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3 **SYMLIN[®]**
4 **(pramlintide acetate) Injection**

5 **Rx only**

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7 **WARNING**

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9 **SYMLIN is used with insulin and has been associated with an increased risk of insulin-**
10 **induced severe hypoglycemia, particularly in patients with type 1 diabetes. When severe**
11 **hypoglycemia associated with SYMLIN use occurs, it is seen within 3 hours following a**
12 **SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy**
13 **machinery, or while engaging in other high-risk activities, serious injuries may occur.**
14 **Appropriate patient selection, careful patient instruction, and insulin dose adjustments**
15 **are critical elements for reducing this risk.**

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24 **DESCRIPTION**

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

32 The structural formula of pramlintide acetate is as shown:

33 $\overbrace{\text{Lys-Cys-Asn-Thr-Ala-Thr-Cys-Ala-Thr-Gln-Arg-Leu-Ala-Asn-Phe-Leu-Val-His-Ser-Ser-Asn-Asn-Phe-Gly-Pro-Ile-Leu-Pro-Pro-Thr-Asn-Val-Gly-Ser-Asn-Thr-Tyr-NH}_2$ acetate
34 (salt) with a disulfide bridge between the two Cys residues.

35 Pramlintide acetate is a white powder that has a molecular formula of $\text{C}_{171}\text{H}_{267}\text{N}_{51}\text{O}_{53}\text{S}_2 \cdot x$
36 $\text{C}_2\text{H}_4\text{O}_2$ ($3 \leq x \leq 8$); the molecular weight is 3949.4. Pramlintide acetate is soluble in water.

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

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CLINICAL PHARMACOLOGY

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Amylin Physiology

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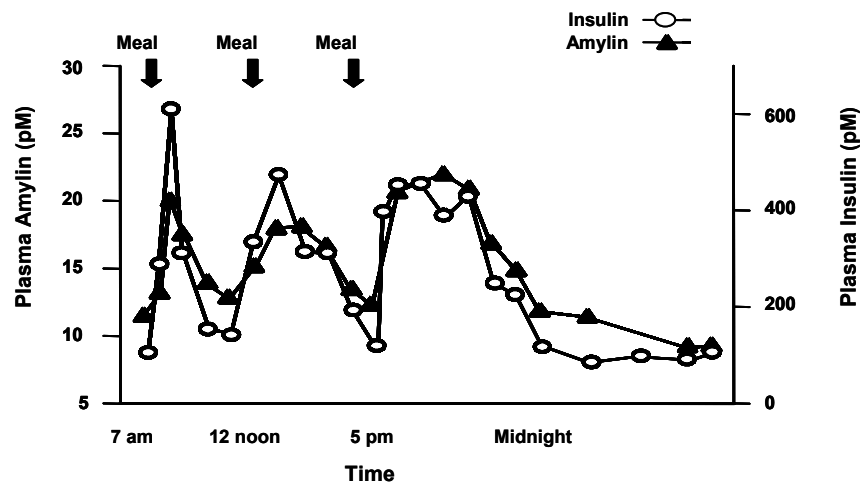
Amylin is co-located with insulin in secretory granules and co-secreted with insulin by pancreatic beta cells in response to food intake. Amylin and insulin show similar fasting and postprandial patterns in healthy individuals (**Figure 1**).

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Figure 1: Secretion Profile of Amylin and Insulin in Healthy Adults

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Amylin affects the rate of postprandial glucose appearance through a variety of mechanisms. Amylin slows gastric emptying (i.e., the rate at which food is released from the stomach to the small intestine) without altering the overall absorption of nutrients. In addition, amylin suppresses glucagon secretion (not normalized by insulin alone), which leads to suppression of endogenous glucose output from the liver. Amylin also regulates food intake due to centrally-mediated modulation of appetite.

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In patients with insulin-using type 2 or type 1 diabetes, the pancreatic beta cells are dysfunctional or damaged, resulting in reduced secretion of both insulin and amylin in response to food.

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Mechanism of Action

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SYMLIN, by acting as an amylinomimetic agent, has the following effects: 1) modulation of gastric emptying; 2) prevention of the postprandial rise in plasma glucagon; and 3) satiety leading to decreased caloric intake and potential weight loss.

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Gastric Emptying. The gastric-emptying rate is an important determinant of the postprandial rise in plasma glucose. SYMLIN slows the rate at which food is released from the stomach to the small intestine following a meal and, thus, it reduces the initial

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68 postprandial increase in plasma glucose. This effect lasts for approximately 3 hours
 69 following SYMLIN administration. SYMLIN does not alter the net absorption of ingested
 70 carbohydrate or other nutrients.

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72 **Postprandial Glucagon Secretion.** In patients with diabetes, glucagon concentrations are
 73 abnormally elevated during the postprandial period, contributing to hyperglycemia.
 74 SYMLIN has been shown to decrease postprandial glucagon concentrations in insulin-using
 75 patients with diabetes.

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77 **Satiety.** SYMLIN administered prior to a meal has been shown to reduce total caloric
 78 intake. This effect appears to be independent of the nausea that can accompany SYMLIN
 79 treatment.

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81 Pharmacokinetics

82 **Absorption.** The absolute bioavailability of a single SC dose of SYMLIN is approximately
 83 30 to 40%. Subcutaneous administration of different doses of SYMLIN into the abdominal
 84 area or thigh of healthy subjects resulted in dose-proportionate maximum plasma
 85 concentrations (C_{max}) and overall exposure (expressed as area under the plasma concentration
 86 curve or (AUC)) (Table 1).

87

88 **Table 1: Mean Pharmacokinetic Parameters Following Administration of Single SC Doses of**
 89 **SYMLIN**

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SC Dose (μg)	AUC _(0-∞) ($\text{pmol} \cdot \text{min}/\text{L}$)	C _{max} (pmol/L)	T _{max} (min)	Elimination t _{1/2} (min)
30	3750	39	21	55
60	6778	79	20	49
90	8507	102	19	51
120	11970	147	21	48

91

92 Injection of SYMLIN into the arm showed higher exposure with greater variability,
 93 compared with exposure after injection of SYMLIN into the abdominal area or thigh.

94

95 There was no strong correlation between the degree of adiposity as assessed by BMI or
 96 skin fold thickness measurements and relative bioavailability. Injections administered
 97 with 6.0-mm and 12.7-mm needles yielded similar bioavailability.

98

99 **Distribution.** SYMLIN does not extensively bind to blood cells or albumin (approximately
 100 40% of the drug is unbound in plasma), and thus SYMLIN's pharmacokinetics should be
 101 insensitive to changes in binding sites.

102

103 **Metabolism and Elimination.** In healthy subjects, the half-life of SYMLIN is
 104 approximately 48 minutes. SYMLIN is metabolized primarily by the kidneys. Des-lys¹
 105 pramlintide (2-37 pramlintide), the primary metabolite, has a similar half-life and is

106 biologically active both *in vitro* and *in vivo* in rats. AUC values are relatively constant with
107 repeat dosing, indicating no bioaccumulation.

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110 **Special Populations.**

111 **Renal Insufficiency:** Patients with moderate or severe renal impairment ($Cl_{Cr} >20$ to
112 ≤ 50 mL/min) did not show increased SYMLIN exposure or reduced SYMLIN clearance,
113 compared to subjects with normal renal function. No studies have been done in dialysis
114 patients.

115

116 **Hepatic Insufficiency:** Pharmacokinetic studies have not been conducted in patients with
117 hepatic insufficiency. However, based on the large degree of renal metabolism (see
118 Metabolism and Elimination), hepatic dysfunction is not expected to affect blood
119 concentrations of SYMLIN.

