The sponsor does not recommend mixing Symlin with any type of insulin in the same syringe. Additionally, the incompatibility that occurs upon mixing with other types of insulin is not visible to the naked eye. Thus, if accidental mixing occurs there will be no way for the patient or health care provider to recognize a problem. It is also common for patients to reuse their insulin syringes due to financial constraints. How can the risk be minimized of syringe reuse and potential mixing of Symlin with other types of insulin?

3.3 Risk of Off-label Use

The DMEDP is concerned about two types of potential off-label use in patients where the benefit/risk profile has not been fully characterized or demonstrated —

[ ]

[ ]

4 RISK MANAGEMENT PLAN

4.1 Overview

The Sponsor proposes several components which include labeling, professional and patient education, surveillance, and limited promotion, during which the Sponsor will limit marketing sales calls to selected physicians. These are described in more detail below.

4.2 Labeling

The sponsor proposes to address the hypoglycemia risk in several sections of the label.

- The following boxed warning outlining the increased risk of severe hypoglycemia when adding Symlin to insulin regimens is being proposed.

DRAFT

- The proposed label also proposes to contraindicate use of pramlintide in "patients with a confirmed diagnosis of gastroparesis —— and/or hypoglycemia unawareness".

Comment: We recommend that the contraindication not be limited to patients that are diagnosed by —— as the method for diagnosis should be determined by the prescribing physician and/or consulting gastroenterologist.

They have also proposed patient selection via labeling.

SYMLIN therapy should be considered in patients with insulin-using type 2 or type 1 diabetes who fulfill the following criteria:

- have failed to achieve adequate glycemic control despite individualized insulin management;
- are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for SYMLIN therapy:

- poor compliance with current insulin regimen;
- poor compliance with prescribed self-blood glucose monitoring;
- have an A1C >9%;
- recurrent severe hypoglycemia requiring assistance during the past 6 months;
- presence of hypoglycemia unawareness;
- —— confirmed diagnosis of gastroparesis;
- require the use of drugs that stimulate gastrointestinal motility;
- pediatric patients.

4.3 RiskMAP Proposal

4.3.1 Limited Promotion

The Sponsor plans to promote Symlin to targeted HCPs skilled in the use of insulin. They do not plan to conduct direct-to-consumer advertising.

Comment: DMEDP has indicated that the Sponsor plans to detail only a limited number of physicians that specialize in diabetes management (e.g., those staffed with dieticians, etc.) However, the strategy that will be utilized to identify such a targeted group has not been specified, as the use of insulin is widespread and not easily linked to one or a few

physician specialties. There is also not a clear plan to ascertain the degree of prescribing that will occur outside of these targeted specialties or practice settings.

4.3.2 Education and Outreach

4.3.2.1 Healthcare Professional Education

Medical education includes a reasonable plan [redacted] education which includes evaluation; however, it is also aimed at the targeted HCP group. [redacted] will also be given to participants.

Comment: As stated above, ODS has concerns about the identification of physicians in such a group; further, healthcare professionals such as nurses and pharmacists are not mentioned, so it is unclear whether HCPs in these professions are to be targeted for education.

The two proposed medical education objectives mainly address the incorporation of Symlin into therapy.

Comment: The sponsor needs to add a specific objective relating to the safety issues of tolerance (nausea) and hypoglycemia, such as:

"Understand the importance of patient selection and instruction to prevent and manage nausea and the risk of severe hypoglycemia".

The [redacted] medical education is offered to all (including nontargeted) HCPs. These groups can request further training from Amylin Medical Science Liaisons and Diabetes Clinical Liaisons. In addition, the sponsor "will engage" various diabetes and diabetes education professional organizations to help them plan how best to communicate with and educate their memberships. Although not clear, it appears that the nontargeted group can [redacted]

4.3.2.2 Patient Education

A Medication Guide (MG) is recommended to instruct patients about the risks of hypoglycemia, how to avoid it, and how to manage it if it should occur. The MG should serve as a primary educational tool for patients and more detailed educational offerings, [redacted] should be nonpromotional and consistent with the MG. Supplemental patient education materials, such [redacted] should include the MG. HCPs who counsel and educate patients receiving Symlin should also be encouraged to utilize the MG.

As the boxed warning states, "Patient selection, patient instruction, and insulin dose adjustments are critical elements [redacted] At a meeting between HFD-180 and ODS on 12/7/04, ODS suggested that a Medication Guide (MG) would be an appropriate tool for this drug product. A MG is a form of patient labeling that is required to be dispensed with each prescription as per 21CFR 208. Content and format are also

specified in the regulation. Drugs that would qualify for a MG must meet one of the following criteria:

- patient labeling could help prevent serious adverse effects,
- the drug product has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product;
- the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The Patient Information Subcommittee (PISC) met January 18, 2005 to discuss the appropriateness of a Medication Guide for Symlin and agreed that the product met the regulatory requirements for a Medication Guide.

The sponsor has been notified of FDA's desire for development of the MG, and they submitted a draft MG to the Agency in December 2004. A separate review of the recently submitted MG will be sent to HFD-510 from ODS/DSRCS.

4.4 Proposed Surveillance Program

The proposed surveillance program will entail a postmarketing observational study (PMOS) and standard pharmacovigilance.

General comment: It in unclear how the sponsor will categorize episodes of "severe hypoglycemia."

The Sponsor should clearly define different manifestations of hypoglycemia and apply such definitions consistently across all proposed studies and patient educational material.

4.4.1 Post-Marketing Observational Study

The Sponsor is proposing to collect data relevant to the safety, tolerability, and effectiveness of Symlin in the "real world" clinical practices of those skilled in the management of diabetes through a PMOS.

Comment: We note the problematic juxtaposition of "real world" and "skilled clinical practices" as the setting for the study. Although the sponsor's RiskMAP would appear to limit prescribing to diabetologists and other clinicians who specialize in diabetes and to whom the company will promote the product, the "real world" will undoubtedly include patients who receive Symlin through clinicians outside of those classified as "skilled" by the sponsor. Thus, the PMOS study as proposed will only provide insight into utilization within participating clinical practices that are skilled. The sponsor does not describe

how these practices will be identified or recruited. It could be argued that a more random sample of clinical practices would afford a more representative estimate for the clinical outcomes the PMOS study seeks to quantify. Although the sponsor outlines the desire to recruit [ ] clinical sites and further provides power calculations around this sample size, it is the representativeness of the sites, in combination with the absolute number, that will provide the best estimate of "real world" practices.

4.4.2 Standard Pharmacovigilance Program

4.4.2.1 Safety Surveillance

The protocol includes a commitment from the Sponsor to conduct standard pharmacovigilance for the Symlin product through collection and review of spontaneous adverse event reports and to "determine the rates of known events (expected) relative to the frequency observed in clinical trials."

Comment: The primary role of traditional, spontaneous adverse event reports-based pharmacovigilance is qualitative identification of rare and unexpected safety concerns associated with a drug product. Certain epidemiologic methods can sometimes be employed to 1) further assess a causal association between drug and event and 2) provide an estimate for the frequency of the adverse event. In contrast to the sponsor's position, spontaneous systems are not designed to assess the rates of known and expected adverse effects of drug therapy. However, adverse event reports may be informative in ascertaining the circumstances leading to hypoglycemia in specific high risk groups or identifying if there is difficulty in reversing hypoglycemia by oral intake of glucose-containing solutions in patients with delayed gastric emptying.

4.4.2.2 Call Center

The sponsor proposes a 1-800-based Call Center where patients and HCPs can discuss questions regarding Symlin.

Comment: Given the complex nature of adding Symlin to a standing regimen of insulin, it seems prudent to have a call center where both patients and clinicians can call to seek clarity for use of Symlin.

4.5 Evaluation Plan

The evaluation component of the RiskMAP is proposed to assess:

[ ]

The sponsor proposes the process metrics summarized the table (reproduced[5]) below.

Table 1: Process Metrics Associated With Foundational Tools/Specific Program Objectives.

Tool	Metrics	Documentation of Compliance With Target
Labeling		Package Insert
Call Center	At launch, Call Center personnel trained on product information for Symlin, including handling Adverse Event and Product Complaint reporting. At launch, toll-free numbers would be operational.	Call Center
Pharmacovigilance	submitted in compliance with regulatory obligations.	Report of the Safety Monitoring
Observational Study		

Comment: The table above summarizes the content of the Symlin RiskMAP and does not present measures of process conformance or process deviation. It could be anticipated that a process measure would include quantitative attributes, such as an estimate of the frequency of severe, Symlin-associated hypoglycemia observed in a representative sample of Symlin users during early therapy and/or an estimate of the frequency of Symlin prescriptions from clinicians outside the "skilled" population that the sponsor seeks to be the major Symlin prescribers. We further recommend the sponsor's evaluation plan include measures to assess prescribing outside of the targeted healthcare professionals as well as prescribing to off-label indications

4.5.2 Outcome Metrics

The Sponsor proposes to determine the frequency of severe hypoglycemia through two sources:

- spontaneously reported adverse events
- The safety summary derived from stimulated adverse event reporting in the PMOS

[5] NDA 21-332 Complete Response (Sept 2004), Risk Minimization Action Plan; p12.

Comment: The Sponsor does not specify a rate of hypoglycemia postmarketing that would be considered excessive and indicative of a safety problem.

4.5.3 Report on RiskMAP to FDA

The Sponsor proposes to report annually on the overall program and to discuss the impact of the RiskMAP as well as potential modifications that might be made after approximately 2 years after launch.

Comment: Reporting to the Agency on the overall program should occur more frequently than annually, at least for the first 2 to 3 years of marketing. Consideration might be given to semi-annual reporting for the first 2-3 years of marketing. Recommendations for modifications in the RiskMAP will be provided by the Agency at such time as sufficient information regarding the RiskMAP performance is known.

5 CONCLUSIONS/RECOMMENDATIONS

There are three major safety issues of concern to the ODS and/or DMEDP: the risk of hypoglycemia particularly in patients with type 1 diabetes or patients with a history of gastroparesis, the potential for medication errors, and the potential for off-label use in patients where the benefit/risk profile has not been characterized or demonstrated.

The Symlin RiskMAP as proposed by the Sponsor was intended to address the risk of hypoglycemia and utilizes healthcare professional and patient education, limited promotion, planned surveillance, as well as a plan to evaluate the RiskMAP. ODS has identified issues regarding each of the Sponsor's proposed tools, as well as issues around the formulation that should be addressed in the completed RiskMAP prior to approval/marketing of the product.

- Regarding Labeling and Packaging:
  - Recommend that the contraindications not be limited to patients that are diagnosed by [
  - [
  - Limit the availability of Symlin to a single concentration and single unit of measure (e.g., units/mL).
  - If a single concentration and/or single unit of measure are not required by the sponsor then a dosing conversion chart is needed in the DOSAGE and ADMINISTRATION section of the professional insert and in the instructions for use section of the patient labeling to avert calculation errors.
  - Include warnings in the PRECAUTIONS section, information for patients subsection and in the DOSAGE and ADMINISTRATION section of the physician insert labeling describing the incompatibility which occurs upon mixing Symlin with other types of insulin. A similar warning should appear

in the patient instructions of use section of the medication guide. Additionally, patients and caregivers should be instructed not to reuse insulin syringes based on this incompatibility.

- Regarding Limited Promotion
  - The Sponsor should clarify how they will identify appropriate prescriber specialties to which this product will be targeted with specific outreach.
- Regarding Education and Outreach:
  - A Medication Guide is recommended and should serve as a primary educational tool for patients. The MG should instruct patients about the risk of hypoglycemia, how to avoid it, and how to manage episodes of hypoglycemia should they occur. The PISC has agreed that the product meets the regulatory requirements for a Medication Guide.
  - The strategy that will be utilized to identify the targeted group of physicians for more in-depth medical education should be specified.
  - The two proposed medical education objectives mainly address the incorporation of Symlin into therapy. We recommend the sponsor add a specific objective relating to the safety issues of intolerance (nausea) and hypoglycemia.
- Regarding the Surveillance Plan
  - The Sponsor should clearly define different manifestations of hypoglycemia and apply such definitions consistently across all proposed postmarketing studies and patient educational material.
  - Recommend that the Sponsor recruit a diverse or random sample of clinical practices which would afford a more representative estimate for the clinical outcomes the PMOS study seeks to quantify
  - Recommend that adverse event reports of hypoglycemia requiring medical intervention from any source (spontaneous or study reports) be submitted to the Agency in an expedited manner (as 15-day report) and be followed-up for pertinent clinical circumstances.
- Regarding the Evaluation Plan
  - The Sponsor's plan to evaluate the Symlin RiskMAP should include a plan to the evaluate the following 2 components:
    - The extent and appropriateness of off-label
    - Prescribing by physicians outside of those that are targeted by the sponsor as being able to titrate patients carefully to avoid hypoglycemia.
  - The sponsor should propose a rate of severe hypoglycemia that they consider appropriate in the postmarketing setting and what interventions they will undertake if that rate is exceeded.

Symlin RMP Review Team:
Allen Brinker, M.D., M.P.H., Epidemiology Team Leader, DDRE
Mary Dempsey, Project Management Officer, ODS IO
Lanh Green, Pharm.D., M.P.H., SE Team Leader, DDRE
Claudia B. Karwoski, Pharm.D., Scientific Coordinator (Detail) ODS IO
Toni Piazza-Hepp, Pharm.D., Deputy Director, DSCRS
Josyln Swann, Pharm.D., Safety Evaluator, DDRE
Kristina Arnwine, Safety Evaluator, DMETS
Denise Toyer, Pharm.D., Deputy Director, DMETS

/S/

Gerald DalPan, MD, MHS, Director, DSRCS

/S/

Carol Holquist, RPh, Director, DMETS

/S/

Mark Avigan, MD, C.M., Director, DDRE

/S/

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400

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

/s/

Mary Dempsey
2/11/05 10:04:39 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/11/05 10:24:24 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Carol Holquist
2/11/05 01:22:41 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
2/11/05 02:13:58 PM
DRUG SAFETY OFFICE REVIEWER

Anne Trontell
2/11/05 05:12:55 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 18, 2005

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Julie Rhee, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review #2 of Medication Guide for Symlin (pramlintide acetate), NDA 21-332

Background

The sponsor submitted a revised draft Medication Guide (MG) for Symlin (pramlintide acetate), NDA 21-332, February 3, 2005, in response to the January 25, 2005, teleconference to discuss their December 17, 2004, draft Medication Guide. The Patient Information Subcommittee (PISC) met January 18, 2005 to discuss the appropriateness of a Medication Guide for Symlin and agreed that the product met the regulatory requirements for a Medication Guide. The PISC also recommended that the MG should be shortened, simplified, focus on Symlin, emphasize the important risk information, and behaviors to avoid while using the product (once these are clearly identified in the professional information (PI)), and that the *Instructions for Use* be simplified and incorporated in the MG.

See the attached Medication Guide for our specific comments and revisions. We have simplified the wording, made it consistent with the PI, and removed unnecessary information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. The revisions are based on draft labeling submitted by the sponsor on February 2, 2005, and revised by the review division February 11, 2005. The Medication Guide should always be consistent with the prescribing information. All

future changes to the PI should also be reflected in the MG.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

6 Page(s) Withheld

_____ § 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/

Jeanine Best
2/18/05 02:45:09 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/18/05 03:25:37 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: ODS (Room 15B-08, PKLN Bldg.)			Julie Rhee, DMEDP, HFD-510	
DATE February 8, 2005	IND NO.	NDA NO. 21-332	TYPE OF DOCUMENT Proposed MedGuide	DATE OF DOCUMENT February 3, 2005
NAME OF DRUG Symlin (pramlintide acetate) injection	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE February 23, 2005
NAME OF FIRM: Amylin Pharmaceuticals, Inc				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the proposed Medication Guide (submitted on February 3, 2005) and provide your inputs. I am also attaching a copy that includes revisions made by our Medical Officer, Dr. Roman Dragos, for your information.

Electronic copy of the February 3 submission is available in EDR. If you need a Word copy with Dr. Draos's revisions, please let me know. Thank you.

This is an NME application and its PUDFA due date is March 20, 2005.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Rhee, H Julie

From: Rhee, H Julie
Sent: Tuesday, February 08, 2005 10:28 AM
To: Rhee, H Julie
Subject: FW: fyi--Symlin risk management plan

-----Original Message-----
From: Roman, Dragos
Sent: Tuesday, February 08, 2005 9:02 AM
To: Rhee, H Julie
Cc: Orloff, David G
Subject: FW: fyi--Symlin risk management plan

Julie,
Could you please forward both versions to ODS? In my version I tried to simplify the writing and present the main ideas as "bullets" with the secondary clarifications in parentheses. I also tried to be explicit to how the treatment (in particular the titration) is being done, following the recommendations that came at the PISC meeting. In addition, I emphasized in most parts that it is the doctor who will make the decisions with sentences like : [illegible] to make the Medguide consistent with the label which stresses repeatedly that the physician will make all pramlintide and insulin changes. I think that by following this path we can accomplish two goals: 1) inform the patient of the complexity of the treatment and 2) establish a need to contact the physician for any management changes and safety issues.

Finally, I tried to live the information at a descriptive level so the patient does not need to interpret anything but rather know when to call (i.e. at any step that requires a change). I also re-arranged some paragraphs that fit better under different headings. As this is a very complex set of instructions, I acknowledge that it is difficult to reach a perfect balance between brevity and being informative. Looking forward to any further suggestions.

Dragos

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

/s/

Julie Rhee
2/8/05 10:48:41 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 28, 2005

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Julie Rhee, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Medication Guide for Symlin (pramlintide acetate), NDA 21-332

Background

The sponsor submitted a Medication Guide (MG) for Symlin (pramlintide acetate), NDA 21-332, December 17, 2004 in response to a request from HFD-510. The Patient Information Subcommittee (PISC) met January 18, 2005 to discuss the appropriateness of a Medication Guide for Symlin and agreed that the product met the regulatory requirements for a Medication Guide. The PISC also recommended that the MG should be shortened, simplified, focus on Symlin, emphasize the important risk information, and behaviors to avoid while using the product (once these are clearly identified in the professional information (PI)), and that the *Instructions for Use* be simplified and incorporated in the MG.

The Division of Medication Errors and Technical Support (DMETS) will be providing further comments in a separate document on [redacted]

Comments and Recommendations

1. Follow the format and content guidelines specified in 21CFR 208 regulations for Medication Guides.
2. The Flesch-Kincaid Reading Level for the proposed Symlin Medication Guide was measured at 10.2 (corresponding to grade level) and the Flesch Reading Ease measured at 49.2%. For optimal comprehension, patient materials should be written at less than an 8th grade reading level, with a reading ease of at least 60% (60% corresponds with an 8th grade reading level). There are many opportunities to simplify the vocabulary and sentence structure in this MG.

About 50% of American adults (90 million people) have difficulty understanding and acting upon health information, notes the Institute of Medicine (IOM) in its April 2004 report, "Health Literacy: A Prescription to End Confusion." The IOM defines health literacy as "The ability to obtain, process, and understand basic health information and services needed to make appropriate health decisions... It also depends upon the skills, preferences, and expectations of health information and care providers: our doctors; nurses; administrators; home health workers; the media; and many others. Health literacy is not to be confused with the ability to read, although at least a quarter of Americans read at the fifth grade level or below, while the majority of patient education materials are written at or above the 10th-grade level

3. C

J

We will be glad to review a revised and simplified MG for Symlin.

Please let us know if you have any questions.

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

/s/

Jeanine Best
1/28/05 11:34:11 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/28/05 05:07:02 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Rhee, H Julie

From: Rhee, H Julie
Sent: Friday, February 25, 2005 1:13 PM
To: 'Zimmer, Donna'
Cc: Data, Joann; Kolterman, Orville; 'mkim@amylin.com'
Subject: Retinopathy study

Hi Donna,

This is to let you know that we've decided not to request retinopathy study as a Phase 4 commitment.

Julie

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: February 16, 2005

To: Donna Zimmer	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** 301-443-9282
Phone number: 858-642-7268	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin

Total no. of pages including cover: 3

Comments:

Attached are Risk management review comments. Please let me know when you expect to respond.

Thank you.

Document to be mailed: YES ☑ NO

1. See the general comments (1) and (3) under the **"Vial Label"**.
2. Revise the sentence to read "1 mL contains: 0.6 mg pramlintide (as acetate), 2.25 mg metacresol, D-mannitol, acetic acid and sodium acetate"
3. Revise the number of vials in the carton to read "4 x 5 mL vials" instead of 1

Appears This Way
On Original

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

/s/

Julie Rhee
2/14/05 04:22:16 PM
CSO

Rhee, H Julie

From: Rhee, H Julie

Sent: Thursday, February 03, 2005 2:26 PM

To: 'dzimmer@amylin.com'

Cc: 'Data, Joann'; 'Brokob, Carolyn'

Subject: Symlin carton/container label comments

Hi Donna,

Here are our recommendations for Symlin carton and vial labels. Please submit the revised labels to the electronic document room.

Please give me a call if you need any further clarification.

Thanks,
Julie

NDA 21-332 Symlin (pramlintide acetate) injection

Date of submission: September 17, 2004

Comments for vial and carton labels

Vial Label:

1. To increase the prominence of the product strength and concentration, the concentration "0.6 mg/mL" should be moved to under the established name. So, it would read:

Symlin
(Pramlintide acetate) Injection
0.6 mg/mL

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

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

Carton Label:

1. See the general comments (1) and (3) under the "**Vial Label**".

2. Revise the sentence to read "1 mL contains: 0.6 mg pramlintide (as acetate), 2.25 mg metacresol, D-mannitol, acetic acid and sodium acetate"

3. Revise the number of vials in the carton to read "4 x 5 mL vials" instead of

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 00-0230-3
September 30, 2004	December 18, 2004 **PDUFA DATE:** March 18, 2005	

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Julie Rhee
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME: **Symlin** (Pramlintide Acetate Injection) 0.6 mg/mL in 5 mL vials, **NDA#:** 21-332	**NDA SPONSOR:** Amylin Pharmaceuticals

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary names, Symlin, [illegible] DMETS considers this a final decision. However, if the approval of the NDA is delayed beyond 90 days the firm should be notified that this name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS also recommends implementation of the labeling revisions outlined in the Section III of this review.

3. DDMAC finds the proprietary name, Symlin, acceptable from a promotional perspective.

/S/

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 24, 2004

NDA#: 21-332

NAME OF DRUG: **Symlin** (Pramlintide Acetate Injection)
0.6 mg/mL in 5 mL vials,
[ ]

NDA HOLDER: Amylin Pharmaceuticals

I. INTRODUCTION:

This consult is in response to a September 30, 2004 request, by the Division of Metabolic and Endocrine Drug Products, to re-review the proposed proprietary drug name, Symlin, regarding potential name confusion with approved proprietary and established drug names as well as pending names. DMETS initially reviewed the proprietary name Symlin and had no objections to the use of the name (see DMETS consult # 00-0230 dated March 21, 2001 and consult # 00-230-1 dated October 28, 2003). In addition, the container labels, carton and package insert labeling, [ ] were reviewed for possible interventions in minimizing medication errors. Per the Approvable letter, all label and labeling issues (including those contained in DMETS' October 28, 2003 review) were deferred until the current review cycle. Therefore, although revised labels and labeling were submitted for review during this cycle, the revisions did not reflect any of DMETS' concerns contained in the October 28, 2003 review.

