

Division of Pharmaceutical Evaluation-II Office of Clinical Pharmacology and Biopharmaceutics

NDA:	21-332	Relevant IND:	39,897
Brand Name:	Symlin™	Generic Name:	Pramlintide Acetate
Concentrations:	Vial – 0.6 mcg/mL sterile injection in 5 mL vials Cartridge – 1.0 mcg/mL sterile injection in 1.5 mL cartridges		
Sponsor:	Amylin Pharmaceuticals, Inc. 9373 Towne Centre Drive, San Diego, CA 92121		
Submission Date:	7-DEC-2000 5-APR-2001	Division Due Date:	6-JUN-2001
Advisory Committee:	26-JUL-2001	PDUFA Date:	7-OCT-2001
CPB Reviewer:	Steven B. Johnson, Pharm.D.		
CPB Team Leader:	Hae-Young Ahn, Ph.D.		
Acknowledgements:	Daniel Davis, M.D.; S.W. Johnny Lau, Ph.D.; Todd Sahlroot, Ph.D.		

EXECUTIVE SUMMARY

On December 7, 2000, Amylin Pharmaceuticals submitted NDA 21-332 in support of Symlin™ (pramlintide acetate) injection. Pramlintide is the synthetic analogue of the 37-amino acid polypeptide, amylin. The proposed mechanism of pramlintide action is complex, with regulation of postprandial glucagon concentrations and altered gastric emptying rate being the most well described. Two formulations of Symlin™ have been proposed for marketing, a 0.6 mg/mL (vial) formulation that will be administered by syringe and a 1.0 mg/mL (cartridge) formulation that will use a “pen” system for administration. Symlin™ has been proposed for use as adjunctive therapy to insulin in patients with type 1 or insulin-requiring type 2 diabetes mellitus (DM).

Included in this application were 28 clinical pharmacology and biopharmaceutics related studies or reports. Of these studies, 19 were used to make the CPB recommendation. Many of the early studies were found to be unacceptable for review due to formulation and/or assay issues. Common to the studies that were utilized in this review included: a formulation pH of 4.0 and/or the use of the current immunoenzymetric assay (IEMA) for pramlintide pharmacokinetic (PK) studies.

The following is a brief description of Symlin™ attributes. First of all, there is a high degree of inter-subject variability for all PK parameters, except $t_{1/2}$ and T_{max} . This drug is absorption rate limited, has a time to maximum pramlintide plasma concentration (T_{max}) of approximately 20 minutes, and a half-life of about 50 minutes. Pramlintide is metabolized to des-lysine pramlintide, which has 100% of the activity as pramlintide, and other none reactive fragments. There is no apparent drug accumulation following multiple doses in either type 1 or type 2 diabetes patients.

In order to take full advantage of pramlintide’s delayed gastric emptying effect, Symlin™ should be administered about 15 minutes before a meal – this timing would correspond with the pramlintide T_{max} . Symlin™ should be administered subcutaneously into the tissue of the anterior abdominal wall only, with a maximum dose of 360 mcg/day – divided BID, TID, or QID.

During the course of this review, a series of questions were generated to address pertinent issues that were thought to be key for the approval of this application. The most prominent of these questions are:

1) Is the analytical method used to detect pramlintide in human plasma precise and accurate?

Yes, the immunoenzymetric assay used to detect human plasma pramlintide exhibits precision and accuracy estimates that are acceptable. However, it should be noted that the samples used in the quality control analysis were sufficiently far enough away from the calibration limits and the lower limit of quantitation as to create some concern about the plasma concentrations that fall between the LLOQ and the lowest quality control sample.

2) Is there any assay interference from endogenous substances or metabolites?

Yes, this assay is susceptible to interference by endogenous amylin, the des-lysine pramlintide metabolite, and human anti-mouse antibody (HAMA). Also, the values reported as pramlintide concentrations are actually pramlintide, the pramlintide metabolite, and amylin.

3) What is the absolute bioavailability of Symlin™?

The bioavailability of a subcutaneously administered dose of Symlin™, relative to an equivalent intravenously administered dose of Symlin™, is approximately 37%. Pramlintide exhibits absorption rate limited pharmacokinetics.

4) What effect does pH, mixing, volume, or concentration have on the bioavailability of Symlin?

The formulation pH has a significant effect on the bioavailability of Symlin™. A formulation pH of 4.7 was shown to exhibit a 25% reduction in bioavailability compared to the to-be-marketed pH 4.0 formulation.

Compatibility studies, that would describe what substances could be mixed with pramlintide, were not performed. However, in interaction studies where pramlintide and insulins were mixed in the same syringe, pramlintide and sometimes insulin pharmacokinetics were significantly altered.

Volume and concentration had no apparent effect on Symlin™ bioavailability.

5) Does Symlin™ exhibit dose proportionality over the entire proposed dosing range, 30 mcg to 180 mcg?

No, Symlin™ does not exhibit dose proportionality over the entire proposed dosing range. However, studies in healthy volunteers and patients with type 1 and type 2 diabetes demonstrate a dose-related exposure. Apparent clearance in normal healthy subjects ranged from 2.36 L/min to 2.87 L/min for the dosing range of 30 mcg to 120 mcg.

6) Given that Symlin™ will be available in two concentrations, are these formulations bioequivalent?

Bioequivalence was established between the cartridge formulation administered by a pen system and the vial formulation administered with a syringe. Ninety-five percent confidence limits were within the 80% to 125% boundaries for both C_{max} and AUC.

7) Since there will be three suppliers of pramlintide material for Symlin™, are there any PK-related concerns about using multiple sources of this protein?

No, there are no outstanding concerns related to the multiple sources of pramlintide. Information submitted in the form of a BE study was sufficient to conclude that pramlintide material from UCB-Bioproducts and Bachem were equivalent. Material from both Bachem and Mallinckrodt was used throughout the development program and was not considered different.

8) Are there any differences between the pramlintide PK profiles of type 1 and type 2 diabetes patients?

Yes, there is a difference between the pramlintide PK profiles of type 1 and type 2 diabetes patients. In the studies evaluated in this application, patients with type 2 diabetes exhibited lower relative pramlintide plasma concentrations than did patients with type 1 diabetes. This fact is reflected in the proposed diabetes type-specific dosing regimens.

9) Pramlintide is renally eliminated, what effect does renal insufficiency have on pramlintide PK?

The exact effect that renal insufficiency has on pramlintide PK cannot be stated with absolute certainty due to the design limitations of the renal study (e.g., parallel design with 3 to 8 subjects per group and inherent inter-subject variability). However, there was no observed trend in the data to suggest that renal insufficiency adversely affects pramlintide PK. It should be kept in mind that pramlintide dosing in humans has spanned 30 mcg to 10 mg in single dose studies.

10) Can pramlintide be mixed with insulin(s)?

No, pramlintide should not be mixed in the same syringe with any insulin. The sponsor evaluated mixing effects of pramlintide with rapid, short, intermediate, and long-acting insulins. The results

suggest that pramlintide PK, and sometimes insulin PK, is compromised when these agents are mixed.

11) Since pramlintide delays gastric emptying time, what effect does Symlin™ have on orally administered medications?

Two studies evaluated the effect Symlin™ has on the PK of Lo/Ovral, an oral contraceptive, and ampicillin, a relatively acid-stable antibiotic. Results indicate that norgestrel, the progestin component of Lo/Ovral, achieves significantly lower and delayed C_{max} values when administered 15 minutes after a dose of Symlin™. However, there was no difference in the extent of norgestrel exposure.

Conversely, pramlintide appeared to have no effect on ampicillin AUC or C_{max}. However, T_{max} was increased by approximately one hour.

The conclusion drawn from these studies would suggest that orally administered drugs that are expected to have a rapid onset of action, or those that are adversely affected (e.g., degraded) by prolonged gastric retention times, should be administered at least one hour prior to dosing pramlintide.

12) What effect does a morning dose of pramlintide have on the gastric emptying of a lunchtime meal?

There was no observed interference of a morning dose of pramlintide on a lunchtime meal eaten approximately 4 hours after pramlintide administration. This is consistent with pramlintide's attributes of a relatively short half-life of pramlintide, ~ 50 minutes, and the fact that there is no indication of pramlintide accumulation.

Based upon the results of the studies that answer the above questions, it has been concluded that Amylin, Inc. has supplied sufficient information to the PK section for Symlin™, NDA 21-332, to have been adequately evaluated.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-292 for Symlin™ (pramlintide acetate) and finds the application acceptable, pending the indicated labeling changes (see **Comments to Sponsor** and **Labeling Changes**).

TABLE of CONTENTS

EXECUTIVE SUMMARY	1
RECOMMENDATION.....	3
TABLE of CONTENTS.....	3
APPENDIX INDEX.....	4
BACKGROUND – (from sponsor).....	4
TERMS and ABBREVIATIONS	5
DRUG CHARACTERISTICS	5
ANALYTICAL	6
HUMAN PK – BIOAVAILABILITY/BIOEQUIVALENCE	7
HUMAN PK – BIOEQUIVALENCE	10
HUMAN PK – TARGET POPULATION	12
HUMAN PK – PLASMA/BLOOD.....	17
HUMAN PK – EX VIVO – Placental Transfer	17
PHARMACODYNAMICS	17
LABELING	19
COMMENTS TO THE SPONSOR.....	19

APPENDIX INDEX

Study #	Title	Page #
137-125	An open-label, randomized, four-period cross-over study in normal volunteers of the bioavailability of selected concentrations of pramlintide in two different formulations.	
137-142	An open-label, randomized, two-period crossover study in healthy volunteers of the bioequivalence of two different formulations and dosage forms of pramlintide.	
137-126	An open-label, randomized, four-period cross-over study of the proportionality of four subcutaneous doses of pramlintide (AC137) administered at a constant volume in normal volunteers.	
137-127	An open-label, single-dose, pharmacokinetic study of pramlintide in type 1 diabetics with renal impairment.	
137-133	A randomized, double-blind, placebo-controlled, single-dose, two-period cross-over study to evaluate the effect of pramlintide on the pharmacokinetics of ethinyl estradiol and norgestrel in healthy female subjects receiving the oral contraceptive ageng Lo/Ovral®.	
137-134	A randomized, double-blind, placebo-controlled, single-dose, two-period cross-over study to determine the effect of pramlintide on the pharmacokinetics of ampicillin in healthy subjects.	
137-130	A randomized, double-blind, single-dose, two-period cross-over study of the safety of pramlintide and lispro insulin administered as two separate subcutaneous injections in conjunction with NPH, Lente, or Ultralente insulin in patients with type 1 diabetes mellitus.	
137-115	An open-label, randomized, cross-over study in type 1 diabetes mellitus of the pharmacokinetics of subcutaneous pramlintide (AC137) and 70/30 insulin mixed together and as separate single injections.	
137-119	An open-label, randomized, five-period cross-over study of the pharmacokinetics of subcutaneous pramlintide (AC137) versus placebo plus NPH and regular insulin mixed together and as separate single injections in patients with type 1 diabetes mellitus.	
137-145	An open-label, randomized, two-period cross-over study in healthy volunteers to test the bioequivalence of pramlintide supplied by two different manufacturers.	
137-143	An open-label assessment of the single dose and multiple dose pharmacokinetic profiles of pramlintide in subjects with type 1 diabetes mellitus.	
137-144	An open-label assessment of the single dose and multiple dose pharmacokinetic profiles of pramlintide in subjects with type 2 diabetes mellitus.	
137-120	An open-label, randomized, five-period cross-over study of the pharmacokinetics of subcutaneous pramlintide (AC137) versus placebo plus isophane and soluble insulin mixed together and as separate single injections in patients with type 1 diabetes mellitus.	
137-118	The effect of single doses of pramlintide on the gastric emptying of two meals.	
137-137	A study to determine the effect of pramlintide on the gastric emptying of subjects with type 2 diabetes mellitus currently requiring insulin.	
REST 98049	Characterization of pramlintide metabolites following bolus subcutaneous administration in type 1 diabetic subjects.	
REST 98044	Characterization of binding of pramlintide to components from rat, dog, rabbit, mouse, and human blood.	

BACKGROUND – (from sponsor)

In people without diabetes, plasma glucose concentrations are tightly regulated by the co-secretion of the hormones amylin and insulin from the pancreatic β -cells in response to nutrient intake, and by the glucagon secretion from pancreatic α -cells in response to a variety of stimuli, including hypoglycemia and elevated concentrations of amino acids. In people with type 1 diabetes, the pancreatic β -cells are usually destroyed by an autoimmune process, leaving patients deficient in both insulin and amylin. In people with type 2 diabetes, insulin resistance leads to an increased demand for insulin, and initially results in increases in β -cell secretion of both insulin and amylin. Over time, β -cell secretion fails, and relative deficiencies of both insulin and amylin occur in conjunction with inappropriate fluctuations in glucose concentrations, overt hyperglycemia, and increased risk of hypoglycemia.

Results of nonclinical and clinical studies indicate that the 37-amino acid polypeptide amylin and the amylin analogue pramlintide contribute to glucose regulation through several mechanisms including reducing the postprandial rise in glucagon concentrations without impeding the glucagon response to insulin-induced hypoglycemia, and regulating the rate of nutrient delivery to the small intestine via an effect on gastric emptying. It has been proposed that amylin's effect on gastric emptying may be exerted via a central mechanism involving specific binding sites in the area postrema of the brain, with outflow through the efferent pathways of the vagus nerve to the gastrointestinal system, rather than by direct action on the stomach. Elevated glucagon concentrations favor increased rates of hepatic glucose release, and a reduction in postprandial glucagon concentrations should result in lower rates of hepatic glucose output during the postprandial period, thus favoring lower postprandial glucose concentrations. It has been demonstrated that hypoglycemia overrides these effects.

Immunoassay of amylin in healthy human volunteers indicates fasting concentrations between 4 and 8 pmol/L, increasing two- to three-fold following ingestion of a mixed meal or an oral glucose load. In patients with type 1 diabetes mellitus, amylin concentrations are near or below the limit of quantitation under fasting conditions and do not increase in response to nutrient stimuli. In patients with type 2 diabetes mellitus or with impaired glucose tolerance, fasting amylin concentrations are comparable to those seen in healthy human subjects. However, the postprandial responses vary considerably. The postprandial responses tend to be decreased in relation to the prevailing level of glycemia and are virtually absent in patients with type 2 diabetes who have progressed to insulin therapy. Amylin deficiency in patients with diabetes mellitus may contribute to impaired glucoregulation.