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121 **Geriatric:** Pharmacokinetic studies have not been conducted in the geriatric population.
122 SYMLIN should only be used in patients known to fully understand and adhere to proper
123 insulin adjustments and glucose monitoring. No consistent age-related differences in the
124 activity of SYMLIN have been observed in the geriatric population (n=539 for patients
125 65 years of age or older in the clinical trials).

126

127 **Pediatric:** SYMLIN has not been evaluated in the pediatric population.

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129 **Gender:** No study has been conducted to evaluate possible gender effects on SYMLIN
130 pharmacokinetics. However, no consistent gender-related differences in the activity of
131 SYMLIN have been observed in the clinical trials (n=2799 for male and n=2085 for
132 female).

133

134 **Race/Ethnicity:** No study has been conducted to evaluate the effect of ethnicity on
135 SYMLIN pharmacokinetics. However, no consistent differences in the activity of
136 SYMLIN have been observed among patients of differing race/ethnicity in the clinical
137 trials (n=4257 for white, n=229 for black, n=337 for Hispanic, and n=61 for other ethnic
138 origins).

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140 **Drug Interactions:** The effect of SYMLIN (120 μ g) on acetaminophen (1000 mg)
141 pharmacokinetics as a marker of gastric-emptying was evaluated in patients with type 2
142 diabetes (n=24). SYMLIN did not significantly alter the AUC of acetaminophen.
143 However, SYMLIN decreased acetaminophen C_{max} (about 29% with simultaneous
144 co-administration) and increased the time to maximum plasma concentration or t_{max}
145 (ranging from 48 to 72 minutes) dependent on the time of acetaminophen administration
146 relative to SYMLIN injection. SYMLIN did not significantly affect acetaminophen t_{max}
147 when acetaminophen was administered 1 to 2 hours before SYMLIN injection. However,
148 the t_{max} of acetaminophen was significantly increased when acetaminophen was
149 administered simultaneously with or up to 2 hours following SYMLIN injection (see
150 PRECAUTIONS, Drug Interactions).

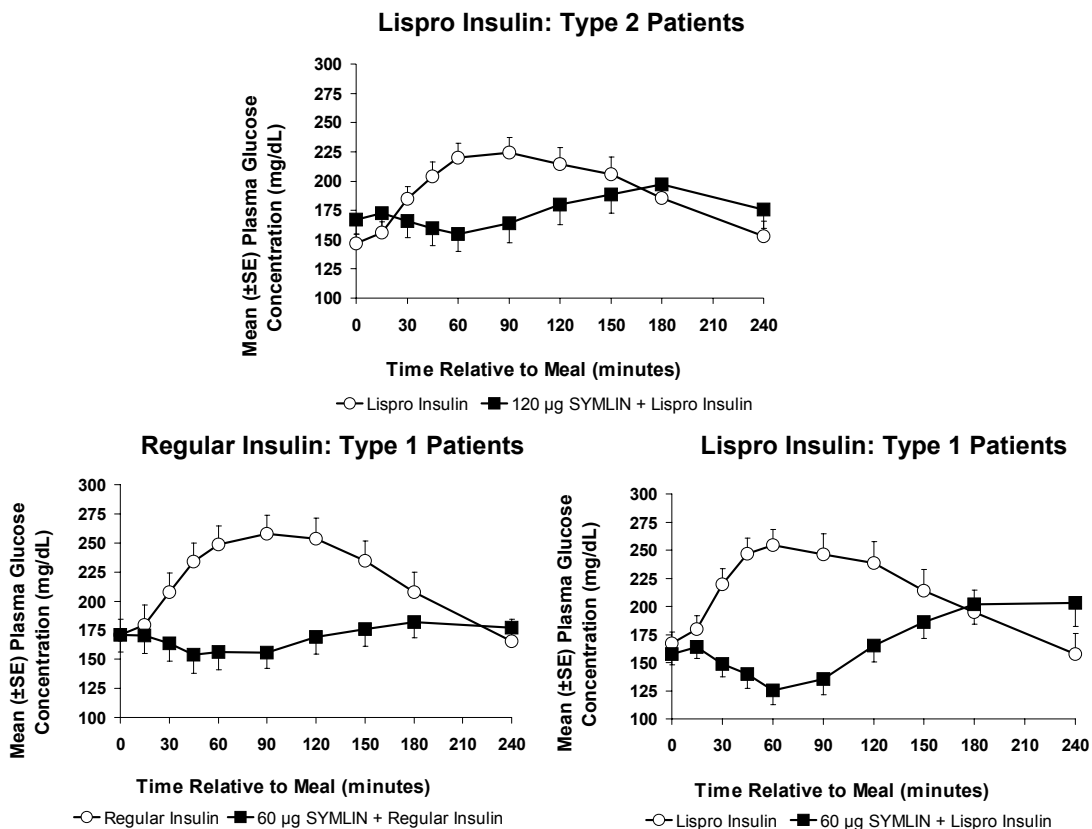
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152 **Pharmacodynamics**

153 In clinical studies in patients with insulin-using type 2 and type 1 diabetes, SYMLIN
 154 administration resulted in a reduction in mean postprandial glucose concentrations, reduced
 155 glucose fluctuations, and reduced food intake. SYMLIN doses differ for insulin-using type 2
 156 and type 1 patients (see DOSAGE AND ADMINISTRATION).

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 158 **Reduction in Postprandial Glucose Concentrations.** SYMLIN administered
 159 subcutaneously immediately prior to a meal reduced plasma glucose concentrations
 160 following the meal when used with regular insulin or rapid-acting insulin analogs (**Figure 2**).
 161 **This reduction in postprandial glucose decreased the amount of short-acting insulin**
 162 **required and limited glucose fluctuations based upon 24-hour glucose monitoring.**
 163 When rapid-acting analog insulins were used, plasma glucose concentrations tended to rise
 164 during the interval between 150 minutes following SYMLIN injection and the next meal (see
 165 DOSAGE and ADMINISTRATION).

166
 167 **Figure 2: Postprandial Plasma Glucose Profiles in Patients With Type 2 and Type 1**
 168 **Diabetes Receiving SYMLIN and/or Insulin**



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 170
 171 **Reduced Food Intake.** A single, subcutaneous dose of SYMLIN 120 µg (type 2) or
 172 30 µg (type 1) administered 1 hour prior to an unlimited buffet meal was associated with
 173 reductions in total caloric intake (placebo-subtracted mean changes of ~23% and 21%,
 174 respectively), which occurred without decreases in meal duration.

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CLINICAL STUDIES

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A total of 5325 patients and healthy volunteers received SYMLIN in clinical studies.

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This includes 1688 with type 2 diabetes and 2375 with type 1 diabetes in short- and

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long-term controlled clinical trials, long-term uncontrolled clinical trials, and an

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open-label study in the clinical practice setting.

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Clinical Studies in Type 2 Diabetes

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The efficacy of a range of SYMLIN doses was evaluated in several placebo-controlled

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and open-label clinical trials in insulin-using patients with type 2 diabetes. Based on

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results obtained in these studies, the recommended dose of SYMLIN for patients with

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insulin-using type 2 diabetes is 120 µg administered immediately prior to major meals.

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Two, long-term (26 to 52 week), randomized, double-blind, placebo-controlled studies of

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SYMLIN were conducted in patients with type 2 diabetes using fixed dose insulin to

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isolate the SYMLIN effect. Demographic and baseline characteristics for the 871

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SYMLIN-treated patients are as follows: mean baseline HbA1c ranged from 9.0 to 9.4%,

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mean age was 56.4 to 59.1 years, mean duration of diabetes ranged from 11.5 to

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14.4 years, and mean BMI ranged from 30.1 to 34.4 kg/m². In both of these studies,

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SYMLIN or placebo was added to the participants' existing diabetes therapies, which

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included insulin with or without a sulfonylurea agent and/or metformin.

