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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-332

Trade Name: Symlin Injection

Generic Name(s): (pramlintide acetate)

Sponsor: Amylin Pharmaceuticals, Inc.

Agent:

Approval Date: March 16, 2005

Indication: Provides for treatment of type 1 or type 2 diabetes as an adjunct to insulin

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-332

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-332

Approval Letter(s)

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) dated December 7, 2000, received December 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMLIN® (pramlintide acetate) Injection, 5 mL vials.

We acknowledge receipt of your submissions dated December 18, 2003, January 7, February 13, May 27, June 21, July 2 and 16, August 9, September 8, 9, and 17, and December 3 and 17, 2004, and January 31, February 2, 3, 7, 9, 11, 16, 17 (2), 18, 24 (3), 25 (2), and 28 (2), and March 1, 3, 7, 8, 9, 10, 14, and 16, 2005.

The September 17, 2004, submission constituted a complete response to our December 17, 2003, action letter.

This new drug application provides for the use of SYMLIN (pramlintide acetate) Injection for the following indications:

- 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 who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling submitted on March 14, 2005, (text for the package insert, text for the Medication Guide, immediate container and carton labels for 5 mL vials). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission as **"FPL for approved NDA 21-332."** Approval of this submission by FDA is not required before the labeling is used.

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. For this application, we are waiving the pediatric study requirement for ages less than or equal to 11 years and deferring pediatric studies for ages 12 to less than or equal to 17 years.

Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment, as outlined in your submission dated March 7 and 16, 2005, is listed below.

1. A study of SYMLIN in adolescents ages 12 to less than or equal to 17 years with type 1 and type 2 diabetes to evaluate the pharmacokinetics and relevant pharmacodynamic effects of different subcutaneous doses of the drug.

   Final Report Submission: September 30, 2007

   For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated **"Required Pediatric Study Commitment."**

We also remind you of your postmarketing study commitment to conduct an observational study as described in your submissions dated March 1 and 9, 2005, and listed below.

2. 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 targeted prescribers.

Protocol Submission:	April 30, 2005
Study Start:	September 30, 2005
Final Report Submission:	September 30, 2008

Submit clinical protocols for these postmarketing commitment studies to your IND for this product. Submit study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered to date into each study. All submissions, including supplements, relating to these

postmarketing study commitments should be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence.**"

Additionally, we remind of your agreements, in your submissions dated February 24 and March 8, 2005, to risk management procedures designed to encourage the safe and effective use of SYMLIN. These agreements include the following:

- No direct-to-consumer advertisement.
- No journal advertisement for one year after SYMLIN is launched.
- Promotion limited primarily to physicians who specialize in diabetes management and are supported by certified diabetes educators.
- Gradual introduction of SYMLIN into the marketplace, with concomitant evaluation of patterns of SYMLIN use by "targeted" and "non-targeted" health care providers. To this end, you will 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.
- Conduct of a postmarketing observational study to assess the potential hypoglycemic risk for SYMLIN in the actual use setting (an effort will be made to also enroll "non-targeted" health care providers").
- Surveillance Plan: reporting of severe hypoglycemic events in an expedited manner for two years or as long as the postmarketing observational study remains ongoing, whichever is longer.
- A 24/7 nationwide call center to assist patients and physicians with the use of SYMLIN.

Submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive

copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
1. Physician insert
2. Medication Guide
3. Carton label for 5 mL vial
4. Immediate container label for 5 mL vial

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-332

Approvable Letter (S)

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) dated December 7, 2000, received December 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symlin® (pramlintide acetate) Injection.

We acknowledge receipt of your submissions dated October 18 and 23, November 15 and 16, and December 10, 2001, February 7, March 22, May 10, and September 3, 2002, and January 31, February 6 (2), May 1, June 16 and 19, July 25, August 22, September 12, 16, and 23, October 2, 14, 16, 21, and 27, and December 10, 2003.

The June 16, 2003, submission constituted a complete response to our October 10, 2001, action letter.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to adequately address the following deficiencies.