TERMS and ABBREVIATIONS

AA -----	Amino acid(s)
Agency -----	Food and Drug Administration
AUC -----	Area under the plasma-concentration-time curve
BA -----	Bioavailability
BE -----	Bioequivalence
BMI -----	Body Mass Index
C _{max} -----	Maximum drug concentration
DMEDP -----	Division of Metabolic and Endocrine Drug Products
OCPB -----	Office of Clinical Pharmacology and Biopharmaceutics
NDA -----	New Drug Application
T _{max} -----	Time of maximum drug concentration (C _{max})
t _{1/2} -----	Drug elimination half-life

DRUG CHARACTERISTICS

Drug Chemistry

Pramlintide acetate is a synthetic analogue of the endogenous human polypeptide, amylin. Pramlintide differs from amylin in its replacement of amino-acid (AA) residues at 25 (alanine), 28 (serine), and 29 (serine) of the 37-AA amylin peptide, with proline residues. These substitutions are purported to increase pramlintide's solubility, and decrease the propensity for aggregation and adhesion, which has been reported with amylin. Pramlintide acetate is an odorless white powder, is soluble in water, has a molecular weight of 3949.9, and a molecular formula of C₁₇₁H₂₆₇N₅₁O₅₃S₂*xC₂H₄O₂, where x is variable. The structural formula is shown below, and includes the disulfide bridge between the two cysteine residues:



Drug Formulation

Multiple formulations (i.e., vial = 26; cartridge = 3) have been described in the development of Symlin™. Of these formulations, AC-0137-F22 (vial) and AC-0137-F28 (cartridge) were chosen for marketing. The formulations for both dosage units are presented in **TABLE 1**:

TABLE 1: Symlin™ Formulations

	Vial – F22	Cartridge – F28
Strength	0.6 mcg/mL (5 mL)	1.0 mcg/mL (1.5 mL)
pH	4.0	4.0
Pramlintide	0.60 g/L	1.00 g/L
Acetate	30 mM	30 mM
Mannitol	43 g/L	43 g/L
Metacresol	2.25 g/L	2.25 g/L
Acetic Acid	1.53 g/L	1.53 g/L
Sodium Acetate Trihydrate	0.61 g/L	0.61 g/L
Water for Injection	QS to 1.0 L or 1.015 kg	QS to 1.0 L or 1.015 kg*
*Meets both the European Pharmacopeia (EP) and United States Pharmacopeia (USP) monographs		

Early pharmacokinetic studies utilized formulations other than those shown above that differed mainly in their relative pH values – those studies were not reviewed. The data that provided the basis for the Clinical Pharmacology and Biopharmaceutics recommendation was generated using the above to-be-marketed formulations.

Additionally, the sponsor is using three suppliers of pramlintide in the manufacture of Symlin™, Bachem, Mallinckrodt, and UCB-Bioproducts (see **HUMAN PK – BIOEQUIVALENCE**).

ANALYTICAL

Is the analytical method used to detect pramlintide in human plasma precise and accurate?

Is there any assay interference from endogenous substances or metabolites?

The detection of pramlintide is dependent upon a validated immunoenzymetric assay (IEMA) method that relies on two monoclonal mouse antibodies (Ab): a capture Ab (F024-4.4) and a detection Ab (F025-27.4). Neither Ab is specific for amylin or pramlintide. Antibody F024-4.4 binds near the amino terminus of pramlintide and Ab F025-27.4 binds to the amidated carboxy terminus of pramlintide. The F025-27.4 Ab is conjugated to alkaline phosphatase and a fluorescent substrate, 4-methylumbelliferyl phosphate (4-MUP). This method is able to detect bound, conjugated antibody, using a microplate fluorometer. Relative fluorescence units (RFU) are correlated with concentration using a calibration curve defined in the same assay. This assay uses the Tripro-amylin EIA kit produced by PerSeptive Diagnostics, Inc, and a microplate fluorometer from Dynatech, Chantilly, VA.

In **TABLE 2**, the quality control samples used in the assays for studies 137-142 and 137-145 are presented. These two studies were chosen because they were the two pivotal bioequivalence studies submitted with this application. Both accuracy and precision were within accepted parameters for these studies. However, there is a concern related to the quality control samples.

Quality control samples were measured at the sponsor defined values of low, middle, and high. However, because the extreme values were far away from the limits of the calibration curve, there exists some doubt about the values obtained at the extremes, especially those plasma pramlintide values that fall between the LLOQ and the lowest quality control sample value. Therefore, because of this issue and the cross-reactivity with endogenous amylin, pharmacokinetic analysis will be confined to C_{max} and AUC_{0-t} .

Assay interference was documented for endogenous amylin and for des-lysine pramlintide with 35% and 100% cross-reactivity, respectively. This cross-reactivity results in a total pramlintide concentration that is actually a combination of amylin, des-lysine pramlintide, and pramlintide. Since under fasting conditions endogenous amylin concentrations are usually undetectable, and the fact that the des-lysine pramlintide

metabolite is equipotent with pramlintide, these findings are not likely to undermine the value of the assay.

TABLE 2 – Assay Quality Control Results from Two Pivotal Bioequivalence Studies

Study		137-142	137-145
LLOQ (pmol/L)		4.5	4.5
Calibration Range		5.4 – 111.1	5.4 – 111.1
Precision (%CV)	12.7	3.7	4.7
	40.6	2.9	
	40.1		4.1
	74.9	4.1	
	79.5		5.0
Accuracy (%)	12.7	104.4	104.2
	40.6	102.4	
	40.1		101.2
	74.9	105.2	
	79.5		101.1
Stability	5 freeze/thaw cycles		
Storage	1 year @ either –20°C or –70°C		
Crossreactivity	35% – amylin; 100% – des-lysine pramlintide		
Homology	92% – amylin; 97% – des-lysine pramlintide		

One important point. This IEMA utilizes monoclonal antibodies from a murine source – and, many humans carry the human anti-mouse antibody (HAMA). HAMA, present in plasma, binds to the mouse antibodies in the assay, which can result in a false signal, either positive or negative. Strategies for reducing this interference include: immunosuppressant therapy, and the use of humanized, polyethylene glycolated, or Fab fragments of antibody agents. The sponsor chose to reduce the HAMA interference by using a diluent that contained a high concentration of non-specific mouse IgG which competes with the specific mouse monoclonal antibodies for the human anti-mouse antibody binding sites.

The above point was raised because several subjects were determined to be unevaluable in several PK studies due to this assay interference. The Agency strongly encourages the sponsor to develop an assay that does not utilize murine antibodies.

HUMAN PK – BIOAVAILABILITY/BIOEQUIVALENCE

Symlin is a parenterally (i.e., subcutaneously) administered sterile solution. As such, knowing the absolute bioavailability is crucial. It is also imperative that there is a good understanding of the effect that physiochemical alterations have on the product's bioavailability. Therefore, there are two primary questions that should be asked:

What is the absolute bioavailability of Symlin™?

What effect does pH, mixing, volume, or concentration have on the bioavailability of Symlin?

Absolute Bioavailability

The absolute bioavailability for Symlin was determined in an open-label, randomized, four-period crossover study (137-125) in 40 (39 completed¹) healthy male subjects between 18 and 41 years of age. The four treatments consisted of: A) 60 mcg (0.1 mL) pH 4.7 pramlintide administered subcutaneously (formulation F11); B) 60 mcg (0.1 mL) pH 4.0 pramlintide administered subcutaneously (formulation F22); C) 60 mcg (0.2 mL) pH 4.0 pramlintide administered subcutaneously (formulation F21); and D) 60 mcg (0.1 mL) pH 4.0 pramlintide administered intravenously (formulation F22). Each of the treatments was separated by a 1-week washout period.

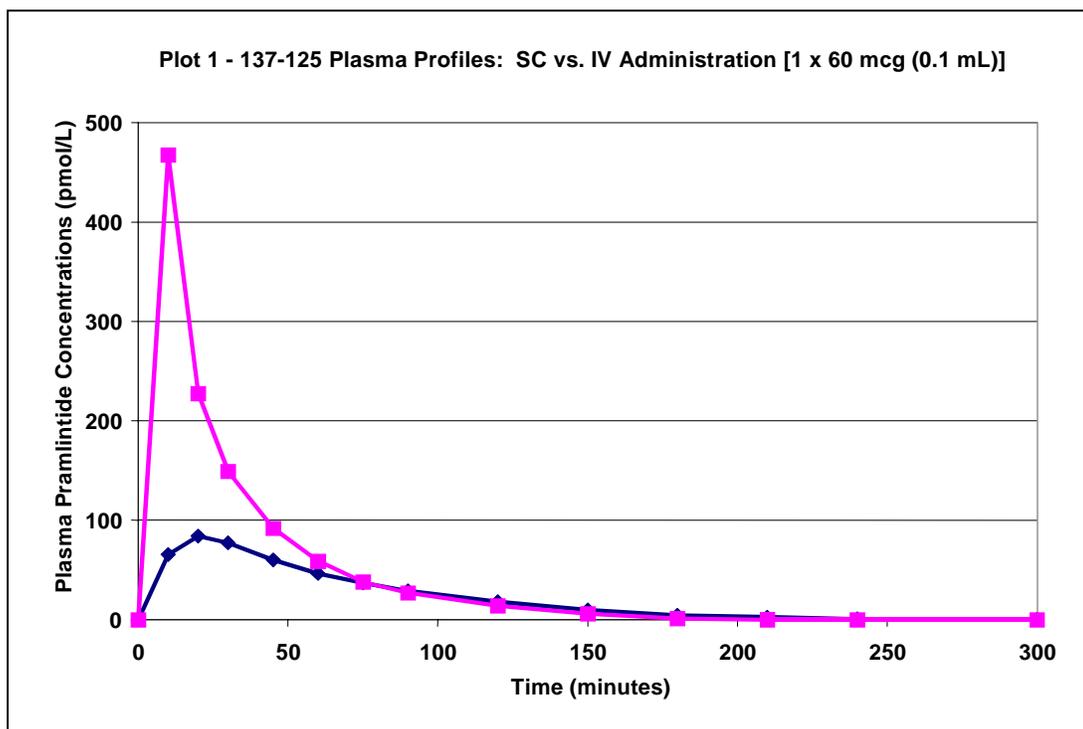
Results, presented in **TABLE 3** and **PLOT 1**, show that the absolute bioavailability (f) of a 60 mcg dose of pramlintide, in a volume of 0.1 mL, administered to healthy volunteers under fasting conditions, is 37%.

However, because the sampling times for the IV administered pramlintide did not include a sufficient number of early time points, the absolute bioavailability of pramlintide may be overestimated.

TABLE 3 – Pramlintide Plasma Concentrations: SC vs. IV Administration

Parameter	Units	Tx B: 60 mcg (0.1 mL) SC pH 4.0			Tx D: 60 mcg (0.1 mL) IV pH 4.0		
		Mean	SD	%CV	Mean	SD	%CV
C _{max}	pmol/L	89.23	24.01	26.9	--	--	--
T _{max}	minutes	20.5	6.51	31.9	--	--	--
AUC _{0-t}	pmol*min/L	6234	2154	34.6	17,950	6834	38.1
AUC _{0-inf}	pmol*min/L	6803	2253	33.1	18,420	6795	36.9
t _{1/2}	minutes	43.6	13.6	31.2	33.4	7.94	23.8
C _{max} / BMI	pmol/L	3.90	1.19	30.5	--	--	--
AUC _{0-t} / BMI	pmol*min/L	272.0	99.39	36.5	789.4	325.4	41.2
AUC _{0-inf} / BMI	pmol*min/L	297.2	103.6	34.9	809.6	324.4	40.1

Analysis was also conducted to determine if body mass index (BMI) had any impact on the coefficient of variation for both C_{max} and AUC. Results do not indicate a significant difference between the uncorrected parameters and those corrected for BMI. This suggests that BMI has little influence on the pharmacokinetics of pramlintide in healthy males.



Effect of pH on Bioavailability

Formulation pH was shown to have a significant effect on the bioavailability of subcutaneously administered pramlintide. In study 137-125, a pH 4.7 formulation (F11) was compared with the to-be-marketed pH 4.0 formulation (F22). Results, as shown in **TABLE 4**, revealed that the pH 4.7 formulation had a 25% reduction in AUC and a 35% decrease in the mean C_{max}, when compared with the pH 4.0 formulation. Because of this pH issue, earlier studies which utilized the pH 4.7 formulation were not considered in this review.

TABLE 4 – Pramlintide Plasma Concentrations: pH 4.7 vs. pH 4.0

Parameter	Units	Tx A: 60 mcg (0.1 mL) SC pH 4.7			Tx B: 60 mcg (0.1 mL) SC pH 4.0		
		Mean	SD	%CV	Mean	SD	%CV
C _{max}	pmol/L	59.70	24.01	40.2	89.23	24.01	26.9
T _{max}	minutes	20.7	13.2	63.8	20.5	6.51	31.9
AUC _{0-t}	pmol*min/L	4485	2206	49.2	6234	2154	34.6
AUC _{0-inf}	pmol*min/L	5193	2208	42.5	6803	2253	33.1
t _{1/2}	minutes	49.3	18.9	38.3	43.6	13.6	31.2
C _{max} / BMI	pmol/L	2.62	1.15	43.9	3.90	1.19	30.5
AUC _{0-t} / BMI	pmol*min/L	195.6	100.3	51.3	272.0	99.39	36.5
AUC _{0-inf} / BMI	pmol*min/L	226.4	99.89	44.1	297.2	103.6	34.9

Effect of Volume on Bioavailability

The effect of the volume of SC injections on pramlintide PK was described in several studies, with the most indicative examples being the single/multiple dose studies conducted in type 1 and type 2 diabetes patients. In study 137-143, patients with type 1 DM were administered either a 0.03 mL, 0.06 mL, or 0.09 mL of the 1.0 mg/mL cartridge formulation. In study 137-144, patients with type 2 DM were administered either a 0.06 mL, 0.09 mL, 0.12 mL, or 0.18 mL of the 1.0 mg/mL cartridge formulation. In both cases, AUC_{0-300 min} and C_{max} values exhibited expected dose related changes (**see HUMAN PK – TARGET POPULATION**). Similar results were observed in the absolute BA study, 137-125, where a 0.1 mL dose of the 0.6 mg/mL vial formulation was compared with 0.2 mL of a 0.3 mg/mL “test” formulation. These combined results suggest that the volume of the injection has no significant impact on the bioavailability of Symlin.