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Table 2 summarizes the composite results across both studies for patients assigned to the

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120-µg dose after 6 months of treatment.

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Table 2: Mean (SE) Change in HbA1c, Weight, and Insulin at 6 Months in the Double-Blind, Placebo-Controlled Studies in Patients With Insulin-using Type 2 Diabetes

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Variable	Placebo	SYMLIN (120 µg)
Baseline HbA1c (%)	9.3 (0.08)	9.1 (0.06)
Change in HbA1c at 6 Months Relative to Baseline (%)	-0.17 (0.07)	-0.57 (0.06)*
Placebo-Subtracted HbA1c Change at 6 Months (%)	NA	-0.40 (0.09)*
Baseline Weight (kg)	91.3 (1.2)	92.5 (1.2)
Change in Weight at 6 Months Relative to Baseline (kg)	+0.2 (0.2)	-1.5 (0.2)*
Placebo-Subtracted Weight Change at 6 Months (kg)	NA	-1.7 (0.3)*
Percent Change in Insulin Doses at 6 Months: Rapid/Short-Acting	+6.5 (2.7)	-3.0 (1.6)*
Percent Change in Insulin Doses at 6 Months: Long-Acting	+5.2 (1.4)	-0.2 (1.3)*

204 * Statistically significant reduction compared with placebo (p-value < 0.05).

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206 In a cohort of 145 patients who completed two years of SYMLIN treatment the baseline
207 subtracted HbA1c and weight reductions were: -0.40% and -0.36 kg, respectively.

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209 **Open-Label Study in the Clinical Practice Setting.** An open-label study of SYMLIN
210 was conducted at the recommended dose of 120 µg in 166 patients with insulin-using
211 type 2 diabetes who were unable to achieve glycemic targets using insulin alone. A
212 flexible-dose insulin regimen was employed in these patients (see DOSAGE and
213 ADMINISTRATION). In this study, patients adjusted their insulin regimen based on
214 pre-and post-meal glucose monitoring. At baseline, mean HbA1c was 8.3%, mean age
215 was 54.4 years, mean duration of diabetes was 13.3 years, and mean BMI was
216 38.6 kg/m². SYMLIN was administered with major meals. SYMLIN plus insulin
217 treatment for 6 months resulted in a baseline-subtracted mean HbA1c reduction of -0.56
218 ± 0.15 % and a baseline-subtracted mean weight reduction of -2.76 ± 0.34 kg. These
219 changes were accomplished with reductions in doses of total, short-acting, and
220 long-acting insulin (-6.4 ± 2.66, -10.3 ± 4.84, and -4.20 ± 2.42 %, respectively).

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222 **Clinical Studies in Type 1 Diabetes**

223 The efficacy of a range of SYMLIN doses was evaluated in several placebo-controlled
224 and open-label clinical trials conducted in patients with type 1 diabetes. Based on results
225 obtained in these studies, the recommended dose of SYMLIN for patients with type 1
226 diabetes is 30 µg or 60 µg administered immediately prior to major meals.

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228 Three, long-term (26 to 52 week), randomized, double-blind, placebo-controlled studies
229 of SYMLIN were conducted in patients with type 1 diabetes (N=1717). Two of these
230 studies allowed only minimal insulin adjustments in order to isolate the SYMLIN effect;
231 in the third study, insulin adjustments were made according to standard medical practice.
232 Demographic and baseline characteristics for the 1179 SYMLIN-treated patients were as
233 follows: mean baseline HbA1c range was 8.7 to 9.0%, mean age range was 37.3 to
234 41.9 years, mean duration of diabetes range was 15.5 to 19.2 years, and mean BMI range
235 was 25.0 to 26.8 kg/m². SYMLIN or placebo was added to existing insulin therapies.

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237 **Table 3** summarizes the composite results across these studies for patients assigned to the
238 30 or 60 µg dose after 6 months of treatment.

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Table 3: Mean (SE) Change in HbA1c, Weight, and Insulin at 6 Months in the Double-Blind, Placebo-Controlled Studies in Patients With Type 1 Diabetes

Variable	Placebo	SYMLIN (30 or 60 µg)
Baseline HbA1c (%)	9.0 (0.06)	8.9 (0.04)
Change in HbA1c at 6 Months Relative to Baseline (%)	-0.10 (0.05)	-0.43 (0.04)*
Placebo-Subtracted HbA1c Change at 6 Months (%)	NA	-0.33 (0.06)*
Baseline Weight (kg)	75.1 (0.6)	76.1 (0.5)
Change in Weight at 6 Months Relative to Baseline (kg)	+0.6 (0.1)	-1.1 (0.1)*
Placebo-Subtracted Weight Change at 6 Months (kg)	NA	-1.7 (0.1)*
Percent Change in Insulin Doses at 6 Months: Rapid/Short-Acting	+1.7 (3.3)	-3.6 (2.9)
Percent Change in Insulin Doses at 6 Months: Long-Acting	+2.5 (1.9)	+1.9 (1.3)

* Statistically significant reduction compared with placebo (p-value < 0.05).

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In a cohort of 73 patients who completed two years of SYMLIN treatment the baseline subtracted HbA1c and weight changes were: -0.35% and 0.60 kg, respectively.

SYMLIN Dose-Titration Trial. A dose-titration study of SYMLIN was conducted in patients with type 1 diabetes. Patients with relatively good baseline glycemic control (mean HbA1c = 8.1%) were randomized to receive either insulin plus placebo or insulin plus SYMLIN. Other baseline and demographics characteristics were: mean age of 41 years, mean duration of diabetes of 20 years, mean BMI of 28 kg/m². SYMLIN was initiated at a dose of 15 µg and titrated upward at weekly intervals by 15-µg increments to doses of 30 µg or 60 µg, based on whether patients experienced nausea. Once a tolerated dose of either 30 µg or 60 µg was reached, the SYMLIN dose was maintained for the remainder of the study (SYMLIN was administered before major meals). During SYMLIN titration, the insulin dose (mostly the short/rapid acting insulin) was reduced by 30-50% in order to reduce the occurrence of hypoglycemia. Once a tolerated SYMLIN dose was reached, insulin dose adjustments were made according to standard clinical practice, based on pre- and post-meal blood glucose monitoring. By 6 months of treatment, patients treated with SYMLIN and insulin and patients treated with insulin and placebo had equivalent reductions in mean HbA1c (-0.47 ± 0.07 % vs. -0.49 ± 0.07 %, respectively); patients on SYMLIN lost weight (-1.33 ± 0.31 kg relative to baseline and -2.6 kg relative to placebo plus insulin-treated patients). SYMLIN-treated patients used less total insulin (-11.7% relative to baseline) and less short/rapid-acting insulin (-22.8% relative to baseline).

268 **Open-Label Study in the Clinical Practice Setting.** An open-label study of SYMLIN
269 was conducted in patients with type 1 diabetes who were unable to achieve glycemic
270 targets using insulin alone. A flexible-dose insulin regimen was employed in these
271 patients after SYMLIN titration was completed (see DOSAGE and
272 ADMINISTRATION). In this study, patients adjusted their insulin regimen based on
273 pre-and post-meal glucose monitoring. At baseline, mean HbA1c was 8.0%, mean age
274 was 42.7 years, mean duration of diabetes was 21.2 years, and mean BMI was
275 28.6 kg/m². SYMLIN daily dosage was 30 µg or 60 µg with major meals.

276
277 SYMLIN plus insulin reduced HbA1c and body weight from baseline at 6 months by a
278 mean of 0.18% and 3.0 kg, respectively. These changes in glycemic control and body
279 weight were achieved with reductions in doses of total, short-acting, and long-acting
280 insulin (-12.0 ± 1.36 , -21.7 ± 2.81 , and -0.4 ± 1.59 %, respectively).

