

# The SYMLIN Support Program<sup>SM</sup> is here for you



## Enroll in the program today to:

- ❖ **Get one-on-one telephone help** from a SYMLIN<sup>®</sup> specialist
- ❖ **Get access to a website** that features helpful tips, stories from people taking SYMLIN, and step-by-step instructions for using the SymlinPen<sup>®</sup>
- ❖ **Receive ongoing education and tools about SYMLIN<sup>®</sup>**, including a welcome package and newsletters
- ❖ Receive a **FREE travel case\*** for your SymlinPen<sup>®</sup>

For more information on the SYMLIN Support Program, call toll free at **1-888-SYMLIN1** (1-888-796-5461) or log on to the website at **www.SYMLINsupport.com**. The program does not take the place of your healthcare provider's advice. Talk with your healthcare provider if you have additional questions.



## YES! Enroll me in the SYMLIN Support Program

### Part 1 Please check your answers to the questions below.

#### 1. Which type of diabetes do you have?

- Type 1 (often diagnosed in children and young adults — treated with insulin)
- Type 2 (most common type of diabetes; often diagnosed in adults — usually treated first with pills)
- Not sure

#### 2. How many years have you been taking insulin?

- Less than 3 years
- 3 years or more
- Not sure

#### 3. Do you check your blood sugar more than once a day?

- Yes
- No
- Not sure



**So that you can receive your travel case, please complete your contact information and mailing address in Part 2 of this form.**

### Part 2 Please provide the following information for delivery and enrollment. Write neatly to ensure that there is no delay.

Title (Mr/Mrs/Ms/Dr): \_\_\_\_\_

Name: \_\_\_\_\_

Address 1: \_\_\_\_\_

Address 2: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_ ZIP: \_\_\_\_\_

E-mail: \_\_\_\_\_

Date of birth (mm-dd-yy): \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_

#### Best time to call (if you would like to receive calls):

- Morning
- Afternoon
- Evening (up to 6:00 PM eastern time; 3:00 PM Pacific time)

Phone: \_\_\_\_\_ Ext: \_\_\_\_\_

Date you started, or plan to start, SYMLIN (mm-dd-yy):

\_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_

Some of the materials from the SYMLIN Support Program can be sent to you by mail or e-mail. How would you like to receive them?

- Mail
- E-mail
- Both

**Now that you have filled out the form, please fax this page to 800-305-0277.**

I understand that the information I am providing may be used for marketing purposes by Amylin Pharmaceuticals, Inc. (Amylin) to provide me with diabetes information and health products, to contact me to see if I'd like to participate in market research activities, and to learn about products and services concerning health conditions. By submitting this form, I consent to these uses and understand that I must be 18 years or older to accept this registration offer.

I understand that I may request to be removed from the contact list by calling **1-888-SYMLIN1 (1-888-796-5461)** or visiting **www.SYMLINsupport.com**.

SYMLIN is an injectable medicine used to control blood sugar after meals in adults with type 2 or type 1 diabetes who take mealtime insulin.

**For Important Patient Safety Information, including information about the risk for severe low blood sugar, please see next page. Also read the accompanying SYMLIN Medication Guide.**

\*Limit: 1 travel case per person.

**Symlin<sup>®</sup>**  
(pramlintide acetate)  
injection

**SymlinPen<sup>®</sup>**  
(pramlintide acetate)  
pen-injector

## Important Patient Safety Information for SYMLIN<sup>®</sup> (pramlintide acetate) Injection

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

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

### Low blood sugar (hypoglycemia)

- **Your chance for low blood sugar is higher if you:**
  - do not reduce your insulin dose before meals at the beginning of SYMLIN treatment, as directed by your doctor.
  - use more SYMLIN or insulin than prescribed by your doctor.
  - change your insulin dose without checking your blood sugar.
  - eat less food than your usual meal.
  - are sick and cannot eat.
  - are more active than usual.
  - have a low blood sugar level before eating.
  - drink alcohol.