Effect of Mixing on Bioavailability

The idea of mixing is an important consideration with Symlin, as it will be used as an adjunct to insulin therapy. With this in mind, the sponsor has conducted numerous studies in which Symlin was mixed in the same syringe with different insulin products (e.g., regular insulin, insulin lispro, NPH insulin, etc.). The overwhelming conclusion from reviewing these studies is that Symlin should not be mixed in the same syringe with insulin because Symlin PK is significantly affected and efficacy will likely be compromised (**see HUMAN PK – EXTRINSIC – Drug-Drug Interactions**).

Also, due to the importance of pH on the bioavailability of Symlin, mixing Symlin in the same syringe with any agent that can potentially alter the pH is not recommended.

Effect of Concentration on Bioavailability

The effect of concentration on bioavailability was evaluated in two studies, 137-125 and 137-142. Study 137-125 compared a single 60 mcg dose at a concentration of 0.1 mL at pH 4.0 (F22 – to be marketed formulation – reference) with a single 60 mcg dose at a concentration of 0.2 mL at pH 4.0 (F21 – test). Results indicate that a doubling of the injection volume, and hence a halving of the concentration, results in a 6.5% reduction in the relative BA (AUC_{0-t}).

Study 137-142, discussed in HUMAN PK – Bioequivalence, demonstrated that a 1.0 mg/mL formulation (cartridge) was bioequivalent to a 0.6 mg/mL formulation (vial). It also showed that the relative bioavailability of the cartridge formulation to the vial formulation was about 97% (AUC_{0-300 min}).

Therefore, small changes in drug concentration do not appear to have a significant impact on the bioavailability of Symlin.

Dose Proportionality

Does Symlin™ exhibit dose proportionality over the entire proposed dosing range, 30 mcg to 180 mcg?

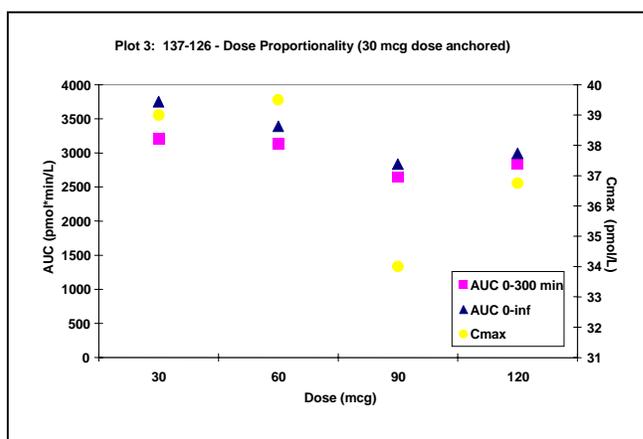
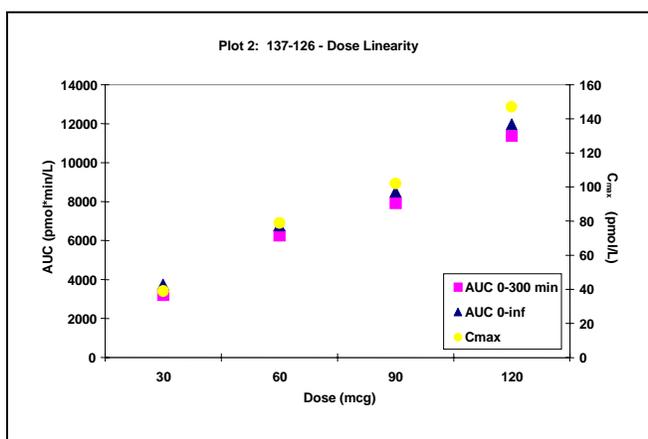
In order to characterize dose proportionality, the sponsor has conducted a randomized four-way crossover study in 40 (38 completed) healthy male subjects using four single subcutaneous doses of pramlintide administered at constant volume (0.2 mL). The treatments were as follows: Tx A – 30 mcg

(as 0.1 mL of formulation F21 (lot 96-0201GB) plus 0.1 mL placebo (lot 95-0504GE); Tx B – 60 mcg (as 0.1 mL of formulation F22 (lot 96-0503JB) plus 0.1 mL placebo (lot 95-05804GE); Tx C – 90 mcg (as 0.1 mL of formulation F24 (lot 96-0506JB) plus 0.1 mL placebo (lot 95-0504GE); and Tx D – 120 mcg (as 0.2 mL of formulation F22 (lot 96-0503JB). Each treatment phase was separated by a 1-week washout period.

Results (TABLE 5) indicate that SC administered pramlintide exhibits near linear kinetics between 30 and 120 mcg in normal healthy subjects – with a definite dose related increase in the PK parameters (see **Plots 2 & 3**). However, this study failed to demonstrate dose proportionality.

TABLE 5 – Pramlintide PK Profiles in Normal Healthy Subjects – Single Dose

Parameter	Units	30 mcg	60 mcg	90 mcg	120 mcg
C _{max}	pmol/L	39.26 ± 9.21	79.44 ± 20.50	102.48 ± 30.23	146.99 ± 35.50
AUC ₀₋₃₀₀	pmol*min/L	3215 ± 1122	6261 ± 2401	7939 ± 2848	11380 ± 3839
T _{max}	min	21.4 ± 8.79	19.5 ± 7.69	19.1 ± 7.70	21.3 ± 8.36
t _½	min	54.9 ± 14.5	49.2 ± 15.3	51.1 ± 20.0	48.1 ± 12.8
Cl (apparent)	L/min	2.36	2.42	2.87	2.67
Mean ± SD					



Two additional studies, 137-143 and 137-144, considered dose linearity and dose proportionality in type 1 and type 2 diabetes patients, respectively. Results were similar to those seen in study 137-126, with linearity being demonstrated between the range of 30 and 180 mcg (see **HUMAN PK – TARGET POPULATION**).

HUMAN PK – BIOEQUIVALENCE

Given that Symlin™ will be available in two concentrations, are these formulations bioequivalent?

Cartridge vs. Vial

Two dosage forms have been proposed for marketing by the sponsor, a cartridge form, to be used with a pen system, and a vial dosage form, to be used for syringe administration. Study 137-142 was conducted to establish bioequivalence between these two dosage forms. In this single center, open-label, randomized, two-period crossover study consisting of two evaluation periods with a 24-hour washout period between dosing events, a single 60 mcg dose administered by pen from the cartridge form (1.0 mg/mL) was compared with a single 60 mcg dose administered by syringe from the vial form (0.6 mg/mL) in 30 subjects (20 females and 10 males). All doses were administered into the subcutaneous tissue of the anterior abdominal wall.

TABLE 6 – Pramlintide PK Parameters: Cartridge Formulation vs. Vial Formulation

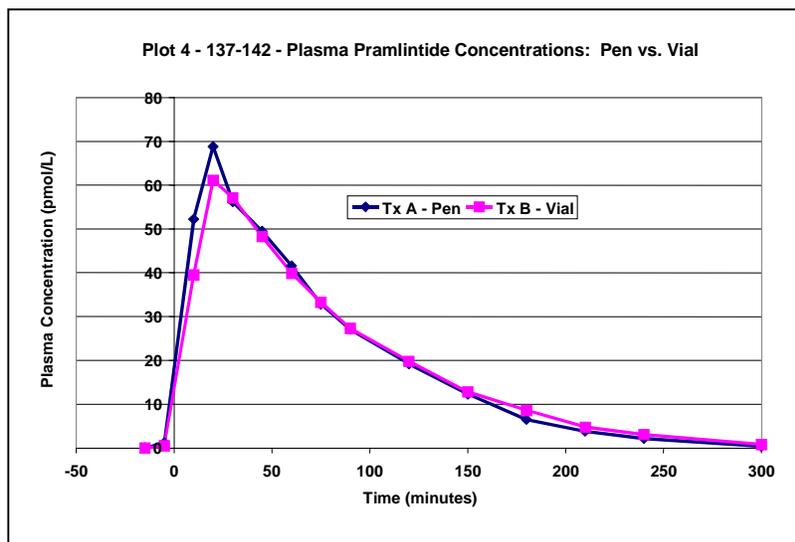
Parameter	Units	Tx A: Pen System 60 mcg @ 1.0 mg/mL			Tx B: Vial (syringe) 60 mcg @ 0.6 mg/mL		
		Mean	SD	%CV	Mean	SD	%CV
C _{max}	pmol/L	71.2	23.75	33.4	65.7	21.89	33.3
T _{max}	minutes	21.8	9.51	43.6	25.2	15.17	60.2
AUC _{0-300 min}	pmol*min/L	5742.0	3366.3	58.6	5695.5	3489.35	61.3
AUC _{0-inf}	pmol*min/L	6532.8	3499.7	53.6	6704.2	3725.05	55.6
t _{1/2}	minutes	52.8	16.51	31.3	59.4	26.55	44.7

TABLE 7 – Pramlintide BE Comparison: Cartridge Formulation vs. Vial Formulation

Parameter	Units	Tx A: Pen System	Tx B: Vial (syringe)	Tx: A/B Ratio ^c	90% CI ^d		p-value ^e
		Mean ^b	Mean ^b		Low	High	
C _{max} ^a	pmol/L	67.3	62.1	108.4	100.0	117.4	0.0986
T _{max}	minutes	20.0	20.0				0.1226 ^f
AUC _{0-300 min} ^a	pmol*min/L	4845	4679	103.6	93.3	115.0	0.5742
AUC _{0-inf} ^a	pmol*min/L	5673	5673	100.0	90.5	110.5	0.9993
t _{1/2}	minutes	52.8	59.4				0.1554

a – Parameters were natural log-transformed before analysis.
b – Means for the test (pen) and reference (syringe) treatment formulations;
 - (geometric means – anti-log of the means of the logs – for natural log-transformed parameters); and
 - (arithmetic means are presented for t_{1/2} and median values presented for T_{max}).
c – Ratio of geometric means calculated as Test/Reference.
d – 90% CI of the geometric means ratio T/R.
e – P-value from ANOVA (sequence, subject-within-sequence, period, & treatment) for testing treatment differences.
f – P-value from the Wilcoxon signed-rank test for the difference of 2 treatment formulations.

Results of this study indicate that the cartridge and vial formulations are bioequivalent when 60 mcg is administered subcutaneously to healthy individuals. This study also suggests that small differences in concentration, i.e., 1.0 mg/mL (cartridge) vs. 0.6 mg/mL (vial), results in non-significant differences in the rate of absorption and no detectable difference in the extent of absorption for this product (see **PLOT 4**).



Since there will be three suppliers of pramlintide material for Symlin™, are there any PK-related concerns about using multiple sources of this protein?

UCB-Bioproducts vs. Bachem Material

There has been a great deal of concern about the adequacy of the chemical characterization of peptides and their associated process impurities. Since the sponsor is proposing that three independent suppliers of pramlintide provide material for Symlin, the Agency has requested comparative bioavailability information. Specifically, a comparison was requested between UCB-Bioproducts material, which has never been used in clinical studies, and either Mallinckrodt or Bachem material, both of which have been used extensively in clinical development and are thought to be equivalent.

As such, the sponsor has submitted a two-way crossover design study (137-145) conducted in 30 normal healthy male and female subjects. Treatments consisted of a single 60 mcg dose from a 1.0 mg/mL formulation in cartridge form with active ingredient manufactured by UCB-Bioproducts [AC137-F28 (99-0603KB)] that was compared with a single 60 mcg dose from a 1.0 mg/mL formulation in cartridge form with active ingredient manufactured by Bachem [AC137-F28 (99-0602KB)].

Results of this study (see **TABLE 8**) clearly show that the F28 cartridge formulation produced from the UCB-Bioproducts pramlintide material is bioequivalent to the F28 cartridge formulation produced from the Bachem material.

TABLE 8 – Pramlintide BE Comparison: UCB-Bioproducts vs. Bachem Pramlintide Material

Parameter	Units	Tx A: UCB	Tx B: Bachem	Tx: A/B Ratio ^c	90% CI ^d		p-value ^e
		Mean ^b	Mean ^b		Low	High	
C _{max} ^a	pmol/L	50.4	51.8	0.97	89.4	105.9	0.5817
T _{max}	minutes	17.8	16.2				0.4747
AUC _{0-300 min} ^a	pmol*min/L	2463.1	2554.4	0.96	85.6	108.6	0.6067
AUC _{0-inf} ^a	pmol*min/L	3631.6	3609.9	1.01	89.6	113.1	0.9279
t _{1/2}	minutes	55.8	56.9				0.8657

a – Parameters were natural log-transformed before analysis.
b – Means for the test (UCB-Bioproducts) and reference (Bachem) treatment formulations;
 - (geometric means – anti-log of the means of the logs – for natural log-transformed parameters); and
 - (arithmetic means are presented for t_{1/2} and T_{max}).
c – Ratio of geometric means calculated as Test/Reference.
d – 90% CI of the geometric means ratio T/R.
e – P-value from ANOVA (sequence, subject-within-sequence, period, & treatment) for testing treatment differences.

HUMAN PK – TARGET POPULATION

Are there any differences between the pramlintide PK profiles of type 1 and type 2 diabetes patients?

Single and multiple dose PK/PD studies were conducted in both type 1 and type 2 diabetes patients. Common findings to both of these studies were: dose linearity over the study-specific dosage ranges, similar confounding factors that led to inconclusive pharmacodynamic conclusions (e.g., incomplete insulin usage records), and no apparent dose accumulation between treatments days 1 and 5. Of note, is the observation that concentrations in type 2 patients tend to be lower than those seen in type 1 patients.

Study 137-143 assessed the single and multiple dose PK profiles of SC administered pramlintide in 11 type 1 diabetes patients. This study was a randomized, three-treatment, three-way crossover design with two dosing frequency groups: three times daily (TID) and four times daily (QID). The group 1 treatments consisted of either 30 mcg, 60 mcg, or 90 mcg pramlintide doses administered SC using the 1.0 mg/mL cartridge formulation and given just prior to breakfast, lunch, and dinner for 4 days followed by a single dose prior to breakfast on the 5th day (13 consecutive doses). The group 2 treatments were similar to the group 1 treatments, but with the addition of a fourth dose administered just prior to an evening snack (17 consecutive doses). Results are presented in **TABLE 9**.