281

282 **INDICATIONS AND USAGE**

283 SYMLIN is given at mealtimes and is indicated for:

284

- 285 • Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin
286 therapy and who have failed to achieve desired glucose control despite optimal
287 insulin therapy.
- 288
289 • Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin
290 therapy and who have failed to achieve desired glucose control despite optimal
291 insulin therapy, with or without a concurrent sulfonylurea agent and/or
292 metformin.

293

294 **CONTRAINDICATIONS**

295 SYMLIN is contraindicated in patients with any of the following:

296

- 297 • a known hypersensitivity to SYMLIN or any of its components, including
298 metacresol;
- 299 • a confirmed diagnosis of gastroparesis;
- 300 • hypoglycemia unawareness.

301

302 **WARNINGS**

303 **Patient Selection**

304 **Proper patient selection is critical to safe and effective use of SYMLIN.** Before
305 initiation of therapy, the patient's HbA1c, recent blood glucose monitoring data, history
306 of insulin-induced hypoglycemia, current insulin regimen, and body weight should be
307 reviewed. SYMLIN therapy should only be considered in patients with insulin-using
308 type 2 or type 1 diabetes who fulfill the following criteria:

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- 310 • have failed to achieve adequate glycemic control despite individualized insulin
311 management;
312 • are receiving ongoing care under the guidance of a health care professional skilled in
313 the use of insulin and supported by the services of diabetes educator(s).

314

315 Patients meeting any of the following criteria should NOT be considered for SYMLIN
316 therapy:

317

- 318 • poor compliance with current insulin regimen;
319 • poor compliance with prescribed self-blood glucose monitoring;
320 • have an HbA1c >9%;
321 • recurrent severe hypoglycemia requiring assistance during the past 6 months;
322 • presence of hypoglycemia unawareness;
323 • confirmed diagnosis of gastroparesis;
324 • require the use of drugs that stimulate gastrointestinal motility;
325 • pediatric patients.

326

327 **Hypoglycemia.** SYMLIN alone does not cause hypoglycemia. However, SYMLIN is
328 indicated to be co-administered with insulin therapy and in this setting SYMLIN
329 increases the risk of insulin-induced severe hypoglycemia, particularly in patients with
330 type 1 diabetes. Severe hypoglycemia associated with SYMLIN occurs within the first
331 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a
332 motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious
333 injuries may occur. Therefore, when introducing SYMLIN therapy, appropriate
334 precautions need to be taken to avoid increasing the risk for insulin-induced severe
335 hypoglycemia. These precautions include **frequent pre- and post-meal glucose**
336 **monitoring combined with an initial 50% reduction in pre-meal doses of**
337 **short-acting insulin (see DOSAGE and ADMINISTRATION).**

338

339 Symptoms of hypoglycemia may include hunger, headache, sweating, tremor, irritability,
340 or difficulty concentrating. Rapid reductions in blood glucose concentrations may induce
341 such symptoms regardless of glucose values. More severe symptoms of hypoglycemia
342 include loss of consciousness, coma, or seizure.

343

344 Early warning symptoms of hypoglycemia may be different or less pronounced under
345 certain conditions, such as long duration of diabetes; diabetic nerve disease; use of
346 medications such as beta-blockers, clonidine, guanethidine, or reserpine; or intensified
347 diabetes control.

348

349 The addition of any antihyperglycemic agent such as SYMLIN to an existing regimen of
350 one or more anti-hyperglycemic agents (e.g., insulin, sulfonylurea), or other agents that
351 can increase the risk of hypoglycemia may necessitate further insulin dose adjustments
352 and particularly close monitoring of blood glucose.

353

354 The following are examples of substances that may increase the blood glucose-lowering
355 effect and susceptibility to hypoglycemia: oral anti-diabetic products, ACE inhibitors,

356 diisopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene,
357 salicylates, and sulfonamide antibiotics.

358

359 Clinical studies employing a controlled hypoglycemic challenge have demonstrated that
360 SYMLIN does not alter the counter-regulatory hormonal response to insulin-induced
361 hypoglycemia. Likewise, in SYMLIN-treated patients, the perception of hypoglycemic
362 symptoms was not altered with plasma glucose concentrations as low as 45 mg/dL.

363

364 **PRECAUTIONS**

365 **General:**

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367 Hypoglycemia (See WARNINGS).

368

369 **Information for Patients:** Health care providers should inform patients of the potential
370 risks and advantages of SYMLIN therapy. Health care providers should also inform
371 patients about self-management practices including glucose monitoring, proper injection
372 technique, timing of dosing, and proper storage of SYMLIN. In addition, the importance
373 of adherence to meal planning, physical activity, recognition and management of
374 hypoglycemia and hyperglycemia, and assessment of diabetes complications. Refer
375 patients to the SYMLIN Medication Guide for additional information.

376

377 Instruct patients on handling of special situations such as intercurrent conditions (illness
378 or stress), an inadequate or omitted insulin dose, inadvertent administration of increased
379 insulin or SYMLIN dose, inadequate food intake or missed meals.

380

381 **SYMLIN and insulin should always be administered as separate injections and**
382 **never be mixed.**

383

384 Women with diabetes should be advised to inform their healthcare professional if they
385 are pregnant or contemplating pregnancy.

386

387 **Renal Impairment:** The dosing requirements for SYMLIN are not altered in patients
388 with moderate or severe renal impairment ($Cl_{Cr} >20$ to ≤ 50 mL/min). No studies have
389 been done in dialysis patients (see CLINICAL PHARMACOLOGY; Special
390 Populations).

391

392 **Hepatic Impairment:** Studies have not been performed in patients with hepatic
393 impairment. However, hepatic dysfunction is not expected to affect blood concentrations
394 of SYMLIN (see CLINICAL PHARMACOLOGY; Special Populations).

395

396 **Allergy: Local allergy.** Patients may experience redness, swelling, or itching at the site
397 of injection. These minor reactions usually resolve in a few days to a few weeks. In
398 some instances, these reactions may be related to factors other than SYMLIN, such as
399 irritants in a skin cleansing agent or improper injection technique.

400

401 **Systemic Allergy.** In controlled clinical trials up to 12 months, potential systemic
402 allergic reactions were reported in 65 (5)% of type 2 patients and 59 (5%) of type 1
403 SYMLIN-treated patients. Similar reactions were reported by 18 (4%) and 28 (5%) of
404 placebo-treated type 2 and type 1 patients, respectively. No patient receiving SYMLIN
405 was withdrawn from a trial due to a potential systemic allergic reaction.

406

407 **Drug Interactions**

408 Due to its effects on gastric emptying, SYMLIN therapy should not be considered for
409 patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents such
410 as atropine) and agents that slow the intestinal absorption of nutrients (e.g., α -glucosidase
411 inhibitors). Patients using these drugs have not been studied in clinical trials.

412

413 SYMLIN has the potential to delay the absorption of concomitantly administered oral
414 medications. When the rapid onset of a concomitant orally administered agent is a
415 critical determinant of effectiveness (such as analgesics), the agent should be
416 administered at least 1 hour prior to or 2 hours after SYMLIN injection.

417

418 In clinical trials, the concomitant use of sulfonylureas or biguanides did not alter the
419 adverse event profile of SYMLIN. No formal interaction studies have been performed to
420 assess the effect of SYMLIN on the kinetics of oral antidiabetic agents.