PRODUCT INFORMATION

Symlin (pramlintide acetate) is a synthetic analogue of human amylin, a pancreatic beta-cell hormone that is secreted along with insulin. Amylin and insulin concentrations are deficient in patients with type I and type II diabetes. Amylin, along with insulin, promotes clearance of nutrients from the plasma into peripheral tissues for utilization and storage. In clinical trials, Symlin has been shown to contribute to improve glucose control through reduction of postmeal glucagon concentrations and modulation of the appearance of meal-derived nutrients (including glucose) into the peripheral circulation. Symlin is indicated as [ ] For type I diabetes mellitus (DM), the initial dose is 30 micrograms (mcg) administered subcutaneously, and the number of Symlin doses per day should be based upon frequency of meals and snacks, not to exceed 4 doses per day. For type II DM, the initial dose is 120 micrograms, based upon frequency of meals and snacks, not to exceed 3 doses per days. Symlin should be given within 15 minutes before meals. [ ] Symlin is also supplied as a 0.6 mg per mL sterile injection in 5 mL vials for use with a syringe.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Symlin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Symlin. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the proprietary name Symlin from a promotional perspective.

2. The Expert Panel identified one proprietary name, Xyrem, as having the potential for confusion with Symlin. The available dosage form and the usual dosage are listed in Table 1 (see below).

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Symlin	Pramlintide acetate injection 0.6 mg/mL in 5 mL vials	Type 1 Diabetes: 30 mcg SQ 15 minutes before a meal, not to exceed 4 doses per day. Type 2 Diabetes: 120 mcg SQ 15 minutes before a meal, not to exceed 3 doses per day.	N/A
Xyrem	Gamma Hydroxybutyrate Oral Solution 500 mg/mL	2.5 grams by mouth at bedtime followed by 2.5 grams 2.5 to 4 hours later titrated up to a maximum of 9 grams/day in divided doses	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Symlin were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

Prescription analysis studies were conducted during the initial ODS review and were not repeated during this review.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Symlin, the primary concerns related to look-alike and sound-alike confusion with Xyrem. The name, Xyrem, was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Symlin in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation. In addition, Xyrem is only available through restricted distribution.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

The sponsor received an approvable letter on December 17, 2003. In a discussion with the project manager, Julie Rhee, on November 16, 2004, DMETS was informed that all label and labeling issues received prior to the issuance of the approvable letter were deferred until the next review cycle. Label and labeling comments contained in the ODS consult # 00-0230-1 dated October 28, 2003 review were not forwarded to the sponsor at that time. Although revised labels and labeling were submitted in this consult, DMETS' concerns have not been addressed. Additionally, upon review of the revised label and labeling, DMETS still has the same label and labeling concerns as previously noted. Therefore our previous comments are repeated below for the Division's convenience.

A. General Comments (5 mL)

1. We have some concerns about the availability of [redacted] 0.6 mg/mL) of this product for use by patients. We believe that only one strength should be available, thus resulting in only one volume of injection being delivered regardless of the packaging formulation used ([redacted] vial). For example, [redacted]

   DMETS notes that there could be difficulty in measuring doses [redacted] to 60 mcg depending upon the type of syringe used. Please comment.

2. We recommend specifying the type of syringe (e.g., insulin, tuberculin, etc) that should be used when administering Symlin 0.6 mg/mL.

   The sponsor includes a conversion table that helps patients and/or healthcare practitioners convert mcg/mL doses to units using a U-100 syringe. This increases the risk of medication errors since patients are now dealing with three different types of measurement (mcg, mL, and units). Additionally, DMETS questions whether patients will be able to accurately measure increments from 2.5 units to 7.5 units (0.025 mL to 0.075 mL) using a U-100 syringe. These units correspond to doses less than 60 mcg. Usually, the increments on U-100 syringes are **numbered** at 10 unit increments (i.e., 10 units, 20 units, through 100 units) and **marked** (hash mark no numbers) at 2 unit increments. Therefore, a patient would need to estimate 2.5 units by placing the plunger between the 2 unit and 4 unit hash mark. This would not be an accurate measure of 2.5 units. Although, this measurement could be made using a U-50 syringe or tuberculin syringe, the sponsor does not make this distinction in the labeling. Please comment.

3. Relocate and increase the prominence of the product strength and concentration (i.e., 0.6 mg per mL [ ]) so that it appears immediately following the proprietary and established name. For example:

   Symlin
   (Pramlintide Injection)
   0.6 mg/mL

4. Each mL of Symlin contains 0.6 mg (vial) [ ] of pramlintide, not pramlintide acetate. We recommend revising the established name as follows:

   Pramlintide Injection

5. Delete the trailing zero on the container labels, carton and package insert labeling (e.g., 1.0 mg) since it may be misinterpreted as 10 if the decimal point is indistinguishable. Revise accordingly.

6. DMETS recommends that the route of administration is spelled out and not abbreviated (e.g., Subcutaneous Use Only instead of SC Use Only). Revise accordingly.

7. Revise the ' [ ] to read "Each mL contains pramlintide acetate equivalent to xx mg pramlintide."

B. Container Labels (5 mL Trade and Professional Sample Vial)

1. See General Comments A-3, A-4, A-6, and A-7.

2. DMETS recommends inclusion of the phrase, "Usual Dosage:" before the statement "See enclosed package insert."

C. Container Labels [ ]

See General Comments A-3 through A-6.

D. Carton Label (5 mL Trade and Professional Sample Vial)

1. General Comments A-3, A-4, A-7, and Comment B-2.

2. We note that the conversion table for using insulin syringes is only included in the package insert labeling and is not included in the patient information sheet. However, if the package insert is removed from the carton the patient would not have access to this information. We recommend that this information be included on the carton labeling.

E. Carton Label [ ]

See General Comments A-3, A-4, A-6 through A-7, and Comment B-2.

F. Shipping Carton [ ]

See General Comments A-3, A-4, A-7, and Comment B-2.

G. Package Insert Labeling

1. See General Comment A-2, A-4 through A-7.

2. DMETS recommends revising the term 'µg' to read 'mcg.' DMETS has received postmarketing medication error reports indicating that the term 'µg' has been misinterpreted as milligrams. Revise accordingly throughout the text of the insert.

3. Dosage and Administration Section

   a. Administration and Regimen Subsection. DMETS questions the need for inclusion of information relating to the visual inspection of insulin especially since Symlin should not be mixed with any type of insulin. Revise accordingly.

   b. Type 1 Diabetes Subsection. DMETS recommends that the statement "The starting dose of SYMLIN is 15 µg, administered immediately prior to meals, up to a maximum of 4 times a day." Be relocated before the statement " Dose titration from 15 µg up to 60 µg in 15 µg increments as tolerated is advised.

4. How Supplied Section

   a. Information relating to administration of Symlin administration 0.6 mg/mL (5) mL should be relocated to the Dosage and Administration section of the package insert.

   b. Table 5, entitled 'Conversion of Symlin Dose to Insulin Unit Equivalents' should contain an introductory/qualifying statement such as 'If you have insulin U-100 syringes available then you can use this syringe to measure Symlin doses by using...

c. Table 5 includes a column that contains the volume (cc or mL). DMETS does not understand the need for this column in this conversion table since patients will likely only use the 'units increment' on a U-100 syringe.

H. Patient Information Sheet

DMETS' comments will be included in the Division of Surveillance, Research, and Communication Support's review of the Patient Information Sheet.

I.

L

2.

a.

b.

c.

7

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

V. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proposed proprietary names, Symlin [redacted]. DMETS considers this a final decision. However, if the approval of the NDA is delayed beyond 90 days the firm should be notified that this name with its associated labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS recommends implementation of the label and labeling comments outlined in Section III of this review.

3. DDMAC finds the proprietary name Symlin acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

/S/

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Linda Kim-Jung, PharmD
Acting Team Leader
Division of Medication Errors and Technical Support

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

/s/

Kristina Arnwine
12/21/04 03:44:50 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
12/21/04 04:18:09 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/21/04 05:44:51 PM
DRUG SAFETY OFFICE REVIEWER

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/1/04

NDA 21-332

Amylin Pharmaceuticals, Inc.
Attention: Joann L. Data, M.D., Ph.D.
Senior Vice President, Regulatory Affairs and Quality Assurance
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121-3030

Dear Dr. Data:

We acknowledge receipt on September 20, 2004 of your September 17, 2004, resubmission to your new drug application for Symlin (pramlintide acetate) injection.

We consider this a complete, class 2 response to our December 17, 2003, action letter. Therefore, the user fee goal date is March 20, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted during the September 7, 2000, pre-NDA meeting for the pediatric study requirement for this application.

If you have any question, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

/S/

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Julie Rhee
10/1/04 09:26:55 AM
Signed for Dr. David Orloff

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 21, 2004
TIME: 3:00 – 4:00 pm
LOCATION: Parklawn Building 3rd floor c/r "Chesapeake"
APPLICATION: NDA 21-332
DRUG NAME: Symlin (pramlintide acetate) injection
TYPE OF MEETING: General
MEETING CHAIR: David Orloff, M.D.
MEETING RECORDER: Julie Rhee
FDA ATTENDEES:

David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products
Roman Dragos, M.D., Medical Officer, DMEDP
Robert Misbin, M.D., Medical Officer, DMEDP
Eddie Gabry, M.D., Medical Officer, DMEDP
Todd Sahlroot, Ph.D., Statistical Team Leader, DMEDP
Lee Pian, Ph.D., Statistician, DMEDP
Julie Rhee, Regulatory Project Manager, DMEDP

EXTERNAL CONSTITUENT ATTENDEES (Amylin Pharmaceuticals):

Ginger Graham, Chief Executive Officer
Dan Bradbury, Chief Operating Officer
Alain Baron, M.D., Senior Vice President, Clinical Research
Joann Data, M.D., Ph.D., Senior Vice President, Regulatory Affairs & QA
Dwayne Elwood, Senior Vice President, Marketing
Orville Kolterman, M.D., Senior Vice President, Clinical Affairs
Joerg Limmer, D.V.M., Senior Director, Medical Affairs
Karen Lutz, Ph.D., Senior Manager, Medical Writing
Larry Shen, Senior Director, Biometrics
Jean Tempke, Associate Director, Project Management
Yan Wang, Ph.D., Senior Statistician
Donna Zimmer, Regulatory Operations, Manager

Amylin Consultants:

[

]

BACKGROUND:

The sponsor submitted an NDA for Symlin (pramlintide acetate injection) on December 7, 2000. The proposed indication is [redacted]

The Agency issued two approvable letters on October 10, 2001, and December 17, 2003. Deficiencies in the October 10, 2001, letter related to unresolved safety issues such as increased risk of (i) severe hypoglycemia relative insulin alone, especially in the first month of therapy, in patients with type 1 or type 2 diabetes, (ii) serious adverse events including motor vehicle accidents and other injuries seen in patients with type 1 diabetes (potentially related to hypoglycemia), and (iii) potential lowering of the threshold for hypoglycemia awareness.

The sponsor responded to the October 10, 2001, approvable letter on June 16, 2003. The Agency issued another approvable letter on December 17, 2003, because the issue of increased risk of hypoglycemia with pramlintide/insulin relative insulin alone had not been fully resolved and because, additionally, essentially equivalent glycemic control was achieved with insulin versus insulin plus pramlintide in the clinical trial submitted in response to the first AE letter.

The sponsor requested a type C meeting on May 27, 2004, to discuss necessary additional information to gain an approval of Symlin. The sponsor also wanted to discuss patient population, education for use of Symlin in patients and physicians, and use of Symlin in patient with type 2 diabetes. Meeting background package was submitted on June 21, 2004.

DISCUSSION POINTS:

1. The Division stated that there seems to be enough data for patients with type 2 diabetes and is willing to consider approving Symlin as an adjunct to insulin for use in patients with type 2 diabetes as a single indication. If the sponsor wishes to proceed along this path, they should propose same and submit a response accordingly to the latest AE letter.

2. The following issues were identified by FDA as requiring resolution prior to approval for use in patients with type 1 diabetes:

    - The increased risk of hypoglycemia with pramlintide/insulin compared to insulin alone is not fully obviated by the revised method of initiation of therapy used in the study reviewed on the second review cycle. The reduction in the incidence of severe hypoglycemia in the open-label clinical trial 137-155 was acknowledged albeit it occurred in the setting of a non-controlled clinical trial. Thus, strictly speaking, there are no data to permit precise quantitation of the hypoglycemia risk of pramlintide/insulin versus insulin alone.

- The Division wishes to discuss the conduct of a new randomized, placebo-controlled, open-label clinical trial in patients with type 1 diabetes comparing pramlintide plus insulin vs. insulin alone was recommended. In the new study, the following information would be gleaned from an adequate and well-controlled trial in the broad target population who might attempt therapy with this agent: efficacy in terms of HbA1c reduction, the absolute risk of hypoglycemia, the overall effect of treatment(s) on weight, insulin dose, and quality of life measured with validated instruments.

- The sponsor made several points, among them:

  - Blinded, placebo-controlled trials of insulin in combination with agents that themselves confer direct hypoglycemic risk and/or enhance the hypoglycemic risk of a given dose of insulin present great problems with regard to establishment of superior efficacy of the combination regimen as well as with regard to the management of hypoglycemic risk among patients in the trial.
  - A group of motivated, well-managed patients with type 1 diabetes exists who desire greater glycemic control but who are stymied by weight gain, hypoglycemia, or complexity of their insulin regimen who are candidates, after consultation with their physicians, for pramlintide.
  - Sponsor has uncontrolled quality of life data supporting a positive effect of pramlintide when added to insulin in patients with type 1 diabetes.
  - The additional daily injection(s) required with use of pramlintide are tolerated by patients who perceive benefits of the treatment (e.g., weight loss, better glycemic control compared to baseline).
  - The pharmacologic activity of pramlintide renders a "smoothing out" or post-prandial glucose fluctuations that simplifies bolus insulin dosing, a reduction in insulin dose, and in many patients, weight loss compared to insulin alone.
  - Optimum safe and effective use of insulin requires collaboration between patient, physician, and other medical professionals. To the extent that use of insulin is an "art" so too is the use of pramlintide plus insulin. As for new insulins that have been introduced to market, sponsor acknowledges that patients and health care professionals caring for them will need to gain experience with pramlintide once it is available.
  - Because of the point immediately proceeding and due to the risk of hypoglycemia, the sponsor is committed to a multifaceted risk-management program for pramlintide that is similar to that in place for Forteo.
  - The sponsor responded that they do not believe additional trial will provide any additional information. However, the sponsor asked if the additional study in patients with type 1 diabetes can be conducted either as a Phase 4 study or under Subpart H.

DECISIONS (AGREEMENTS) REACHED:

1. The sponsor agreed to submit a proposal for placebo-controlled, unblended study in patients with type 1 diabetes. This is not a complete response to our December 17, 2003, approvable letter.

2. The sponsor agreed to submit any additional data they have on patients with type 2 diabetes. No specific commitment was made on the part of the sponsor to propose a single indication in type 2 diabetes.

3. The proposed Risk Management Plan (including a boxed warning, limitation of the treatment to patients who failed to achieve glycemic control despite having optimized their insulin regimen, physician and patient education, no consumer advertising, postapproval safety study focused on safety outcomes,etc.) is acceptable for review.

4. The subpart H "route" is not an option for approval of pramlintide.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Timing of the additional study in patients with type 1 diabetes was not decided and needs further discussion.

ATTACHMENTS/HANDOUTS:

3 Page(s) Withheld

✓ § 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/

Julie Rhee
8/20/04 02:30:24 PM

6/16/04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-332	Efficacy Supplement Type SE-	Supplement Number N/A	
Drug: Symlin (pramlintide acetate) injection)		Applicant: Amylin Pharmaceuticals, Inc.	
RPM: Julie Rhee		HFD-510	Phone # 827-6424

Application Type: (x) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
User Fee Goal Dates	March 20, 2005 (**Sunday**)
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number _____
• User Fee waiver	(x) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) _____
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) _____
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No

• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(x) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(x) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (x) No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	2/14/05

General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE 12/16/03
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (x) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling	Included
• Original applicant-proposed labeling	Included (dated 9/17/04)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC—1/25/05 DMETS—12/21/04 DSRCS—~~Pending~~ 2/19/05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Included
• Applicant proposed	Included (dated 9/17/04)
• Reviews	Included
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included
❖ Memoranda and Telecons	Included
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	3/7/00
• Pre-Approval Safety Conference (indicate date; approvals only)	3/10/05,
• Other (End of NDA review)	11/21/01
❖ Advisory Committee Meeting	
• Date of Meeting	7/26/01
• 48-hour alert	Included
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Pending (as of 2/10/05)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	~~Pending (as~~ of 2/10/05) 2/23/05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	~~Pending (as of 2/10/05)~~ 2/23/05
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	2/11/05
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included
❖ Demographic Worksheet *(NME approvals only)*	Not needed
❖ Statistical review(s) *(indicate date for each review)*	Included (11/13/03)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Included (2/9/05)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Included
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Included
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Included (8/1/01)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Included (7/12/01)
❖ Facilities inspection (provide EER report)	Date completed: 12/8/03 (x) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (x) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Included (9/5/01)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	Included (7/9/01)
❖ CAC/ECAC report	N/A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-332

6/9/04

Amylin Pharmaceuticals, Inc.
Attention: Joann L. Data, M.D., Ph.D.
Sr. Vice President, Regulatory Affairs and Quality Assurance
9373 Towne Centre Drive, Suite 250
San Diego, CA 92121

Dear Dr. Data:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symlin (pramlintide acetate) injection.

We also refer to your May 27, 2004, correspondence, received May 28, 2004, requesting a meeting to the discuss use of Symlin in insulin-using patients with type 2 diabetes as the "patient population".

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: July 21, 2004
Time: 3:00 – 4:00 pm
Location: Parklawn Building 3rd floor conference room "Chesapeake"
CDER participants (tentative):
Robert Meyer, M.D., Director, Office of Drug Evaluation II
David Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products
Dragos Roman, M.D., Medical Officer, DMEDP
Robert Misbin, M.D., Medical Officer, DMEDP
Jon Sahlroot, Ph.D., Statistical Team Leader, Office of Biometrics II
Julie Rhee, Regulatory Project Manager, DMEDP

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at rheej@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Julie Rhee at 827-6424 or the division secretary at 827-6432.

Provide the background information for this meeting (two copies to the NDA and 10 desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 21, 2004, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Julie Rhee
6/9/04 08:25:55 AM

MEMORANDUM OF TELE-CONFERENCE MINUTES

MEETING DATE: January 14, 2004

TIME: 3:00 – 4:00 pm

APPLICATION: NDA 21-332 Symlin™ (pramlintide acetate)

MEETING CHAIR: David Orloff, M.D., Director, DMEDP

MEETING RECORDER: Julie Rhee, Regulatory Project Manager, DMEDP

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name
David Orloff, M.D.	Director	Division of Metabolic and Endocrine Drug Products
Roman Dragos, M.D.	Medical Reviewer	DMEDP
Julie Rhee	RPM	DMEDP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES: Amylin Pharmaceuticals, Inc.

External Attendee	Title
Joann Data, M.D., Ph.D.	Senior Vice President, Regulatory Affairs and QA
Orville Kolterman, M.D.	Senior Vice President, Clinical Affairs
Alain Baron, M.D.	Senior Vice President, Clinical Research
David Maggs, M.D.	Executive Director, Medical Affairs
Dwayne Elwood	Senior Vice President, Marketing
Larry Shen, Ph.D.	Senior Director, Biometrics
Dan Bradbury	Chief Operating Officer

BACKGROUND:

The sponsor had submitted an NDA for Symlin on December 7, 2000. The proposed indication is [redacted]

The Agency issued an approvable letter on October 10, 2001. The approvable letter recommended to address an increased risk of severe hypoglycemia, difference in bioavailability, safe and effective timing of Symlin and insulin administration relative to food ingestion, and the effect of concomitant Symlin administration on the pharmacokinetics of oral hypoglycemic agents before Symlin can be approved.

On June 16, 2003, the sponsor submitted a complete response to the October 10, 2001, approvable letter. The Agency issued a second approvable letter on December 17, 2003, because of unacceptable risk management for the use of pramlintide with insulin.

On December 18, 2003, the sponsor submitted a tele-conference request to further discuss the specific requirements needed for Symlin approval. The sponsor provided a background material for the tele-conference on January 7, 2004.

DISCUSSION POINTS:

1. The tele-conference was focused on (1) patient population selection and (2) method of use for Symlin.

2. The sponsor proposes a label-driven launch education program and only physicians familiar with the use of Symlin will decide who is an appropriate candidate for pramlintide therapy.

3. The Division informed the sponsor that although the January 7, 2004, response attempts to address the deficiencies stipulated in the December 17, 2003, approvable letter, Study 137-155 is an uncontrolled, open-label, observation study and the Study does not address the Division's concern. The Division does not object if the sponsor plans to submit Study 137-155 data along with other information for review.

4. The Division stated that they agree that pramlintide is pharmacologically active and that, given this activity, in can result in lowering of HbA1c in DM1 and DM2. However, at present, the Division is not satisfied that Symlin is safe and effective for the treatment of DM1 and DM2 in conjunction with insulin.

5. When the sponsor was challenged about their conviction that pramlintide is safe and effective, the sponsor responded that they believe that it is safe and effective in a well selected patient population.

   The sponsor stated that dealing with severe hypoglycemia in insulin treated patient population cannot be avoided. The sponsor also stated that hypoglycemia is induced by insulin in this patient population. The Division asked the sponsor to provide data that hypoglycemia is caused by misuse of insulin. The Division agrees that Symlin-associated hypoglycemia in patients taking combination insulin and Symlin is mediated through insulin action. This is related to the mechanism of action of Symlin and represents a risk of the drug above and beyond that of insulin therapy alone.

6. The sponsor was asked what pramlintide does other than being pharmacologically active for people on insulin. The Division also reminded the sponsor that more data is needed to show what pramlintide does beyond reduction in insulin use, given that, despite this fact, Symlin used in combination with insulin is associated with a risk of severe hypoglycemia above that with insulin alone in a trial in which equivalent glycemic control was achieved with both treatment regimens.

7. The sponsor stated that pramlintide would not be recommended for all patients. Initiation of pramlintide therapy is for people who know how to use insulin. Pramlintide helps some patients who run into barriers, i.e., weight gain or wide fluctuations of blood glucose level.

8. [redacted]

[redacted]

9. The sponsor is at liberty to ask pramlintide users to submit their testimonials.

TELE-CONFERENCE MINUTES

Addendum to the tele-conference minutes: Following to the January 30, 2004, telephone conversation between Dr. David Orloff of the Division and Dr. Joann Data at Amylin, there was a face-to-face meeting on February 2, 2004. The Division's attendees were Dr. David Orloff, Dr. Dragos Roman, and Julie Rhee. Representatives from Amylin were Dr. Orville Kolterman, Dr. Joann Data, and Dr. Karen Lutz, Senior Manager, Medical Writing.