TABLE 9 – Pramlintide PK Profiles in Type 1 Diabetes Patients – Single & Multiple Dosing

Parameter	Day	30 mcg TID	60 mcg TID	90 mcg TID	30 mcg QID	60 mcg QID	90 mcg QID
C_{max} (pmol/L)	1	41.9 ± 22.9	64.5 ± 23.7	99.4 ± 31.4	36.5 ± 10.2	66.9 ± 25.0	123.9 ± 40.5
	5	37.6 ± 22.8	74.4 ± 20.0	92.7 ± 26.7	40.7 ± 20.0	70.7 ± 23.3	98.6 ± 30.1
T_{max} (hr)	1	0.273 ± 0.0753	0.365 ± 0.237	0.321 ± 0.115	0.274 ± 0.0751	0.276 ± 0.0794	0.273 ± 0.072
	5	0.328 ± 0.120	0.334 ± 0.113	0.288 ± 0.083	0.249 ± 0.002	0.278 ± 0.080	0.275 ± 0.082
AUC_{0-t} (pmol*hr/L)	1	32.86 ± 28.40	74.14 ± 34.26	118.5 ± 65.37	20.10 ± 11.46	51.67 ± 33.37	115.9 ± 54.29
	5	26.45 ± 21.93	79.68 ± 48.98	104.8 ± 63.53	24.20 ± 18.76	63.88 ± 49.83	102.0 ± 41.77
AUC_{0-inf} (pmol*hr/L)	1	81.37 ± 22.17	102.6 ± 37.4	144.2 ± 65.74	48.88 ± ?	72.01 ± 37.82	129.1 ± 55.74
	5	64.96 ± 9.63	117.2 ± 44.39	136.3 ± 66.70	66.43 ± 15.99	98.34 ± 56.22	124.1 ± 46.12
t_{1/2} (hr)	1	1.12 ± 1.01	0.970 ± 0.337	0.774 ± 0.281	0.595 ± ?	0.656 ± 0.169	0.645 ± 0.165
	5	0.726 ± 0.239	0.789 ± 0.326	0.722 ± 0.230	0.713 ± 0.173	0.724 ± 0.303	1.02 ± 1.02
k_{el} (1/hr)	1	0.887 ± 0.374	0.796 ± 0.278	1.03 ± 0.423	1.16 ± ?	1.13 ± 0.316	1.14 ± 0.284
	5	1.02 ± 0.282	1.00 ± 0.384	1.03 ± 0.281	1.00 ± 0.243	1.07 ± 0.342	1.03 ± 0.496
Mean ± SD							

Study 137-144 assessed the single and multiple dose PK profiles of SC administered pramlintide in 12 type 2 diabetes patients. This study was a randomized, three-treatment, three-way crossover design with two dosing frequency groups: two times daily (BID) and three times daily (TID). The group 1 treatments consisted of either 60 mcg, 120 mcg, or 180 mcg pramlintide doses administered SC using the 1.0 mg/mL cartridge formulation (lot # 97-0403KB) and given just prior to breakfast and dinner for 4 days followed by a single dose prior to breakfast on the 5th day (9 consecutive doses). The group 2 treatments included 60 mcg, 90 mcg, and 120 mcg doses of pramlintide administered just prior to breakfast, lunch, and dinner (13 consecutive doses). Results are presented in **TABLE 10**.

TABLE 10 – Pramlintide PK Profiles in Type 2 Diabetes Patients – Single & Multiple Dosing

Parameter	Day	60 mcg BID	120 mcg BID	180 mcg BID	60 mcg TID	90 mcg TID	120 mcg TID
C_{max} (pmol/L)	1	50.8 ± 20.3	117.4 ± 116.4	151.3 ± 67.2	36.4 ± 18.5	55.7 ± 25.7	74.0 ± 24.6
	5	55.9 ± 24.6	97.8 ± 34.0	137.3 ± 36.4	42.2 ± 20.2	60.1 ± 24.4	77.2 ± 28.2
T_{max} (hr)	1	0.331 ± 0.107	0.341 ± 0.105	0.368 ± 0.221	0.290 ± 0.072	0.253 ± 0.008	0.260 ± 0.030
	5	0.284 ± 0.072	0.324 ± 0.124	0.339 ± 0.224	0.255 ± 0.009	0.301 ± 0.105	0.275 ± 0.071
AUC_{0-t} (pmol*hr/L)	1	62.39 ± 61.98	143.0 ± 139.9	179.4 ± 129.9	32.24 ± 46.23	53.93 ± 52.15	76.24 ± 54.37
	5	61.18 ± 52.32	123.1 ± 97.40	189.0 ± 147.8	35.06 ± 38.05	59.66 ± 46.52	91.19 ± 77.00
AUC_{0-inf} (pmol*hr/L)	1	119.1 ± 86.42	201.6 ± 160.0	201.0 ± 140.4	201.5 ± 111.6	124.9 ± 85.32	119.2 ± 79.45
	5	133.7 ± 67.68	163.4 ± 111.0	232.1 ± 166.2	107.7 ± 67.12	129.2 ± 63.29	152.4 ± 102.7
t_{1/2} (hr)	1	1.24 ± 0.774	1.24 ± 0.832	0.926 ± 0.496	2.72 ± 1.49	1.38 ± 1.20	1.10 ± 0.778
	5	1.52 ± 1.09	1.02 ± 0.502	0.981 ± 0.406	1.42 ± 1.40	1.43 ± 0.991	1.15 ± 0.543
k_{el} (1/hr)	1	0.699 ± 0.301	0.760 ± 0.408	0.907 ± 0.385	0.300 ± 0.165	0.725 ± 0.338	0.811 ± 0.338
	5	0.594 ± 0.249	0.828 ± 0.369	0.814 ± 0.297	0.791 ± 0.425	0.615 ± 0.243	0.686 ± 0.231
Mean ± SD							

Comparison of tables 6 and 7 would suggest that, on average, patients with type 2 diabetes tend to exhibit lower total exposure than do patients with type 1 diabetes, when administered the same dose. It should also be noted that there is incredible variation in the PK parameters. This variability may be due to the route of administration, administration technique, and/or differences in body type.

Pramlintide is renally eliminated, what effect does renal insufficiency have on pramlintide PK?

Effect of Renal Insufficiency on Pramlintide PK

The sponsor conducted a study in order to evaluate the effect of renal insufficiency on pramlintide PK, based upon a rat nephrectomy model, a study that showed that basal levels of amylin were significantly higher in lean, non-diabetic patients with renal failure on chronic hemodialysis, and the fact that diabetes is a leading cause of renal disease.

Study 137-127 evaluated the PK of pramlintide in an open-label, parallel design study in 21 type 1 DM patients with varying degrees of renal function. Individuals were stratified by renal function into 1 of 4 categories based on creatinine clearance (CrCl): CrCl ≥ 90 mL/min; CrCl 60-89 mL/min; CrCl 30-59

mL/min; and CrCl < 30 mL/min. Each of the patients self-administered a single 60 mcg dose of pramlintide into the subcutaneous tissue of the anterior abdominal wall.

Based on the results of this study (**TABLE 11**), the sponsor concluded that “impaired renal function has no significant influence on pramlintide PK; therefore no dosing adjustment is required.” However, it should be noted that because of the high inter-subject variability and the few number of patients enrolled in this parallel design study, there can be no definitive conclusion regarding dosing adjustment (i.e., this study is inconclusive). Therefore, dosing of patients with compromised renal function should be individualized based on efficacy and tolerability.

TABLE 11 – Renal Insufficiency – Plasma Pramlintide Parameters in Type 1 DM Patients

AUC _{0-inf} (pmol*min/L)	Group I	Group II	Group III	Group IV
N	6	8	4	3
Mean ± SD	8396 ± 4360	5128 ± 2655	10538 ± 7064	5650 ± 4197
Min, max	2080, 12346	1764, 9199	3100, 19877	850, 8627
C _{max} (pmol/L)				
Mean ± SD	84.17 ± 30.69	60.70 ± 30.58	86.10 ± 57.02	60.93 ± 35.00
Min, max	52.4, 138.3	33.2, 112.5	31.9, 139.8	26.1, 96.1
T _{max} (min)				
Mean ± SD	34.2 ± 23.06	21.9 ± 8.43	30.0 ± 20.41	15.0 ± 5.00
Min, max	10, 75	10, 30	15, 60	10, 20
t _½ (min)				
Mean ± SD	49.4 ± 10.85	64.3 ± 54.78	80.7 ± 21.94	49.4 ± 35.11
Min, max	32, 63	27, 198	55, 105	19, 88
Cl/F				
Mean ± SD	169.7 ± 147.9	236.1 ± 139.78	135.5 ± 111.65	438.2 ± 559.71
Min, max	75, 443	100, 523	46, 297	107, 1084

Group I = CrCl ≥ 80 mL/min; Group II = CrCl 50-80 mL/min; Group III = CrCl 30-50 mL/min; Group IV = < 30 mL/min

Drug-Drug Interactions

Symlin and Insulins

Can Symlin™ be mixed in the same syringe with insulin(s)?

The primary indication for Symlin™ is as an adjunct to insulin therapy. Since both pramlintide and insulin are administered via the subcutaneous route, for convenience (e.g., fewer daily injections), it would be ideal if the two could be mixed in the same syringe. With this in mind, the sponsor has conducted 4 studies (137-130, 137-115, 137-119, & 137-120) in which type 1 diabetes patients were administered pramlintide and insulin(s) at the same time but in different syringes, or pramlintide and insulin(s) in the same syringe. The insulins that were evaluated in these studies included: Regular, NPH, Lente, Ultralente, & 70/30 (see **APPENDIX**).

The results of these studies, as a whole, strongly indicate that when pramlintide is administered in the same syringe with any insulin product, that both pramlintide and insulin pharmacokinetics can be substantially altered (see **TABLES 12 & 13**). This would then preclude the practice of “mixing” for reasons of compromised pramlintide and insulin efficacy. This conclusion is in line with that of the sponsor. The labeling will clearly indicate that Symlin™ should not be mixed with any insulin product (see **LABELING COMMENTS**).

TABLE 12 – Plasma Pramlintide PK: Symlin™ Mixed with R or NPH Insulin vs. Alone

Parameters	Units	A	B	C
		30 mcg Symlin + R Insulin	30 mcg Symlin + NPH Insulin	30 mcg Symlin
C _{max}	pmol/L	37.30 ± 20.38	33.21 ± 20.20	42.43 ± 20.32
AUC _{0-t}	pmol*min/L	1669 ± 1383	1513 ± 1200	1626 ± 1160
T _{max}	min	22.8 ± 9.83	32.3 ± 15.4	18.5 ± 9.07
t _{1/2}	min	51.7 ± 14.6	45.4 ± 13.8	47.1 ± 28.6
Mean ± SD				

TABLE 13 – Comparison: Symlin mixed with R or NPH Insulin vs. Alone

Parameters	Units	A vs. C		B vs. C	
		PE	90% CI	PE	90% CI
C _{max}	pmol/L	86.2	73.1 – 99.4	77.2	64.0 – 90.3
AUC _{0-t}	pmol*min/L	98.9	76.7 – 121.1	91.1	68.9 – 113.3
Mean ± SD					

Symlin and Lo/Ovral or Ampicillin**Since pramlintide delays gastric emptying time, what effect does Symlin™ have on orally administered medications?**

As previously described, one of pramlintide's primary mechanisms of action is to delay gastric emptying time. Therefore, it is conceivable that if an orally administered drug were administered concomitantly with pramlintide, an interaction may occur such that the object drug's efficacy could be compromised. With this in mind, the sponsor has conducted two drug-drug interaction studies to determine the effect that pramlintide has on an oral contraceptive (OC), Lo/Ovral™ and a relatively acid-stable antibiotic, ampicillin.

Study 137-133 evaluated the effect of pramlintide on the PK of ethinyl estradiol and norgestrel in healthy female subjects receiving Lo/Ovral (30 mcg ethinyl estradiol + 300 mcg norgestrel). In this randomized, two-period crossover design study, 18 females on OC treatment were subcutaneously administered either a placebo injection (lot # 96-0302JE) or a 90 mcg dose of Symlin™ (lot # 96-0503JB – F22 – 0.6 mg/mL) 15 minutes before administration of a single dose of Lo/Ovral™ (Lot # 9978046, expiration: 3/2000).

Results as presented in **TABLE 14** showed no statistically significant differences in the PK profile of ethinyl estradiol on any of the calculated PK parameters. In contrast, the norgestrel component of Lo/Ovral™ did exhibit significant differences when administered with Symlin™ (see **TABLE 15**). The C_{max} for norgestrel was reduced by about 30% and the time to C_{max} was delayed by 45 minutes; AUC was similar between treatments.

TABLE 14 – Effect of Symlin on Lo/Ovral (ethinyl estradiol) Pharmacokinetics

ETHINYL ESTRADIOL	Lo/Ovral	Lo/Ovral + Symlin	p-value ^a	Ratio or LSMeans Difference	95% CI	
					Low	High
InAUC_{0-24 hours} (pg*min/L)						
LS Means (SE) ^a	10.4 (0.1)	10.4 (0.1)	0.981	100.3%	79.4%	126.6%
GEO LS Means ^b	32990.2	33076.8				
InAUC_{0-inf} (pg*min/L)						
LS Means (SE) ^a	10.8 (0.1)	10.9 (0.1)	0.389	109.5%	88.1%	136.0%
GEO LS Means ^b	49544.0	54227.8				
InC_{max} (pg/L)						
LS Means (SE) ^a	4.6 (0.1)	4.6 (0.1)	0.842	98.5%	84.3%	115.2%
GEO LS Means ^b	101.2	99.7				
T_{max} (min)						
LS Means (SE) ^a	74.0 (14.1)	101.9 (14.1)	0.176	27.9	-13.9	69.7
t_{1/2} (min)						
LS Means (SE) ^a	413.1 (64.4)	468.8 (64.4)	0.412	55.6	-84.8	196.0

^a = Based on ANOVA model which includes terms for sequence, subject within sequence, period and treatment
^b = Geometric means are the antilogs of the means of the natural logarithmic transformed endpoints.