421

422 **Mixing SYMLIN and Insulin**

423 The pharmacokinetic parameters of SYMLIN were altered when mixed with regular,
424 NPH, and 70/30 premixed formulations of recombinant human insulin immediately prior
425 to injection. **Thus, SYMLIN and insulin should not be mixed and must be**
426 **administered separately.**

427

428 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

429 **Carcinogenesis.** A two-year carcinogenicity study was conducted in CD-1 mice with
430 doses of 0.2, 0.5, and 1.2 mg/kg/day of SYMLIN (32, 67, and 159 times the exposure
431 resulting from the maximum recommended human dose based on area under the plasma
432 concentration curve or AUC, respectively). No drug-induced tumors were observed. A
433 two-year carcinogenicity study was conducted in Sprague-Dawley rats with doses of
434 0.04, 0.2, and 0.5 mg/kg/day of SYMLIN (3, 9, and 25 times the exposure resulting from
435 the maximum recommended human dose based on AUC, respectively). No drug-induced
436 tumors were observed in any organ.

437

438 **Mutagenesis.** SYMLIN was not mutagenic in the Ames test and did not increase
439 chromosomal aberration in the human lymphocytes assay. SYMLIN was not clastogenic
440 in the *in vivo* mouse micronucleus test or in the chromosomal aberration assay utilizing
441 Chinese hamster ovary cells.

442

443 **Impairment of Fertility.** Administration of 0.3, 1, or 3 mg/kg/day of SYMLIN (8, 17,
444 and 82 times the exposure resulting from the maximum recommended human dose based
445 on body surface area) had no significant effects on fertility in male or female rats. The

446 highest dose of 3 mg/kg/day resulted in dystocia in 8/12 female rats secondary to
447 significant decreases in serum calcium levels.

448

449 **Pregnancy**

450 **Teratogenic Effects: Pregnancy Category C.** No adequate and well-controlled studies
451 have been conducted in pregnant women. Studies in perfused human placenta indicate
452 that SYMLIN has low potential to cross the maternal/fetal placental barrier. Embryofetal
453 toxicity studies with SYMLIN have been performed in rats and rabbits. Increases in
454 congenital abnormalities (neural tube defect, cleft palate, exencephaly) were observed in
455 fetuses of rats treated during organogenesis with 0.3 and 1.0 mg/kg/day (10 and 47 times
456 the exposure resulting from the maximum recommended human dose based on AUC,
457 respectively). Administration of doses up to 0.3 mg/kg/day SYMLIN (9 times maximum
458 recommended dose based on AUC) to pregnant rabbits had no adverse effects in
459 embryofetal development; however, animal reproduction studies are not always
460 predictive of human response. SYMLIN should be used during pregnancy only if it is
461 determined by the healthcare professional that the potential benefit justifies the potential
462 risk to the fetus.

463

464 **Nursing Mothers**

465 It is unknown whether SYMLIN is excreted in human milk. Many drugs, including
466 peptide drugs, are excreted in human milk. Therefore, SYMLIN should be administered
467 to nursing women only if it is determined by the health care professional that the
468 potential benefit outweighs the potential risk to the infant.

469

470 **Pediatric Use**

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

472

473 **Geriatric Use**

474 SYMLIN has been studied in patients ranging in age from 15 to 84 years of age,
475 including 539 patients 65 years of age or older. The change in HbA1c values and
476 hypoglycemia frequencies did not differ by age, but greater sensitivity in some older
477 individuals cannot be ruled out. Thus, both SYMLIN and insulin regimens should be
478 carefully managed to obviate an increased risk of severe hypoglycemia.

479

480 **ADVERSE REACTIONS**

481 Adverse events (excluding hypoglycemia, discussed below) commonly associated with
482 SYMLIN when co-administered with a fixed dose of insulin in the long-term,
483 placebo-controlled trials in insulin-using type 2 patients and type 1 patients are presented
484 in **Table 4** and **Table 5**, respectively. The same adverse events were also shown in the
485 open-label clinical practice study, which employed flexible insulin dosing.

486

487 **Table 4: Treatment-Emergent Adverse Events Occurring With \geq 5% Incidence and**
488 **Greater Incidence With SYMLIN Compared With Placebo in Long-Term,**

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491**Placebo-Controlled Trials. Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Insulin-Using Type 2 Diabetes, 120 µg)**

	Long-Term, Placebo-Controlled Studies		Open-Label, Clinical Practice Study
	Placebo + Insulin (n%) (N=284)	SYMLIN + Insulin (n%) (N=292)	SYMLIN + Insulin (n%) (N=166)
Nausea	34 (12)	81 (28)	53 (30)
Headache	19 (7)	39 (13)	8 (5)
Anorexia	5 (2)	27 (9)	1 (<1)
Vomiting	12 (4)	24 (8)	13 (7)
Abdominal Pain	19 (7)	23 (8)	3 (2)
Fatigue	11 (4)	20 (7)	5 (3)
Dizziness	11 (4)	17 (6)	3 (2)
Coughing	12 (4)	18 (6)	4 (2)
Pharyngitis	7 (2)	15 (5)	6 (3)

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498**Table 5: Treatment-Emergent Adverse Events Occurring With ≥5% Incidence and Greater Incidence with SYMLIN Compared to Placebo in Long-Term, Placebo-Controlled Studies. Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Type 1 Diabetes, 30 or 60 µg)**

	Long-Term, Placebo-Controlled Studies		Open-Label, Clinical Practice Study
	Placebo + Insulin (n%) (N=538)	SYMLIN + Insulin (n%) (N=716)	SYMLIN + Insulin (n%) (N=265)
Nausea	92 (17)	342 (48)	98 (37)
Anorexia	12 (2)	122 (17)	0 (0)
Inflicted Injury	55 (10)	97 (14)	20 (8)
Vomiting	36 (7)	82 (11)	18 (7)
Arthralgia	27 (5)	51 (7)	6 (2)
Fatigue	22 (4)	51 (7)	12 (4.5)
Allergic Reaction	28 (5)	41 (6)	1 (<1)
Dizziness	21 (4)	34 (5)	5 (2)

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Most adverse events were gastrointestinal in nature. In patients with type 2 or type 1 diabetes, the incidence of nausea was higher at the beginning of SYMLIN treatment and decreased with time in most patients. The incidence and severity of nausea are reduced when SYMLIN is gradually titrated to the recommended doses (see DOSAGE and ADMINISTRATION).

Severe Hypoglycemia507
508
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510

SYMLIN alone (without the concomitant administration of insulin) does not cause hypoglycemia. However, SYMLIN is indicated as an adjunct treatment in patients who use mealtime insulin therapy and co-administration of SYMLIN with insulin can increase the risk of insulin-induced hypoglycemia, particularly in patients with type 1 diabetes

511 (see Boxed Warning). The incidence of severe hypoglycemia during the SYMLIN
512 clinical development program is summarized in **Table 6** and **Table 7**.

513

514 **Table 6: Incidence and Event Rate of Severe Hypoglycemia in Long-Term,**
515 **Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With**
516 **Insulin-Using Type 2 Diabetes**
517

	Long-Term, Placebo-Controlled Studies (No Insulin Dose-Reduction During Initiation)				Open-Label, Clinical Practice Study (Insulin Dose-Reduction During Initiation)	
	Placebo + Insulin		SYMLIN + Insulin		SYMLIN + Insulin	
	0-3 Months (n=284)	>3-6 Months (n=251)	0-3 Months (n=292)	>3-6 Months (n=255)	0-3 Months (n=166)	>3-6 Months (n=150)
Severe Hypoglycemia						
Patient-Ascertained*						
Event Rate (event rate/patient year)	0.24	0.13	0.45	0.39	0.05	0.03
Incidence (%)	2.1	2.4	8.2	4.7	0.6	0.7
Medically Assisted**						
Event Rate (event rate/patient year)	0.06	0.07	0.09	0.02	0.05	0.03
Incidence (%)	0.7	1.2	1.7	0.4	0.6	0.7

518 * Patient-ascertained severe hypoglycemia: Requiring the assistance of another individual (including aid in
519 ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection, intravenous
520 glucose, or other medical intervention.