The action items from this meeting are as follows:

i. In the absence of compelling evidence from adequate and well-controlled trials that Symlin is safe and effective in combination with insulin and offers benefits that outweigh risks when compared to therapeutically equivalent insulin-alone treatment regimens, the Agency is not prepared to approve the NDA for Symlin.
ii. Symlin is pharmacologically active in DM1 and DM2, resulting in lowering of HbA1c when compared to a fixed insulin-only treatment regimen. In a treatment regimen in which insulin dose was adjusted to obviate hypoglycemia and then titrated to achieve

optimum glycemic control, insulin-Symlin combination patients experienced more severe hypoglycemia with no better glycemic control than insulin-alone-treated patients. The sponsor believes [redacted]

[redacted]. The effect [redacted] has not been established. If the sponsor is interested in proposing [redacted] Symlin in combination with insulin, further discussions regarding [redacted] will be necessary.

iii. With regard to addressing the efficacy of Symlin in lowering HbA1c beyond that of insulin alone as well as, potentially, [redacted] the Division suggests that the sponsor consider a randomized blinded, placebo-controlled, withdrawal study in patients stable on Symlin-insulin under good glycemic control.

iv. Amylin stated that patients on pramlintide use 28% less short acting insulin. However, the Division responded that despite insulin dose-sparing, there was an increase in severe hypoglycemia.

v. Objective of future studies should be to document clinically meaningful value of pramlintide as an adjunct therapy to insulin and consider the following items:
   a. [redacted]
   b. Insulin sparing, and
   c. Improved safety.

vi. The sponsor is reminded to submit a complete response, not a partial response, to the December 17, 2003, approvable letter.

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

/s/

Julie Rhee
2/13/04 04:30:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-332

Amylin Pharmaceuticals, Inc.
Attention: Joann L. Data, M.D., Ph.D.
Sr. Vice President
Regulatory Affairs and Quality Assurance
9373 Towne Centre Drive, Suite 250
San Diego, CA 92121

Dear Dr. Data:

Please refer to the tele-conference between representatives of your firm and FDA on January 14, 2004. The purpose of the tele-conference was to clarify some of the issues in our December 17, 2003, action letter.

The official minutes of that tele-conference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of January 14, 2004, tele-conference minutes

Office Director's Sign-Off Memorandum

Date:	Wednesday, December 17, 2003
NDA:	21-332
Sponsor:	Amylin Pharmaceuticals
Proprietary Name:	Symlin (pramlintide acetate) injection
Date of submission:	Resubmission date: June 17th, 2003 Original submission: Dec. 8, 2000

Introduction: This is the second cycle for this drug product, which is an analogue of a naturally occurring hormone, amylin, that is co-secreted from the pancreas along with insulin. It's intended physiologic results is a lowering of glucose, at least in part mediated by a suppression of glucagon release postprandially and through delayed GI transit/gastric emptying.

I am in substantial agreement with Dr. Orloff's excellent Division Director's memo of 12/10/03 summarizing this action and therefore will keep this document quite brief. The original clinical trials of Symlin used pre-prandial SQ administration as an adjunct to relatively fixed doses of basal and bolus insulin. While they confirmed a small but meaningful hypoglycemic effect of Symlin used in this manner, they also showed more episodes of serious hypoglycemia. One potential manifestation of this effect was an excess of motor vehicle accidents observed in Symlin-treated patients. It was unclear from these trials if this increase in hypoglycemia was due to the better glucose control achieved in the Symlin group and therefore would be no worse than upward titration of insulin to achieve similar improvements in glycemia. There was also some question of whether Symlin might effect the patient's ability to detect impending hypoglycemia.

The sponsor largely answered the latter question by PD studies which showed that Symlin did not apparently impair autonomic signs nor symptoms of hypoglycemia. They also presented placebo-controlled studies that both allowed for a reduction in insulin with initiation of pramlintide and adjustment of bolus and basal insulin. These studies, which excluded patients with a history of notable hypoglycemia in the previous 6-months, were designed for the two treatment groups to achieve similar glycemic improvement, which indeed they did (though there was a numeric trend towards control being marginally better with insulin/placebo). However, there were still excessive numbers of patients with protocol-defined severe hypoglycemic episodes with pramlintide compared to placebo patients, despite similar levels of glycemic improvement. The overall rate of hypoglycemia was lower in these trials, perhaps due to restricted entry criteria, but there was still a clear numerical disadvantage for pramlintide when more severe episodes were compared.

Given the current set of studies showing that pramlintide does not afford any benefit not otherwise achievable with insulin (with insulin alone requiring fewer SQ injections at that), and a serious safety risk in excess of insulin that resulted in the original data set in an excess of MVAs, this product has an unfavorable risk-benefit profile and cannot be

approved for the indication sought in the populations proposed. The sponsor will need to identify a population in whom this risk-benefit ratio is favorable to get the product approved (like type-II diabetics not yet requiring insulin).

See Dr. Orloff's memo and other reviews for full details of this and the prior action.

/S/

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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

/s/

Robert Meyer
12/17/03 09:49:07 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: December 2, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-332
Symlin (pramlintide acetate) injection
Amylin Pharmaceuticals
Adjuctive therapy to insulin in DM1 and DM2

SUBJECT: 2nd cycle NDA review issues and recommended action

Background

This application received an AE action in October 2001, based primarily on a deficiency related to safety. Specifically, in the 26- and 52-week phase 3 trials, designed such that insulin dose was held constant except as indicated by hypoglycemia, there was a substantially higher incidence of severe hypoglycemia among patients treated with pramlintide/insulin than with insulin/placebo, more so in DM1 but also in DM2 patients.

The original phase 3 trials were structured in order to permit a demonstration of improved glycemic control with the combination over that with insulin alone. And indeed, consistent with the well-documented pharmacology of the drug, the demonstration was successful. That is, patients receiving the combination showed a mean reduction from baseline in HbA1c of approximately 0.3 percentage units relative to insulin alone. Of critical importance in evaluating the meaningfulness of this treatment effect in support of pramlintide clinical utility is the fact that, as implied above, standard-of-care adjustments of insulin dose to achieve glycemic goals were not integrated into the management of patients in these trials. To repeat, the studies were designed to demonstrate a "win" for pramlintide with the hypothesis driven by the knowledge that pramlintide would ultimately reduce total caloric intake and/or absorption due to effects on appetite/nausea and gastric emptying. As stated above, pramlintide "won." What was left unanswered from an efficacy standpoint by this trial was whether glycemic control with insulin alone, equivalent or superior to that with the combination, could have been achieved by simply allowing for dose adjustments of basal and bolus insulins according to standard clinical practice. Trial 150 submitted in response to the AE action established not surprisingly that, indeed, this was possible. In short, the results of trial 150 support a conclusion that pramlintide adds nothing in terms of glycemic control in type 1 or type 2 DM beyond what can be accomplished with insulin alone. Furthermore, though modest reductions in insulin dose are necessary when adding pramlintide to the antidiabetic regimen, pramlintide has no known insulin-agonist or insulin-sensitizing activity and so obviously does not obviate the need for insulin in DM1 or in "insulin-requiring" DM2 patients.

With regard to safety, as above, counterbalancing the marginally greater efficacy of pramlintide/insulin vs. fixed-dose insulin alone observed in the original phase 3 program was the finding of a marked increased incidence of severe hypoglycemia in pramlintide-treated patients, particularly in the DM1 patients (25% pramlintide, 18% placebo, overall), and most marked in the early, pramlintide-titration phase, of the studies. The significance of this enhanced hypoglycemia risk was borne out by the distressing finding of a marked increase in motor vehicle accidents among pramlintide-treated DM1 patients (4-8 times the incidence over insulin alone), as many of the accidents were clearly or plausibly related to hypoglycemia. The extent to which the increased risk of hypoglycemia with pramlintide could be explained by the enhanced glycemic control over insulin alone and the extent to which such risk could be obviated or managed by reductions in insulin dose during titration to maximum tolerated dose of pramlintide were questions left unanswered by the original phase 3 program.

On the first review cycle, the Endocrine and Metabolic Drugs Advisory Committee recommended against approval pending further studies of safe methods of initiation and maintenance of therapy with pramlintide (i.e., timing relative to meals and insulin, dose titration, insulin dose-reduction to obviate hypoglycemia). In consultation with the Division, the sponsor has conducted such studies, including a pivotal 29-week clinical safety (i.e., hypoglycemia risk) study in DM1. In contrast to the previous trials, this study was designed with protocol-specified algorithms for pramlintide gradual upward dose titration and for adjustment of insulin dose during pramlintide intitation and during maintenance pramlintide therapy after maximum tolerated dose of pramlintide was achieved. Furthermore, from the standpoint of drug therapeutic effect, the trial was designed to permit optimization of glycemic control in patients not yet at ADA goal with a requirement for interpretability of the safety (hypoglycemia) data wholly dependent on "equivalent" (non-inferior) efficacy of pramlintide to placebo. Not unexpectedly, this "goal" of the trial was achieved. Indeed, the finding of "equivalent" therapeutic effects of regimens employing insulin only and insulin plus pramlintide (in concert with the increased incidence of severe hypoglycemia among pramlintide-treated patients in the trial, as in the previous studies) bears critically on the consideration of the place for pramlintide as an adjunct to insulin therapy in DM1 and DM2 as proposed by the sponsor.

Clinical Safety and Efficacy

This resubmission included the results of a single phase 3 study (137-150), as described above. In addition, results of small studies investigating, among other things, 1) the effects of pramlintide on hypoglycemia awareness and neuroglycopenic responses (no effect), 2) bioavailability of pramlintide administered at different anatomical sites, and 3) effect of timing of pramlintide administration relative to meals and insulin in postprandial glucose dynamics. The antigenicity of drug sourced from a previously untested facility was also assayed in trial 150, and was satisfactory.

In study 150, over 29 weeks of therapy, the average placebo-subtracted weight loss (i.e., relative to insulin alone) with pramlintide was ~2.5 kg. As expected, pramlintide-treated patients used less total insulin (~10-12%), with the greatest reduction in bolus insulin (~25% mean reduction in daily dose). With respect to glycemic control, overall mean reductions in HbA1c were essentially the same for both treatment groups, though the percent of insulin-alone patients

achieving HbA1c $\leq$ 7% and maintaining a stable reduction of $\geq$ 0.5 HbA1c percentage units relative to baseline was somewhat higher than among insulin-pramlintide-treated patients. In short, the single "benefit" of adding pramlintide to the regimen was a modest mean weight loss relative to insulin alone.

The incidence of severe hypoglycemia, defined as requiring IV administration of glucose, IM administration of glucagon, third-party intervention to obtain treatment, or experiencing a life-threatening situation as a result of the event, was about double in the pramlintide group compared to the insulin-alone group during both the initiation phase of the study (2.7% in the insulin-alone group and 4.7% in the insulin/pramlintide group) and in the maintenance phase (17.% pramlintide, 8.4% insulin alone). Over the entire course of the study, the incidence of severe hypoglycemia was 10.2% for insulin-alone patients and 21.6 for insulin-pramlintide patients. This increased risk was therefore persistent over the course of therapy, and was thus not effectively obviated by downward insulin dose adjustment during pramlintide initiation, nor did it wane completely once the patient was on a stable, "tolerated" dose of pramlintide. These rates represent a modest decreased incidence in both treatment groups compared to the experience in the previous phase 3 trials in which insulin dose was not downward adjusted per protocol specifically to prevent hypoglycemia. Therefore, it is reasonable to conclude that the method of initiation of pramlintide therapy implemented in study 150 was partially successful in enhancing the safety of the drug. Nevertheless, it is important to note that patients were screened into this trial based on an entry criterion that their glycemic control be stable and that they not have experienced severe hypoglycemia in the 6 months prior to enrollment. So, while the absolute rates of severe hypoglycemia are low and below those observed in the original phases 3 studies, they nevertheless represent a substantial increase over the patients' experience in the 6 months preceding the study (certainly not totally unexpected with concerted efforts at improved glycemic control). Most importantly, though, there seems little question of an unprevented, and unavoidable until proven otherwise, marked increased incidence of severe hypoglycemia associated with the use of pramlintide.

The dose-limiting tolerability factor for pramlintide is nausea and is a major cause of drug discontinuation. Furthermore, it appears that nausea induction correlates with efficacy. This pharmacologic "response" marks those patients who will reduce caloric intake, and who potentially will have the most marked delays in gastric emptying and delivery of nutrients to the portal circulation. As such, however, these are precisely the individuals who have the highest risk for hypoglycemia, which seems logically to result from one very simple mechanism: an imbalance between insulin dose and glucose delivery from the gut to the blood. It is clear therefore, that the efficacy of pramlintide and the hypoglycemic risk associated with its use cannot be dissociated and that, for all intents and purposes, adding pramlintide to the medical regimen of a diabetic will tend only to complicate the use of insulin. That is, if the pramlintide is effective, it will significantly add to the known but obviously totally acceptable risk of insulin, a critically necessary drug, hypoglycemia. This Catch-22 results, by definition, in an unacceptable risk-benefit profile for pramlintide.

Labeling

Not applicable in light of AE action

Biopharmaceutics

NDA #21-332 (second cycle)
Drug: Symlin (pramlintide injection)
Proposal: adjunct to insulin in DM1 and DM2
12/10/03

See OCPB review. Biopharmaceutics deficiencies addressed, though the investigation into differences in bioavailability across target populations have not been conclusive.

Pharmacology/Toxicology
No new issues.
Chemistry/ Microbiology
See ONDC review.

DSI/Data Integrity
No clinical site inspections were requested or performed.

Financial disclosure
The financial disclosure information is in order per Dr. Roman's review.
ODS/nomenclature
No issues

Recommendation
Approvable. Risk versus benefit is unfavorable for type 1 DM and for type 2 DM treated with insulin due to increased risk of hypoglycemia absent any advantages re: glycemic control. Sponsor must identify a target population in which benefit outweigh risks.

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

/s/

David Orloff
12/10/03 02:22:27 PM
MEDICAL OFFICER

Robert Meyer
12/10/03 03:43:31 PM
MEDICAL OFFICER
I am in substantial agreement with Dr. Orloff's memorandum.

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 10, 2003

FROM: David Hoberman, Ph.D., consultant SGE

SUBJECT: Non-inferiority of pramlintide/insulin to insulin/placebo in Study 137-150. NDA 21-332

TO: Dragos Roman, M.D. (HFD-510)

Subsequent to the Advisory Committee meeting for Symlin (pramlintide), the FDA requested the sponsor (Amylin) to conduct a safety study to determine whether titrated regimens of pramlintide would reduce the incidence of severe hypoglycemia compared to the incidence of severe hypoglycemia found in the randomized pramlintide groups in the original NDA trials. In the latter trials, patients were randomized to placebo, 30 µg pramlintide, or 60 µg pramlintide, added on to insulin. In contrast, during a 4-week Initiation Period in the new study (137-150), patients were randomized to placebo or pramlintide added on to insulin. Patients started at 15 µg and titrated up to a maximum of 60 µg through 30 µg and 45 µg (or matching placebo). Eventually, all pramlintide-randomized patients were on 30 µg or 60 µg. Those who stayed on 30 µg were those whose nausea did not allow them to advance upward in dose. An additional difference between the original NDA trials and trial 137-150 was that in the latter trial, a patient's insulin could be adjusted, whereas in the NDA trials, investigators were encouraged to keep each patient's insulin doses as stable as possible over the course of the trial. Consequently, the design of trial 137-150 more accurately reflects the actual usage of insulin in practice.

The primary clinical comparison in this trial was the incidence of severe hypoglycemia in both treatment groups. There was no statistical plan to formally compare them. However, the sponsor agreed to enroll enough patients to ensure that the pooled pramlintide group would pass a non-inferiority test with a margin of .4% in change of HbA_{1C} from baseline. Thus, it must be shown that the mean decrease from baseline in HbA_{1C} in the placebo/insulin group was not more than .4% more than the decrease in the pooled pramlintide group. As a result of my conversations with the Medical Officer, Dragos Roman, HFD-510, this memo addresses only the issue of whether the trial met the non-inferiority standard.

Out of 295 randomized patients (placebo N=147, pramlintide N=148), 286 had data available for analysis of HbA_{1C} (placebo N=143, pramlintide N=143). The analysis plan stated an ANCOVA with study site and HbA_{1C} randomization stratum as factors along with unspecified covariates. In the LOCF analysis, the raw means were -.47% in the placebo group and -.39% in the pramlintide group. The lsmean estimates from the linear model were -.49% and -.47%, respectively, both with standard errors of .07%.

The sponsor then reports a one-sided 95% confidence upper bound of +.19% for the treatment difference (pramlintide change from baseline minus placebo change from baseline) which falls within the .4% non-inferiority margin. This reviewer has these comments:

1) A two-sided 95% upper bound clearly falls below .4%.

2) If the raw means are used (producing a greater numerical advantage to the placebo group), the upper bound rises to .28%, still below .4%.

3) If only completers are used, the results of the model are essentially the same are using the LOCF analysis.

4) There was no evidence of treatment by randomization stratum interaction.

Conclusions

Sensitivity analyses performed by this reviewer confirm that trial 137-150 provides evidence that pramlintide, as administered in this trial, provides mean HbA_{1C}-lowering which is not more than .4% less than that of insulin, alone as administered in this trial.

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

/s/

Todd Sahlroot
11/13/03 04:24:21 PM
BIOMETRICS
concur with Dr. Hoberman

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE

OFFICE OF DRUG SAFETY

Memorandum

DATE: October 31, 2003

TO: David Orloff, M.D.
Director, Division of Endocrine and Metabolic Drug Products (DMEDP), HFD-510

FROM: Office of Drug Safety
Division of Drug Risk Evaluation (DDRE), HFD 430
Division of Surveillance, Research, and Communication Support (DSRCS), HFD 420

SUBJECT: Feedback on RMP for Symlin® (pramlintide acetate).

IND/NDA#: NDA 21-332

EXECUTIVE SUMMARY

The purpose of this review is to provide feedback on the Risk Management Plan (RMP) for Symlin® (pramlintide acetate). The RMP describes the healthcare provider educational plan as well as other strategies to use with healthcare providers and patients to manage the risk of pramlintide. The RMP does state a goal and provide objectives for a number of the strategies.

The overall goal of the RMP is to reduce the occurrence of severe hypoglycemia in patients using pramlintide. The core of the RMP is the healthcare provider educational plan. However, the RMP does not specify an approach for titration of dose and/or frequency of administration of pramlintide to appropriately manage diabetes and avoid hypoglycemia. Additional strategies for healthcare providers [ ] and patients [ ], which are part of this RMP, are being studied [ ]. The RMP also includes various communication formats and [ ].

The objective for the education plan is to maximize the ability of the physicians and diabetes educators to initiate patients on pramlintide. Objectives are also given for:

- [ ]
- [ ]
- [ ]
- [ ]

- [ ]
- Various communication formats – to make all essential information available to everyone need it.

Objectives are not provided for the prescribing information sheet or guidelines.

Proposed evaluations are presented for the [ ] plan. There is no mention of evaluating the other patient and healthcare provider strategies or the overall goal of the RMP (to reduce the occurrence of severe hypoglycemia in patients using pramlintide).

ODS has several suggestions for the sponsor to consider. These suggestions are listed in the Considerations for Sponsor section.

DOCUMENT STRUCTURE

This document is divided into six sections: Introduction, Epidemiologic Comments, Education Components Comments, Evaluation Comments, Considerations for Sponsor, and References. The Education Components section has three sub-sections: target audience, patient strategies, and healthcare provider strategies. An introduction is presented first. Dr. Brinker next provides epidemiologic comments; Ms. Best, Dr. Lechter, and Ms. Wheelock present education components comments; and Dr. Staffa presents evaluation comments. The final comment section consists of a summary of considerations for the sponsor. A reference section concludes the document.

I. INTRODUCTION

Symlin® (pramlintide acetate) has been submitted for review by the DMEDP. In clinical trials, nausea and hypoglycemia has been observed in insulin-using patients taking pramlintide. The risk of severe hypoglycemia in insulin-using patients has resulted in the sponsor submitting a RMP. The goal of this program is to reduce the occurrence of severe hypoglycemia in patients using pramlintide.

II. EPIDEMIOLOGIC COMMENTS

Pramlintide acetate treatment as an adjunctive therapy to insulin includes an increased risk for episodes of clinically significant nausea and/or vomiting and hypoglycemia. As stated under Section 3.9.5 (page 142) of the pramlintide resubmission, the "main goal of the pramlintide risk management program (RMP) is to reduce the occurrence of severe hypoglycemia in patients using [pramlintide]." Section 3.9.5 also includes (and highlights) general pharmacovigilance activities. Nonetheless, a comprehensive strategy that identifies specific groupings of patients who are at increased risk for the adverse events described above or that will effectively inform physicians and patients on how to manage these risks has not been presented. Of particular concern is the likely occurrence of insulin-induced hypoglycemic reactions in patients with nausea/vomiting or slowed gastric emptying (both potential side-effects of pramlintide acetate). Rapid reversal of hypoglycemia by oral intake of glucose containing solutions (e.g. orange juice) may be somewhat limited due to these pramlintide-associated effects. In addition, patients with underlying diabetic gastroparesis may be particularly vulnerable to exaggerated gastric emptying slowing effects of the agent and thus be at increased risk to develop episodes of nausea and vomiting or hypoglycemia. An effective risk management program should address these concerns.

Several important but otherwise general issues the reviewing division may wish to consider include:

1. Incorporation of any clinical parameters (e.g., dose, titration of dose, frequency of administration, stopping rules) used in the clinical development program into all approved product labeling in addition to the package insert.
2. Restriction of the indicated population to that included in the clinical development program, to include **contraindication** of patient subsets excluded from the clinical development program. As above, this information would also need to be incorporated into all approved product labeling, not just the package insert.

III. EDUCATION COMPONENTS COMMENTS

The sponsor has a wide array of educational strategies targeting patients, physicians, and diabetes educators. For patients, the sponsor has proposed t

sponsor proposes the use of Information

, and guidelines.

All of the physician and patient strategies are grounded in adult learning (Houle, 1996; Knowles, Holton, & Swanson, 1998), patient education (Redman, 1988), educational psychology (Ormrod, 1999; Woolfolk, 1993) and instructional design (Dick & Carey, 1996) principles and theory. Additionally, the physician strategies are supported by current research for the use of a) multifaceted interventions (Figueiras, Sastre, & Gestal-Otero, 2001; Grimshaw et al., 2001; Wyszewianski & Green, 2000), b) practice-enabling interventions (Davis, Thomson, Oxman, & Haynes, 1992; Davis, Thomson, Oxman, & Haynes, 1995), c) group learning (Parboosingh, 2002; Pereles, Lockyer, & Fidler, 2002), and c) information seeking and on-line learning (Casebeer, Bennett, Kristofco, Carillo, & Centor, 2002). The strategies for diabetic patients are supported by research on education and self-monitoring interventions (Padgett, Mumford, Hynes, & Carter, 1988) as well as self-management education (Norris, Lau, & Smith, 2002).