Clinical Safety and Efficacy:

1. Increased risk of hypoglycemia with pramlintide/insulin relative to insulin alone

   The original Phase 3 trials were designed to permit a demonstration of improved glycemic control with pramlintide/insulin compared to insulin alone. Usual care adjustments of insulin dosing to achieve glycemic goals were not generally integrated into the management of patients in these trials. These studies showed a substantially higher incidence of severe hypoglycemia among patients treated with pramlintide/insulin compared with patients treated with insulin/placebo. While this was particularly true of Type 1 diabetics, it was also seen in Type 2 patients. The previously submitted data supported a conclusion that pramlintide was superior in efficacy compared to placebo as an adjunct to fixed-dose insulin. However, left

unanswered were the questions (1) can glycemic control with insulin alone that is equivalent or superior to that with the combination be achieved by simply allowing for dose adjustment of basal and bolus insulins according to usual practice, (2) to what extent can the increased risk of severe hypoglycemia with pramlintide/insulin be explained by the enhanced glycemic control over insulin alone, and (3) to what extent can such risk be obviated or managed by reductions in insulin dose during titration to maximum tolerated dose of pramlintide.

Trial 150 addressed all three questions in a study in which insulin dose adjustments to glycemic goals were directed per protocol. Results showed that:

- therapeutic regimens employing insulin/placebo and insulin/pramlintide were comparable in terms of measures of glycemic control,

- despite no additional improvement in glycemic control, pramlintide/insulin was still associated with an increased risk of protocol-defined severe hypoglycemic episodes compared to insulin/placebo, and

- the increased risk of severe hypoglycemia associated with pramlintide/insulin therapy relative to insulin/placebo occurred during both the initiation and maintenance phases of the trial. The risk of severe hypoglycemia was not effectively obviated by downward insulin dose adjustment during pramlintide initiation, nor did the risk wane completely once the patient was on a stable, "tolerated" dose of pramlintide.

We accept that the overall rates of severe hypoglycemia in Study 150 represent modest decreases compared to the rates observed in the previous Phase 3 trials. Therefore, it is reasonable to conclude that the method of initiation of pramlintide therapy implemented in Study 150 was partially successful in enhancing the safe use of the drug. However, it is also important to note that patients were required to have stable glycemic control at study entry, including no episodes of severe hypoglycemia in the prior six months. So, while the absolute rates of severe hypoglycemia were low across treatment groups and below those observed in the original Phase 3 studies, they represented a substantial increase over the patients' experience in the six months preceding the study (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/insulin compared to insulin/placebo in this study, as was observed in prior studies.

In conclusion, the totality of the pramlintide clinical trial data suggests that the efficacy of pramlintide and the risk of hypoglycemia associated with its use in combination with insulin cannot be dissociated. In addition, adding pramlintide to the medical regimen of an insulin-treated patient with diabetes confers no benefit in terms of enhanced glycemic control (or any other identified, clinically meaningful measure) that could not otherwise be achieved by intensification of the insulin regimen. In fact, the trial results suggest that the addition of pramlintide will tend only to complicate the use of insulin. That is, if a patient responds to pramlintide, the drug will significantly add to the known risk of hypoglycemia that is associated with use of insulin. In short, these facts render an unacceptable risk-benefit

profile for pramlintide when used in combination with insulin in the treatment of patients with type 1 or type 2 diabetes mellitus.

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).

Labeling:

2. We reserve full comment on the labeling until the application is otherwise approvable. However, the wording of the pregnancy category should be revised as specified in our letter of October 10, 2001, including use of the "Pregnancy Category C" heading.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Endocrine and Metabolic Drug Products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Although not approvability issues, we have the following recommendations for your consideration:

Clinical Pharmacology:

A. The primary pharmacodynamic (PD) endpoint was the plasma glucose concentration-time curve from time zero to last time point ($AUC_{0\text{-}4hr}$). However, AUC was not an optimal PD endpoint because of the averaging nature between below and above the baseline (fasting glucose level).

B. The abdomen, arm, and thigh were proposed as injection sites. The exposure after injection into the thigh was not different from exposure after injection into the abdomen. However, for obese patients, pramlintide exposure as AUC was 20-36% higher after injection into the arm compared to injection into the abdomen. Therefore, for obese patients, the arm should only be cautiously recommended as an alternative injection site because of considerations of further increased risk of hypoglycemia due to the higher exposure.