521 ** Medically assisted severe hypoglycemia: Requiring glucagon, IV glucose, hospitalization, paramedic
522 assistance, emergency room visit, and/or assessed as an SAE by the investigator.

523

524 **Table 7: Incidence and Event Rate of Severe Hypoglycemia in Long-Term,**
525 **Placebo-Controlled and Open-Label, Clinical Practice Studies in Patients With**
526 **Type 1 Diabetes**
527

	Long-Term, Placebo-Controlled Studies (No Insulin Dose-Reduction During Initiation)				Open-Label, Clinical Practice Study (Insulin Dose-Reduction During Initiation)	
	Placebo + Insulin		SYMLIN + Insulin		SYMLIN + Insulin	
	0-3 Months (n=538)	>3-6 Months (n=470)	0-3 Months (n=716)	>3-6 Months (n=576)	0-3 Months (n=265)	>3-6 Months (n=213)
Severe Hypoglycemia						
Patient-Ascertained*						
Event Rate (event rate/patient year)	1.33	1.06	1.55	0.82	0.29	0.16
Incidence (%)	10.8	8.7	16.8	11.1	5.7	3.8
Medically Assisted**						
Event Rate (event rate/patient year)	0.19	0.24	0.50	0.27	0.10	0.04
Incidence (%)	3.3	4.3	7.3	5.2	2.3	0.9

528 * Patient-ascertained severe hypoglycemia: Requiring the assistance of another individual (including aid in
529 ingestion of oral carbohydrate); and/or requiring the administration of glucagon injection,
530 intravenous glucose, or other medical intervention.

531 ** Medically assisted severe hypoglycemia: Requiring glucagon, IV glucose, hospitalization, paramedic
532 assistance, emergency room visit, and/or assessed as an SAE by the investigator.
533

534 **OVERDOSAGE**

535 Single 10 mg doses of SYMLIN (83 times the maximum dose of 120 µg) were
536 administered to three healthy volunteers. Severe nausea was reported in all three
537 individuals and was associated with vomiting, diarrhea, vasodilatation, and dizziness. No
538 hypoglycemia was reported. SYMLIN has a short half-life and in the case of overdose,
539 supportive measures are indicated.

540

541

DOSAGE AND ADMINISTRATION

542 **SYMLIN dosage differs depending on whether the patient has type 2 or type 1**
543 **diabetes (see below).** When initiating therapy with SYMLIN, initial insulin dose
544 reduction is required in all patients (both type 2 and type 1) to reduce the risk of
545 insulin-induced hypoglycemia. As this reduction in insulin can lead to glucose
546 elevations, patients should be monitored at regular intervals to assess SYMLIN
547 tolerability and the effect on blood glucose, so that **individualized** insulin adjustments
548 can be initiated. If SYMLIN therapy is discontinued for any reason (e.g., surgery or
549 illnesses), the same initiation protocol should be followed when SYMLIN therapy is
550 re-instituted (see below).

551

552

Initiation of SYMLIN therapy

553

Patients With Insulin-using Type 2 Diabetes

554

**In patients with insulin-using type 2 diabetes, SYMLIN should be initiated at a dose
555 of 60 µg and increased to a dose of 120 µg as tolerated.**

556

Patients should be instructed to:

557

- 558 • Initiate SYMLIN at 60 µg subcutaneously, immediately prior to major meals;
- 559 • Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix
560 insulins (70/30) by **50%**;
- 561 • Monitor blood glucose frequently, including pre- and post-meals and at bedtime;
- 562 • Increase the SYMLIN dose to 120 µg when no clinically significant nausea has
563 occurred for 3-7 days. **SYMLIN dose adjustments should be made only as
564 directed by the health care professional.** If significant nausea persists at the 120 µg
565 dose, the SYMLIN dose should be decreased to 60 µg;
- 566 • Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is
567 achieved and nausea (if experienced) has subsided. **Insulin dose adjustments
568 should be made only as directed by the health care professional;**
- 569 • Contact a health care professional skilled in the use of insulin to review SYMLIN and
570 insulin dose adjustments at least once a week until a target dose of SYMLIN is
571 achieved, SYMLIN is well-tolerated, and blood glucose concentrations are stable.

571

572

Patients With Type 1 Diabetes

573

**In patients with type 1 diabetes, SYMLIN should be initiated at a dose of 15 µg and
574 titrated at 15-µg increments to a maintenance dose of 30 µg or 60 µg as tolerated.**

575

Patients should be instructed to:

- 576 • Initiate SYMLIN at a starting dose of 15 µg subcutaneously, immediately prior to
577 major meals;
- 578 • Reduce preprandial, rapid-acting or short-acting insulin dosages, including fixed-mix
579 insulins (e.g., 70/30) by **50%**;
- 580 • Monitor blood glucose frequently, including pre- and post-meals and at bedtime;
- 581 • Increase the SYMLIN dose to the next increment (30 µg, 45 µg, or 60 µg) when no
582 clinically significant nausea has occurred for at least 3 days. **SYMLIN dose**
583 **adjustments should be made only as directed by the health care professional.** If
584 significant nausea persists at the 45- or 60-µg dose level, the SYMLIN dose should be
585 decreased to 30 µg. If the 30-µg dose is not tolerated, discontinuation of SYMLIN
586 therapy should be considered;
- 587 • Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is
588 achieved and nausea (if experienced) has subsided. **Insulin dose adjustments**
589 **should be made only as directed by the health care professional;**
- 590 • Contact a health care professional skilled in the use of insulin to review SYMLIN and
591 insulin dose adjustments at least once a week until a target dose of SYMLIN is
592 achieved, SYMLIN is well-tolerated, and blood glucose concentrations are stable.
- 593

594 **Once Target Dose of SYMLIN Is Achieved in Type 2 or Type 1 Patients**

595 After a maintenance dose of SYMLIN is achieved, both insulin-using patients with type 2
596 diabetes and patients with type 1 diabetes should be instructed to:

597

- 598 • Adjust insulin doses to optimize glycemic control once the target dose of SYMLIN is
599 achieved and nausea (if experienced) has subsided. **Insulin dose adjustments**
600 **should be made only as directed by a health care professional;**
- 601 • Contact a health care professional in the event of recurrent nausea or hypoglycemia.
602 An increased frequency of mild to moderate hypoglycemia should be viewed as a
603 warning sign of increased risk for severe hypoglycemia.
- 604

605 **Administration**

606 SYMLIN should be administered subcutaneously immediately prior to each major meal
607 (≥ 250 kcal or containing ≥ 30 g of carbohydrate).

608

609 To administer SYMLIN from vials, use a U-100 insulin syringe (preferably a 0.3 mL [0.3
610 cc] size) for optimal accuracy. If using a syringe calibrated for use with U-100 insulin,
611 use the chart below (**Table 8**) to measure the microgram dosage in unit increments. **Do**
612 **not mix SYMLIN with insulin.**

613

614 **Table 8: Conversion of SYMLIN Dose to Insulin Unit Equivalents**

615

Dosage Prescribed (µg)	Increment Using a U-100 Syringe (Units)	Volume (cc or mL)
15	2.5	0.025
30	5.0	0.050
45	7.5	0.075
60	10.0	0.100
120	20.0	0.200

616

617 Each SYMLIN dose should be administered subcutaneously into the abdomen or thigh.

618 Injection sites should be rotated so that the same site is not used repeatedly. The

619 injection site selected should also be distinct from the site chosen for any concomitant

620 insulin injection. Each SYMLIN injection should be administered subcutaneously to

621 abdomen or thigh (administered into the arm is not recommended because of variable

622 absorption).