TABLE 15– Effect of Symlin on Lo/Ovral (norgestrel) Pharmacokinetics

NORGESTREL	Lo/Ovral	Lo/Ovral + Symlin	p-value ^a	Ratio or LSMeans Difference	95% CI	
					Low	High
InAUC_{0-24 hours} (ng*min/L)						
LS Means (SE) ^a	7.4 (0.1)	7.4 (0.1)	0.646	98.2	90.4%	106.7%
GEO LS Means ^b	1658.3	1628.6				
InAUC_{0-inf} (ng*min/L)						
LS Means (SE) ^a	8.0 (0.1)	8.1 (0.1)	0.188	107.1	96.3%	119.2%
GEO LS Means ^b	3070.2	3288.8				
InC_{max} (ng/L)						
LS Means (SE) ^a	1.5 (0.1)	1.5 (0.1)	< 0.001	68.9	60.4%	78.5%
GEO LS Means ^b	4.7	3.2				
T_{max} (min)						
LS Means (SE) ^a	68.9 (11.7)	114.2 (11.7)	0.014	45.3	10.9	79.6
t_{1/2} (min)						
LS Means (SE) ^a	1780 (205)	2054 (205)	0.197	274.9	-162	712

^a = Based on ANOVA model which includes terms for sequence, subject within sequence, period and treatment
^b = Geometric means are the antilogs of the means of the natural logarithmic transformed endpoints.

The second drug-interaction study (137-134), which evaluated delayed gastric emptying, was a double-blind, placebo-controlled, single-dose, two-period crossover design study in 12 (11 completed) healthy male and female subjects. Subjects were given either placebo (lot # 96-032JE) plus a single 2 x 250 mg oral dose of ampicillin (batch # 54763 B; expiration 8/2002) or a single 90 mcg subcutaneously administered dose of Symlin™ (lot # 96-0503JB – F22 – 0.6 mg/mL) plus oral ampicillin. Results (**TABLE 16**) show that pramlintide has no significant impact on the AUC or C_{max} of ampicillin, but similar to the Lo/Ovral™ study, T_{max} was increased by approximately one hour.

TABLE 16 – Effect of Symlin on Ampicillin Pharmacokinetics

AMPICILLIN	Ampicillin	Ampicillin + Symlin	p-value ^a	Ratio or LSMeans Difference	95% CI	
					Low	High
InAUC_{0-8 hours} (mcg*min/L)						
LS Means (SE) ^a	6.7 (0.1)	6.6 (0.1)	0.553	95.7	81.5%	112.4%
GEO LS Means ^b	782.3	748.9				
InAUC_{0-inf} (mcg*min/L)						
LS Means (SE) ^a	6.7 (0.1)	6.6 (0.1)	0.559	95.8	81.5%	112.5%
GEO LS Means ^b	792.9	1.6 (0.1)				
InC_{max} (mcg/L)						
LS Means (SE) ^a	1.5 (0.1)	1.6 (0.1)	0.380	108.3	89.0%	131.9%
GEO LS Means ^b	4.7	5.1				
T_{max} (min)						
LS Means (SE) ^a	110.0 (12.7)	176.2 (12.7)	0.003	66.2	29.1	103.3
t_{1/2} (min)						
LS Means (SE) ^a	59.1 (3.2)	51.0 (3.2)	0.046	-8.2	-16.2	-0.2

^a = Based on ANOVA model which includes terms for sequence, subject within sequence, period and treatment
^b = Geometric means are the antilogs of the means of the natural logarithmic transformed endpoints.

Individually, the results from these studies are relatively unremarkable – especially given that the extent of absorption was not affected by pramlintide in either case. However, both of these agents, ampicillin and Lo/Ovral™, are used chronically and are not dependent upon rapid drug action, as are many oral pain medications, etc. Therefore, as the sponsor has recommended, concomitant medications susceptible to delayed gastric emptying times should be administered at least one-hour before administration of Symlin™.

HUMAN PK – PLASMA/BLOOD

An *in vitro* protein binding study of pramlintide in animal and human blood and plasma. A mean of 37% of pramlintide tracer spiked into whole blood was bound to cells, with the remaining in the unbound in the plasma fraction. Thirty-three percent was bound to soluble plasma components, which leaves approximately 40% total pramlintide available for receptor binding.

HUMAN PK – EX VIVO – Placental Transfer

Placental transfer was evaluated in placentas from normal term vaginal or cesarean section deliveries. Placentas were perfused as an open, non-circulating, system for 90 to 120 minutes and then as a closed, circulating, system for an additional 90 to 120 minutes. Concentrations in the perfusate ranged from 206 to 458 pmol/L.

No detectable pramlintide was detected on the fetal side after 120 minutes of the open-loop perfusion stage. One sample of fetal perfusate, during the closed loop phase, had detectable pramlintide at 60 minutes, but was undetectable at 90 minutes. These *ex vivo* results suggest that fetal exposure to pramlintide *in utero* is low.

PHARMACODYNAMICS

What effect does a morning dose of pramlintide have on the gastric emptying of a lunchtime meal?

Effect of Pramlintide on Gastric Emptying

Delay gastric emptying time is one of the two well described mechanisms of pramlintide action. Gastric emptying, as a pharmacodynamic (PD) endpoint, was formally evaluated in two studies (also see **HUMAN PK – EXTRINSIC – Drug-Drug Interactions**). The first of these studies, 137-118, determined the dose-response relationship of single doses of pramlintide on the rate of gastric emptying of the liquid and solid components of a radio-labeled standardized meal (500 kcal – 55% CHO; 35% fat, 10% protein) and to determine if a dose of pramlintide administered 15 minutes before breakfast has a “carry-over” effect on the emptying of the lunch time meal. This four-way cross-over study in 14 (11 evaluable) type 1 diabetes

patients compared treatments of 30 mcg, 60 mcg, and 90 mcg (lot # 95-0902GB – F21 – 0.3 mg/mL formulation) with placebo (lot # 95-0504GE).

Results of this study showed that when pramlintide is administered 15 minutes before a standardized breakfast consisting of a liquid component, 3-ortho-methyl-glucose (3-OMG) labeled milkshake, and a solid meal, ^{99m}Techetium-amberlite resin labeled pancake, gastric emptying time was significantly delayed compared with placebo. The time to maximum plasma 3-OMG concentration (T_{max}) was increased from about 80 minutes for placebo to 200 minutes for the 90 mcg dose (see **TABLE 17**). The time to achieve half-gastric emptying was similarly increased (see **TABLE 18**). There was no observed “carry-over” effect of the morning pramlintide dose to the lunch time meal.

TABLE 17 – Liquid Meal – Plasma 3-OMG PK Parameters by Treatment (n = 11)

Breakfast (1st meal)	Placebo	30 mcg	60 mcg	90 mcg
AUC_{0-240 min} (mmol*min/L)				
Arithmetic mean	41.2	31.0	26.6	29.7
p-value vs placebo	NA	0.0057	0.0005	0.0028
C_{max} (mmol/L)				
Arithmetic mean	0.26	0.20	0.20	0.21
p-value vs placebo	NA	0.0004	0.0008	0.0051
T_{max} (min)				
Arithmetic mean	81.8	170.9	200.0	191.1
p-value vs placebo	NA	0.0006	0.0001	0.0001
Lunch (2nd meal)	Placebo	30 mcg	60 mcg	90 mcg
AUC_{240-480 min} (mmol*min/L)				
Arithmetic mean	57.9	62.3	60.1	59.9
p-value vs placebo	NA	0.3389	0.6669	0.4977
C_{max} (mmol/L)				
Arithmetic mean	0.33	0.34	0.33	0.33
p-value vs placebo	NA	0.6960	0.7775	0.8379
T_{max} (min)				
Arithmetic mean	318.2	316.4	322.0	308.9
p-value vs placebo	NA	0.8157	0.9782	0.5282

NA = not applicable; p-values from t-tests for multiple comparisons following ANOVA

TABLE 18 – Solid Meal – Gastric Emptying Parameters by Treatment (n = 11)

Breakfast (1st meal)	Placebo	30 mcg	60 mcg	90 mcg
Half-Emptying Time (min)				
Arithmetic mean	128.6	187.2	200.1	214.5
p-value vs placebo	NA	0.0002	0.0001	0.0001
Lag Time (min)				
Arithmetic mean	32.5	54.4	56.4	70.3
p-value vs placebo	NA	0.0173	0.0130	0.0001
Lunch (2nd meal)	Placebo	30 mcg	60 mcg	90 mcg
Half-Emptying Time (min)				
Arithmetic mean	136.9	138.5	140.6	145.4
p-value vs placebo	NA	0.7497	0.7497	0.2590
Lag Time (min)				
Arithmetic mean	34.2	46.5	40.0	48.2
p-value vs placebo	NA	0.1938	0.5772	0.1353

NA = not applicable; p-values from t-tests for multiple comparisons following ANOVA

The second gastric emptying study, 137-137, consisted of a two-way crossover design in 10 type 2 diabetes patients that were administered either placebo (lot # 97-0101GE) or a 90 mcg dose of pramlintide (lot # 96-1002JB – F24 – 0.9 mg/mL) 15 minutes prior to a ^{99m}Techetium breakfast (381 kcal – 48% CHO, 26% fat, & 26% protein). The results, as presented in **TABLE 19**, demonstrate that pramlintide significantly increases the half-emptying time and lag time of a solid meal in patients with type 2 diabetes compared with placebo.

TABLE 19 - Solid Meal – Gastric Emptying Parameters

Breakfast	Placebo	90 mcg
Half-Emptying Time (min)		
Arithmetic mean	80.50	127.00
p-value vs placebo	NA	0.0011
Lag Time (min)		
Arithmetic mean	17.00	28.80
p-value vs placebo	NA	0.0232

NA = not applicable; p-values from standard ANOVA for 2x2 crossover

LABELING

Labeling will be addressed in an amendment to this review that will be submitted after the Advisory Committee Meeting scheduled for July 26, 2001. Attached is the sponsor's proposed labeling.

COMMENTS TO THE SPONSOR

The immunoenzymetric assay (IEMA) used to detect human plasma pramlintide exhibited reasonable precision and accuracy estimates. However, the samples used in the quality control analysis were sufficiently far enough away from the calibration limits and the lower limit of quantitation as to create some concern about the plasma concentrations that fall between the lower limit of quantitation (LLOQ) and the lowest quality control sample. In addition, the LLOQ appeared to be highly variable between studies. Hence, the reported plasma values that fall on the lower end of the plasma profile curve are not considered reliable.

There is also the issue of using a non-specific assay to characterize the pharmacokinetics of pramlintide. As you have pointed out in your submission, we're actually looking at pramlintide, the pramlintide metabolite(s), and any endogenous material, when describing pramlintide PK. However, the relative contribution of each component is not well described. There is also the potential for additional interference from the human anti-murine antibody (HAMA).

With these issues in mind, the Office of Clinical Pharmacology and Biopharmaceutics strongly suggests that you consider developing a more specific assay for pramlintide that overcomes the described limitations of the IEMA.

Steven B. Johnson, Pharm.D.
CPB Reviewer

Hae-Young Ahn, Ph.D.
CPB Team Leader

Draft Sign-off: _____

Final Sign-off: _____

Briefing Date: 01-JUN-2001

Briefing Attendees:

Hae-Young Ahn, Gerald Fetterly, Hank Malinowski, Saul Malozowski, Mei-Ling Chen, Larry Lesko, Sang Chung, Arzu Selen, John Hunt, and Mehul Mehta.

SYMLIN™

brand of pramlintide acetate injection

DESCRIPTION

SYMLIN™ (pramlintide acetate) is a synthetic analogue of human amylin, a pancreatic beta-cell hormone that is secreted along with insulin, and has actions that complement those of insulin in maintaining metabolic control. SYMLIN, as adjunctive therapy to insulin, can improve glycemic control in people with type 1 or insulin-using type 2 diabetes without increasing insulin requirements, promoting weight gain, or increasing the risk of hypoglycemia.

SYMLIN is an amylinomimetic agent, the first member of a new class of therapeutic compounds that differs in chemical structure and pharmacologic actions from insulin, sulfonylureas, metformin, thiazolidinediones, meglitinides, or the alpha-glucosidase inhibitors. Pramlintide is a 37-amino acid polypeptide with proline replacements at positions 25 (alanine), 28 (serine), and 29 (serine) of human amylin.

The structural formula of pramlintide acetate is as shown:


Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH₂ acetate (salt) with a disulfide bridge between the two Cys residues.

Pramlintide acetate is a white powder that has a molecular formula of C₁₇₁H₂₆₇N₅₁O₅₃S₂ • x C₂H₄O₂ (x is variable). The molecular weight of C₁₇₁H₂₆₇N₅₁O₅₃S₂ is 3949.4. Pramlintide acetate is soluble in water.

SYMLIN is formulated as a clear sterile solution for subcutaneous (SC) administration, containing pramlintide as the acetate salt, metacresol as a preservative, acetic acid, sodium acetate, mannitol, and water for injection. SYMLIN has a pH of 4.0. In cartridges for use with the SymlinPen™ delivery devices, each milliliter of SYMLIN contains 1.0 mg of pramlintide (as pramlintide acetate). In vials, each milliliter of SYMLIN contains 0.6 mg of pramlintide (as pramlintide acetate).

CLINICAL PHARMACOLOGY

Amylin is a naturally occurring hormone, synthesized by the pancreatic beta cells and stored in secretory granules with insulin. Amylin and insulin are cosecreted in response to food intake, providing an amylin signal proportional to meal size. Amylin is a neuroendocrine hormone that acts at specific binding sites in the area postrema of the brain. Activation of these binding sites results in signaling through efferent pathways of the vagus nerve to modulate postmeal glucagon concentrations and the appearance of meal-derived nutrients (including glucose) in the peripheral circulation.