One of the positive aspects of the RMP is the use of *knowledge-oriented*

strategies. Using a variety of educational strategies meets the learning needs of various individuals and facilitates not only knowledge and understanding but also use. Furthermore, the RMP proposes to use instructional strategies

Comments on the education components of the RMP include the target audience, patient strategies, and healthcare provider strategies.

TARGET AUDIENCE

The sponsor has identified a target audience of physicians and affiliated certified diabetes educators; however, it is unclear how physicians and certified diabetes educators will be identified and targeted for administration of the education programs.

We recommend that the sponsor detail the sampling frame and recruitment strategies, as well as any sub-populations of physicians or diabetes educators that would be missed using the proposed strategy.

PATIENT STRATEGIES

The Patient Package Insert (PPI) has been reviewed by DSRCS and comments have been forwarded under separate cover. See PPI review consult dated October 30, 2003.

The RMP does not mention the use of the PPI. Because the PPI contains comprehensive information based on the prescribing information, we recommend that the PPI be the primary communication tool for patients using pramlintide. We also recommend that the sponsor consider evaluating the PPI in achieving the communication objectives, which are presented in the major headers.

We have reviewed [illegible] e for type 1 diabetes and have the following comments:

- All patient materials should be written at a 6th to 8th grade reading comprehension level in order to reach a broad range of patients, including those with lower literacy. The sample brochure presented has a Flesch-Kincaid grade level of 9.9 with and sentences averaging 17 words apiece. There are numerous opportunities to simplify the language and to shorten sentences.

[illegible]

[illegible]

We recommend that [illegible] lower reading grade level and are used as an adjunct educational/risk communication strategy.

For the [illegible] we recommend that the sponsor:

- provide information about the development [illegible]
- identify the communication objective(s)
- outline the study design for the use of [illegible] in evaluating the effectiveness of the booklets
- provide instructions [illegible]
- [illegible]

[illegible] are useful for tracking doses, blood sugar levels, and reactions. If used properly, these — have a dual function as 1) a classical conditioning tool facilitating patients' learning about

the use and monitoring of pramlintide and insulin and 2) an aid for patients and healthcare providers in proper dose adjustments of pramlintide and insulin.

We recommend that these [ ] be patient user-friendly and easy to understand, especially for those patients with low literacy. Since this strategy is currently being studied in a Phase 3B clinical utility study, we also recommend that the sponsor present evaluation data for the objectives of the . — (assessing which treatment regimens are working, contact with the care-giver, and monitoring warning signs of nausea and hypoglycemia).

HEALTHCARE PROVIDER STRATEGIES

The sponsor has identified a number of strategies for physicians and diabetic educators. These strategies include: information [

] guidelines.

As part of the commercial launch of pramlintide, the sponsor is planning [

]

The sponsor states that an assessment tool will be employed to measure the success of the educational program. We recommend that the sponsor describe the tool and the study design plan for evaluating the objective of the education program (maximize the ability of physicians and diabetes educators to initiate patients on pramlintide).

The sponsor is developing other communication formats
the education program. The sponsor does not provide [

]

The sponsor also mentions the development and use of . [

] Since these strategies are currently being studied in a Phase 3B clinical utility study, we recommend that the sponsor present evaluation data for the following strategies' objective:

- Healthcare provider information — enable those responsible for designing patient regimens and education programs to do so
- — to permit review of the critical treatment procedures and issues underlying physiology
- — to provide a clinical link to physicians and diabetes educators to insure the timely flow of new information as well as provide contact with clinical experts.

IV. EVALUATION COMMENTS

The overall goal of the RMP is to reduce the occurrence of severe hypoglycemia in patients using pramlintide. Evaluation strategies are provided for the patient — and healthcare provider educational plan. The sponsor states that an assessment tool will be used before and after the educational program to quantitatively measure the success of the program.

Given that the main goal of the RMP is to reduce the risk of hypoglycemia in patients using pramlintide, it would be appropriate to design a risk management evaluation plan in which the risk of hypoglycemia in patients using this product is evaluated both at baseline and periodically after the education program is launched. An "acceptable" level of risk should be defined and agreed upon *a priori* so that it can be determined whether the program meets that goal.

Strategies for monitoring the incidence of hypoglycemia among patients using pramlintide should be described, with particular attention to the ascertainment of this outcome, since it can be problematic. For example, it is often underrepresented in automated health care databases due to both coding issues (severe vs. mild) and the urgency with which care is often required for serious hypoglycemia. This urgency can result in patients seeking emergency care, which can impact the capture of this outcome in databases based on insurance plan data.

Given that dosing and titration of dose are integral pieces of the risk management strategy for this product, strategies for capturing information on dosing in the population of patients using the product should be described.

V. CONSIDERATIONS FOR THE SPONSOR

The following points are summarized from the previous sections, and are considerations for the sponsor to include in the RMP.

1. The sponsor should consider incorporating any clinical parameters (e.g., dose, titration of dose, frequency of administration, stopping rules) used in the clinical development program into all approved product labeling in addition to the package insert.

2. The sponsor should consider restricting the indicated population to that included in the clinical development program, to include **contraindication** of patient subsets excluded from the clinical development program. As above, this information would also need to be incorporated into all approved product labeling, not just the package insert.

3. The sponsor should consider a program to monitor the frequency of hypoglycemic events in patients on pramlintide therapy.

4. The sponsor should consider and describe strategies for capturing information on dosing in the population of patients using the product.

5. For the education program target audience, the sponsor should detail the sampling frame and recruitment strategies, as well as any sub-populations of physicians or diabetes educators that would be missed using the proposed strategy.

6. The PPI should be the primary communication tool for patients using pramlintide. The sponsor should consider evaluating the PPI as a risk communication tool.

7. The [ ] should be developed with a lower reading grade level (6^{th} –8^{th} grade) and be used as an adjunct to the PPI as an educational/risk communication strategy.

8. [ ]

9. The [redacted] should be user-friendly and easy to understand, especially for those patients with low literacy. Since this strategy is currently being studied in a Phase 3B clinical utility study, the sponsor should present evaluation data for the [redacted] objectives (assessing which treatment regimens are working, contacting with the care-giver, and monitoring warning signs of nausea and hypoglycemia).

10. The sponsor should describe the assessment tool and the study design plan for evaluating the education program's objective (maximize the ability of physicians and diabetes educators to initiate patients on pramlintide).

11. At least one of the "other communication formats" should serve as a primary alternate for the education program and should therefore have the same objective and content of the educational program. Additionally, this communication format should be evaluated for the education program's objective (maximize the ability of physicians and diabetes educators to initiate patients on pramlintide). The other communication formats should be evaluated for meeting the informational needs of those accessing them.

12. For the other strategies [redacted] which are currently being studied in a Phase 3B clinical utility study, the sponsor should present evaluation data for the following strategies' objective:
    - Healthcare provider information [redacted] to enable those responsible for designing patient regimens and education programs to do so
    - [redacted] - to permit review of the critical treatment procedures and issues underlying physiology
    - [redacted] - to provide a clinical link to physicians and diabetes educators to insure the timely flow of new information as well as provide contact with clinical experts.

13. [redacted]

14. The sponsor should define an "acceptable" level of risk and design a risk management evaluation plan in which the risk of hypoglycemia in patients using this product is evaluated both at baseline and periodically after the education program is launched.

VI. REFERENCES

Casebeer, L., Bennett, N., Kristofco, R., Carillo, A., & Centor, R. (2002). Physician internet medical information seeking and on-line continuing education use patterns. J Contin.Educ.Health Prof., 22, 33-42.

Davis, D. A., Thomson, M. A., Oxman, A. D., & Haynes, R. B. (1992). Evidence for the effectiveness of CME. A review of 50 randomized controlled trials. JAMA, 268, 1111-1117.

Davis, D. A., Thomson, M. A., Oxman, A. D., & Haynes, R. B. (1995). Changing physician performance. A systematic review of the effect of continuing medical education strategies. JAMA, 274, 700-705.

Dick, W. & Carey, L. (1996). The Systematic Design of Instruction. New York, NY: HarperCollins College.

Figueiras, A., Sastre, I., & Gestal-Otero, J. J. (2001). Effectiveness of educational interventions on the improvement of drug prescription in primary care: a critical literature review. J Eval.Clin Pract, 7, 223-241.

Grimshaw, J. M., Shirran, L., Thomas, R., Mowatt, G., Fraser, C., Bero, L., Grilli, R., Harvey, E., Oxman, A., & O'Brien, M. A. (2001). Changing provider behavior: An overview of systematic reviews of interventions. Med Care, 39, II2-II45.

Houle, C. O. (1996). The Design of Education. San Francisco, CA: Jossey-Bass.

Knowles, M. S., Holton, E. F., & Swanson, R. A. (1998). The Adult Learner. Houston, TX: Gulf.

Norris, S. L., Lau, J., & Smith, S. J. (2002). Self-management education for adults with type 2 diabetes. A meta-analysis of the effect of gylcemic control. Diabetes Care, 25, 1159-1171.

Ormrod, J. E. (1999). Human Learning. Upper Saddle River, NJ: Merrill Prentice Hall.

Padgett, D., Mumford, E., Hynes, M., & Carter, R. (1988). Meta-analysis of the effects of educational and psychosocial interventions on management of diabetes mellitus. J.Clin.Epidemiology, 41, 1007-1030.

Parboosingh, J. T. (2002). Physician communities of practice: Where learning and practice are inseparable. J Contin.Educ.Health Prof., 22, 230-236.

Pereles, L., Lockyer, J., & Fidler, H. (2002). Permanent small groups: group dynamics, learning, and change. J Contin.Educ.Health Prof., 22, 205-213.

Redman, B. K. (1988). The Process of Patient Education. St. Louis, MO: C.V. Mosby Company.

Woolfolk, A. E. (1993). Educational Psychology. Needham Heights, MA: Allyn & Bacon.

Wyszewianski, L. & Green, L. A. (2000). Strategies for changing clinicians' practice patterns. A new perspective. J Fam Pract, 49, 461-464.

/S/

Mark Avigan, M.D., Acting Director
Division of Drug Risk Evaluation (DDRE), HFD 430
Office of Drug Safety

/S/

Toni Piazza – Hepp, Pharm.D., Acting Director
Division of Surveillance, Research, and Communication Support (DSRCS), HFD 410
Office of Drug Safety

ODS Review Team

Jeanine Best, M.S.N., R.N., P.N.P., Patient Product Information Specialist, DSRCS

Allen Brinker, M.D., Medical Officer Epidemiology Team Leader, DDRE

Karen Lechter, J.D., Ph.D., Social Science Analyst, DSRCS

Judy A. Staffa, Ph.D., R.Ph., Epidemiology Team Leader, DSRCS

Leslie D. Wheelock, M.S., R.N., Associate Director for Communication, DSRCS

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

/s/

Mary Dempsey
11/3/03 06:34:14 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
11/4/03 09:38:01 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
11/4/03 10:16:11 AM
DRUG SAFETY OFFICE REVIEWER

Rhee, H Julie

From: Roman, Dragos
Sent: Friday, October 24, 2003 2:57 PM
To: Rhee, H Julie
Subject: Addendum to Amylin question

One additional question: how many sites were involved in trial 137-150 and a breakdown of severe hypoglycemia events by site.
Thanks,
Dragos

Appears This Way
On Original

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

/s/

Julie Rhee
10/27/03 09:52:46 AM
CSO

Rhee, H Julie

From: Roman, Dragos
Sent: Friday, October 24, 2003 2:52 PM
To: Rhee, H Julie
Cc: Orloff, David G
Subject: Data request

Julie,
I need some clarifications from Amylin.
1) I could not find any tabulation on patient compliance with respect to pramlintide use in study 137-150. Can they point me to where these data are in the submission and, if not present, can they present us a brief but informative summary in a table format?
2) After reviewing the financial disclosure documents I need information from the study site where Dr. Steven Edelman was principal investigator. The information should include (1) the site number, (2) the number and patient identifier for the patients contributed to the trial, (3) a list of the serious adverse events and severe hypoglycemic episodes contributed by the site.
Thanks,
Dragos

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

/s/

Julie Rhee
10/27/03 09:49:13 AM
CSO

11 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Rhee, H Julie

From: Roman, Dragos
Sent: Friday, September 26, 2003 4:32 PM
To: Rhee, H Julie
Cc: Orloff, David G
Subject: Additional data for pramlintide NDA

Julie,
I need some additional information from the folks from Amylin Pharmaceuticals. This information may be in the NDA or not. If present in the NDA I appreciate their help in locating it. If not I need the following:

Study 137-150
1) A break down of severe hypoglycemia (incidence and annual event rate) in each treatment group (pramlintide vs. placebo) by short acting insulin (lispro, aspart) on one hand and regular insulin on the other hand. The data should be presented for the initiation period (0-4 weeks), maintenance period (week 4-week 29) and for the whole duration of the trial. In addition to the pramlintide to placebo comparison the data should also be presented for the 30mcg vs. the 60 mcg subgroup. The data can be presented in a format similar to Table 25 of study 137-150 entitled "Severe Hypoglycemia Incidence and Annual Event Rate (DCCT, Study 137-150, and Type 1 Long-term Controlled Trials 137-112, 137-117, 137-121; ITT Recommended Doses)"

2)A break down of severe hypoglycemia (incidence and annual event rate) in each treatment group (pramlintide vs. placebo) by treatment modality (CSII vs. MDI). The data should be presented for the initiation period (0-4 weeks), maintenance period (week 4-week 29) and for the whole duration of the trial. The data can be presented in a format similar to Table 25 of study 137-150 entitled "Severe Hypoglycemia Incidence and Annual Event Rate (DCCT, Study 137-150, and Type 1 Long-term Controlled Trials 137-112, 137-117, 137-121; ITT Recommended Doses)"
3) Incidence of nausea broken down by treatment modality (CSII vd. MDI).

Study 137-151
The range of glucose concentrations the table **Mean (SD) Incremental Plasma Glucose Concentrations (mg/dL) Following a Standardized Breakfast by Study Group and by Treatment** presented in the synopsis of the study.

Thanks,
Dragos

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

/s/

Julie Rhee
9/26/03 05:14:06 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: September 26, 2003

To: Joann L. Data, M.D., Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** (301) 443-9282
Phone number: 858-642-7324	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin

Total no. of pages including cover: 2

Comments: Additional clinical information request. Please submit the requested information no later than October 3, 2003, if possible at all. Thank you.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☑ NO

NDA 21-332 Symlin (pramlintide acetate)

Additional clinical information request

1. Study 137-150:

   a. A break down of severe hypoglycemia (incidence and annual event rate) in each treatment group (pramlintide vs. placebo) by short acting insulin (lispro, aspart) on one hand and regular insulin on the other hand. The data should be presented for the initiation period (0-4 weeks), maintenance period (week 4-week 29) and for the whole duration of the trial. In addition to the pramlintide to placebo comparison the data should also be presented for the 30mcg vs. the 60 mcg subgroup. The data can be presented in a format similar to Table 25 of study 137-150 entitled "Severe Hypoglycemia Incidence and Annual Event Rate (DCCT, Study 137-150, and Type 1 Long-term Controlled Trials 137-112, 137-117, 137-121; ITT Recommended Doses)"

   b. A break down of severe hypoglycemia (incidence and annual event rate) in each treatment group (pramlintide vs. placebo) by treatment modality (CSII vs. MDI). The data should be presented for the initiation period (0-4 weeks), maintenance period (week 4-week 29), and for the whole duration of the trial. The data can be presented in a format similar to Table 25 of study 137-150 entitled "Severe Hypoglycemia Incidence and Annual Event Rate (DCCT, Study 137-150, and Type 1 Long-term Controlled Trials 137-112, 137-117, 137-121; ITT Recommended Doses)".

   c. Incidence of nausea broken down by treatment modality (CSII vd. MDI).

2. Study 137-151:

   The range of glucose concentrations the table Mean (SD) Incremental Plasma Glucose Concentrations (mg/dL) Following a Standardized Breakfast by Study Group and by Treatment presented in the synopsis of the study.

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

/s/

Julie Rhee
9/26/03 05:11:41 PM
CSO

MEMORANDUM OF TELECON

DATE: March 24, 2003

APPLICATION NUMBER: NDA 21-332, Symlin (pramlintide acetate)

BETWEEN:

Name: Ms. Donna Zimmer,
Phone: (858) 642-7268
Representing: Manager, Regulatory Affairs at Amylin Pharmaceuticals, Inc.

AND

Name: Julie Rhee, Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: February 6, 2003, submission (2)

The sponsor submitted two correspondences on February 6, 2003, with questions concerning Format and Content for their resubmission of the NDA in response to the approvable letter dated October 10, 2001.

I. Resubmission Format Questions (February 6, 2003 submission):

1. Amylin plans to submit the NDA resubmission in electronic NDA format. Is this acceptable to the Agency?

   FDA's response: Yes

2. Amylin plans to submit the Archival copy of the NDA resubmission in electronic format as was provided for the initial submission? Is this acceptable to the Agency?

   FDA's response: Yes

3. Amylin plans to provide the *Table of Contents* in the format that was used in the initial NDA. The numbering sequence will continue from where the initial NDA numbering ended as seen in Attachment 1. Is the draft table of contents format acceptable to the Agency, including numbering sequence?

   FDA's response: Yes

4. Amylin plans to submit a list of clinical investigators utilized since the original submission for Item 8.1 (List of Investigators, List of INDs and NDAs) representing those studies in the resubmission. Is this acceptable to the Agency?

   FDA's response: Yes

5. Amylin plans to submit a list of clinical investigators utilized since the original submission for Section 19 – Financial Information, for those studies in the resubmissiom. In addition, Amylin will provide finacial information for studies 137-111; 137-112, 137-117, and 137-123 as cited in the NDA 21-332 "approvable" letter dated October 10, 2001, Attachment 2. Is this acceptable to the Agency?

   FDA's response: Yes

II. Resubmission Content Questions (February 6, 2003, submission):

1. On page 2 of the NDA 21-332 "approvable" letter dated October 10, 2001 (Attachment 1), under Manufacturing Facilities, it is noted that all facilities listed in the application must be found acceptable by FDA investigators, and specifically states on page 3, Item No. 9, "A satisfactory inspection of the [ ] site is required." Would the Agency please acknowledge to Amylin that the [ ] facility located in [ ] has been found acceptable by FDA investigators?

   FDA's response: Inspection of [ ] is acceptable.

2. It is Amylin's plan to update selected ISS tables as part of the *safety update* to include pooled data from all the studies submitted in the NDA and 120-Day Safety Update, and studies 137-146, 137-147, 137-150, 137-151, 137-152, 137-153, and 137-154. Separate tables will be provided for allcontinuing studies, including 137-140, 137-149, and 137-150E. Does the Agency agree with this approach?

   FDA's response: Pooled data is acceptable only for safety update. Ms. Zimmer stated that she is going to get a clarification of their question from Dr. Data.

3. Amylin does not plan to recreate the entire ISS, but rather summarize how the additional studies have further elucidated the safety profile of Symlin. Does the Agency agree with this approach?

   FDA's response: Yes

4. Likewise, Amylin does not plan to recreate the Application Summary, but rather summarize the impact of the learnings from the new studies. Does the Agency agree with this approach?

   FDA's response: Yes

5. Amylin plans to revise the label and thus the annotated label. Our plan is to annotate the label as we did in the original application. Where new language comes from the results of the new clinical data, the annotation will go to the summary of the study

findings and at the second level to the individual study reports. Is this acceptable to the Agency?

FDA's response: Yes

[

]

[

]

Appears This Way
On Original

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

/s/

Julie Rhee
3/26/03 09:58:43 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 21, 2001

To: Joann Data, M.D., Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** (301) 443-9282
Phone number: 858-552-2200	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin
FDA version of the November 21, 2001, meeting minutes

Total no. of pages including cover:

Comments:

The official minutes of the November 21, 2001, meeting are enclosed. You are responsible for notifying the Agency of any significant differences in understanding regarding the meeting outcomes.

Document to be mailed: ☐ YES ☑ NO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 21, 2001
TIME: 12:00 – 1:30 pm
LOCATION: Parklawn Building 3rd floor c/r "K"
APPLICATION: NDA 21-332 Symlin™ (pramlintide acetate injection)
TYPE OF MEETING: End of NDA review
MEETING CHAIR: David Orloff, M.D.
MEETING RECORDER: Julie Rhee, Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
John Jenkins, M.D.	Director	Office of Drug Evaluation II, HFD-102
David Orloff, M.D.	Director	DMEDP, HFD-510
Dragos Roman, M.D.	Medical Officer	DMEDP, HFD-510
David Hoberman, Ph.D.	Statistician	Division of Biometrics II, HFD-715
Hae-Young Ahn, Ph.D.	Biopharm Team Leader	Division of Pharmaceutical Evaluation II, HFD-870
Steven Johnson, Pharm.D.	Biopharm Reviewer	Division of Pharmaceutical Evaluation II, HFD-870
Julie Rhee	Project Manager	DMEDP, HFD-510

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Mr. Joe Cook	President and CEO	Amylin Pharmaceuticals, Inc.
Joann Data, M.D., Ph.D.	Sr. VP, Regulatory and Quality Assurance	Amylin
Orville Kolterman, M.D.	Sr. VP, Clinical Affairs	Amylin
Mr. John Wood	Director, Regulatory Affairs	Amylin
Terrie Burrell, Ph.D.	Clinical Investigator	Amylin
Larry Shen, Ph.D.	Director, Biostatistics	Amylin
Ms. Donna Zimmer	Manager, Regulatory Submissions	Amylin
Mr. Mark Fineman	Director, Clinical Sciences	Amylin
Ms. Jean Tempke	Associate Director, Project Management	Amylin
Mr. Tom Bicsak	Associate Director, Medical Writing	Amylin
	Consultant	
	Consultant	
	Consultant	

BACKGROUND:

The NDA 21-332 Symlin™ (pramlintide acetate) was submitted on December 7, 2000, as an [redacted]

An Advisory Committed (AC) meeting was held for the NDA on July 26, 2001. The committee voted against the approval of the NDA and recommended that the sponsor conduct additional studies to address the safe and effective use of Symlin in patients with Type 1 and Type 2 diabetes. The committee's major concern was the risk of hypoglycemia, particularly during the first 4 weeks of treatment, and most marked in the patient with Type 1 diabetes. The sponsor proposed to address the committee's concern by adjusting the starting dose of Symlin and by downward adjustment of insulin dose until tolerance to Symlin develops.

On August 21, 2001, the sponsor requested a meeting to discuss issues identified during the AC meeting as well as in the forthcoming action letter and provided the meeting background material on October 23, 2001. The Agency issued an approvable letter on October 10, 2001.

QUESTIONS AND ANSWERS:

The following is a list of the sponsor's questions and the Agency's responses in the order of discussion during the meeting:

Question 5: Does the Agency agree that the proposed body composition and injection site bioavailability study addresses the Agency's question?

FDA's response: The study design appears to be acceptable. However, there should be approximate equal numbers of patients who are lean and obese (e.g., BMI <24 and ≥24, respectively) patients.

Question 6: Does the Agency agree that the proposed pharmacodynamic study design to assess optimal dose timing addresses the Agency's question?