623

- 624 • **SYMLIN and insulin should always be administered as separate injections.**
- 625 • **SYMLIN should not be mixed with any type of insulin.**
- 626 • **If a SYMLIN dose is missed, do not give an additional injection.**
- 627 • **Always use a new syringe and needle to give SYMLIN and insulin injections.**

628

629 **Discontinuation of Therapy**

630 SYMLIN therapy should be discontinued if any of the following occur:

- 631 • Recurrent unexplained hypoglycemia that requires medical assistance;
- 632 • Persistent clinically significant nausea;
- 633 • Noncompliance with self-monitoring of blood glucose concentrations;
- 634 • Noncompliance with insulin dose adjustments;
- 635 • Noncompliance with scheduled health care professional contacts or recommended
- 636 clinic visits.

637

638 **Preparation and Handling**

639 SYMLIN should be inspected visually for particulate matter or discoloration prior to

640 administration whenever the solution and the container permit.

641

642 **HOW SUPPLIED**

643 SYMLIN is supplied as a sterile injection in 5 mL vials, containing 0.6 mg/mL
 644 pramlintide (as acetate), for use with a syringe. To administer SYMLIN from vials, use a
 645 U-100 insulin syringe (preferably a 0.3 mL [0.3 cc] size). If using a syringe calibrated
 646 for use with U-100 insulin, use the chart (**Table 8**) in the DOSAGE AND
 647 ADMINISTRATION section to measure the microgram dosage in unit increments. **Do**
 648 **not mix SYMLIN with insulin.**

649

650 SYMLIN Injection is available in the following package size:

651 5 mL vials (NDC 66780-110)

652

653 **STORAGE**

654 **Unopened (not in-use) Vials:** Before use, SYMLIN vials should be refrigerated, 36°F to
655 46°F (2°C to 8°C), and protected from light. Do not freeze. If a vial has been frozen or
656 overheated, throw it away.

657

658 **Opened (in-use) Vials:** Opened vials in use (punctured) can be kept either refrigerated
659 or at room temperature for up to 28 days as long as the temperature is not greater than
660 77°F (25°C). Opened vials, whether or not refrigerated, must be used within 28 days.
661 Discard after 28 days.

662

663 Storage conditions and stability are summarized in **Table 9**:

664

665 **Table 9: Storage Conditions and Stability of SYMLIN (5 mL Vials)**

666

	Unopened (not in-use) Refrigerated	Open (in-use) Refrigerated or Room Temperature
5 mL Vial	Until Expiration Date	Use Within 28 days

667

668

669 Vials are manufactured for:

670 Amylin Pharmaceuticals, Inc.

671 San Diego, CA 92121 USA

672 1-800-349-8919

673 <http://www.symlin.com>

674

675 **Rx only**

676

677

1 **Medication Guide**

2
3 **SYMLIN[®] (SĪM-lĭn)**
4 **(pramlintide acetate) Injection**

5 Read the Medication Guide that comes with SYMLIN before you start using it and each time
6 you get a refill. There may be new information. This Medication Guide does not take the place
7 of talking to your doctor about your medical condition or treatment.

8 **What is the most important information I should know about SYMLIN?**

- 9 • **SYMLIN is used with insulin to lower blood sugar, especially high blood sugar that**
10 **happens after meals.**
- 11 • **SYMLIN is given at mealtimes. The use of SYMLIN does not replace your daily**
12 **insulin but may lower the amount of insulin you need, especially before meals.**
- 13 • **Even when SYMLIN is carefully added to your mealtime insulin therapy, your**
14 **blood sugar may drop too low, especially if you have type 1 diabetes. If this low**
15 **blood sugar (severe hypoglycemia) happens, it is seen within 3 hours after a**
16 **SYMLIN injection. Severe low blood sugar makes it hard to think clearly, drive a**
17 **car, use heavy machinery or do other risky activities where you could hurt yourself**
18 **or others.**
- 19 • **SYMLIN should only be used by people with type 1 and type 2 diabetes who:**
- 20 • already use their insulin as prescribed, but still need better blood sugar control.
- 21 • will follow their doctor's instructions exactly.
- 22 • will follow up with their doctor often.
- 23 • will test their blood sugar levels before and after every meal, and at bedtime.
- 24 • understand how to adjust SYMLIN and insulin doses.

25 **What is SYMLIN?**

26 SYMLIN is an injectable medicine for adults with type 1 and type 2 diabetes to control blood
27 sugar. SYMLIN slows down the movement of food through your stomach. This affects how fast
28 sugar enters your blood after eating. SYMLIN is always used with insulin to help lower blood
29 sugar during the 3 hours after meals.

30 **Who should not use SYMLIN?**

31 **Do not use SYMLIN if you:**

- 32 • cannot tell when your blood sugar is low (hypoglycemia unawareness).
- 33 • have a stomach problem called gastroparesis. This is when your stomach does not empty as
34 fast as it should.
- 35 • are allergic to SYMLIN or any ingredients in SYMLIN. See the end of this Medication
36 Guide for a complete list of ingredients.

37 **SYMLIN has not been studied in children.**

38 **What should I tell my doctor before starting SYMLIN?**

39 **Tell your doctor about all of your medical conditions including if you:**

- 40 • **are pregnant or planning to become pregnant.** It is not known if SYMLIN can harm your
41 unborn baby. You and your doctor will decide how to best control your blood sugar levels
42 during pregnancy.
- 43 • **are breastfeeding.** It is not known if SYMLIN passes into your milk and if it can harm your
44 baby. You and your doctor will decide the best way to feed your baby if you are using
45 SYMLIN.

46 **Keep a list of all the medicines you take. Tell your doctor about all the medicines you take**
47 **including prescription and non-prescription medicines, vitamins, and herbal supplements.**
48 SYMLIN can slow down how other medicines pass through your stomach and may affect how
49 much of them get into your body. Therefore, you may have to change the times you take certain
50 medicines.

51 **How should I use SYMLIN?**

- 52 • **You must use SYMLIN exactly as prescribed. The amount of SYMLIN you use will**
53 **depend on whether you have type 1 or type 2 diabetes.** You and your doctor will decide if
54 you can use SYMLIN.
- 55 • **Never mix SYMLIN and insulin.** You must use different syringes for SYMLIN and insulin
56 because insulin can affect SYMLIN when the two are mixed together.
- 57 • Injecting SYMLIN is similar to injecting insulin. **Inject SYMLIN under the skin**
58 **(subcutaneously) of your stomach area (abdomen) or upper leg (thigh).** Inject SYMLIN
59 at a site that is more than 2 inches away from your insulin injection. Allow SYMLIN to
60 warm to room temperature before injecting. Use a U-100 insulin syringe (best to use 0.3 mL
61 [0.3 cc] size) to draw-up and inject SYMLIN. Always use a new syringe and needle for each
62 SYMLIN injection.
- 63 • The dose of SYMLIN that your doctor prescribes should be one in the table below. Use this
64 table to match your SYMLIN dose to insulin syringe units:

Find Your Dose in micrograms (µg)	Draw Up This Amount in U-100 Insulin Syringe (units)
15	2.5
30	5.0
45	7.5
60	10.0
120	20.0

- 65
- 66 • Do not use SYMLIN if the liquid in the vial looks cloudy.
 - 67 • If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and
68 you may not be able to eat the amount of food you usually eat. Pay careful attention to the

69 amount of insulin you use at this time as you may be at more risk for low blood sugar.
70 Contact your doctor for guidance.

- 71 • If you miss or forget a dose of SYMLIN, wait until the next meal and take your usual dose of
72 SYMLIN at that meal. Do not take more than your usual dose of SYMLIN.