### How should I use SYMLIN?

- **When you first start SYMLIN, your doctor should tell you to reduce the dose of insulin you take before meals by 50 percent.** Future insulin changes should be directed by your doctor based on blood sugar testing.
- The amount of SYMLIN you use will depend on whether you have type 2 or type 1 diabetes.
- **Never mix SYMLIN and insulin.**
- **Injecting SYMLIN is similar to injecting insulin. Inject SYMLIN under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh) and at least 2 inches away from your insulin injection site.**
- **Do not transfer SYMLIN from the pen-injector to a syringe. This could result in a higher dose than intended, because SYMLIN in the pen-injector is a different strength than SYMLIN in the vial.**
- If you miss or forget a dose of SYMLIN, wait until the next meal and take your usual dose of SYMLIN at that meal. Do not take more than your usual dose of SYMLIN.
- Do not take SYMLIN if you plan to eat a meal with fewer than 250 calories or less than 30 grams of carbohydrate. Do not inject SYMLIN if you skip a meal.
- Opened pen-injectors or vials in use can be refrigerated or kept at a room temperature up to 86°F for up to 30 days.

### What are the possible side effects of SYMLIN?

- Low blood sugar (hypoglycemia) is a potentially serious side effect (see **Low blood sugar (hypoglycemia)** section).
- Nausea is the most common side effect with SYMLIN. Mild nausea is more likely during the first weeks after starting SYMLIN and usually does not last long. It is very important to start SYMLIN at a low dose and increase it as directed by your doctor. If nausea continues or bothers you, call your doctor right away.
- Tell your doctor if you have any side effects that bother you or that do not go away.

Be sure to read the accompanying *Medication Guide* before using SYMLIN. For more information, please see the Patient Instructions for Use, which came with your pen-injector or vial. This and other important information is also available at [www.SYMLIN.com](http://www.SYMLIN.com).

Live Customer Support is available Monday through Friday from 9 AM to 6 PM eastern time at **1-800-349-8919**.



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**Symlin<sup>®</sup>**  
(pramlintide acetate)  
injection

**SymlinPen<sup>®</sup>**  
(pramlintide acetate)  
pen-injector

# Symlin<sup>®</sup>

(pramlintide acetate)  
injection

## Medication Guide

### SYMLIN<sup>®</sup> (SĪM-lin) (pramlintide acetate) injection

Read the Medication Guide and the "Patient Instructions for Use" that come with your SYMLIN product before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

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

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

#### What is SYMLIN?

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

#### Who should not use SYMLIN?

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

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

SYMLIN has not been studied in children.

#### What should I tell my doctor before starting SYMLIN?

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

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

**Keep a list of all the medicines you take. Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and**

**herbal supplements.** SYMLIN can slow down how other medicines pass through your stomach and may affect how much of them get into your body. You may have to change the times you take certain medicines.