FDA's response: The proposed study appears to be acceptable but the Agency reserves the final comments until the protocol is reviewed. The Agency suggested that the dose timing study be conducted before any other clinical studies.

Question 7: Does the Agency agree that conducting one additional drug-drug interaction study during the review process would address the noted Agency concern?

FDA's response: Yes. Any potential limitations in drug-drug interaction information are to be handled as a labeling issue.

Question 1a: Does the Agency agree that Study 137-150 entitiled "A Randomized, Multicenter, Triple-Blind, Placebo-Controlled Study to Investigate the Safety and Effectiveness of Pramlintide in Subjects With Type 1 Diabetes Mellitus", as described, addresses Agency concerns that are generally limited to the type 1 population?

DISCUSSION:

1. Although the efficacy of Symlin has been demonstrated, hypoglycemic events during Symlin treatment need to be evaluated in the context of efficacy (i.e., a clinical trial that proves efficacy of pramlintide treatment over insulin alone).

2. Refer to the attached overhead for "Severe Hypoglycemia (requirements for data analysis)" which contains information that must be collected in Study 137-150. The overhead represents the minimum data needed to be collected in order to analyze hypoglycemia in patients with type 1 diabetes. The Agency recommended that such a study should be conducted in the U.S.

3. The sponsor could consider a non-inferiority study design because the efficacy of Symlin has already been demonstrated. If such a design is used, it may be difficult to address risk vs benefit in the event of excess hypoglycemic events in the Symlin-plus-insulin group vs insulin alone. In addition, in the context of non-inferiority for HbA1c, the absence of a signal of excess hypoglycemia with Symlin will be difficult to weigh if it is attributable merely to a reduction in insulin dose. The Agency recommended that no matter which study design is employed, adjustment of insulin regimen should be allowed in accordance with standard clinical practice. Symlin dose at steady state should remain fixed.

   If the sponsor plans to pursue a non-inferiority study, the suggested sample size is at least 100 patients per group based on 80% power calculation.

   Although the Agency previously had requested one-year study, we are willing to accept a study of shorter duration but require 6-months at steady-state Symlin dose.

FDA's response: No. The Agency recommends an efficacy study that, if successful, would allow analysis of hypoglycemia in context of efficacy. Refer to the attached copy of the overhead titled "Clinical Trial Design-Type 1 Diabetes" for a possible study design.

Question 1b: Does the Agency agree that there will be no long-term study conducted in the type 2 population?

DISCUSSION:

Extrapolation of hypoglycemic data from patients with type 1 patients to type 2 patients is acceptable. However, if retinopathy data from patients with type 1 diabetes cannot be extrapolated to patients with type 2 diabetes, a study in patients with type 2 diabetes may be required.*

FDA's response: This issue is still under discussion internally.*

* *See Post Meeting Note at the end of this minutes.*

Question 3: Would the Agency reconsider its position regarding the need for additional information on the effect of Symlin™ on diabetic retinopathy?

DISCUSSION:

Since data on natural history of retinopathy in patients with type 1 and type 2 diabetes exist, the sponsor may conduct study using historical data as a control. However, it is undecided whether or not it is acceptable to study retinopathy in patients with type 2 diabetes or to extrapolate data from type 1 patients to type 2 patients.

FDA's response: No. The Agency has not decided as what would constitute an appropriate trial to address the safety signal on retinopathy. Additional information on the effect of Symlin on diabetic retinopathy is needed. However, it has not been decided if data from type 1 patients could be extrapolated to type 2 patients. It also has not been decided if a study to evaluate the effect of Symlin on diabetic retinopathy could be done as a Phase 4 commitment.*

* See Post Meeting Note at the end of this minutes.

Question 2: Would the Agency reconsider its position regarding the effect of Symlin™ on hypoglycemia unawareness?

DISCUSSION:

1. Analysis of individual patient hypoglycemia awareness scores generated during the 14-day study (Study AP93-08) identifies a signal of hypoglycemia unawareness in the 100 µg Symlin arm. This signal is outlined in the attached copy of the overhead on Hypoglycemia rating-study AP93-08.

2. The Agency requested that the sponsor conduct a hyperinsulinemic hypoglycemic clamp study with concomitant measurement of glycemic threshholds for symptoms and counterregulatory responses. The study must include Symlin doses around the dose regimens anticipated in the clinical use (including 30μg and 60 μg). Symlin serum drug levels should be measured and correlated with the findings of the study. This study can be done simultaneously with clinical studies.

FDA's response: No. See the above discussion.

Question 4: Does the Agency agree that the inclusion of — material and assessment of anti-pramlintide antibodies in the proposed clinical studies, coupled with existing antibody data on — material, addresses the Agency concerns?

FDA's response: Yes.

Question 11: Is the proposed approach to submitting a Safety Update when additional information is available acceptable to the Agency?

FDA's response: Yes.

Question 12a: [
]

FDA's response: —

Question 12b: [
]

FDA's response: [
]

Question 8: Is the explanation outlined above regarding financial disclosure information for the stated studies acceptable to the Agency?

FDA's response: The handout to the sponsor is attached to this minutes.

Question/Statement 9: Amylin will work with the Agency to address any other outstanding concerns related to this inspection and the observations in [
] Form FDA 483.

FDA's response: An acceptable establishment inspection is needed before the application is approved.

Question 10a: Is the proposed approach to labeling acceptable to the Agency?
Question 10b: Are the proposed revisions outlined above to the Agency wording for the Carcinogenicity labeling acceptable?
Question 10c: Are the proposed revisions outlined above to the Agency wording for the Impairment of Fertility labeling acceptable?
Question 10d: Are the proposed revisions to the Agency wording for the Pregnancy labeling outlined above acceptable?

FDA's response: It is premature to discuss the labeling now. The Agency will discuss the labeling when the application is approvable.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Although the following issues had not been decided during the meeting, the Agency's recommendations are outlined below in the "Post Meeting Note concerning retinopathy".

1. Whether or not to study retinopathy in patients with type 2 diabetes or to extrapolate data from type 1 patients to type 2 patients.
2. Whether or not retinopathy study could be conducted as Phase 4 commitment.

Post Meeting Note concerning retinopathy:

1. Retinopathy study can be conducted as a Phase 4 commitment.
2. The duration of the study should be three years in patients with either type 1 or type 2 diabetes.
3. The suggested sample size is 500 patients.
4. An open-label, concurrent untreated control design is acceptable.
5. The best type of follow-up is 7 field photographs performed at baseline, months 3, 6, 9, 12, 18, 24, and 36.

Attachments: 1. Dr. Roman's overhead presentation
2. Financial Disclosure information (response to question 8)

Clinical Trial Design-Type 1 Diabetes

- Population: Well-control!ed patients with type 1 diabetes.
- Type of study: Efficacy study with detailed descriptive analyses of safety data of interest (hypoglycemia and retinopathy).
- Primary efficacy endpoint: HbA1C. Pramlintide treatment arms (30 gg and 60 gg) must show: 1) lower HbA1C at the end of the trial compared to HbA1C at baseline and 2) a 0.3 % (absolute value AND statistically significant) lower HbA1C in the treatment arms compared to the placebo arm at the end of the trial. Importantly, the mean of HbA1C in the pramlintide arm at the end of the trial must be !ess than 8 %.
- Duration of the trial must be at least 6 months for pramlintide at steady state.
- Retinopathy data should be recorded as fundoscopic photographs at least at baseline and at the end of the trial. Incidence of patients with retinopathy progression from background to proliferative type must be reported.
- Standardized meal challenges with postprandial glucose concentration measurements at the beginning, end and intermediary timepoints.

Severe Hypoglycemia (requirements for data analysis)

- Severe hypoglycemia: use the same definition as in previous studies (assisted hypoglycemia).

- Record the time of occurrence (in particular with respect to mealtime and administration of insulin).

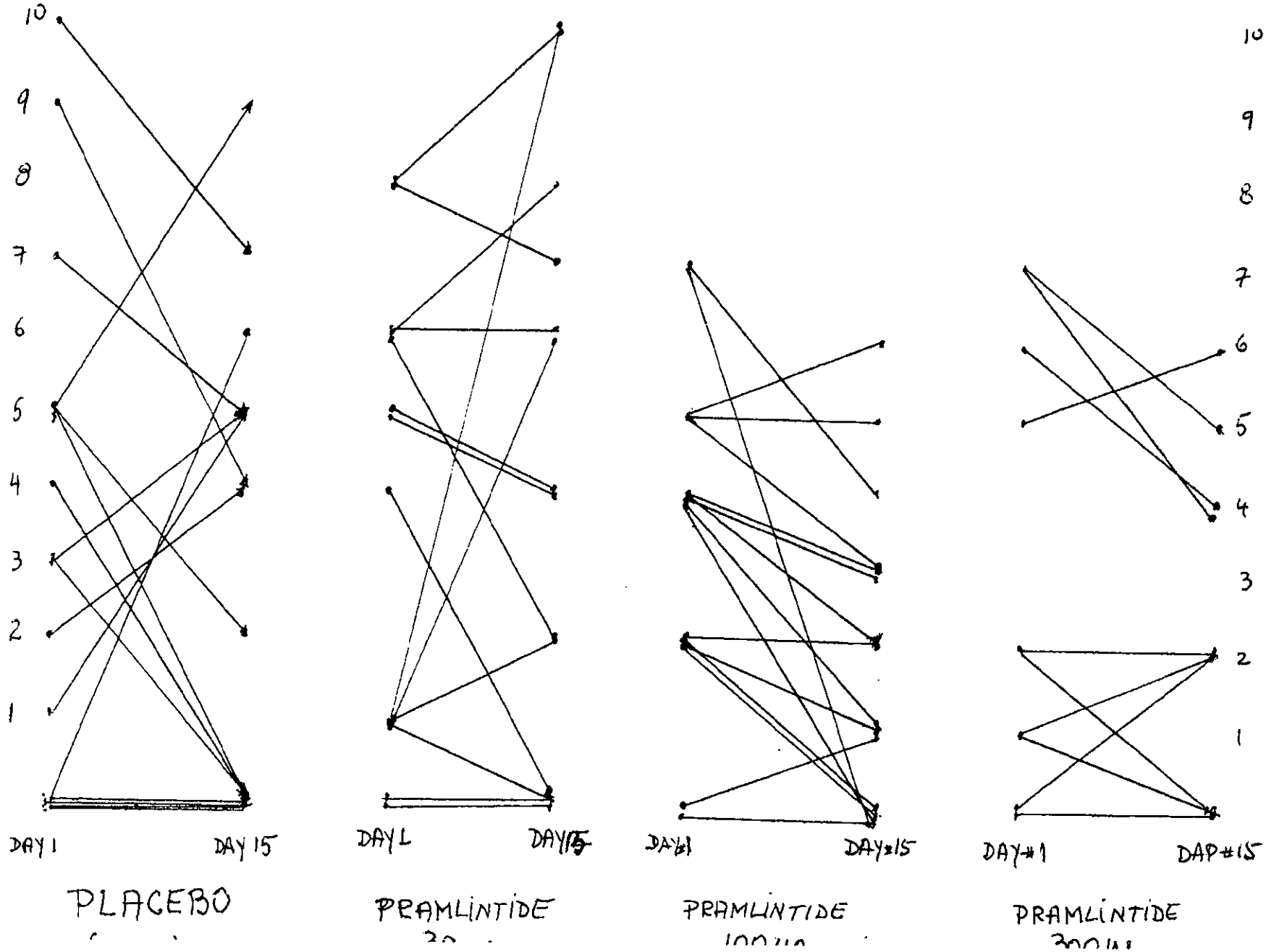
- Record hypoglycemia which occurs in the context of driving (including MVAs), or in association with trauma (e.g. falls, fractures, lacerations, etc).

- Report as patient incidence (temporal distribution within the trial and relationship with patients' HbA1C values).

- Report also as event rates (temporal distribution within the trial and relationship with patients' HbA1C values).

Serious Adverse Events associated with hypoglycemia: report incidence, temporal distribution within the trial and relationship with patients' HbA1C values.

HYPOGLYCEMIA RATING - STUDY AP93-08



The Financial Disclosure section should address the following four kinds of financial payments for covered studies:

1. OUTCOME PAYMENTS (payment dependent on outcome of the study):

   Study completed before 2/2/99: REQUIRED
   Study completed after 2/1/99: REQUIRED

2. PROPRIETARY INTEREST (patents/trademark/copyright/licensing agreement in the product):

   Study completed before 2/2/99: REQUIRED
   Study completed after 2/1/99: REQUIRED

3. EQUITY INTEREST (stock ownership/stock options, see 21CFR 54.2(b)):

   For publicly traded companies (interest greater than $50,000 during the time the investigator is carrying out the study and for 1 year following completion of the study):

   Study completed before 2/2/99: Not required (for multicenter studies, all sites must have been completed before 2/2/99)
   Study completed after 2/1/99: REQUIRED

   For non-publicly traded companies (i.e., value can't be easily determined):

   Study completed before 2/2/99: REQUIRED
   Study completed after 2/1/99: REQUIRED

4. SIGNIFICANT PAYMENTS OF OTHER SORTS (e.g., honoraria, consultation fees, research grants, compensation in the form of equipment) that have a total value greater than $25,000 (during the time the investigator is conducting the study and for one year following completion of the study), exclusively of the costs of conducting the clinical study or other clinical studies. If payment was made after 2/1/99, the applicant should report for the time period the study was being conducted and for 12 months after.

   Study completed before 2/2/98: Not required
   Study completed 2/2/98 - 2/1/99: Report payments made between 2/2/99 and 12 months after the study completion date (e.g., if study completed 12/31/98, report payments made 2/2/99 12/31/99)
   Study completed after 2/1/99: REQUIRED

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

/s/

David Orloff
12/21/01 03:02:09 PM

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

/s/

Julie Rhee
12/21/01 04:06:09 PM
CSO

Rhee, H Julie

From: Orloff, David G
Sent: Wednesday, November 28, 2001 5:54 PM
To: Roman, Drago; Rhee, H Julie
Subject: FW: questions about diabetic retinopathy

Dragos and Julie,
We did promise the sponsor that we would get back to them on the retinopathy issue. From Wiley's response, it seems that there is no utility to a short term study. I would be OK with a long-term study in type 1, to be completed as a Phase 4 commitment. Wiley recommends a concurrent control. He suggests 500 patients for 3 years.

So, we can convey to the sponsor that we want a phase 4 commitment for a study of the effects on symlin on retinopathy. The study can be in type 1 or type 2 DM, should be 3 years in duration, and should enroll approx 500 patients. An open-label, concurrent untreated control design is acceptable.

DGO

-----Original Message-----
From: Chambers, Wiley A
Sent: Thursday, November 22, 2001 9:59 PM
To: Orloff, David G
Cc: Roman, Drago; Jenkins, John K
Subject: RE: questions about diabetic retinopathy

-----Original Message-----
From: Orloff, David G
Sent: Tuesday, November 20, 2001 6:07 PM
To: Chambers, Wiley A
Cc: Roman, Drago; Jenkins, John K
Subject: questions about diabetic retinopathy

Wiley,
In the phase 3 trials in Type 2 DM for one of our pending NDAs (Symlin), there was a weak but troubling signal in the AE database suggesting possible risk of progression of proliferative changes. Specifically, across 3 placebo-controlled trials, each with 3 doses of drug, in a single high dose arm, the incidence of AEs in this regard was about twice that of the other arms and the control. (Dragos, I don't have the numbers of events or patients easily accessible. You may want to comment on how many patients/cases this is based on). That arm involved the highest dose in any of the trials. There was no prospective plan to investigate effects on retinopathy (ie, no baseline or follow up exams or photos). These were spontaneous AEs.

As we move forward with this program, we are requiring a repeat study in Type 1 DM to address safe use of the drug with respect to hypoglycemia risk. We are considering asking that they do baseline and follow up retinal surveillance (photos) in a random subset of patients in placebo and drug groups in this 6-12 month trial.

Questions:
1. Are the retinopathic findings, course of disease, etc. in Type 1 and Type 2 sufficiently similar to permit extrapolation from T1 to T2 and thus obviate the need to do a formal study in Type 2?

Response: Retinopathy findings, course of disease, etc as far as the eye is concerned is the same in Type 1 and Type 2. There should be no problem extrapolating from one to the other with respect to the eye.

2. We realize that the trial size and duration we would propose in either diabetic population (T1 or T2) will only exclude a substantial increased risk. However, are we likely to have too low a background incidence of retinopathy in a Type 1 (relative to Type 2) cohort to further bias the study toward a negative result (no evidence of harm induced)?

Diabetic retinopathy is most closely correlated with duration of diabetes. The longer the duration of diabetes, the more likely the patients are to have retinopathy and more likely they are to progress to higher levels of retinopathy. The most difficult thing in the review of your products is that changes to tighter diabetic control, particularly more rapid changes to tighter control have a higher chance of increasing retinopathy in the short run. If the product being studied is particularly effective, it is likely to have an increased rate of retinopathy in a short term trial. Short term in this case is less than 3 years. It is for this reason that our Division requires products trying to get an indication for the treatment, reduction or prevention of diabetic to conduct trials of at least 3 years.

Obviously, this does not mean that all cases of increased diabetic retinopathy are good things, but I am not sure that you are going to be able to separate out, good from bad increases in diabetic retinopathy in short term studies.

3. Is the short-term natural history of diabetic retinopathy sufficiently characterized such that an open-label observational study in type 2 would be of use?

The natural history of diabetic is well characterized, but this characterization includes a variability which is too high to study in less than about 500 patients. This natural history would not include changes in diabetic control. As mentioned above, rapid tighter control is likely to increase retinopathy over the short term.

I think the bottom line in this case will be that the changes observed so far are sufficient to warrant a phase 4 study. The study design would be better if it is concurrently controlled, but should really be conducted for at least 3 years. The best type of follow-up is 7 field photographs performed at baseline, months 3, 6, 9, 12, 18, 24 and 36.

I would be happy to discuss this further with you at your convenience.

Wiley

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

/s/

Julie Rhee
12/11/01 09:04:03 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 9, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-332
Symlin (pramlintide)
Amylin Pharmaceuticals

SUBJECT: Addendum to Division Director memo dated October 1, 2001

This memo is intended to address several outstanding issues related to the Symlin NDA not covered in my memorandum dated October 1, 2001.

A. Drug substance and drug product

1. Pramlintide acetate is manufactured at three different sites: [ ] The pivotal clinical trials to date have utilized drug product made from only the first 2 sites. An issue was raised at the pre-NDA meeting with regard to bridging studies necessary to qualify drug product made from [ ] pramlintide. This has been addressed by studies including amino acid analysis and structural characterization to verify that all three peptide products are identical. In addition, the three drug substances are identical with regard to "bio-identity," that is, in a binding assay to a specific amylin tissue binding site. Peptide degradants resulting under "stressed" conditions are not "active" in this binding assay.
2. The major impurities in both the drug substance (none greater than —, specifications — pure for all three sources) and drug product are peptide degradants. The drug product, regardless of source, has a specification of — purity at release.
3. The major specific peptide degradants differ between the products made from the material from the 3 sources. However, an Ames test of material from all three sources revealed no genotoxic potential. Consistent with ICH guidance, due to the extreme low absolute dose of these degradants, pharm/tox does not feel that additional qualifying toxicology studies will yield useful results and therefore recommends against further testing.
4. Dr. Roman reviewed the antigenicity data (page 69-71 of his review). The antibody response to drug product made from [ ] material was studied in long term trials in Types 1 and 2 diabetes. The percentage of patients with at least one positive test for anti-pramlintide antibodies (by ELISA) ranged, at proposed doses, between 5 and 10%. Two short (14-day) studies in a small number of patients using — material were ongoing at the time of the Dr. Roman's review. No patients had yet tested positive for anti-pramlintide antibodies.

Recommendation:
In conclusion, no further toxicology studies are warranted. The sponsor should be encouraged to use [redacted] Symlin in upcoming trials of safety and efficacy and to include testing for anti-pramlintide antibodies after at least 6-months of treatment in approximately 100 patients.

B. Need for Executive Carcinogenicity Committee concurrence on conclusion of "no drug-related tumors'

1. Dr. Alavi has scheduled the Symlin carcinogenicity studies for discussion at the October 30, 2001, meeting of ECAC.
2. The primary reviewer and team leader concur on the conclusion of "no drug-related tumors" based on review of 2-year studies in mouse and rat.
3. Dr. El Hage has suggested that, if preferred, the labeling with regard to carcinogenicity findings may be withheld until ECAC concurrence is officially obtained.

Recommendation:
The labeling comments can be conveyed in the action letter. These are preliminary and are subject to change as required by the data. This is conveyed in the letter.

C. Drug interaction studies

1. Dr. Roman has commented on the paucity of interpretable "drug-interaction" data in the NDA. The specific issue raised with Symlin relates to pharmacokinetics of orally administered drugs, whose absorption may be delayed and/or reduced by concomitant administration of pramlintide, a drug that acts principally by delaying gastric emptying.

Recommendation:
The above issue should be addressed as a deficiency in the action letter, with general guidance to propose and seek Division concurrence on a battery of "interaction" studies to include drugs likely to be used by the populations in whom Symlin will be prescribed, and specifically addressing whether only rate or rate and extent of absorption are affected for drugs for which either or both are important for therapeutic efficacy or safety.

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

/s/

David Orloff
10/9/01 08:17:20 PM
MEDICAL OFFICER

ADRA Rev #1 of Action Package for NDA 21-332, Symlin (pramlintide acetate) Inj

Reviewer: Lee Ripper, HFD-102 Date: October 3 *and 10*, 2001
Date received in HFD-102: October 2, 2001
Action goal date: October 5, 2001 UF GOAL DATE: October 10, 2001

Indication: [redacted]

Action type: AE RPM: Julie Rhee, 7-6424/Kati Johnson, 7-6380
Drug Classification: 1S Date original NDA received: Dec 8, 2000
505(b)(1) application
Patent Info: Received, acceptable
EER: UN 10/5/01
Clinical Inspection Summary: 7/13/01, studies acceptable.
OPDRA review of tradename: Acceptable 3/21/01
DDMAC review of PI: Not done
Debarment statement: Acceptable
EA: Categorical exclusion
Financial disclosure information/review: See comment #2 below.

1. Dr. Orloff needs to enter his DD review into DFS.

   Done.

2. Financial Disclosure: The MOR lists 6 Phase 3 controlled studies as contributing efficacy data. Financial disclosure information was submitted for only two of these (121, 122). The letter needs to request F.D. information for the remaining four (111, 112, 117, 123).

   Added to letter.

3. Facility Inspections: Withhold issued on [redacted] site on 10/5/01. Needs to be added to letter.

   Added to letter.

4. CMC Rev #2 objects to the [redacted] on the labels as promotional. Julie Rhee is checking with DDMAC for their position on such symbols. In the past, DDMAC has said symbols cannot intervene between the trade name and the established name, but they have not objected to the placement of symbols in other label locations and many labels now have such symbols. In this case, the symbol is to the right of the trade name with the established name under the trade name.

Follow-up: Mark Askine in DDMAC considers the symbol to be intervening material. Dr. Jenkins considers it to be promotional because of the relationship it implies between insulin and pramlintide. Current wording in letter as unacceptable because it is promotional will remain. Since this is an approvable letter with a number of deficiencies, the applicant will be able submit a response if it does not agree.