Risk Management Plan (RMP):

C. Please include the following requests in your RMP when you submit your response:

1. 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. 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. Consider a program to monitor the frequency of hypoglycemic events in patients on pramlintide therapy.

4. Consider and describe strategies for capturing information on dosing in the population of patients using the product.

5. For the target audience of the education program, 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 patient package insert (PPI) should be the primary communication tool for patients using pramlintide. Please consider evaluating the PPI as a risk communication tool.

7. The [ ] 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. [ ]
   - Provide information about
   - Identify the communication objective(s)
   - Outline the study design for the use [ ]
   - Provide instructions [ ]
   - [ ]

9. The [ ] should be user-friendly and easy to understand, especially for patients with low literacy. Present evaluation data from the ongoing Phase 3B clinical utility study for the objectives of the sheets (assessing which treatment regimens are working, contacting the care-giver, and monitoring warning signs of nausea and hypoglycemia).

10. Describe the assessment 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).

11. At least one of the "other communication formats" should serve as a primary alternative for the education program and should therefore have the same objective and content as the educational program. Additionally, this communication format should be evaluated for the objective of the education program (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 [ ] which are currently being studied in a Phase 3B clinical utility study, present evaluation data for the following strategies' objective:

    - Healthcare provider information [ ] - to 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.

13. [ ]

14. 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.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Endocrine and Metabolic Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
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/

Robert Meyer
12/17/03 09:50:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-332

10/10/01
AE

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) dated December 7, 2000, received December 8, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMLIN™ (pramlintide acetate) Injection.

We acknowledge receipt of your submissions dated January 19 and 25, February 5 and 9, April 5 and 10, May 9, 18, 21, 25, 29 (2), and 31, June 1, 11, and 12, July 8, 9 (2), 16, 20, and 31, August 1, 9, 10, 16, 20, 21, 24, and 30, and September 4, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues:

Clinical Safety and Efficacy:

A. 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 profile of Symlin™ 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 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.

B. 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 safety issues discussed in (1), above.

C. 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.

D. The antibody response to Symlin™ produced by using drug substance manufactured by — has not been adequately characterized.

Clinical Pharmacology and Biopharmaceutics:

E. The reduced bioavailability of pramlintide observed in patients with Type 2 diabetes relative to those with Type 1 diabetes supports differential dosing between the two populations. The difference in bioavailability may be related to skin thickness, amount of subcutaneous fat, and/or site of injection. A clearer understanding of the mechanism(s) responsible for the observed difference is necessary to guide the safe use of the drug (e.g., in lean patients with Type 2 diabetes).

F. The optimally safe and effective timing of Symlin™ and insulin administration relative to food ingestion has not been established.

G. The effect of concomitant Symlin™ administration on the pharmacokinetics of orally administered drugs requires further characterization.

Financial Disclosure:

H. Financial disclosure information was not submitted for all covered clinical studies.

Manufacturing Facilities:

I. All facilities listed in the application must be found acceptable by FDA investigators.

Information necessary to address these deficiencies is listed below. You are strongly encouraged to confer with the Division of Metabolic and Endocrine Drug Products prior to design and initiation of studies designed to address these deficiencies.

Clinical Safety and Efficacy:

1. Additional studies in patients with Type 1 and Type 2 diabetes must be conducted to investigate the safety and effectiveness of Symlin™ under conditions in which patients receive treatment with insulin and life-style modification in accordance with recommendations of the American Diabetes Association, and target, in consultation with their physicians, optimal improvement in glycemic control over the course of a 12-month trial. These trials should be placebo-controlled and should involve careful titration of Symlin™ to a steady-state dose to be maintained for at least the last 6 months of study. Clearly, the dose of insulin may need to be adjusted during the titration phase of the study to obviate hypoglycemia. Insulin dose should then be adjusted to achieve optimum control. In light of the risks identified in trials to date, careful and complete ascertainment of events to establish the incidence of hypoglycemia, motor vehicle accidents, or

injuries, among other adverse outcomes, across treatment groups should be a critical aspect of the trial designs.