#### How should I use SYMLIN?

- **You must use SYMLIN exactly as prescribed. The amount of SYMLIN you use will depend on whether you have type 2 or type 1 diabetes.** You and your doctor will decide if you can use SYMLIN.
- It is important for you to carefully read, understand and follow the "Patient Instructions for Use" that comes along with this Medication Guide and your SYMLIN.
- **SYMLIN is available in vials and two SymlinPen<sup>®</sup> pen-injectors. Your doctor will prescribe the type of SYMLIN that is right for you.**
  - If you have been using the SYMLIN vial with an insulin syringe and you are changing to the SymlinPen<sup>®</sup> pen-injector: **Your doctor will prescribe the SymlinPen<sup>®</sup> pen-injector that is right for you, tell you how much SYMLIN to inject and when to inject it.**
  - **It is important that you understand how to inject the right SYMLIN dose. Read the "Patient Instructions for Use" carefully BEFORE giving your first dose with the SymlinPen<sup>®</sup> pen-injector. The SYMLIN in the pen-injector is a different strength than the SYMLIN in the vial.**
- The way you inject SYMLIN is similar to the way you inject insulin. **Inject SYMLIN under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh).** Inject SYMLIN at a site that is more than 2 inches away from your insulin injection. Do not inject SYMLIN and insulin in the same site.
- To help reduce the chances of getting a reaction at the injection site, allow SYMLIN to come to room temperature before injecting.
- Use a new needle for each SYMLIN injection.
- **Never mix SYMLIN and insulin.** Insulin can affect SYMLIN when the two are mixed together.
- Do **not** use SYMLIN if the liquid looks cloudy.
- If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and you may not be able to eat the amount of food you usually eat. If you take more SYMLIN than your prescribed dose, pay careful attention to the amount of insulin you use because you may be at more risk for low blood sugar. Contact your doctor for guidance.
- If you miss or forget a dose of SYMLIN, wait until the next meal and take your usual dose of SYMLIN at that meal. **Do not take more than your usual dose of SYMLIN.**

#### Using SYMLIN and insulin with Type 2 Diabetes

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

#### Using SYMLIN and insulin with Type 1 Diabetes

1. Start SYMLIN at 15 mcg injected under your skin, just before major meals. A major meal must have at least 250 calories or 30 grams of carbohydrate.
2. When starting SYMLIN, reduce your rapid-acting or short-acting insulin, including fixed-mix insulin such as 70/30, used before meals by **50 percent**. This means half of the dose you usually use. All insulin changes should be directed by your doctor.
3. You must check your blood sugar before and after every meal and at bedtime.
4. Increase your dose of SYMLIN to 30 mcg on your doctor's instructions if you have not had any nausea for 3 days or more. If you have nausea with SYMLIN at 30 mcg, call your doctor right away. Your doctor may decide that you should stop SYMLIN.
5. Increase your dose of SYMLIN to 45 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 30 mcg dose.

6. Increase your dose of SYMLIN to 60 mcg on your doctor's instructions if you have not had any nausea for 3 days or more while using the 45 mcg dose.
7. Call your doctor right away if you are bothered with nausea on the 45 mcg or 60 mcg dose. Your doctor may decide that you should reduce SYMLIN to the 30 mcg dose.
8. Your doctor may make changes to your insulin doses to better control your blood sugar once you are on a dose of SYMLIN that is right for you. All insulin changes should be directed by your doctor.

### Staying on SYMLIN

- Once you reach your recommended dose of SYMLIN, talk to your doctor about changing your insulin doses to better control your blood sugar. You may have to increase your long-acting insulin to prevent high blood sugar (hyperglycemia) between meals. **Insulin changes should always be directed by your doctor based on blood sugar testing.**
- Call your doctor if nausea or low blood sugar continues while on your recommended dose of SYMLIN. Low blood sugar that happens often is a warning sign of possible severe low blood sugar, especially if you have type 1 diabetes.
- **If you stop taking SYMLIN for any reason, such as surgery or illness, talk to your doctor about how to re-start SYMLIN.**

### When should I not use SYMLIN?

#### Do not use SYMLIN if:

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

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

### What should I avoid while taking SYMLIN?

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

### What are the possible side effects of SYMLIN?

#### Low blood sugar (hypoglycemia)

- **SYMLIN is used with insulin to lower your blood sugar, but your blood sugar may drop too low, especially if you have type 1 diabetes.** See "What is the most important information I should know about SYMLIN?"
- When starting SYMLIN, reduce your doses of insulin before meals as recommended by your doctor to reduce the chance of low blood sugar. You and your doctor should talk about a plan to treat low blood sugar. You should have fast-acting sugar (such as hard candy, glucose tablets, juice) or glucagon with you at all times. Call your doctor if you have low blood sugar more often than normal or severe low blood sugar.