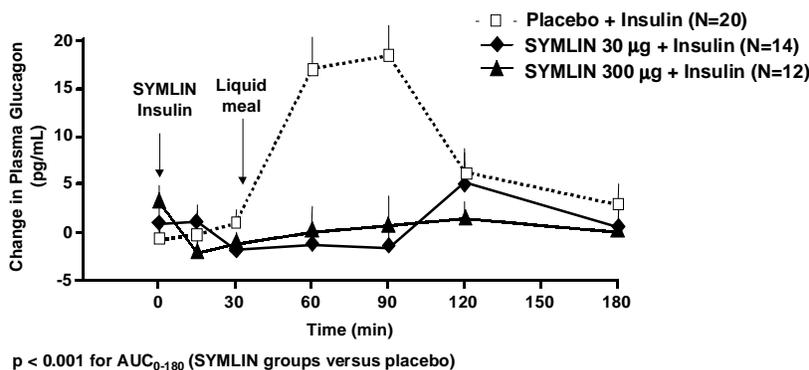
In people with type 1 diabetes, the pancreatic beta cells are destroyed, resulting in deficiencies in both insulin and amylin. In people with type 2 diabetes, beta cell failure occurs with a background of insulin resistance. As beta cells fail, insulin and amylin concentrations become abnormally low for the accompanying glucose concentrations. Thus both type 1 and type 2 diabetes exhibiting beta cell failure manifest elevated glucose concentrations with exaggerated glucose swings throughout the day. When beta cell failure is recognized clinically and insulin therapy is initiated, amylin replacement therapy should also be considered.

Mechanism of Action of Improved Glucose Control

In clinical studies in patients with diabetes who use insulin, SYMLIN has been shown to contribute to improved glucose control through: regulation of postmeal glucagon concentrations to prevent the abnormal postprandial rise seen in people with diabetes, and modulation of the appearance of meal-derived nutrients (including glucose) in the peripheral circulation. These effects are complementary to insulin, which promotes clearance of nutrients from the plasma into peripheral tissues for utilization and storage.

- **Normalization of Postprandial Glucagon Secretion.** In people with diabetes, glucagon concentrations are abnormally elevated during the postprandial period. This contributes to postprandial hyperglycemia by increasing release of glucose from the liver into the peripheral circulation. SYMLIN has been shown to return postprandial glucagon concentrations to normal in patients with diabetes (Figure 1). SYMLIN does not modify the glucagon response to hypoglycemia, thus keeping the important counter-regulatory responses to hypoglycemia intact.

Figure 1. Change in Mean Plasma Glucagon Following a Liquid Meal After 14 Days of SYMLIN + Insulin or Placebo + Insulin TID in Patients With Type 1 Diabetes



- **Coordination of Nutrient Delivery.** In people with diabetes, glucose concentrations are abnormally elevated, especially during the postprandial period. Following the administration of a single SC dose of 30, 60, or 90 µg of SYMLIN in addition to their usual insulin dosage, patients with type 1 diabetes demonstrated a dose-dependent reduction in the rate of delivery of food from the stomach to the small intestine (gastric emptying rate). The time required for half the food to leave the stomach was increased by approximately 1 to 1½ hours compared with placebo administration.

In patients with type 2 diabetes who use insulin, administration of a single SC dose of 90 µg of SYMLIN demonstrated similar effects. These alterations in nutrient delivery provide better coordination with the activity profiles of short-acting insulins consistent with reduced swings in plasma glucose concentrations.

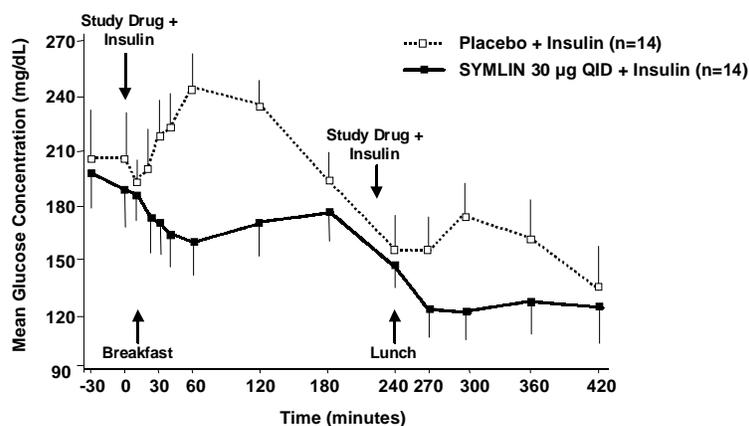
Effect on Postprandial Glucose Concentrations

Consistent with these findings, SYMLIN administration has been shown to result in a reduction in postprandial plasma glucose concentrations.

In a 14-day study in patients with type 1 diabetes, SYMLIN 30 µg administered four times daily resulted in a statistically significant reduction in 24-hour mean plasma glucose concentrations by study end compared to placebo (reduction of 29 mg/dL compared to placebo).

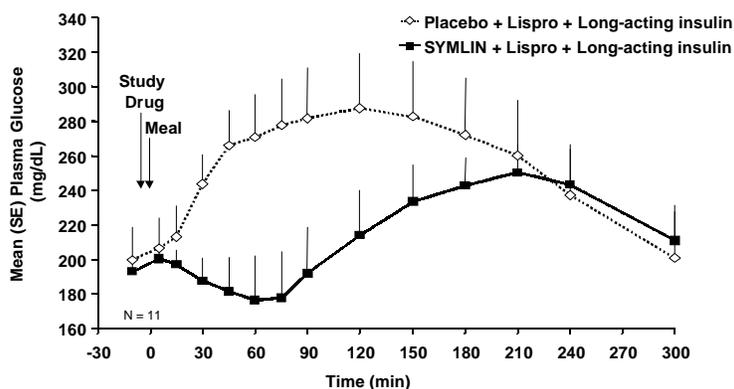
A 28-day crossover study in patients with type 1 diabetes assessed the effect of SYMLIN 30 µg + insulin and placebo + insulin administered four times daily on postprandial glucose concentrations following breakfast and lunch on the 28th day of treatment. Following both meals, patients receiving SYMLIN + insulin did not experience a postprandial rise in glucose concentrations, while those receiving placebo + insulin did (p=0.001 and p=0.02 for breakfast and lunch, respectively) (Figure 2). These results also suggest a reduction in the swings of plasma glucose concentrations that often characterize this population.

Figure 2. Mean Plasma Glucose During a 7-Hour Period After 28 Days of SYMLIN 30 µg + Insulin or Placebo + Insulin QID in Patients With Type 1 Diabetes



Postprandial glucose profiles were also compared in a separate study following administration of a single 60 µg dose of SYMLIN or placebo with insulin lispro and a long-acting insulin (NPH, Lente[®] or Ultralente[®]). This double-blind crossover study enrolled patients with type 1 diabetes who maintained their usual insulin regimens that included insulin lispro prior to study entry. Postprandial glucose concentrations were lower following SYMLIN + their usual insulin regimen (insulin lispro + long-acting insulin treatment) compared with placebo + their usual insulin regimen (Figure 3).

Figure 3. Mean Postprandial Plasma Glucose Following Single Dose of SYMLIN 60 µg + Insulin Lispro and Long-Acting Insulin or Placebo + Insulin Lispro and Long-Acting Insulin in Patients with Type 1 Diabetes



Pharmacodynamics

In short-term clinical studies in patients with type 1 diabetes, SYMLIN treatment resulted in a reduction in mean postprandial and 24-hour plasma glucose concentrations. In mid-term and long-term studies, SYMLIN administration resulted in reduction of fructosamine and HbA_{1c} (see CLINICAL STUDIES).

In a 28-day study in patients with type 1 diabetes, SYMLIN administration in addition to usual insulin therapy resulted in greater mean reductions from baseline in fructosamine concentrations by study end compared to placebo + insulin. This difference was statistically significant for the SYMLIN 30 µg and 60 µg + insulin groups compared with insulin alone.

Similarly in a 28-day study in patients with type 2 diabetes using insulin, three regimens of SYMLIN (30 µg QID, 60 µg TID or QID) administered with usual insulin regimens resulted in statistically significant mean reductions in fructosamine by study end compared with adding placebo to usual insulin regimens.

Preservation of counter-regulatory responses during hypoglycemia. In four placebo-controlled studies of patients with type 1 diabetes employing a controlled hypoglycemia challenge induced with intravenous insulin, the onset and degree of hypoglycemia were no greater, and the recovery following hypoglycemia

was no different following SYMLIN administration compared with placebo administration. The counter-regulatory hormonal response to hypoglycemia was preserved during SYMLIN administration.

Reduction of body weight. SYMLIN administration has been shown to reduce body weight in type 1 and insulin-using type 2 diabetes, as described in Clinical Studies. This effect was most pronounced in overweight patients (BMI ≥ 27 kg/m²). Lean patients (BMI < 23 kg/m²) with type 1 diabetes maintained their weight.

Pharmacokinetics

The absolute bioavailability of a 60 μ g SC dose of SYMLIN was determined to be approximately 40% that of an equivalent intravenous dose in healthy subjects.

Bioequivalence has been established between the 0.6 mg/mL formulation (0.1 mL with a vial and syringe) and the 1.0 mg/mL formulation (0.06 mL with a cartridge and pen delivery device). SYMLIN is not tightly bound to cells or albumin, with overall free drug concentrations at approximately 40%, and thus should be insensitive to changes in binding sites.

SYMLIN administered SC in four different doses to healthy subjects produced dose-proportionate C_{max} , and relatively constant T_{max} and $t_{1/2}$ (Table 1).

Table 1. Mean Pharmacokinetic Parameters Following Administration of Single SC Doses of SYMLIN

Subcutaneous Dose (μ g)	C_{max} (pmol/L)	T_{max} (min)	$t_{1/2}$ (min)
30	39	21	55
60	79	20	49
90	102	19	51
120	147	21	48

AUC values were also dose proportionate.

Absorption and Bioavailability

Absorption: SYMLIN demonstrates linear, absorption-rate limited pharmacokinetics in healthy subjects and in patients with type 1 diabetes or insulin-using type 2 diabetes.

Distribution: The distribution as indicated by the AUC values is dose proportional when given by SC injection. AUC values were relatively constant over time with repeat dosing, indicating no bioaccumulation.

Metabolism: SYMLIN is primarily metabolized by the kidneys. Des-lys¹ pramlintide (2-37 pramlintide), the primary metabolite, is biologically active in several in vitro assays and in vivo in rats. Other plasma metabolites (15-37, 16-37, 17-37 and 24-37 pramlintide) are not reactive in studies of in vitro binding.

Elimination: In rats, the plasma half-life of both pramlintide and des-lys¹ pramlintide was shown to be prolonged when blood flow to the kidney was interrupted by ligation. Insignificant amounts of pramlintide and des-lys¹ pramlintide have been detected in the urine of normal rats.

Special Populations

Renal insufficiency

Impaired renal function has little or no influence on SYMLIN pharmacokinetics and no dose adjustment is required (see DOSAGE AND ADMINISTRATION).

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.

Age

SYMLIN has been studied in patients ranging in age from 16 to 84 years of age, including 512 patients 65 years of age or older, and 29 patients between the ages of 16 and 18. No age-related differences in the activity of SYMLIN have been observed.

Gender

SYMLIN has been studied in 2531 male patients and 1884 female patients. No gender-related differences in the activity of SYMLIN have been observed.

Race/Ethnicity

SYMLIN has been studied in patients of different races/ethnic origins, including white (n=3923), black (n=195), Hispanic (n=244), and other ethnic origins (n=53). No differences in the activity of SYMLIN have been observed among patients of differing ethnic origins.

CLINICAL STUDIES

A total of 4415 patients have received SYMLIN in clinical studies, 3482 of these (1970 with type 1 diabetes, 1512 with type 2 diabetes, the majority insulin-using) in short- or long-term controlled clinical trials or in long-term uncontrolled clinical trials.

Clinical Studies in Type 1 Diabetes

Three long-term, double-blind, placebo-controlled studies of SYMLIN were conducted in patients with type 1 diabetes (N=1717). SYMLIN total daily dosage ranged from 120 to 270 µg given in regimens of 30 µg or 60 µg QID, 60 µg or 90 µg TID, or 90 µg BID.

In each of these studies, SYMLIN or placebo was added to existing insulin therapies. No attempt was made to standardize insulin regimens prior to study entry. During the studies, patients were asked to maintain their usual dietary and exercise patterns. In practice, insulin regimens were changed as needed to maintain glycemic control. Improved glucose control, as measured by change in HbA_{1c} from baseline, was the primary endpoint in each study.

Results from one long-term study (Study A) are representative of results with other studies and are presented in Table 2. In this study, the mean duration of diabetes across treatment arms ranged from 18 to 19 years, and mean HbA_{1c} at study entry was 8.9 to 9.0%. Mean weight at baseline was approximately 77 kg and approximately equal numbers of men and women participated in the study.

Table 2. Glucose Control, Insulin Use, and Weight Parameters in a 52-week Double-Blind Placebo-Controlled Study in Type 1 Diabetes

Timepoint/Parameter	Study A		
	Placebo + Insulin (n=106)	SYMLIN 60 µg TID + Insulin (n=100)	SYMLIN 60 µg QID + Insulin (n=108)
Mean Change from Baseline at Week 26			
HbA _{1c} (%)	-0.2	-0.5*	-0.4
Insulin use (% change) ¹	3.5	-0.1	-4.2
Weight (kg)	0.7	-1.2*	-1.0*
Mean Change from Baseline at Week 52			
HbA _{1c} (%)	0.1	-0.4*	-0.3*
Insulin use (% change) ¹	-0.3	-2.5	-6.1
Weight (kg)	0.8	-0.3*	-0.6*

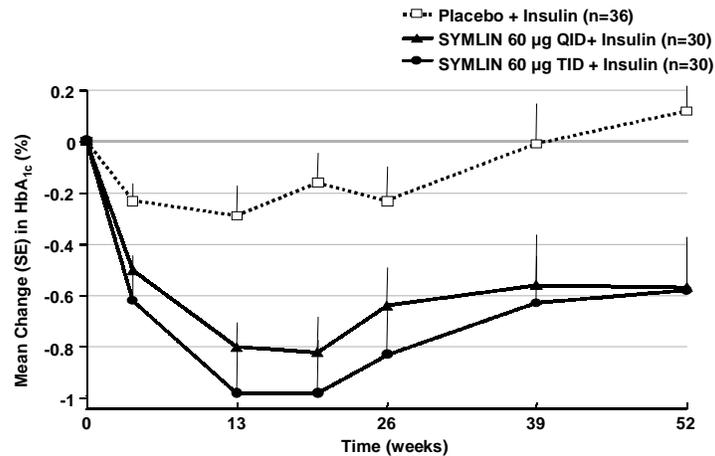
* Statistically significant difference from placebo + insulin.

¹ Relative change from baseline; statistical difference between treatments not assessed for this variable.