2. The possibility that Symlin™ may alter (lower) the threshold for hypoglycemia awareness or otherwise affect patient response to hypoglycemia must be formally investigated. Hypoglycemia should be induced by intravenous insulin infusion, and the glycemic threshold at which signs and symptoms develop should be determined at baseline and after five days of dosing with Symlin™ versus placebo in a cohort of well-controlled patients with Type 1 diabetes or in non-obese normal volunteers.

3. In the new long-term studies described above (see #1), retinal examination and photography should be performed at baseline and at endpoint in a substantial subset of patients. Inclusion and exclusion criteria related to degree of baseline retinopathy should be developed, and safety monitoring for proliferative changes at an intermediate time point (e.g., 6 months) is recommended.

4. Future studies of the safety and efficacy of Symlin™ should include arms receiving —— derived drug product and should include testing for anti-pramlintide antibodies after at least 6 months of treatment in approximately 100 patients.

Clinical Pharmacology and Biopharmaceutics:

5. The effects of body composition and injection site on the bioavailability of Symlin™ should be investigated.

6. Studies should be conducted to determine the optimally safe and effective timing of Symlin™ and insulin dosing relative to meals.

7. You should propose and seek concurrence from the Division of Metabolic and Endocrine Drug Products on a battery of "interaction" studies to include orally administered drugs likely to be used by the populations in whom Symlin™ will be prescribed, and specifically addressing whether only rate or both rate and extent of absorption are affected for drugs for which either or both are important for therapeutic efficacy or safety.

Financial Disclosure:

8. 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.

Manufacturing Facilities:

9. A satisfactory inspection of the [redacted] site is required.

Labeling:

10. Submit revised draft labeling that includes the following changes. We reserve further comment until the application is otherwise approvable.

    a. The inclusion of the [ ] as part of the proprietary name is considered promotional and is not acceptable under 21 CFR 201.56. Therefore, any use of the [ ] on the labeling should be deleted.

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

    c. **Carcinogenesis, Mutagenesis, Impairment of Fertility:**

    Carcinogenicity: A two-year carcinogenicity study was conducted in CD-1 mice with doses of 0.2, 0.5 and 1.2 mg/kg/day (32, 67, and 159 times the maximum recommended human dose based on AUC, respectively). No drug-induced tumors were observed in any organ. A two-year carcinogenicity study was conducted in Sprague-Dawley rats with doses of 0.04, 0.2 and 0.5 mg/kg/day (3, 9, and 20 times the maximum recommended human dose based on AUC, respectively). No drug-induced tumors were observed in any organ.

    Mutagenesis: Symlin™ was not mutagenic in the Ames test and did not increase chromosomal aberration in the human lymphocytes assay. Symlin™ was not clastogenic in the in vivo mouse micronucleus test or in the chromosomal aberration assay utilizing Chinese hamster ovary cells.

    Impairment of Fertility: Administration of 0.3, 1, or 3 mg/kg/day of pramlintide (8, 27, and 82 times the maximum recommended human dose based upon body surface area) had no significant effects on fertility in male or female rats. The highest dose of 3 mg/kg/day resulted in dystocia in 8/12 dams secondary to significant decreases in serum calcium levels.

    d. **Pregnancy:** *Teratogenic effects: Pregnancy category C:*

    Embryofetal toxicity studies with pramlintide have been performed in rats and rabbits. Increases in congenital anomalies (neural tube defect, cleft palate, exencephaly) were observed in fetuses of rats treated during organogenesis with 0.3 and 1.0 mg/kg/day (10 and 47 times the maximum recommended human dose based on AUC, respectively). Administration of doses up to 0.3 mg/kg/day pramlintide (9 times the maximum recommended human dose based on AUC) to pregnant rabbits had no adverse effects in embryofetal development. No adequate and well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, Symlin™ should be used during pregnancy only if clearly needed.

Safety Update:

11. Submit all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

    a. Describe in detail any significant changes or findings in the safety profile.

    b. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

        - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

        - Present tabulations of the new safety data combined with the original NDA data.

        - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

        - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

    c. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

    d. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

    e. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

    f. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

    g. Provide English translations of current approved foreign labeling not previously submitted.

Although not required for approval, we recommend [redacted]

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
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/

John Jenkins
10/10/01 11:57:21 AM
Concur with Dr. Orloff's recommendations that this application is approvable pending resolution of the deficiences listed in the action letter.