#### Your chance for low blood sugar is higher if you:

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

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

**Nausea:** Nausea is the most common side effect with SYMLIN. Mild nausea is more likely during the first weeks after starting SYMLIN and usually does not last long. It is very important

to start SYMLIN at a low dose and increase it as directed by your doctor. See "How should I use SYMLIN?" If nausea continues or bothers you, call your doctor right away.

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

SYMLIN also can cause reactions at the injection site including redness, minor bruising, or pain. See the detailed "Patient Instructions for Use." Follow the directions under "How should I use SYMLIN?" to reduce the chance of an injection site reaction.

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

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

### How should I store SYMLIN?

- Store SYMLIN that has not been opened in the refrigerator, between 36°F to 46°F (2°C to 8°C), until you are ready to use it. Protect SYMLIN from light.
- After a vial or pen-injector has been used for the first time, it can be refrigerated or kept at a temperature up to 86°F (30°C) for 30 days. Do not leave **above** 86°F (30°C). Any vial or pen-injector in use should be thrown away after 30 days, even if it still has medicine in it.
- Unused SYMLIN (opened or unopened) should not be used after the expiration (EXP) date printed on the carton and the label.
- **Do not freeze SYMLIN. Do not use SYMLIN if it has been frozen.**

**Keep SYMLIN and all medicines out of the reach of children.**

### General information about the safe and effective use of SYMLIN

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

This Medication Guide summarizes the most important information about SYMLIN. Also see the "Patient Instructions for Use" on using the SymlinPen® pen-injector or vial. You can ask your doctor for more about SYMLIN, including information that is written for doctors.

More information on SYMLIN can be found at <http://www.SYMLIN.com>.

SYMLIN Customer Service is available 24 hours a day at 1-800-349-8919.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### What are the ingredients in SYMLIN?

**Active ingredient:** pramlintide acetate

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

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*This Medication Guide has been approved by the U.S. Food and Drug Administration.*

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Manufactured for Amylin Pharmaceuticals, Inc.

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1-800-349-8919

<http://www.SYMLIN.com>

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## Drug Interactions

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

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

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

## Mixing SYMLIN and Insulin

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

## Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

**Impairment of Fertility.** Administration of 0.3, 1, or 3 mg/kg/day of SYMLIN (8, 17, and 82 times the exposure resulting from the maximum recommended human dose based on body surface area) had no significant effects on fertility in male or female rats. The highest dose of 3 mg/kg/day resulted in dystocia in 8/12 female rats secondary to significant decreases in serum calcium levels.

## Pregnancy

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

## Nursing Mothers

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

## Pediatric Use

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

## Geriatric Use

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

## ADVERSE REACTIONS

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

**Table 4: Treatment-Emergent Adverse Events Occurring With  $\geq 5\%$  Incidence and Greater Incidence With SYMLIN Compared With Placebo in Long-Term, Placebo-Controlled Trials. Incidence of the Same Events in the Open-Label Clinical Practice Study (Patients With Insulin-Using Type 2 Diabetes, 120 mcg)**

	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)

**Table 5: Treatment-Emergent Adverse Events Occurring With  $\geq 5\%$  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 mcg)**

	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)

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 Hypoglycemia

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

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

	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	
Severe Hypoglycemia	0-3 Months (n=284)	>>-6 Months (n=251)	0-3 Months (n=292)	>>-6 Months (n=255)	0-3 Months (n=166)	>>-6 Months (n=150)
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

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

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

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

	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	
Severe Hypoglycemia	0-3 Months (n=538)	>>-6 Months (n=470)	0-3 Months (n=716)	>>-6 Months (n=576)	0-3 Months (n=265)	>>-6 Months (n=213)
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

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

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

## Post Marketing Experience

Since market introduction of SYMLIN, the following adverse reactions have been reported. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General: Injection site reactions.