HbA_{1c} and Results Summary. SYMLIN + insulin produced greater reductions from baseline in HbA_{1c} at Weeks 26 and 52 compared with those observed with placebo + insulin. These reductions in HbA_{1c} in the SYMLIN + insulin groups were achieved without increases in total daily insulin doses. Body weight decreased among patients treated with SYMLIN + insulin, compared with mean increases in weight among patients treated with placebo + insulin. The improvement in glucose and reduction in body weight, along with reduced insulin use in the SYMLIN + insulin groups compared with those receiving placebo + insulin, were maintained throughout a 52-week period.

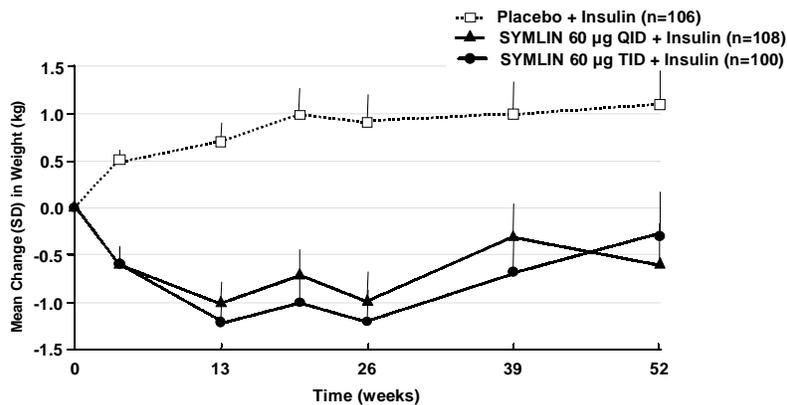
Insulin Use. Because of the variability in insulin use, and the effect that adjusting insulin doses may have on HbA_{1c}, a subgroup of patients who did not change the type or number of insulin injections from baseline, and maintained their daily insulin dose within ±10% of baseline usage during the study was prospectively identified in Study A. This stable insulin usage subgroup was defined to better isolate the effect of SYMLIN in this type 1 diabetes population. At every post-treatment visit, patients in this subgroup who received SYMLIN + insulin experienced a significantly greater mean reduction in HbA_{1c} from baseline than did the placebo + insulin recipients. At Week 52, the mean difference in HbA_{1c} from baseline for placebo + insulin recipients in this subgroup compared with SYMLIN + insulin recipients was 0.7% (Figure 4).

Figure 4. Change in HbA_{1c} From Baseline Through 1 Year for Stable Insulin Usage Subgroups Receiving SYMLIN + Insulin or Placebo + Insulin in Type 1 Diabetes Study A



Weight. On average, patients receiving SYMLIN + insulin lost weight while patients receiving placebo + insulin gained weight (Figure 5). These differences were statistically significant at every visit tested.

Figure 5. Change in Weight From Baseline Through 1 Year for Patients Receiving SYMLIN + Insulin or Placebo + Insulin in Type 1 Diabetes Study A



On average, patients with a BMI <23 kg/m² at study entry who received SYMLIN + insulin maintained body weight.

For those who entered the study with a BMI ≥27 kg/m², SYMLIN + insulin recipients on average experienced a clinically meaningful and statistically significant mean decrease from baseline in body weight at study end compared with placebo + insulin recipients, who experienced a mean increase in body weight.

Effect on Lipid Profile. SYMLIN did not cause any adverse effects on lipid concentrations in patients with type 1 diabetes.

Long-Term Use

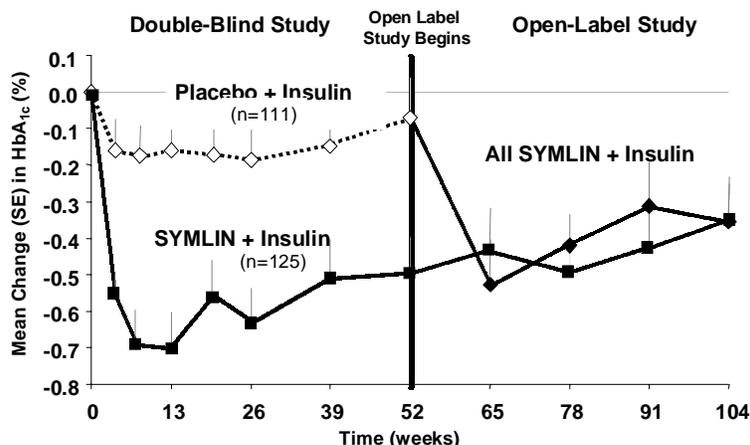
In controlled and uncontrolled studies of SYMLIN, 106 patients with type 1 diabetes received SYMLIN for 2 years or longer.

Approximately 70% (236 of 342) of participants who had completed a 1-year double-blind study volunteered to continue in an open-label extension study of SYMLIN.

The data from this extension study indicate that the effects of SYMLIN are sustained throughout an additional 1 year of observation, with improved glucose control (Figure 6).

There was also a mean decrease in body weight relative to original study baselines.

Figure 6. Change in HbA_{1c} for Patients in 1-Year Double-Blind Study Who Enrolled in an Open-Label Extension Study



Type 1 Diabetes Summary. SYMLIN (at dosages of 30 and 60 µg QID, and 60 µg TID) used as an adjunct to insulin therapy in patients with type 1 diabetes resulted in improved glucose control (reductions in postprandial hyperglycemia and HbA_{1c}) and reduced body weight without an increase in insulin usage. These results were observed for up to 1 year during adequate and well-controlled studies, and were observed for at least one additional year in an open-label study.

Clinical Studies in Insulin-Using Type 2 Diabetes

Three long-term, double-blind, placebo-controlled studies of pramlintide acetate were conducted in patients with type 2 diabetes who use insulin (N=1693). SYMLIN total daily dosage ranged from 90 to 450 µg given in regimens of 90 µg or 120 µg BID, and 30 µg, 60 µg, 75 µg, 90 µg or 150 µg TID. In each of these studies, SYMLIN or placebo was added to the participants' existing diabetes therapies, which included insulin and may have included selected oral hypoglycemic agents. No attempt was made to standardize insulin regimens or any other component of patients' usual therapy prior to study entry. During the studies, patients were asked to maintain their usual dietary and exercise patterns. In practice, insulin regimens were changed as needed to maintain glycemic control. Improved glucose control, as measured by change in HbA_{1c} from baseline, was the primary endpoint in each study.

Results from one long-term study (Study B) are representative of results from other studies and are presented in Table 3. In this study, the mean duration of diabetes across treatment arms ranged from 11 to 12 years, and mean HbA_{1c} at study entry ranged from approximately 9.0 to 9.3%. Mean weight at baseline ranged from 97 to 101 kg, and approximately equal numbers of men and women participated in the study.

Table 3. Glucose Control, Insulin Use, and Weight Parameters in a 52-week Double-Blind Placebo-Controlled Study in Insulin-Using Type 2 Diabetes

Timepoint/Parameter	Placebo + Insulin (N=109)	SYMLIN 120 µg BID + Insulin (N=122)
Mean Change from Baseline at Week 26		
HbA _{1c} (%)	-0.3	-0.7*
Insulin use (% change) ¹	2.7	-0.8
Weight (kg)	0.2	-1.5*
Mean Change from Baseline at Week 52		
HbA _{1c} (%)	-0.1	-0.7*
Insulin use (% change) ¹	3.2	3.3
Weight (kg)	0.7	-1.4*

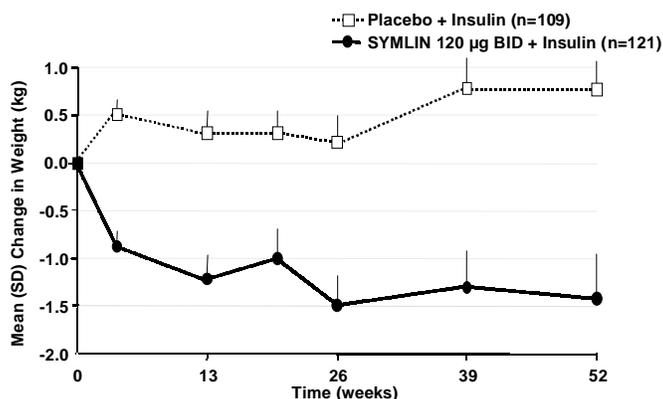
* Statistically significant difference from placebo + insulin.

¹ Relative change from baseline; statistical difference between treatments not assessed for this variable.

HbA_{1c} and Results Summary. SYMLIN + insulin produced greater reductions from baseline in HbA_{1c} at Weeks 26 and 52 compared with those observed with placebo + insulin. Body weight decreased among patients treated with SYMLIN + insulin, compared with mean increases in weight among patients treated with placebo + insulin. The improvement in glucose and reduction in body weight among SYMLIN + insulin recipients compared with those receiving placebo + insulin were maintained throughout the 52-week study period.

Body Weight. On average, patients treated with SYMLIN + insulin lost weight while patients receiving placebo + insulin, gained weight (Figure 7). These differences were statistically significant at every visit tested.

Figure 7. Change in Weight From Baseline Through 1 Year For Patients Receiving SYMLIN + Insulin or Placebo + Insulin in Insulin-Using Type 2 Diabetes Study B



SYMLIN + insulin recipients who were overweight (BMI ≥ 27 kg/m²) at study entry experienced a clinically meaningful and statistically significant mean decrease from baseline in body weight at study end compared with overweight placebo + insulin recipients, who experienced a mean increase in body weight.

Effect on Lipid Profile. SYMLIN did not cause any adverse effects on lipid concentrations in patients with type 2 diabetes.

Long-Term Use

In controlled and uncontrolled studies of SYMLIN, 155 patients with type 2 diabetes who use insulin received SYMLIN for 2 years or longer. Over 75% (300 of 381) of participants who had completed a 1-year double-blind study volunteered to continue in an open-label extension study of SYMLIN. The data from this extension study indicate that the effects of SYMLIN are sustained throughout an additional one year of observation, with improved glucose control and a mean decrease in body weight relative to original study baselines.

Insulin-Using Type 2 Diabetes Summary. Results from studies of SYMLIN supporting the use of dosages of 90 and 120 µg BID, and 60 and 120 µg TID used as an adjunct to insulin therapy in patients with type 2 diabetes resulted in improved glucose control (reductions in HbA_{1c}) and reduction in body weight observed for up to one year during adequate and well-controlled studies. SYMLIN-induced reductions in HbA_{1c} and weight have been shown to persist for an additional year in an open-label study.

Achieving Glucose Control Targets with SYMLIN

The proportion of patients who achieved target HbA_{1c} concentrations by study end was higher with SYMLIN + insulin than with placebo + insulin at all time points measured in Study A (type 1 diabetes) and Study B (insulin-using type 2 diabetes) (Table 4).

Table 4. Percent of Patients Achieving HbA_{1c} Targets By Study End (52 Weeks) in Two Double-Blind Placebo-Controlled Studies

	Placebo + Insulin (n=145)	SYMLIN 60 µg TID + Insulin (n=146)	SYMLIN 60 µg QID + Insulin (n=146)
Type 1 Diabetes Study A¹			
Achieve HbA _{1c} of 8% or less	30%	51%	52%
Achieve HbA _{1c} of 7% or less	4%	14%	13%

	Placebo + Insulin (n=151)	SYMLIN 120 µg BID + Insulin (n=155)	SYMLIN 90 µg BID + Insulin (n=166)
Insulin-Using Type 2 Diabetes Study B¹			
Achieve HbA _{1c} of 8% or less	30%	51%	46%
Achieve HbA _{1c} of 7% or less	5%	14%	10%

¹ Includes only patients who had baseline HbA_{1c} values above this target.

INDICATIONS AND USAGE

SYMLIN is indicated as adjunctive therapy to insulin to improve glycemic and metabolic control in people with type 1 or type 2 diabetes mellitus with or without oral hypoglycemic agents.

SYMLIN should be added to patients' existing diabetes treatment regimens, which should include nutritional counseling, exercise, and weight management as needed. Weight management is important not only in the primary treatment of diabetes, but also to maintain the efficacy of drug therapy. SYMLIN has been shown to reduce body weight in people with diabetes.

CONTRAINDICATIONS

SYMLIN is contraindicated in patients with known hypersensitivity to this product or any of its components, including metacresol.

PRECAUTIONS

SYMLIN should not be used by patients with known hypersensitivity to metacresol.

Hypoglycemia

Hypoglycemia was not observed during the administration of up to 10 mg of SYMLIN as a single agent and would not be expected based on its mechanism of action. There was no increase in the rate of severe hypoglycemia in long-term controlled clinical studies. However, patients receiving SYMLIN with insulin may be at risk for insulin-induced hypoglycemia, and a reduction in the dose of insulin (primarily pre-meal short-acting insulin preparations) or an alteration in insulin regimen may be necessary if hypoglycemia occurs.

Information for Patients

Patients should be informed of the potential risks and advantages of SYMLIN and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, a regular exercise program, and regular measurement of blood glucose, HbA_{1c}, and renal function.

SYMLIN should be taken within 15 minutes before meals.

SYMLIN therapy should be used in addition to insulin. When adding SYMLIN therapy into regimens with insulin and oral hypoglycemic agents, the risks of insulin- or oral hypoglycemic agent-induced hypoglycemia, its symptoms and treatment, and conditions that predispose its development should be

explained to the patient. While the patient's usual instructions for hypoglycemia management do not need to be changed, these instructions should be reviewed and reinforced when initiating SYMLIN therapy.

SYMLIN should be given as a separate injection and should not be mixed with any type of insulin.

SYMLIN has the potential to delay the absorption of orally administered medications. When time to peak effect of orally administered drugs is critical, the concomitant drug should be administered at least one hour prior to SYMLIN.

Drug Interactions

Drugs that alter gastrointestinal motility (e.g., erythromycin, metoclopramide, and anticholinergic agents such as atropine) and agents altering intestinal absorption of nutrients (e.g. alpha-glucosidase inhibitors) should be used cautiously with SYMLIN.

Because altering gastric motility may have an effect on the absorption of concomitantly administered drugs, it was important to determine whether SYMLIN alters the pharmacokinetics of common concomitantly administered drugs. Specific studies described below addressed these issues directly. A clinical review of adverse events, categorized by concomitant medications that were taken during clinical trials, was also done and revealed no particular safety concerns.