5. Carcinogenicity review was not completed until recently and has not been taken to the ECAC. As part of our commitment to do a complete review, ECAC/CAC review should take place during the review cycle the carcinogenicity studies are reviewed.

6. See additional comments on letter.

C:\Data\Wpfiles\N21332AE.doc

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

/s/

Leah Ripper
10/10/01 11:18:34 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 1, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-332
Symlin (pramlintide)
Amylin Pharmaceuticals

SUBJECT: NDA review issues and recommended action

Background

Symlin is a 37 amino acid synthetic analogue of human amylin, a human pancreatic polypeptide that is co-secreted with insulin from the beta cell. The sequence of pramlintide differs from amylin by the substitution of proline residues for the native amino acids at three sites. In patients with Type 1 diabetes and absent pancreatic beta cell function, amylin is absent from the plasma. In patients with longstanding Type 2 diabetes and marked beta cell insufficiency, fasting plasma amylin concentrations may still be normal, but, notably, the normal post-prandial increase in portal and systemic concentrations of the hormone is absent.

In preclinical and phase 1 human studies, pramlintide has been shown to inhibit gastric emptying and post-prandial nutrient absorption when administered subcutaneously prior to a meal. In part rationalized as replacement therapy, pramlintide has been developed for mealtime administration in Type 1 and Type 2 diabetes, as an adjunct to insulin (it must be administered separately—the two peptides require different buffering conditions) with an anticipated effect to lower glycemic exposure via an effect on post-prandial glucose excursions and thereby lower HbA1c.

By and large, the phase 3 trials of this drug, comparing in Type 1 and Type 2 diabetes the efficacy and safety of insulin plus pramlintide to insulin plus placebo, were designed such that adjustments in insulin dosage were not permitted. Even in the two trials (one in each disease) that permitted adjustments "consistent with good medical practice," patients did not achieve tight glycemic control according to established guidelines aimed at reducing diabetic complications. This fact is important considering the primary safety issue that arises with this product—hypoglycemia.

Clinical

Efficacy

The efficacy of pramlintide in Type 1 and Type 2 diabetes mellitus was studied in 6 phase 3, blinded, randomized, placebo-controlled trials (3 each in Type 1 and Type 2). The efficacy data from these trials are summarized and analyzed in the reviews by Drs. Misbin and Hoberman. In

both populations, across all the studies, the mean, placebo-subtracted change from baseline in HbA1c in pramlintide treated patients was approximately 0.3 percentage units. Though modest, this effect was consistently observed. Analyses by categorical response from baseline, specifically of so-called durable responders ($\geq$ 0.5% reduction in HbA1c at end of study—26 or 52 weeks) as shown in figures 2-5 of Dr. Hoberman's review, reconfirms the effect of drug. Specifically, for the Type 1 patients, across three studies, anywhere from 2 to nearly 4 times the percentage durable response rate was observed among the patients treated with pramlintide (up to ~37%) than with placebo, albeit with no apparent dose response and with no difference in the mean decrease in HbA1c between durable responders treated with drug versus placebo. In the Type 2 diabetes trials, the percent durable responders with pramlintide is as much as doubled (up to 40%) relative to placebo, with a clear dose effect on response rate. Finally, the average percent reduction in HbA1c for the durable responders was approximately 1.2% for the Type 1 patients and closer to 1.4% for the Type 2.

Safety

While clearly effective, albeit only to a modest extent across the intent-to-treat populations, in the studies conducted thus far, this efficacy comes at the expense of an unacceptable safety profile, specifically related to risk of hypoglycemia. Whether this is related to the method of use employed in the trials to date, specifically the failure to permit adjustments in insulin dose, particularly early in treatment, remains to be proven. In the trials of both Type 1 and Type 2 diabetes, though much more dramatically so in the Type 1 trials, there was an increased incidence relative to placebo of severe hypoglycemia requiring third party intervention.

From Table 14 (page 37) of Dr. Roman's review, we see that over the course of the 26- and 52-week studies, among the Type 1 patients, 25% of pramlintide patients compared to 18% of placebo patients experienced at least one episode of hypoglycemia requiring third-party intervention. For the Type 2 patients, the incidence rates were 9% for pramlintide and 6% for placebo. Table 15 in Dr. Roman's review further clarifies the extent of this adverse effect of pramlintide therapy. It shows the number of subjects with hypoglycemic episodes according to numbers of events per subject, and clearly demonstrates that in both Type 1 and Type 2 diabetes, for virtually any given number of hypoglycemic events experienced, there were markedly more patients on pramlintide than on placebo.

The increased risk of serious hypoglycemia is most marked in the early weeks of treatment. Nevertheless, the increased incidence relative to placebo clearly persists throughout the treatment periods, most marked among the Type 1 patients. Overall, while the absolute incidence of serious adverse events coded as hypoglycemia was higher among the Type 1 patients than among the Type 2 patients treated with pramlintide, an increase relative to placebo was observed in both patient groups. It is important to note again that this increased incidence occurred in the context of only modest mean changes in HbA1c from baseline and in a range well above levels targeted under current guidelines for optimum diabetes care.

The potential clinical significance of this increased risk of hypoglycemia is demonstrated by a finding on further exploration of the safety database of a marked increased incidence, again most notable among the Type 1 diabetics (4-8 fold relative to placebo) of motor vehicle accidents (MVA) associated with hypoglycemia. This outcome further validates the surrogate of low

glucose level with third party intervention as a marker of significant risk and certainly indicates that further investigation of the safe use of pramlintide is required.

The finding of hypoglycemia with Symlin is not unexpected in light of pharmacodynamic studies in patients with Type 1 diabetes showing decreases in postprandial glucose, as opposed to the expected positive spikes, in those treated with insulin plus pramlintide (see page 13 of Dr. Misbin's review). However, Drs. Misbin and Roman have raised the question of whether hypoglycemia unawareness might contribute to the increased risk of accidental injury seen in the pramlintide subjects. Drs. Misbin and Roman recommend that definitive studies be performed to assess whether pramlintide may cause hypoglycemia unawareness. This seems a reasonable and important avenue to pursue with regard to explaining the rash of MVAs seen in the Type 1 patients treated with pramlintide, and a phenomenon that should be excluded as further investigations into the safe and effective use of the drug ensue.

Finally, in one of the studies of Type 2 diabetes, a dose-related effect on the incidence of progression of diabetic retinopathy was observed. Though not seen in the other trials of Type 1 and Type 2 diabetes, the apparent dose-response for this adverse event relied on the marked increased incidence (10.4% of patients) in the 150 mcg TID dose group in this study, a dose higher than administered in any other trial. This finding prompts the recommendation that retinal surveillance be an aspect of future trials of this product.

Labeling
Preliminary labeling comments from ONDC and Pharm/Tox are included in the action letter. Comments on other sections of the label await response to the deficiencies listed in the letter, as further pharmacokinetic and clinical efficacy and safety trials are deemed necessary prior to approval.

Biopharmaceutics
OCPB finds the biopharmaceutics section of the NDA acceptable. However, there are differences in the PK profiles of pramlintide after SQ injection between patients with Type 1 and Type 2 diabetes. Specifically, the bioavailability of pramlintide in Type 2 diabetes is approximately one-half that in Type 1. This is reflected in the dosing scheme for this drug. This is based on separate studies of 10-12 patients each. Dr. Johnson implies in his review that this may be due to differences in technique of administration or differences in skin thickness (adiposity). Dr. Misbin and Dr. Johnson have recommended further investigations of this phenomenon.

Pharmacology/Toxicology
No target organ toxicity was identified in preclinical models except for injection site lesions. The drug was not teratogenic, embryotoxic, or carcinogenic. The drug is approvable from the standpoint of pharmacology/toxicology.

Chemistry/ Microbiology
The CMC package with regard to drug substance and drug product is acceptable as per ONDC.

[ ]

The site inspections completed and reviewed to date are all acceptable. As of the date of this memorandum, the report and recommendation regarding the inspection of the site at [ ] is pending. This site is listed as the finished dosage labeler, finished dosage manufacturer, and finished dosage packager.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.
Microbiology recommends approval based on sterility assurance.

DSI/Data Integrity
Four sites were inspected and the case report forms for 51 patients were compared to source data. Forms 483 were issued for minor deviations at all four sites. The data from all 4 sites were deemed acceptable by DSI.

Dr. Misbin refers on page 7 of his review to one of the sites, at which "16 records were reviewed of the 35 patients randomized." He also refers to another site at which 21 records were examined. These descriptions are inconsistent with the report in the action package from Roy Blay, DSI. Dr. Misbin cites misreporting of one case of hypoglycemia and one MVA. This information is not cited in the DSI report.

However, an email from Roy Blay dated September 10, 2001, states that at one of the sites, one subject experienced a hypoglycemic episode that was reported to the sponsor but not recorded in the clinic notes or the Case Report Form. In addition, he cites another subject as being involved in a motor vehicle accident that did not result in injury, but which was also not, apparently, properly recorded.

As the drug is not to be approved and as additional clinical safety and efficacy studies are to be required, to include methods for complete capture of MVAs and other accidental injury, the issue of Symlin safety will be revisited. Investigational sites for the new trials will require inspection.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts. This is summarized in Dr. Misbin's review.

OPDRA (ODS)/nomenclature
In a review dated March 5, 2001, OPDRA (ODS) has no objections to the name "Symlin." Should this application be approved, the name will have to be re-evaluated.

Advisory Committee
This application was discussed before the Endocrine and Metabolic Advisory Committee on July 26, 2001. The committee voted nearly unanimously that the efficacy of pramlintide had been established in Type 1 and Type 2 diabetes. However, they further voted that insufficient

information could be derived from the trials to date, due to their design, to guide physicians in the effective use of the drug, citing the need for additional study, with allowances for flexible insulin dosing to effect glycemic control according to established guidelines.

With regard to safety, for both Type 1 and Type 2 diabetes, the committee voted that the safety profile of the drug had not been adequately defined and implied that there were inadequate data, therefore, to guide physicians and patients in the safe use of the drug.

Finally, the vote was 8 to 1 against approval for Type 1 diabetes and 6 to 3 against approval for Type 2 diabetes.

Discussion

Drs. Misbin and Roman have pointed out that the persistent increased incidence of hypoglycemia is observed in the context of "waning" efficacy with regard to mean HbA1c. While this may be true, I would suggest that this "waning" efficacy does not necessarily negate the potential clinical utility of this drug. Indeed, the observation, discussed in detail in Dr. Roman's review, that those patients, Type 1 diabetics in particular, who experience nausea in association with pramlintide dosing, in a large percentage of cases, continue to do so throughout the course of the study, suggests that the pharmacologic effect of the drug persists (i.e., there is no obvious tachyphylaxis). The finding of "waning" efficacy is typical of a number of diabetes trials reviewed in this Division and may simply represent the effects of more intensive attention by patients to their disease and compliance with the overall medical regimen early in the trial. In the Symlin trials as in trials of other anti-diabetic drugs, a "u-shaped" progression in HbA1c level over the course of the study is seen in the placebo groups as well as in the active treatment groups, albeit more exaggerated in the latter. The observation of "waning" effectiveness in a clinical trial does not, by definition, define a therapy as ineffective or only temporarily effective in actual clinical use.

Dr. Misbin has raised the issue that the demonstrated modest efficacy of Symlin in both Type 1 and Type 2 diabetes is in patient populations with mean baseline HbA1c of ~9% and that, in large part secondary to restriction imposed by the design of the studies, there are no data to address efficacy under conditions of optimum, ADA-guided treatment of diabetes mellitus. While this is certainly true, it does not invalidate the proof of principle of efficacy of Symlin relative to placebo discussed above.

I agree completely, though, that further studies are needed, on the one hand to characterize more fully the efficacy, but most importantly to establish a safe treatment algorithm, if possible, including methods of initiation of therapy as well as titration of pramlintide and insulin, and perhaps monitoring for continued pharmacodynamic effect, in patients, whether Type 1 or Type 2, treated with this combination.

In addition, while the safety profile of pramlintide, specifically with regard to absolute hypoglycemia risk, appears more favorable for Type 2 diabetes than for Type 1, the finding of increased risk relative to placebo, particularly in the first month, in Type 2 diabetics and the presumed common mechanism of action to affect glycemic control in both Type 1 and Type 2 diabetes, all suggest that the difference in risk is simply a matter off degree. Whether in Type 1

or Type 2 diabetes, the lack of clinical experience to date with a treatment algorithm designed to minimize the risk of hypoglycemia is a critical deficiency of this NDA that must be addressed prior to approval.

Conclusions and Recommendations
This NDA is approvable pending addressing of the following issues raised in review:

Clinical efficacy and safety
The efficacy data from the trials submitted to the NDA support the potential utility of Symlin as an adjunct to insulin therapy in Type 1 and Type 2 diabetes mellitus. However, as used in the studies to date, the safety of pramlintide is unacceptable. Specifically, there was an increased risk of severe hypoglycemia relative to insulin alone, particularly in the first month of therapy, in trials of Type 1 and Type 2 diabetes, as well as an increased risk of serious adverse events including motor vehicle accidents and other injuries seen in the Type 1 trials. Particularly concerning is the potential role of Symlin in the deaths of several patients in the trials of Type 1 diabetes. The safety and effectiveness of Symlin requires further investigation and characterization in patients with Type 1 and Type 2 diabetes under treatment conditions consistent with generally accepted practice in which patients adjust their insulin regimens to optimize glycemic control.

In light of these adverse outcomes and because investigations to date have not excluded a role for Symlin in hypoglycemia unawareness or in altering the threshold for recognition or reaction to hypoglycemia, this phenomenon should be ruled out as further investigations of the safety and effectiveness of Symlin proceed.

In study 137-111 in patients with Type 2 diabetes, an apparent dose-dependent incidence of progression of diabetic retinopathy was observed in the Symlin groups. This potential risk requires further characterization in trials in which retinal monitoring is part of protocol-defined follow-up in an adequate subset of patients.

Biopharmaceutics
Development of a more specific assay for pramlintide, pramlintide metabolite(s), and endogenous amylin is suggested by OCPB, though not stated as a requirement for approval.

In addition, OCPB and the clinical team recommend investigations of the effects of body composition on pramlintide bioavailability. The use of a higher dose in patients with Type 2 diabetes is based on the finding of lower bioavailability in that population, though if this is solely a function of lean body mass or abdominal obesity, then dosage may have to be adjusted for a relatively lean Type 2 diabetic to obviate the risk of hypoglycemia. Finally, studies to determine the optimally safe and effective timing of Symlin and insulin relative to food ingestion should be a component of further development of Symlin.

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

/s/

David Orloff
10/8/01 01:55:51 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-332 /SE_____ - _____

Drug Symlin™ (pramlintide acetate) Applicant Amylin Pharmaceuticals, Inc

RPM Julie Rhee Phone 827-6424

☑505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: ☑S ☐P

Pivotal IND: 39,897

Application classifications:
Chem Class 1S
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary : 8-Oct-2001
Secondary: 8-Dec-2001

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☐ User Fee Paid
  ☑ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... N/A
  Original proposed labeling (package insert, patient package insert) ..... ✓
  Other labeling in class (most recent 3) or class labeling..... N/A
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☑ No
  Immediate container and carton labels ..... ✓
  Nomenclature review ..... ✓

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☐ Materials requested in AP letter

- Post-marketing Commitments
  - Agency request for Phase 4 Commitments ..... N/A
  - Copy of Applicant's commitments .....

- Was Press Office notified of action (for approval action only)? ..... ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper .....

- Patent
  - Information [505(b)(1)] ..... ✓
  - Patent Certification [505(b)(2)] ..... N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] .....

- Exclusivity Summary ..... N/A

- Debarment Statement ..... ✓

- Financial Disclosure
  - No disclosable information ..... ✓
  - Disclosable information – indicate where review is located .....

- Correspondence/Memoranda/Faxes ..... ✓

- Minutes of Meetings ..... ✓
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting 9/7/00
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting ..... ✓
  - Date of Meeting ..... July 26, 2001
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript ..... ✓

- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

- Clinical review(s) and memoranda X

Continued ⇨

- Statistical review(s) of carcinogenicity studies X
- CAC/ECAC report ..... N/A

Appears This Way
On Original

Electronic Mail Message

Date: 9/10/01 3:24:55 PM
From: Robert Misbin (MISBINR)
To: Julie Rhee (RHEEJ)
Cc: Dragos Roman (ROMAND)
Cc: Saul Malozowski (MALOZOWSKIS)
Cc: Steve Johnson (JOHNSONST)
Subject: symlin deficienies

Julie

How is this. Ask Steve and Dragos for their input.

b0b

21-332 deficiency

1 Pramlintide treatment resulted in a small but statistically significant reduction in HbA1c in patients whose baseline is about 9%, provided that their insulin regimen remained constant or nearly so. We have little data on pramlintide in patients whose HbA1c is 8% or less, even though HbA1c of 8% or less is the minimally acceptable goal established by the ADA. It has not been established that pramlintide is safe and effective for treating diabetes in accordance with the generally accepted practice in which patients are allowed to adjust their insulin regimen to optimize glycemic control.

2 The risk of hypoglycemia appears to be increased in patients taking pramlintide relative to patients on insulin alone. Hypoglycemia in pramlintide-treated patients appears be associated with motor vehicle accidents and trauma.

3 Clinical pharmacology studies raise the concern about the possibility that a five-day exposure to pramlintide could cause hypoglycemia unawareness.

4 Studies have failed to establish a dose-response relationship. It is not clear how pramlintide should be dosed. There is no explanation why the bioavailablity of pramlintide in patients with type 2 diabetes is lower than in type 1 diabetes.

4 The possibility of a dose-related progression of diabetic retinopathy in patients with type 2 diabetes on pramlintide was raised by the results of one study.

Additional studies needed for an approvable package are summarized as follows:

Phase 2 studies:

1) Investigate hypoglycemia unawareness

Hypoglycemia should be induced by an intravenous insulin infusion. The rate of infusion should be gradually increased until the patient exhibits signs/symptoms of hypoglycemia. If no signs/symptoms of hypoglycemia develop, the infusion should be terminated when the blood glucose concentration falls to 2 mM. **The object of the study is to determine the plasma glucose threshold at which signs/symptoms of hypoglycemia develop.** Samples should be obtained for

determination of glucose and pramlintide levels. Glucose threshold values at baseline should be compared to values obtained after five days of pramlintide 120 ug tid or placebo. The timing of the pramlintide dose and the insulin infusion should be planned so that the peak pramlintide concentration and glucose nadir will occur at nearly the same time. Subjects should be instructed not to drive or operate machinery during the five days of treatment. Even better would be to perform the study on a clinical research ward. The study should be done in patients with type 1 diabetes who are in reasonably good control (HbA1c 6.5- 8.5 on constant insulin regimen) or in non-obese normal volunteers

2) Bioavailability

The Sponsor should determine why the bioavailability of pramlintide is so much lower in patients with type 2 diabetes than in patients with type 1 diabetes. One presumes that the difference in bioavailability is related to the distribution of body fat, but this has not been clearly established – (Julie add the stuff about the assay specificity here)

Phase 3 studies

The Sponsor should perform two pivotal studies (one in type 1and one in type 2 diabetes) to determine if pramlintide improves glycemic control under conditions in which patients receive treatment with insulin and life-style management in accordance with the recommendations of the American Diabetes Association. These should be 12-month placebo-controlled trials with reduction in hemoglobin A1c levels as the primary measure of efficacy. In order to avoid hypoglycemia in patients with type 1 diabetes, the starting dose of pramlintide should be 15 ug tid with titrations to 30 ug, and 60 ug tid (or 10 ug qid with titration up to 30 ug qid). The dose of pramlintide should remain constant for the last 6 months of the study. Reduction in HbA1c from baseline without an increase in hypoglycemia should be criteria for a successful trial. . For the trial to be considered positive, HbA1c levels should be lower at endpoint than at baseline. In order to prevent hypoglycemia

early in the trial, it might be advisable to instruct patients to reduce their short acting preprandial insulin dose when starting test drug. After the first week on test drug, patients should be instructed to adjust their insulin dose as needed to achieve good glycemic control. They should be informed both in writing and verbally of the finding that pramlintide appears to increase the risk of hypoglycemia and motor vehicle accidents. They should be advised to avoid driving or use of machinery.

Retinal photography should be performed at baseline and at endpoint with a fundoscopic exam at about 6 months. Inclusion criteria should be developed to exclude patients believed to have clinically important or unstable retinopathy.

Prior to initiating the pivotal study in patients with type 2 diabetes, the Sponsor needs to perform the PK study described above. Results of this study will be needed to provide a rationale for dose selection in a pivotal trial. The Sponsor should consider including obese insulin-treated patients who are also taking metformin (2g/d or greater) in their pivotal study.

Julie

Include info from Dragos about how he wants to safety data to be reported.

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

/s/

Julie Rhee
9/10/01 05:54:40 PM
CSO

Electronic Mail Message

Date: 9/10/01 3:48:41 PM
From: Blay, Roy A (BLAYR@A1)
To: Rhee, H Julie (RHEEJ@A1)
Cc: Misbin, Robert I (MISBINR@A1)
Cc: Malozowski, Saul N (MALOZOWSKIS@A1)
Subject: NDA 21-332, Symlin, Adverse events

A letter dated April 16, 2001, was sent to Dr. Clinkingbeard noting that subject # 2216 experienced a hypoglycemic episode that was reported to the sponsor but not recorded in the clinic notes or the Case Report Form.

In reviewing my old e-mails, I have a record of subject # 923 from Dr. Whitehouse's site being involved in a motor vehicle accident that did not result in injury. The investigator stated that the accident was "maybe" related to treatment. This incident was not mentioned in the letter to Dr. Whitehouse that was issued June 11, 2001.

The above information should be sufficient for the sponsor to contact the sites to obtain whatever information they may need. It is my understanding and confirmed in discussions with my colleagues that we do not release our inspection reports of clinical investigators to sponsors. If they wish to obtain this information, they will need to submit a request through FOI.

I hope this is helpful. Please let me know if I can be of further assistance.

Roy

-822-headers:
.eived: from cdsx02.cder.fda.gov
("port 3007"@cdsx02.cder.fda.gov [150.148.145.221])
by mail.cder.fda.gov (PMDF V6.0-24 #37497)
with ESMTP id <01K86E3UQTUY95MO4L@mail.cder.fda.gov>; Mon,
10 Sep 2001 15:48:01 -0400 (EDT)
Received: by cdsx02.cder.fda.gov with Internet Mail Service (5.5.2653.19)
id <S2F97G8H>; Mon, 10 Sep 2001 15:47:37 -0400
X-Mailer: Internet Mail Service (5.5.2653.19)

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

/s/

Julie Rhee
10/2/01 08:50:55 AM
CSO

Electronic Mail Message

Date: 9/7/01 4:42:41 PM
From: Robert Misbin (MISBINR)
To: David Orloff (ORLOFFD)
To: Julie Rhee (RHEEJ)
To: Saul Malozowski (MALOZOWSKIS)
To: Dragos Roman (ROMAND)
Cc: Roy Blay (BLAYR)
Subject: amylin letter of August 30

Julie

re: Inspection results:

Amylin has requested the EIR relating to the two patients mentioned in my briefing document.