73 **Using SYMLIN and insulin with Type 2 Diabetes (see the Table above)**

- 74 1. Start SYMLIN at 60 µg injected under your skin, just before major meals. A major meal
75 must have at least 250 calories or 30 grams of carbohydrate.
- 76 2. Reduce your rapid-acting or short-acting insulin doses before meals by **50 percent**,
77 including fixed-mix insulins such as 70/30. This means half of the dose you usually use.
- 78 3. You must check your blood sugar before and after every meal and at bedtime.
- 79 4. Increase your dose of SYMLIN to 120 µg on your doctor's instructions if you have not
80 had any nausea for 3 days or more.
- 81 5. Tell your doctor right away if you have nausea with the 120 µg dose. Your doctor will
82 tell you how to adjust your dose of SYMLIN.
- 83 6. Your doctor may make changes to your insulin doses to better control your blood sugar
84 once you are using the 120 µg dose of SYMLIN. All insulin changes should be directed
85 by your doctor.

86 **Using SYMLIN and insulin with Type 1 Diabetes (see the Table above)**

- 87 1. Start SYMLIN at 15 µg injected under your skin, just before major meals. A major meal
88 must have at least 250 calories or 30 grams of carbohydrate.
- 89 2. When starting SYMLIN, reduce your rapid-acting or short-acting insulin doses before
90 meals by **50 percent**, including fixed-mix insulins such as 70/30. This means half of the
91 dose you usually use. All insulin changes should be directed by your doctor.
- 92 3. You must check your blood sugar before and after every meal and at bedtime.
- 93 4. Increase your dose of SYMLIN to 30 µg on your doctor's instructions if you have not
94 had any nausea for 3 days or more. If you have nausea with SYMLIN at 30 µg, call your
95 doctor right away. Your doctor may decide that you should stop SYMLIN.
- 96 5. Increase your dose of SYMLIN to 45 µg on your doctor's instructions if you have not
97 had any nausea for 3 days or more while using the 30 µg dose.
- 98 6. Increase your dose of SYMLIN to 60 µg on your doctor's instructions if you have not
99 had any nausea for 3 days or more while using the 45 µg dose.
- 100 7. Call your doctor right away if you are bothered with nausea on the 45 µg or 60 µg dose.
101 Your doctor may decide that you should reduce SYMLIN to the 30 µg dose.
- 102 8. Your doctor may make changes to your insulin doses to better control your blood sugar
103 once you are on a dose of SYMLIN that is right for you. All insulin changes should be
104 directed by your doctor.

105 **Staying on SYMLIN**

- 106 • Once you reach your recommended dose of SYMLIN, talk to your doctor about changing
107 your insulin doses to better control your blood sugar. You may have to increase your
108 long-acting insulin to prevent high blood sugar (hyperglycemia) between meals. **Insulin**
109 **changes should be directed by your doctor based on blood sugar testing.**
- 110 • Call your doctor if nausea or low blood sugar continues while on your recommended dose of
111 SYMLIN. Low blood sugar that happens often is a warning sign of possible severe low
112 blood sugar, especially if you have type 1 diabetes.
- 113 • **If you stop taking SYMLIN for any reason, such as surgery or illness, call your doctor.**
114 **SYMLIN should be restarted as described above in “How should I use SYMLIN?”**

115 **When should I not use SYMLIN?**

116 **Do not use SYMLIN if:**

- 117 • Your blood sugar is too low.
- 118 • You do not plan to eat. Do not inject SYMLIN if you skip a meal.
- 119 • You plan to eat a meal with less than 250 calories or 30 grams of carbohydrate.
- 120 • You are sick and can't eat your usual meal.
- 121 • You are having surgery or a medical test where you cannot eat.
- 122 • You are pregnant or breastfeeding and have not talked to your doctor.

123 Talk to your doctor if you have any of these conditions.

124 **What should I avoid while taking SYMLIN?**

- 125 • Do not drive or operate dangerous machinery until you know how SYMLIN affects your
126 blood sugar. Low blood sugar makes it hard to think clearly, drive a car, use heavy
127 machinery or do other risky activities where you could hurt yourself or others. Discuss with
128 your doctor what activities you should avoid.
- 129 • Alcohol may increase the risk of low blood sugar.
- 130 • **Your doctor will tell you which medicines you can take while using SYMLIN. Do not**
131 **take other medicines that slow stomach emptying.**

132 Always have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon available
133 to treat low blood sugar.

134 **What are the possible side effects of SYMLIN?**

135 **Low blood sugar (hypoglycemia)**

- 136 • **SYMLIN is used with insulin to lower your blood sugar, but your blood sugar may**
137 **drop too low, especially if you have type 1 diabetes.** See “What is the most important
138 information I should know about SYMLIN?”

- 139 • When starting SYMLIN, reduce your doses of insulin before meals as recommended by your
140 doctor to reduce the chance of low blood sugar. You and your doctor should talk about a
141 plan to treat low blood sugar. You should have fast-acting sugar (such as hard candy,
142 glucose tablets, juice) or glucagon with you at all times. Call your doctor if you have low
143 blood sugar more often than normal or severe low blood sugar.

144 **Your chance for low blood sugar is higher if you:**

- 145 • do not reduce your insulin dose before meals at the beginning of SYMLIN treatment, as
146 directed by your doctor.
- 147 • use more SYMLIN or insulin than prescribed by your doctor.
- 148 • change your insulin dose without checking your blood sugar.
- 149 • eat less food than your usual meal.
- 150 • are sick and cannot eat.
- 151 • are more active than usual.
- 152 • have a low blood sugar level before eating.
- 153 • drink alcohol.

154 **Nausea:** Nausea is the most common side effect with SYMLIN. Mild nausea is more likely
155 during the first weeks after starting SYMLIN and usually does not last long. It is very important
156 to start SYMLIN at a low dose and increase it as directed by your doctor. See “How should I
157 use SYMLIN?” If nausea continues or bothers you, call your doctor right away.

158 **Other Side Effects:** SYMLIN also may cause the following side effects: decreased appetite,
159 vomiting, stomach pain, tiredness, dizziness, or indigestion.

160 SYMLIN also can cause reactions at the injection site including redness, minor bruising, or pain.
161 Follow the directions under “How should I use SYMLIN?” to reduce the chance of an injection
162 site reaction.

163 Tell your doctor if you have any side effects that bother you or that do not go away.

164 These are not all the side effects with SYMLIN. Ask your doctor or pharmacist for more
165 information.

166 **How should I store SYMLIN?**

- 167 • Store SYMLIN vials in the refrigerator until you open them.
- 168 • Opened vials can be refrigerated or kept at room temperature for up to 28 days. Any opened
169 vial should be thrown away after 28 days, even if it still has medicine in it.
- 170 • Throw away any vial that is out-of-date, has been frozen, heated above room temperature
171 (77°F/25°C) or left at room temperature for more than 28 days.
- 172 • **Keep SYMLIN and all medicines out of the reach of children.**

173 **General information about the safe and effective use of SYMLIN**

174 Medicines are sometimes prescribed for conditions other than those described in a Medication
175 Guide. Do not use SYMLIN for a condition for which it was not prescribed. Do not give
176 SYMLIN to other people, even if they have the same symptoms that you have. It may harm
177 them.

178
179 This Medication Guide summarizes the most important information about SYMLIN. If you
180 would like more information, talk with your doctor. You can ask your doctor or pharmacist for
181 information about SYMLIN that is written for health professionals.

182
183 More information on SYMLIN can be found at <http://www.symlin.com>.
184 SYMLIN Customer Service is available 24 hours a day at 1-800-349-8919.

185 **What are the ingredients in SYMLIN?**

186 **Active ingredient:** pramlintide acetate

187 **Inactive ingredients:** metacresol, D-mannitol, acetic acid, and sodium acetate.

188
189 *This draft Medication Guide is pending approval by the U.S. Food and Drug Administration.*

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191 Literature issued March 2005.

192
193 **Manufactured for Amylin Pharmaceuticals, Inc.**
194 **San Diego CA 92121, USA**
195 **1-800-349-8919**
196 **<http://www.symlin.com>**

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