Ampicillin: Ampicillin is a widely prescribed orally administered antibiotic for which plasma C_{max} and AUC are considered important pharmacokinetic measures related to absorption. Because ampicillin efficacy relies on achieving concentrations in excess of those needed to kill the infecting organism at the site of infection, a study of the effect of concomitant administration of SYMLIN and ampicillin was undertaken. In this healthy volunteer study, administration of a single oral 500-mg dose of ampicillin 15 minutes after a single dose of SYMLIN (90 μ g) did not alter the C_{max} or AUC for ampicillin. Consistent with the demonstrated effects of SYMLIN on rate of nutrient delivery from the stomach, the T_{max} for ampicillin was delayed by approximately 60 minutes. This delay in peak antibacterial effect should be considered in special circumstances where time to peak effect is important.

Oral Contraceptives: The efficacy of low-dose oral contraceptives relies on adequate absorption of the estrogen and progestin components of the drug. Therefore a study of the effect of concomitant administration of SYMLIN and a low-dose oral contraceptive on the pharmacokinetics of its two components (ethinyl estradiol 30 μ g and norgestrel 300 μ g) was undertaken. In this healthy volunteer study, administration of a single dose of the contraceptive with a single dose of SYMLIN (90 μ g) did not alter C_{max} , $AUC_{(0-inf)}$, or $t_{1/2}$ of ethinyl estradiol compared with administration with placebo. T_{max} was delayed by 30 minutes, but the difference was not statistically significant. For norgestrel, T_{max} was delayed by approximately 45 minutes and C_{max} was reduced by approximately 30% following treatment with SYMLIN, but $AUC_{(0-inf)}$ and $t_{1/2}$ were not altered. No dosage adjustment of oral contraceptives is recommended with SYMLIN use.

Insulin Lispro: Use of insulin lispro results in peak serum insulin concentrations that occur earlier and are higher than those achieved with regular insulin. Therefore, a study to assess the safety of concomitant administration of insulin lispro and SYMLIN was undertaken. In patients with type 1 diabetes, administration of a single dose of SYMLIN (60 μ g) with a dose of insulin lispro and long-acting insulin (NPH, Lente[®], or Ultralente[®]) resulted in lower postprandial glucose concentrations compared with use of insulin lispro and long-acting insulin alone. (See CLINICAL PHARMACOLOGY—Effects on Postprandial Glucose Concentrations)

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: No evidence of a SYMLIN-related tumorigenic effect was seen when SYMLIN was administered SC for 2 years to mice at doses up to 1.2 mg/kg/day or to rats at doses up to 0.5 mg/kg/day. Based on relative systemic exposure (AUC values) for subjects with type 1 diabetes at the maximum anticipated dose of 360 μ g/day (90 μ g QID), the high dose in the mouse represented a 159-fold excess. The high dose in the rat represented a 25-fold excess. For subjects with type 2 diabetes at the maximum anticipated dose of 360 μ g/day (120 μ g TID), the high dose in the mouse represented a 274-fold excess while the high dose in the rat represented a 43-fold excess.

Mutagenesis: SYMLIN was not mutagenic in the Ames test (maximum exposure $\geq 5,000$ $\mu\text{g}/\text{plate}$) and did not increase chromosomal aberration in the human lymphocytes assay (maximum exposure 1,670 $\mu\text{g}/\text{mL}$) nor was it clastogenic in this or in the Chinese hamster ovary cell assay. These in vitro studies were done with and without metabolic activation. An in vivo bone marrow micronucleus test conducted in mice at 250 mg/kg was negative for clastogenic responses.

Impairment of Fertility: Fertility was not compromised in rats when SYMLIN was administered SC to males and females at 3 mg/kg/day. In subjects with type 1 diabetes at the maximum anticipated dose of 360 $\mu\text{g}/\text{day}$ (90 μg QID), this represented a 115-fold excess based on mg/m²/day and a typical human weight of 77 kg. In subjects with type 2 diabetes and a typical weight of 100 kg, the dose in rats represented a 150-fold excess.

Pregnancy

Pregnancy Category B. SYMLIN was not teratogenic or embryotoxic at doses up to 3 mg/kg in the rat or rabbit. Based on mg/m²/day calculation in 77 kg subjects with type 1 diabetes, the dose in rats represents a 115-fold excess over the maximum anticipated human daily dose while the rabbit dose represents a 208-fold excess. For 100 kg subjects with type 2 diabetes, the excess in rats represented a 150-fold excess while for rabbits it represented a 272-fold excess. SYMLIN did not cross the placental barrier in rats, and very little SYMLIN crossed the placental barrier in rabbits. Ex vivo placental perfusion studies have shown that SYMLIN does not cross the human placental barrier. In perinatal/postnatal studies in the rat, SYMLIN had no effect on the physical or neurodevelopment or reproductive performance of the F₁ generation and had no effect on the F₂ fetuses. The no effect dose for neonates was 1.0 mg/kg.

There are no adequate and well-controlled studies of SYMLIN in pregnant women. SYMLIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose concentrations during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose concentrations as close to normal as possible.

Nursing Mothers

It is not known whether SYMLIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SYMLIN is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of SYMLIN in pediatric patients have not been established.

Geriatric Use

SYMLIN was studied in 512 patients aged 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

A total of 4415 patients have been treated with SYMLIN; of these, 2109 were treated for 6 months or longer, 1350 for 12 months or longer, and 261 for 2 years or longer. In general adverse events associated with SYMLIN were mild, transient, and did not require discontinuation of therapy. The incidence of withdrawals due to adverse events during the clinical trials was 12% for SYMLIN-treated patients and 5% for placebo-treated patients.

Hypoglycemia

Hypoglycemia has not been observed during the administration of up to 10 mg SYMLIN as a single agent in healthy volunteers, and would not be expected based on the mechanism of action. In the SYMLIN studies, severe hypoglycemia was defined using the criteria developed for the Diabetes Control and Complications Trial (DCCT), which captured events requiring the assistance of another individual. These data, expressed as event rate per subject-year of exposure, represent concrete, objective endpoints whereas other measures of hypoglycemia are more subjective.

There was no difference in the event rate per subject-year for severe hypoglycemia among patients with type 1 diabetes who received SYMLIN + insulin (1.1) compared with those who received placebo + insulin (1.1). Likewise, there was no difference in the event rate per subject-year for severe hypoglycemia among patients with type 2 diabetes who received SYMLIN + insulin (0.2) and placebo + insulin recipients

(0.2). These event rates are based upon the long-term controlled studies of SYMLIN in type 1 and insulin-using type 2 diabetes.

The overall incidence of severe hypoglycemia was slightly higher in SYMLIN recipients compared to placebo + insulin recipients (25 vs. 18% respectively in type 1; 9 vs. 6% in type 2). After the first 4 weeks of therapy, the incidence of severe hypoglycemia was reduced in both groups.

Additionally, after the first 4 weeks of treatment, the event rate per subject-year for severe hypoglycemia in the SYMLIN + insulin recipients was lower than that observed in placebo + insulin recipients in type 1 studies. Thus with long-term use of SYMLIN, the risk of severe hypoglycemia was not increased.

The addition of any anti-hyperglycemic agent to an existing insulin regimen may require adjustments to the insulin regimen to optimize overall glycemic control, while balancing the risk for hypoglycemia. Since this is difficult to implement in the context of a clinical trial, it is not unexpected to see an initial increase in hypoglycemia that dissipates over the initial weeks of therapy as appropriate adjustments to the treatment regimen are made.

Other Adverse Events

The most frequent treatment-emergent adverse events (except hypoglycemia) in long-term controlled clinical studies are shown in Table 5. Events with $\geq 5\%$ incidence in either SYMLIN or placebo recipients for which the incidence is greater for SYMLIN-treated patients are shown (total, and severe as assessed by the investigator). Hypoglycemia is discussed separately (see Hypoglycemia).

Table 5. Frequent Treatment-Emergent Adverse Events (Except Hypoglycemia) With $\geq 5\%$ Incidence and Greater Incidence for SYMLIN Groups in Long-Term Controlled Clinical Studies

	Placebo N=958		SYMLIN N=2452	
	Total	Severe	Total	Severe
Nausea	16%	1%	37%	5%
Anorexia	3%	0%	13%	1%
Vomiting	6%	<1%	10%	1%
Abdominal Pain	7%	<1%	8%	1%
Fatigue	4%	<1%	7%	<1%
Dizziness	4%	<1%	5%	<1%
Dyspepsia	3%	<1%	5%	<1%

The most common adverse events associated with SYMLIN use are nausea, anorexia, and vomiting, with the majority of events reported as mild or moderate. These symptoms are generally associated with the initiation of therapy, are transient, and resolve spontaneously during continued treatment. They were related to dose, and were more apparent in patients with type 1 diabetes than in patients with type 2 diabetes. Improvement in glycemic control and reduction in body weight with SYMLIN therapy occurred independent of nausea.

In long-term controlled trials in patients with type 1 diabetes, approximately 12% of SYMLIN patients withdrew due to gastrointestinal reactions compared with 1% of placebo recipients. In controlled trials in patients with insulin-using type 2 diabetes, approximately 3% of SYMLIN patients withdrew due to gastrointestinal reactions compared with 2% of placebo recipients.

Patients with documented gastroparesis were excluded from SYMLIN clinical trials. Therefore, the effects of using SYMLIN in patients with known gastroparesis are unknown. The use of SYMLIN in these and other patients with erratic glucose control should be undertaken cautiously, with appropriate monitoring, as the risk for hypoglycemia may be increased.

Because gastrointestinal events during therapy initiation appear to be related to dose, they may be mitigated by dose reduction and by reminding patients to take SYMLIN within 15 minutes before meals (see DOSAGE AND ADMINISTRATION).

Fatigue and dizziness are common symptoms of hypoglycemia, and the incidence of these adverse events may be secondary to hypoglycemia reported during clinical studies.

A systematic search of the SYMLIN safety database was performed to identify events that are typical of drug-induced reactions or unusual in the absence of drug therapy. Thrombocytopenia was found to occur in one SYMLIN recipient (<0.1%) and one placebo recipient (<0.1%). Acute renal failure was reported for three SYMLIN recipients (<0.1%) and one placebo recipient. None of these events was found to be reasonably associated with SYMLIN use.

There were no observed differences in reported adverse events based on patient age, ethnic background, or gender.

DRUG ABUSE AND DEPENDENCE

There is no pharmacologic evidence to suggest an abuse potential for SYMLIN.

OVERDOSAGE

One SYMLIN overdose (a single dose of 225 µg, 2.5 times the intended dose of 90 µg) was reported during clinical studies, with no associated adverse events.

SYMLIN has been administered in doses up to 10 mg (83 times the maximum recommended dose of 120 µg) in three healthy volunteers. Nausea was reported in all three patients, with vomiting, diarrhea, vasodilation, and dizziness reported in two patients each.

DOSAGE AND ADMINISTRATION

SYMLIN has been shown to contribute to improved glucose control through reduction of postmeal glucagon concentrations and modulation of the appearance of meal-derived nutrients (including glucose) into the peripheral circulation. The effects of SYMLIN are complementary to insulin, which promotes clearance of nutrients from the plasma into peripheral tissues for utilization and storage. Thus, patients' individual meal frequency and insulin regimens should be taken into account when initiating or adjusting SYMLIN therapy.

The management of antidiabetic therapy should be individualized. Patients should initially remain on their usual insulin regimens, with or without oral hypoglycemic agents. SYMLIN therapy should be administered before meals. Following initiation of SYMLIN therapy, insulin doses may need to be adjusted to further optimize glycemic control and minimize hypoglycemia. Doses of preprandial short-acting insulins may need to be decreased to reduce the risk for hypoglycemia while it may be appropriate to increase doses of intermediate and/or long-acting insulins to achieve the desired level of glucose control. Blood glucose monitoring should be employed as needed to guide these changes.

SYMLIN should be given as a separate injection and should not be mixed with any type of insulin.

Initiation of Therapy:

Type 1 Diabetes

SYMLIN therapy should be initiated at 30 µg per dose, administered as a separate subcutaneous injection. The number of SYMLIN doses per day should be based upon frequency of meals and snacks, not to exceed 4 doses per day. SYMLIN should be given within 15 minutes before a meal.

Type 2 Diabetes

SYMLIN therapy should be initiated at 120 µg per dose, administered as a separate subcutaneous injection. The number of SYMLIN doses per day should be based upon frequency of meals, not to exceed 3 doses per day. SYMLIN should be given within 15 minutes before a meal.

SYMLIN Dose Adjustment:

SYMLIN therapy should be adjusted to optimize glycemic and weight control, or to minimize gastrointestinal side effects. For a given dose of SYMLIN, plasma concentrations achieved tend to be lower in patients with type 2 diabetes than in patients with type 1 diabetes.

In patients with type 1 diabetes, doses of 30 and 60 µg have demonstrated efficacy in clinical trials. Desired therapeutic responses were also achieved with doses of 90 µg; however, this dose was not well-tolerated by some patients due to gastrointestinal side effects (primarily nausea).

In patients with type 2 diabetes treated with insulin, a dose of 120 µg was effective and well-tolerated. While doses of 60 and 90 µg were effective in some patients in clinical trials, the effects tended to be less robust.

Special Situations:

No dosage adjustment is required for elderly patients.

No dosage adjustment is required for patients with impaired renal function.

Safety and effectiveness in patients under 16 years of age have not been established.

HOW SUPPLIED

SYMLIN is supplied as a 1.0 mg/mL sterile injection in 1.5 mL cartridges for use with the SymlinPen™ 30-60 or the SymlinPen™ 120 delivery device.

SYMLIN is also supplied as a 0.6 mg/mL sterile injection in 5 mL vials for use with a syringe. To administer SYMLIN from vials, use a 1 mL (1 cc) or smaller volume syringe for optimal accuracy. If using a syringe calibrated for use with U-100 insulin, use the chart below to measure the microgram dosage in unit increments.

Dosage Prescribed	Volume (cc or mL)	Increment Using a U-100 Syringe
30 µg	0.05	5 units
60 µg	0.1	10 units
90 µg	0.15	15 units
120 µg	0.2	20 units

STORAGE

Before use, SYMLIN vials and cartridges should be stored refrigerated, 2°C to 8°C (36°F to 46°F), and protected from light. Do not freeze vials or cartridges.

When in use, SYMLIN vials and cartridges may be stored at room temperature, 25°C (77°F) or below for up to 28 days.

Rx only