The patient with hypoglycemia was at Dr Clinkingbeard's site

The patient with a motor vehicle related event (reported only as hypoglycemia) was from Dr Whitehouse's site.

I am sending a copy of this e mail to Roy Blay so that he can forward the EIR's to you. You can send them along to Amylin.

bOb

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

/s/

Julie Rhee
10/2/01 08:54:25 AM
CSO

Electronic Mail Message

Date: 7/30/01 1:16:49 PM
From: Blay, Roy A (BLAYR@A1)
To: Rhee, H Julie (RHEEJ@A1)
Subject: NDA 21-332 Clinical Summary

I'm not sure what's happening. I've sent it three times, but in the process, the attachment is separated from my message and doesn't go forward. One more time!

<<21332.doc>>

Roy

11 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: August 1, 2001

To: Joann Data, M.D., Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** (301) 443-9282
Phone number: 858-642-7324	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin Injection (pramlintide acetate)
CMC review comments for the drug product.

Total no. of pages including cover: 2

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed:

NDA 21-332 Symlin™ Injection (pramlintide acetate)

Date of submission: December 7, 2000

Chemistry, Manufacturing, and Controls review (for drug product) comments

I. Specifications:

Since biological activity has not been presented for related compounds, these compounds should be referred to in the specifications as "Product-related Impurities" rather than "Related Substances". A revised specification sheet should be submitted.

II. Methods Validation:

The drug product validation methods are described by reference to the drug substance validation methods and separate standard operating procedures (SOPs) for sample preparation. A stand-alone section for the drug product validation methods should be provided.

III. Labeling:

Carton labels:

1. The [redacted] to the right of the drug name, in both the immediate container and the carton labels, should be removed.
2. The carton label of the 0.6 mg/mL strength should read "5 mL Vial" [redacted]

Package Insert:

1. In the Description Section, a range for "x" [redacted] should be given.
2. The DOSAGE AND ADMINISTRATION Section should contain the following statement: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permits".
3. The name and address of the drug product manufacturer (or the sponsor's headquarters) should be part of the How Supplied Section.

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

/s/

Julie Rhee
8/1/01 04:34:30 PM
CSO

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** August 1, 2001
Re: 7/31/01 submission Background: After I had left for the day on July 27, Ms. Zimmer left a voice mail on my answering machine requesting a meeting or a t-con sometime this week (week of 7/30). I called her back on Monday (7/30) and informed her that I need a written meeting request, according to the MaPP, before I could schedule it. I also mentioned that because of vacation schedule, we won't be able to meet with them until September. I have not received the meeting request yet. In the 7/31/01 letter, Dr. data refers to have a meeting soon after Dr. Orloff returns to the office. ********** I called Dr. Data to inform her that I have not received a meeting request yet. But since Dr. Data was not available, I spoke with Ms. Zimmer and informed her that we have not received a meeting request yet. Ms. Zimmer informed me that they are working on the request and asked if it could be a Type A meeting. I stated that since the NDA has already been submitted and, therefore, the drug development is not depended on the outcome of this meeting, I don't think it would be qualified as a Type A meeting. I informed her that it would be a Type C meeting. However, I informed her that that doesn't mean we'll delay scheduling the meeting. I also stated that I would schedule the meeting as soon as everyone is available. --- **Name: Julie Rhee**	**NDA#:** 21-332 **Telecon/Meeting initiated by:** O FDA **By:** Telephone **Product Name:** Symlin **Firm Name:** Amylin **Name and Title of Person with whom conversation was held:** Ms. Donna Zimmer Manager Regulatory Submissions **Phone:** (858) 642-7268

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

/s/

Julie Rhee
8/1/01 01:31:15 PM
CSO

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** July 30, 2001
Background: The sponsor left a voice mail on my phone late last Friday afternoon requesting a meeting or a t-con this week to discuss the NDA data base. I returned the call this morning and asked for a written meeting request as outlined in the MaPP. I also informed them that because of vacation schedule, the earliest we could meet would be in September. ********** Dr. Saul Malozowski and I called Dr. Data and discussed the following: 1. The Agency does not have any concern regarding data integrity and is waiting for the Division of Scientific Investigation's report. If there is any question, we'll get back to the sponsor. 2. Submit two undisclosed cases, which were mentioned during the 7/26/01 Advisory Committee meeting, for our review. 3. Dr. Malozowski commended the sponsor for their prompt response to our information requests in the past. --- **Name: Julie Rhee**	**NDA#:** 21-332 **Telecon/Meeting initiated by:** O FDA **By:** Telephone **Product Name:** Symlin **Firm Name:** Amylin Pharmaceuticals **Name and Title of Person with whom conversation was held:** Joann Data, M.D., Ph.D. **Phone:**

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

/s/

Julie Rhee
7/31/01 12:04:05 PM
CSO

11 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Rhell

Food and Drug Administration
Rockville MD 20857

JUL 19 2001

Kenneth Boren, M.D.
560 W. Brown Road, Suite 3006
Mesa, Arizona 85201-3225

Dear Dr. Boren:

Between April 3 and April 12, 2001, Mr. Randall Johnson, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #137-121) of the investigational drug, Symlin™ (pramlintide acetate) performed for Amylin Pharmaceuticals, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that there was a deviation from pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

You did not obtain updated informed consent for those subjects who had previously provided informed consent prior to 1998. The protocol was revised to include additional clinic visits in an amendment dated January 6, 1998; however, those subjects who gave consent prior to 1998 were not re-consented, as would have been required given the protocol revision.

We appreciate the cooperation shown Mr. Henry during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

John R. Martin M.D.

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-510/Doc. Room/NDA 21-332
HFD-510/Rhee
HFD-510/Misbin
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #010403
HFD-46/Blay
HFD-46/Martin
HFR-PA250/Kozick
HFR-PA2565/Koller
HFR-PA2530/Johnson

Field Classification: VAI
Headquarters Classification:

_____1)NAI
__x__2)VAI (no response required)
_____3)VAI-R (30 day response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

__x_inadequate consent form
____inadequate drug accountability
____deviation from protocol
____inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

E:/blay/boren.rab
r/d: drafted/rab/7.13.01
reviewed by:jrm:7/18/01
final type:jau:7/18/01

Note to Review Division:

Our review of the inspection report and associated exhibits provided to us regarding the inspection of this clinical investigator concludes that the data at this site appears to be acceptable for use in support of the NDA submission. 30 subjects enrolled in the study. 26 subjects completed the study. The investigator reviewed 23 of the case report forms. Our final classification of this inspection is Voluntary Action Indicated (VAI).

3 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 3, 2001

To: Ms. Donna Zimmer	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** (301) 443-9282
Phone number: 858-552-2200	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin

Total no. of pages including cover: 2

Comments:

CMC review comments. Please let me know when we could expect your response. Thank you.

Document to be mailed: ☐ YES ☑ NO

NDA 21-332 Symlin (pramlintide acetate)

Date of submission: December 7, 2000

Chemistry, Manufacturing, and Controls review comments

Based upon our review of NDA #21-332, we have the following additional information requests on the drug substance:

1. With respect to bioassay (bioidentity) for pramlintide, the test method as well as the testing results, which were previously submitted to IND #39,987, should be provided.

2. [ ] programs are given in Tables 3, 4 and 5 (pp. 61 to 62 in Vol. 1.15). Please clarify which of these [ ] programs is used for the method of [ ] during identity testing and determination of potency, purity, and related substance content in bulk drug substance.

3. As noted on pages 73 and 74 (Vol. 1.15), there are two methods used to calculate the assay value for each drug substance lot. [ ] Please clarify whether [ ]

4. Regarding the HPLC column used for quantitative determination of [ ] contents, the following information should be provided:

   i. Column material [ ]

   ii. Particle size and pore size

5. The GC method [ ] is utilized for quantitative determination of [ ] in pramlintide acetate. Please clarify [ ]

6. Please clarify which test (e.g., peptide mapping, sequencing, bioassay) is used for lot-to-lot release of the drug substance.

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

/s/

Julie Rhee
7/3/01 07:08:09 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 17, 2001

To: Joann Data, Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** (301) 443-9282
Phone number: 858-552-2200	**Phone number:** (301) 827-6424

Subject: Discipline Review Completed for NDA 21-332 Symlin™

Total no. of pages including cover: 2

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☑ NO

NDA 21-332 Symlin™

Date of submission: April 10, 2001

Microbiology review comment

Reference is made to your amended New Drug Application dated 10 April 2001 for NDA 21-332, Symlin™ (pramlintide acetate). The submission was reviewed for microbiological issues concerning sterility assurance and the following issues were not completely addressed. Please provide an amendment to address the following concerns.

Results of the [redacted] should be submitted, reviewed, and found acceptable prior to approval of the application. These data should be submitted as soon as they are available.

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

/s/

Julie Rhee
5/17/01 03:50:06 PM
CSO

Electronic Mail Message

Date: 5/9/01 10:33:25 AM
From: Julie Rhee (RHEEJ)
To: dzimmer@amylin.com
Subject: FWD: Delivery Notification: Delivery has failed

Hi Donna,

It happened again--I hit "Reply" button and received the error message.

By the way, could you please let me know number of patients who are on Symlin in the extension study?

Thanks,

Julie

Electronic Mail Message

Date: 5/9/01 10:07:00 AM
From: Julie Rhee 301-827-6424 FAX 301 (RHEEJ@A1)
Subject: Re: Amylin NDA - 21-332 - Additional Clinical Review Questions - Revi sed Page 3

Hi Donna,

Yes. Please include Question 7 in your response.

Thanks,

Julie

>Hi Julie,
>Thank you for the revised page 3 sent via fax. If there are any
questions
>from our clinical group, I'll let you know tomorrow. I did read your
note
>that you have asked that the revised page 3 (May 8th) replace the
previous
>page 3 (May 3). I did notice that question 7 is now not noted on the
>revised page 3. Do you want to add question 7 on this page so that the
same
>information appears as it did previously, with the exception of the
revised
>changes?
>Thanks.
>Donna

his is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Rhee
5/9/01 10:59:24 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 8, 2001

To: Joann Data	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-625-0737	**Fax number:** (301) 443-9282
Phone number: 858-552-2200	**Phone number:** (301) 827-6424

Subject: NDA 21-332 Symlin™
Please replace Page 3 of our 5/3/01 fax with the attached Page 3 (revised 5/8/01).

Total no. of pages including cover: 2

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☑ NO

5. Please provide the following analysis concerning **sponsor-defined hypoglycemia** in the long-term clinical trials of type 1 and type 2 diabetes:

	First 4 weeks		4 weeks to the end of the study		Whole study	
	Pramlintide	Placebo	Pramlintide	Placebo	Pramlintide	Placebo
Number and incidence of subjects with at least one episode of hypoglycemia						
Patient time (years)						
Number of hypoglycemic events						
Number of hypoglycemic events per one year of patient time						

Please provide the above table format for type 1 diabetes (one cumulative table for all three type 1 diabetes trials, and one table for each individual trial: 137-121, 137-112, and 137-117) and for type 2 diabetes (one cumulative table, and one separate table for each individual long term trial: 137-122 and 137-123).

6. Please fill in the information for the following table **and list if the event was associated with hypoglycemia.**

	Type 1 diabetes		Type 2 diabetes	
	Pramlintide (number of subjects)	Placebo (number of subjects)	Pramlintide (number of subjects)	Placebo (number of subjects)
Motor vehicle accidents				
Other accidents (bicycle, power tools, falls, fractures,etc.).				

* Please include **all forms of driving related events** (including events that did result in property damage, traffic violations, near missed collisions, etc.); **please provide patient and study number (including narrative or electronic path to the individual subject information).**

Electronic Mail Message

Date: 5/3/01 10:08:33 AM
From: Dragos Roman 301-827-6430 FAX (ROMAND@A1)
To: H JULIE RHEE (FDACD) (RHEEJ@A1)
Subject: symlin

New final version. Dragos

Appears This Way
On Original

During the review process of NDA 21-332 (pramlintide acetate) several questions have come up which require further clarification. In order to answer these questions in a timely fashion, we are attaching a list of specific information requests and analyses that will help substantially the review process. It would greatly facilitate the progress of our review if you could provide this information within the next few weeks. We apologize, in advance, if these matters have already been dealt with in the submission. Please, fill free to send the individual analyses as they become available to you in order to be looked at promptly and efficiently. Also, please feel free to contact us for any clarifications deemed necessary.

1. The inclusion criteria regarding stability of insulin dose are unclear. In study 123, for example, the study report states that insulin dose could not have changed by more than 10% within 2 months of the 4 week placebo-run in. But later, it states that insulin dose should not have changed by more than 20% before randomization. Please explain this discrepancy.

2 The early responder analysis appears to be a useful way to identify the major effects of the drug. In trial 117, Table 14 vol. 157 gives the proportion of ITT population who are "early responders" (defined as reduction in HBA1c of at least 0.5% units at 4 weeks), changes from baseline to endpoint in HbA1c, weight and insulin dose, and the rate of hypoglycemia through out the study. Please revise these tables to provide the following:

Baseline HbA1c and reduction at 4 weeks

Rate of hypoglycemia and incidence for the first four weeks only

Comments on analysis to detect differences between pramlintide and placebo

Please provide six such revised tables, one for each of the phase 3 trials. Also, please provide two additional tables (one for the trials in type 1 and one for the trials in type 2) in which data from the three individual trials are pooled (pool the placebo arms from each of the three trials and all the pramlintide arms).

Overall Efficacy in "Early Glycemic responder" subgroup
(vol. 157 table 14)

	Placebo	90 bid	60 tid	90 tid
% of ITT	25%	41%	44%	44%
Baseline HbA1c	?	?	?	?
Change				
HbA1c 26 wks	-0.48	-0.42	-0.55	-0.49
Insulin, units	+1.9	-2.0	-4.1	+0.6
Weight, kg	+1.0	-0.4	-2.0	-1.6
Severe Hypoglycemia 0-26 weeks	0.2	2.2	1.0	2.1

	Placebo	90 bid	60 tid	90 tid
% of ITT	25%	41%	44%	44%
Change				
HbA1c 4 wks	?	?	?	?
Insulin, units	?	?	?	?
Weight, kg	?	?	?	?
Severe Hypoglycemia 0-4 weeks	?	?	?	?

3. Tables 24 and 57 of the integrated summary of efficacy use the ITT population to show the relationship between nausea and HbA1c. Please give tables for the evaluable population. Tables 28 and 59 use the evaluable population to show the relationship between nausea and weight loss. Please give tables for the ITT population.

4 Please search the data base to identify patients who may have experienced

medication errors regarding insulin or pramlintide.

5. Please provide the following analysis concerning **sponsor-defined hypoglycemia** in the long-term clinical trials of type 1 and type 2 diabetes:

	First 4 weeks		4 weeks to the end of the study		Whole study	
	Pramlintide	Placebo	Pramlintide	Placebo	Pramlintide	Placebo
Number and percentage of subjects with hypoglycemia						
Patient time (years)						
Incidence (per year)						
Number of hypoglycemic events						
Number of hypoglycemic events per one year of patient time						

Please provide this table format for type 1 diabetes (one cumulative table for all three type 1 diabetes trials, and one table for each individual trial: 137-121, 137-112, and 137-117) and for type 2 diabetes (one cumulative table, and one separate table for each individual long term trial: 137-122 and 137-123).

6. Please fill in the information for the following table **and list if the event was**

associated with hypoglycemia.

	Type 1 diabetes		Type 2 diabetes	
	Pramlintide (number of subjects)	Placebo (number of subjects)	Pramlintide (number of subjects)	Placebo (number of subjects)
Motor vehicle accidents				
Other accidents (bicycle, power tools, falls, fractures,etc.).				

* Please include **all forms of driving related events** (including events that did result in property damage, traffic violations, near missed collisions, etc.); **please provide patient and study number (including narrative or electronic path to the individual subject information).**

7. Please provide the following information for the subjects involved in the **endpoint hypoglycemic challenge** in studies AP93-02, AP93-03, AP93-08:

AP93-02 Trial		Pramlintide serum level for each subject	Pramlintide dose prior to the challenge for each subject (to be correlated with the individual serum level from the previous column)
Peak hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=3)		
	Subjects **unaware** of symptoms of hypoglycemia (=9)		
Trough hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=6)		
	Subjects **unaware** of symptoms of hypoglycemia(=6)		

AP93-03 Trial		Pramlintide serum level for each subject	Pramlintide dose prior to the challenge for each subject (to be correlated with the individual serum level from the previous column)
Peak hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=13)		
	Subjects **unaware** of symptoms of hypoglycemia (=7)		
Trough hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=8)		
	Subjects **unaware** of symptoms of hypoglycemia(=4)		

For the **AP93-08** trial:

	Individual pramlintide serum level(endpoint)	Individual hypoglycemia rating (baseline and endpoint for each subject, to be correlated with the serum level from previous column)
Pramlintide 30g group (=14 subjects)		
Pramlintide 100g group (=16 subjects)		
Pramlintide 300g group (=10 subjects)		

Please, cross-reference all the information to the data location in the electronic NDA submission.

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

/s/

Julie Rhee
5/3/01 10:37:22 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: May 3, 2001

To: Joann Data, M.D., Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 858-552-2212	**Fax number:** (301) 443-9282
Phone number: 858-552-2200	**Phone number:** (301) 827-6424

Subject: Discipline Review Completed for NDA 21-332 Symlin
Additional clinical information request

Total no. of pages including cover: 6

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☑ NO

NDA 21-332 Symlin™ (pramlintide acetate)

Date of submission: December 7, 2000

Additional information request (Clinical)

During the review process of NDA 21-332 (pramlintide acetate), several questions have come up which require further clarification. In order to answer these questions in a timely fashion, we are attaching a list of specific information requests and analyses that will help substantially the review process. It would greatly facilitate the progress of our review if you could provide this information within the next few weeks. We apologize, in advance, if these matters have already been dealt with in the submission. Please, fill free to send the individual analyses as they become available to you in order to be looked at promptly and efficiently. Also, please feel free to contact us for any clarifications deemed necessary.

1. The inclusion criteria regarding stability of insulin dose are unclear. In study 123, for example, the study report states that insulin dose could not have changed by more than 10% within 2 months of the 4 week placebo-run in. But later, it states that insulin dose should not have changed by more than 20% before randomization. Please explain this discrepancy.

2. The early responder analysis appears to be a useful way to identify the major effects of the drug. In trial 117, Table 14 vol. 157 gives the proportion of ITT population who are "early responders" (defined as reduction in HBA1c of at least 0.5% units at 4 weeks), changes from baseline to endpoint in HbA1c, weight and insulin dose, and the rate of hypoglycemia through out the study. Please revise these tables to provide the following:

   i. Baseline HbA1c and reduction at 4 weeks.
   ii. Rate of hypoglycemia and incidence for the first four weeks only.
   iii. Comments on analysis to detect differences between pramlintide and placebo.

   Please provide six such revised tables, one for each of the phase 3 trials. Also, please provide two additional tables (one for the trials in type 1 and one for the trials in type 2) in which data from the three individual trials are pooled (pool the placebo arms from each of the three trials and all the pramlintide arms).

Overall Efficacy in "Early Glycemic responder" subgroup (vol. 157 table 14)

	Placebo	90 bid	60 tid	90 tid
% of ITT	25%	41%	44%	44%
Baseline HbA1c	?	?	?	?
Change				
HbA1c 26 wks	-0.48	-0.42	-0.55	-0.49
Insulin, units	+1.9	-2.0	-4.1	+0.6
Weight, kg	+1.0	-0.4	-2.0	-1.6
Severe Hypoglycemia 0-26 weeks	0.2	2.2	1.0	2.1

	Placebo	90 bid	60 tid	90 tid
% of ITT	25%	41%	44%	44%
Change				
HbA1c 4 wks	?	?	?	?
Insulin, units	?	?	?	?
Weight, kg	?	?	?	?
Severe Hypoglycemia 0-4 weeks	?	?	?	?

3. Tables 24 and 57 of the integrated summary of efficacy use the ITT population to show the relationship between nausea and HbA1c. Please give tables for the evaluable population. Tables 28 and 59 use the evaluable population to show the relationship between nausea and weight loss. Please give tables for the ITT population.

4 Please search the data base to identify patients who may have experienced medication errors regarding insulin or pramlintide.

5. Please provide the following analysis concerning **sponsor-defined hypoglycemia** in the long-term clinical trials of type 1 and type 2 diabetes:

	First 4 weeks		4 weeks to the end of the study		Whole study	
	Pramlintide	Placebo	Pramlintide	Placebo	Pramlintide	Placebo
Number and percentage of subjects with hypoglycemia						
Patient time (years)						
Incidence (per year)						
Number of hypoglycemic events						
Number of hypoglycemic events per one year of patient time						

Please provide the above table format for type 1 diabetes (one cumulative table for all three type 1 diabetes trials, and one table for each individual trial: 137-121, 137-112, and 137-117) and for type 2 diabetes (one cumulative table, and one separate table for each individual long term trial: 137-122 and 137-123).

6. Please fill in the information for the following table **and list if the event was associated with hypoglycemia.**

	Type 1 diabetes		Type 2 diabetes	
	Pramlintide (number of subjects)	Placebo (number of subjects)	Pramlintide (number of subjects)	Placebo (number of subjects)
Motor vehicle accidents				
Other accidents (bicycle, power tools, falls, fractures,etc.).				

* Please include **all forms of driving related events** (including events that did result in property damage, traffic violations, near missed collisions, etc.); **please provide patient and study number (including narrative or electronic path to the individual subject information).**

7. Please provide the following information for the subjects involved in the **endpoint hypoglycemic challenge** in studies AP93-02, AP93-03, AP93-08:

AP93-02 Trial		Pramlintide serum level for each subject	Pramlintide dose prior to the challenge for each subject (to be correlated with the individual serum level from the previous column)
Peak hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=3)		
	Subjects **unaware** of symptoms of hypoglycemia (=9)		
Trough hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=6)		
	Subjects **unaware** of symptoms of hypoglycemia(=6)		

AP93-03 Trial		Pramlintide serum level for each subject	Pramlintide dose prior to the challenge for each subject (to be correlated with the individual serum level from the previous column)
Peak hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=13)		
	Subjects **unaware** of symptoms of hypoglycemia (=7)		
Trough hypoglycemia challenge group	Subjects **aware** of symptoms of hypoglycemia(=8)		
	Subjects **unaware** of symptoms of hypoglycemia(=4)		

For the **AP93-08** trial:

	Individual pramlintide serum level(endpoint)	Individual hypoglycemia rating (baseline and endpoint for each subject, to be correlated with the serum level from previous column)
Pramlintide 30µg group (=14 subjects)		
Pramlintide 100µg group (=16 subjects)		
Pramlintide 300µg group (=10 subjects)		

Please, cross-reference all the information to the data location in the electronic NDA submission.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** April 6, 2001
I called Ms. Zimmer and informed her that we're sending an information request letter to one of their DMF holder, [ ] She asked me if I could tell her what the issues are and I said I couldn't since DMF is confidential. I suggested that she contact the DMF holder and discuss it with them. --- **Name: Julie Rhee**	**NDA#:** 21-332 **Telecon/Meeting initiated by:** ○ FDA **By:** Telephone **Product Name:** Symlin **Firm Name:** Amylin Pharmaceutical **Name and Title of Person with whom conversation was held:** Ms. Donna Zimmer Regulatory Affairs **Phone:** (858) 642-7268

/s/

Julie Rhee
4/6/01 01:09:41 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: March 28, 2001

To: Joann Data, M.D., Ph.D.	**From:** Julie Rhee
Company: Amylin Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (858) 625-0737	**Fax number:** (301) 443-9282
Phone number: (858) 642-7324	**Phone number:** (301) 827-6424

Subject: Discipline Review for NDA 21-332 Symlin

Total no. of pages including cover: 3

Comments: Please let me know when I could expect your response. Thank you.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed:

NDA 21-332 Symlin™ (pramlintide acetate)

Date of submission: December 7, 2000

Microbiology Review #1 Comments

Reference is made to your New Drug Application dated 7 December 2000, for NDA 21-332, Symlin™ (pramlintide acetate). The submission was reviewed for microbiological issues concerning sterility assurance and the following issues were not completely addressed. Please provide an amendment to address the following concerns.

1. [ ]. The maximum holding time from [ ] of the drug product solution used to fill vials is —. This difference should be explained.

2. [

]

3. The media fill experiment used to validate [ ] for the product should be explained in greater detail. For example: At what temperature was the media held? Was the media filled into vials? How was the media examined?

4. [ ] sterilization validation of [ ] used to close the 5-mL vials was conducted using —. It has been shown that [ ] If possible, validation studies should be completed with [ ]

5. The [ ] time for the bulk product should be incorporated into media fill validations.

6. The application states that [ ] may be used for [ ] sterilization. Only validation data for sterilization [ ] were provided. Validation data for the sterilization of these components in [ ] should be provided.

7. Validation data demonstrating the [ ] should be provided.

8. Sterilization validation of the [ ] used [ ] It has been shown that [ ]. If possible, validation studies should be completed [ ]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

/s/

Julie Rhee
3/28/01 03:29:34 PM
CSO

AMYLIN PHARMACEUTICALS

Joann Data, M.D., Ph.D.
AMYLIN PHARMACEUTICALS, INC
9373 Towne Centre Drive, Suite 250
San Diego, CA 92121
Tel: 858/642-7324
Fax: 858/625-0737

FAX TRANSMISSION

DATE: March 29, 2001

TO: Ms. Julie Rhee, Project Manager
FDA/CDER

FAX NO: (301) 443-9282

FROM: Joann Data
Senior Vice President, Regulatory Affairs & QA

RE: Discipline Review for NDA 21-332 Symlin

Number of pages being transmitted including this sheet: 1

Julie,

Thank you for your fax dated March 28, 2001 regarding the microbiology review of NDA 21-332. The questions/issues raised by the Agency have been forwarded to the appropriate people within Amylin to handle. I have been informed that we will be able to provide rather rapid turnaround for questions 1, 2 and 5. I will be able to provide you with a fixed date on Monday, April 2. Questions 3, 4, 6, 7 and 8 will require additional work particularly with our vendors. Our goal is to have some tentative dates by April 2 regarding those responses. I will follow-up with you on Tuesday, April 3 to provide you with more specific information.

We plan to fax back the answers and also send as a supplement to the NDA. Should the reviewer(s) prefer to have a telephonic discussion of the questions, Amylin would be willing to provide answers in that manner as well either before or after the above mentioned submission.

Joann

If you do not receive the entire transmission, please call Donna Zimmer at (858) 642-7268.

Electronic Mail Message

e:	1/26/01 4:24:56 PM	
rom:	Roy Blay	(BLAYR)
To:	Robert Misbin	(MISBINR)
Cc:	Julie Rhee	(RHEEJ)
Subject:	NDA 21-332, Symlin, Study Site Closure	

I requested inspection information from two sites for each of the two phase 3 studies (#s 112 and 121). Ms. Zimmer of Amylin called me today and said [ ] has closed. I will still get the information that was generated at this site, but, of course, it is now impossible to conduct an inspection there. Since we can't do an inspection there, we cannot verify the data. Therefore, you may wish to consider whether this data should be used in support of the NDA.

I plan on picking another site to substitute for [ ] Please call me if you have any questions.

Roy

MEMORANDUM OF MEETING MINUTES

Meeting Date: January 17, 2001
Time: 3:00 – 3:30 p.m.
Location: Parklawn Bldg. 14B45
Application: NDA 21-332 Symlin™ (pramlintide acetate)
Sponsor: Amylin Pharmaceuticals, Inc.
Type of Meeting: NDA filing
Meeting Recorder: Julie Rhee
Attendees:

David Orloff, M.D., Director, DMEDP
Saul Malozowski, M.D., Medical Team Leader, DMEDP
Robert Misbin, M.D., Medical Officer, DMEDP
Dragos Roman, M.D., Medical Officer, DMEDP
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP
Chien-Hua Niu, Ph.D., Chemist, DMEDP
Jeri El-Hage, Ph.D., Pharm/Tox Team Leader, DMEDP
Fred Alavi, Ph.D., Pharmacologist, DMEDP
Hae-Young Ahn, Ph.D., Biopharm Team Leader, DOP II
Todd Sahlroot, Ph.D., Statistical Team Leader, DOB II
David Hoberman, Ph.D., Statistician, DOB II
Roy Blay, Ph.D., Clinical Investigator, DSI
Kathleen Reedy, Health Scientist Administrator, Advisory Committee Staff
Julie Rhee, Project Manager, DMEDP

Proposed Indication:

[

]

Discussions:

1. The application is fileable from the following disciplines:
   a. Clinical
   b. Pharm/Tox
   c. Chemistry
   d. Biopharm
   e. Statistical
   f. Microbiology (by e-mail)

2. Studies 112 and 121 are chosen for a clinical audit.

3. Since Symlin™ is a first one in its class, the NDA will be discussed at the July 26, 2001, Advisory Committee meeting. Symlin™ requires additional injections since it is indicated as an adjunct therapy to insulin and cannot be mixed with insulin.

4. Executive summary for clinical, pharm/tox, biopharm, and statistical sections need to be forwarded to Ms. Reedy by June 22 in preparation for the July 26 AC meeting. A target date for the executive summary completion is June 1.

5. A target date for CMC and microbiology review completion is June 22, 2001.

Conclusions:

1. NDA is filed. The primary UF due date is October 8 and the secondary due date is December 8, 2001.

2. This NDA is to be discussed at the July 26, 2001, AC meeting. A target date for executive summary completion for all disciplines, except chemistry and microbiology, are June 1.

R/D by JRhee 1/31/01
Concurred by: Malozowski 1-31-01/Roman 1-31-01/Alavi 2-5-01/Misbin 2-6-01/Ahn 2-6-01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-332

12/17/00

Amylin Pharmaceuticals, Inc.
Attention: Joann L. Data, M.D., Ph.D.
Sr. Vice President, Regulatory Affairs and Quality Assurance
9373 Towne Centre Drive, Suite 250
San Diego, CA 92121

Dear Dr. Data:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Symlin (pramlintide acetate) Injection
Review Priority Classification:	Standard (S)
Date of Application:	December 7, 2000
Date of Receipt:	December 8, 2000
Our Reference Number:	NDA 21-332

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 6, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 8, 2001, and the secondary user fee goal date will be December 8, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55, please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Enid Galliers
12/17/00 08:11:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-332

Amylin Pharmaceuticals, Inc.
Attention: Joann L. Data, M.D., Ph.D.
Senior Vice President, Regulatory Affairs and Quality Assurance
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121-3030

Dear Dr. Data:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symlin (pramlintide acetate) injection.

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2004. The purpose of the meeting was to discuss overall development program of Symlin.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of the July 21, 2004, meeting minutes

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive, Suite 250
San Diego, CA 92121

2. TELEPHONE NUMBER *(Include Area Code)*

(858) 552-2200

3. PRODUCT NAME

SYMLIN™ Injection (pramlintide acetate)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

N/A

6. LICENSE NUMBER / NDA NUMBER

N021332

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. *HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?* ☒ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Mark J. Foldi	Vice President, CFO	12/1/00

FORM FDA 3397 (5/98)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 1 2000

Joann L. Data, M.D., Ph.D.
Senior Vice President
Regulatory Affairs and Quality Assurance
Amylin Pharmaceuticals, Inc.
9373 Towne Centre Drive
Suite 250
San Diego, CA 92121

RE: Amylin Pharmaceuticals, Inc., New Drug Application 21-332
Small Business Waiver Request 2001.003

Dear Dr. Data:

This letter responds to your August 1, 2000, letter requesting a waiver of the human drug application fee for the new drug application (NDA) for pramlintide acetate injection under the small business waiver provision of section 736(d)(1)(E)[1] of the Federal Food, Drug, and Cosmetic Act (the Act)[2] (Waiver Request 2001.003). For the reasons described below, the Food and Drug Administration (FDA) grants the request from Amylin Pharmaceuticals, Inc. (Amylin), for a small business waiver of the application fee.

According to your waiver request, Amylin currently employs fewer than 500 individuals, including employees of your affiliates. Amylin did not name any affiliates in its waiver request. You also state that the pramlintide injection application will be the first human drug application Amylin will submit to the Agency for review.

Under the Act, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[3] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets two criteria: first, a business must employ fewer than 500 persons, including employees of

---

[1]21 U.S.C. 379h(d)(1)(E).

[2]Sections 735 and 736 of the Act (21 U.S.C. 379g and 379h).

[3]"The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly - (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

its affiliates, and second, the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant a small business waiver to Amylin is based on the findings outlined below. First, by letter dated November 6, 2000, the Small Business Administration (SBA) determined that Amylin had fewer than 500 employees, including those of its affiliate, Amylin Europe Ltd. Second, according to FDA records, the marketing application for pramlintide acetate injection, NDA 21-332, will be the first human drug application, within the meaning of the Act, to be submitted to FDA by Amylin Pharmaceuticals, Inc., or its affiliates. Consequently, your request for a small business waiver of the application fee for pramlintide acetate injection is granted.

FDA records show that NDA 21-332 has not yet been submitted. Please include a copy of this letter with your NDA when it is submitted. If FDA refuses to file the application or Amylin withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Amylin should contact this office, approximately 90 days before it expects to resubmit its marketing application, to determine whether Amylin continues to qualify for a waiver.

If any billing questions arise concerning the marketing application, please contact Beverly Friedman or Michael Jones at 301-594-2041.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this small business waiver, please contact Beverly Friedman at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

Meeting Date: September 7, 2000
Time: 3:30 – 5:00 pm
Location: Parklawn Bldg 3rd fl c/r "Potomac"
Application: IND 39,897 Pramlintide
Sponsor: Amylin Pharmaceuticals
Type of Meeting: Pre-NDA (clinical)
Meeting Chair: David Orloff, M.D.
Meeting Recorder: Julie Rhee
Attendees:

FDA:
John Jenkins, M.D., Director, Office of Drug Evaluation II
David Orloff, M.D., Director, Div. of Metabolic and Endocrine Drug Products
Saul Malozowski, M.D., Medical Team leader, DMEDP
Robert Misbin, M.D., Medical Officer, DMEDP
William Lubas, M.D., Medical officer, DMEDP
Jeri El-Hage, Ph.D., Pharmacology Team Leader, DMEDP
Fred Alavi, Ph.D., Pharmacology Reviewer
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP
Chien Hua Niu, Ph.D., Chemist, DMEDP
Todd Sahlroot, Ph.D., Statistical Team Leader, DMEDP
Lee Pian, Ph.D., Statistician, DMEDP
Hae-Young Ahn, Ph.D., Biopharm Team Leader, DMEDP
Steven Johnson, Pharm.D., Biopharm Reviewer, DMEDP
George Liao, Regulatory Health Information Specialist, ODE II
Julie Rhee, Project Manager, DMEDP

Amylin Pharmaceuticals, Inc.
Mr. Joe Cook, Jr., Chairman and CEO
Dr. Orville Kolterman, Senior Vice President, Clinical Affairs
Dr. Joann Data, Senior Vice President, Regulatory Affairs and Quality Assurance
Dr. George Overend, Senior Director, International Regulatory Strategy
Mr. Marty Brown, Senior Vice President, Operations
Dr. Richard Hiles, Senior Director, Preclinical Development
Mr. Christopher Mitchell, Documentation Technologist
Dr. [redacted] Consultant
[redacted]

Discussions:

1. The sponsor plans to market — 15 ml vials presentation.

2. Most of the clinical studies have been done using raw material supplied by — Pharmacokinetics studies (studies 143 and 144) are ongoing using raw material supplied by — Efficacy studies with — raw material have not been conducted.

3. — synthesis is different from the synthesis of — synthesis — whereas the synthesis of — phase. Synthesis of — is similar but is not identical.

4. The sponsor plans to use raw material supplied by — in the to be marketed formulation. Raw material from different sources will not be mixed in formulation of drug product.

5. Establishment of a bridge between the — material and — raw material was discussed and complete resolution was not reached.

6. The sponsor is to submit a plan on how to bridge — material for safety and efficacy. This will not delay the NDA submission for — material.

7. The NDA for — should include the following:

   a Clinical comparability,
   b Safety and effectiveness, and
   c Proposed analysis plan.

8. Clinical data generated from — material could be submitted (1) as a separate NDA with cross reference to the original NDA or (2) as a supplement once the NDA for — material is approved.

9. The sponsor was asked to perform exploratory analyses of differences in outcomes between the — raw materials in the pivotal studies. The sponsor will examine within-patient differences in patients who received both products and between-patient differences in patients who received only one product.

10. NDA submission is expected in November 2000.

11. Bookmarks should be included in the Table of Contents.

12. Whether or not to present the NDA at Advisory Committee meeting will be decided during the NDA filing meeting.

13. The Agency is willing to defer pediatric studies for pramlintide until the NDA is approved.

14. [ ]

Sponsor's questions/FDA's responses

1. Does the Agency concur with the proposed format of the Safety Pharmacology section in the NDA?

FDA response: It appears to be acceptable.

2. Does the Agency concur with this tabular display and format for the ADME studies in the NDA?

FDA response: It appears to be acceptable.

3. Does the Agency concur that the toxicology package is sufficient to support filing of the NDA?

FDA response: It appears to be acceptable.

4. Is this format described for data presentation for the toxicology section acceptable to the Agency?

FDA response: It appears to be acceptable.

5. Does the Agency wish to receive a package that describes the toxicokinetic profile of pramlintide in animals prior to the NDA submission?

FDA response: No, the toxicokinetic data can be submitted with the NDA.

6. Does the Agency concur that the preclinical items identified by the Agency as part of the development of pramlintide have been addressed?

FDA response: Yes, the preclinical testing program for Symlin appears to be complete.

7. Does the Agency concur with the proposed approach to providing PK addenda for these clinical studies?

FDA response: It appears to be acceptable.

8. Does the Agency concur with the proposed approach to providing data from studies 137-143 and 137-144?

FDA response:It appears to be acceptable.

9. Does the Agency concur that these studies will be adequate to qualify —— material?

FDA response: Antigenicity studies are needed for the material obtained from the different supplier. One antigenicity study from each supplier is sufficient. (see also discussion section)

10. Does the Agency agree with this grouping and proposed positioning of information in Item 6?

FDA response: It appears to be acceptable. However, please include 2 or 3 pages synopsis for each PK study.

11. Does the Agency concur that the Amylin clinical development program accurately reflects feedback received from the Agency?

FDA response:

a No. However, data should be provided for a review.
b NDA should be a complete application at the time of the submission.
c When NDA is submitted, carcinogenicity study data should be submitted electronically for biometric's review.

12. Does the Agency concur with the demographic and disposition overview proposed for the ISS?

FDA response: The demographic and disposition overview proposed for the ISS appear to be acceptable.

13. Does the Agency concur with the overall layout of the Demographic and Subject Disposition Tables?

FDA response: The overall layout of the Demographic and Subject Disposition Tables appear to be acceptable.

14. Does the Agency agree with the proposed presentation scheme for patient profiles?

FDA response: Yes.

15. Does the Agency find acceptable the proposed font size?

FDA response: Seven points font size is too small. The Agency recommends a minimum of 9 or 10 points font size.

Decisions (agreements) reached:

1. The sponsor is to submit their bridging plan for — raw material to — — raw material.

2. NDA should be a complete application at the time of the submission.

3. NDA for ——— material could be submitted before the studies with — material are completed. NDA for — material could be handled as a separate NDA or as a supplement. If the sponsor opts to submit a separate NDA for — material, they could cross reference CMC and pharm/tox sections of the original NDA (for ——— material) for the new NDA.

Unresolved issues or issues requiring further discussion:

After the meeting, the Agency decided to have an internal follow-up meeting concerning bridging of — material to ——— material. I called Dr. Data on 9/12/00 and left a message about our upcoming internal meeting and asked her to wait before they proceed with their bridging plan.

On September 27, I called Dr. Data again and informed her that we're going to have another internal meeting on 10/10/00 to discuss the qualification requirements for their — raw material. However, CMC structural characterization and antigenicity studies data for — raw material should be included in the upcoming NDA. I agreed to get back to her following our 10/10/00 internal meeting.

/S/

Julie Rhee
Minutes Preparer

/S/

David Orloff, M.D.
Chair Concurrence

Attachments: Copy of the sponsor's overhead presentation.

cc: Original IND 39,897
HFD-510/Div. Files
HFD-510/Malozowski/Misbin/Moore/Niu/El-Hage/Alavi
HFD-870/Ahn/Johnson
HFD-715/Sahlroot/Pian

Drafted by: JRhee 9/20/00
Initialed by: Sahlroot 9-20-00/El-Hage 9-20-00/ Ahn 9-28-00/Alavi 9-28-00/Niu 10-4-00/Lubas 10-4-00/Moore 10-4-00
Waiting response from: Malozowski/Misbin/Johnson/Pian
F/T by::
File name: c:/IND 39897/9_7_00 pre NDA meeting minutes

MEETING MINUTES

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 8, 1998
Time: 1:30 – 3:00 pm
Location: Parklawn Building 3rd floor Conference Room "M"
Application: IND 39,897 Pramlintide
Sponsor: Amylin Pharmaceuticals
Type of Meeting: Clinical Discussion
Meeting Chair: Solomon Sobel, M.D.
Meeting Recorder: Julie Rhee
Attendees:
FDA:

Solomon Sobel, M.D., Director, DMEDP
Saul Malozowski, M.D., Acting Medical Team Leader, DMEDP
Robert Misbin, M.D., Medical Officer
Todd Sahlroot, Ph.D., Statistical Team Leader, DOB II
Lee Pian, Ph.D., Statistician, DOB II
Edward Nevius, Ph.D., Director, DOB II
Julie Rhee, Project Manager, DMEDP

Amylin:

Joseph Cook, Jr., Chairman and CEO
Orville Kolterman, M.D., Senior Vice President, Clinical Affairs
Sydney Gilman, Ph.D., Director, Regulatory Affairs
Larry Shen, Ph.D., Biostatistics

Discussion Points:

Question 1: We propose limiting the efficacy analysis to two dose regimens 、 μg BID and 120 μg BID). Both the efficacy and safety of the 60 μg TID treatment arm will be assessed and reported. Do you agree?

1. The sponsor stated that their reason for removing 60 μg TID treatment arm from the primary endpoint is based on dose size and dose frequency.

2. Exclusion of the 60 μg TID arm from data assessment is acceptable to the Agency. However, The data of the excluded dose can not and will not be accepted as efficacious and no claim could be made based upon these findings.

Question #2: With the exclusion of the 60 μg TID arm, we propose the use of the Fisher's protected LSD procedure to compare each pramlintide group against placebo. With only three treatment groups, this procedure controls the experiment wise error at the α=0.05 level. Do you agree?

The proposed statistical method is acceptable.

Question #3:We propose the prospective introduction of a predictive early response criterion (i.e., a reduction of HbA1c of ≥ 0.5% at Week 4) as a key secondary endpoint to better delineate the beneficial clinical profile of the drug. Do you agree?

1. The proposal is acceptable to the Agency with the exception of replacing the word "prospective" with "advance". The sponsor stated that they do not plan to look at the data in advance.

   Also, the word "key" should be deleted.

2. The Agency suggested that the sponsor examine durable responders among the early responders as a secondary endpoint.

3. The sponsor stated that they chose week 4 for predictive early response criterion because week 4 is the first time HbA1c is measured and also because week 4 is the first time changes in HbA1c can be detected.

4. Pramlintide patients had increased response in HbA1c reduction by two-fold at week 26. Placebo group (insulin only) increased daily insulin dose while patients in 120 μg BID treatment arm decreased their insulin intake.

5. The Agency recommended that the sponsor evaluate weight loss during the first 4 weeks after dosing. The sponsor mentioned that nausea did not cause weight loss and appeared to be related to dose response.

6. The sponsor stated that even if they excluded patients with weight loss, changes in HbA1c reduction were similar in all groups.

7. Insulin adjustment was not done once patients were randomized.

8. A description of all randomized patients achieving predictive early response criterion should be provided.

Question #4: Upon completion of collection of all primary endpoint data (6-month HbA1c), Amylin intends to carry out an administrative analysis of the primary endpoint along with inspection of the available 9 and 12 month HbA1c data. This data will be reviewed by senior executives not involved in the conduct of the trial. This activity is not an interim analysis and no statistical penalty should be assessed. Do you agree?

1. There is no statistical penalty since primary analysis is done at 6-month. The results of administrative analysis will not be disseminated to public and will be confined to the senior executives at the company for a business purpose.

2. The sponsor does not plan to change the conduct of studies even if after 26-weeks data do not demonstrate efficacy

3. The Agency expressed skepticism that the application would be approvable even if the current ongoing studies turn out to be positive. Two Phase 3 studies in type 2 diabetes have been negative. In type 1 diabetes, one Phase 3 study has been positive and one Phase 3 study has been negative. Thus, even if the ongoing studies are both positive, the final result of three positive and three negative studies does not meet our standard of approvability. The sponsor responded that the Agency was correct in stating that the three previous studies were negative by strict statistical standards but pointed out that some of the arms in these studies were positive. The sponsor stated that they hoped that FDA would be willing to examine the application in its entirety, and consider in a broad sense whether the drug was safe and effective. The Agency agreed with the sponsor but that it was premature to discuss these broad issues because the studies were still underway.

Hypoglycemia:

Increased hypoglycemia is a manifestation of pramlintide efficacy by lowering glucose and there is no safety concern.

Agreements reached:

In general, the Agency agreed with the sponsor's proposal and there were no undecided items.

Minutes Preparer:

Chair Concurrence:

cc: Original
HFD-510/Div. Files
HFD-510/Malozowski/Misbin
HFD-715/Nevius/Sahlroot/Pian

Drafted by: JRhee 12-23-98
Initialed by: Misbin 12-23-98/Sahlroot 12-30-98/Sobel 1-4-99/Pian 1-4-99/Malozowski 1-5-99
final: JRhee 1-5-99

MEETING MINUTES

3 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/

108 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/