## OVERDOSAGE

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

## DOSAGE AND ADMINISTRATION

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

### Initiation of SYMLIN therapy

#### Patients With Insulin-Using Type 2 Diabetes

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

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

## Patients With Type 1 Diabetes

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

Patients should be instructed to:

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

### Once Target Dose of SYMLIN is Achieved in Type 2 or Type 1 Patients

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

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

### Administration

SYMLIN should be administered subcutaneously immediately prior to each major meal ( $\geq 250$  kcal or containing  $\geq 30$  g of carbohydrate).

SYMLIN should be at room temperature before injecting to reduce potential injection site reactions. Each SYMLIN dose should be administered subcutaneously into the abdomen or thigh (administration into the arm is not recommended because of variable absorption). Injection sites should be rotated so that the same site is not used repeatedly. The injection site selected should also be distinct from the site chosen for any concomitant insulin injection.

- SYMLIN and insulin should always be administered as separate injections.
- SYMLIN should not be mixed with any type of insulin.
- If a SYMLIN dose is missed, wait until the next scheduled dose and administer the usual amount.

### SymLinPen<sup>®</sup> pen-injector

The SymLinPen<sup>®</sup> pen-injector is available in two presentations:

- SymLinPen<sup>®</sup> 60 pen-injector for doses of 15 mcg, 30 mcg, 45 mcg and 60 mcg.
- SymLinPen<sup>®</sup> 120 pen-injector for doses of 60 mcg and 120 mcg.

See the accompanying Patient Instructions for Use for instructions for using the SymLinPen<sup>®</sup> pen-injector.

- The patient should be advised:
- to confirm they are using the correct pen-injector that will deliver their prescribed dose;
  - on proper use of the pen-injector, emphasizing how and when to set up a new pen-injector;
  - not to transfer SYMLIN from the pen-injector to a syringe. Doing so could result in a higher dose than intended, because SYMLIN in the pen-injector is a higher concentration than SYMLIN in the SYMLIN vial;
  - not to share the pen-injector and needles with others;
  - that needles are not included with the pen-injector and must be purchased separately;
  - which needle length and gauge should be used;
  - to use a new needle for each injection.

### SYMLIN vials

To administer SYMLIN from vials, use a U-100 insulin syringe (preferably a 0.3 mL [0.3 cc] size) for optimal accuracy. If using a syringe calibrated for use with U-100 insulin, use the chart below (Table 8) to measure the microgram dosage in unit increments.

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

Dosage Prescribed (mcg)	Increment Using a U-100 Syringe (Units)	Volume (cc or mL)
15	2½	0.025
30	5	0.05
45	7½	0.075
60	10	0.1
120	20	0.2

**Always use separate, new syringes and needles to give SYMLIN and insulin injections.**

### Discontinuation of Therapy

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

- Recurrent unexplained hypoglycemia that requires medical assistance;
- Persistent clinically significant nausea;
- Noncompliance with self-monitoring of blood glucose concentrations;
- Noncompliance with insulin dose adjustments;
- Noncompliance with scheduled healthcare professional contacts or recommended clinic visits.

### Preparation and Handling

SYMLIN should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and the container permit.

### HOW SUPPLIED

SYMLIN is supplied as a sterile injection in the following dosage forms:

- 1.5 mL disposable multidose SymLinPen<sup>®</sup> 60 pen-injector containing 1000 mcg/mL pramlintide (as acetate).
- 2.7 mL disposable multidose SymLinPen<sup>®</sup> 120 pen-injector containing 1000 mcg/mL pramlintide (as acetate).
- 5 mL vial, containing 600 mcg/mL pramlintide (as acetate), for use with an insulin syringe.

To administer SYMLIN from vials, use a U-100 insulin syringe (preferably a 0.3 mL [0.3 cc] size). If using a syringe calibrated for use with U-100 insulin, use the chart (Table 8) in the DOSAGE AND ADMINISTRATION section to measure the microgram dosage in unit increments.

## Do not mix SYMLIN with insulin.

SYMLIN Injection is available in the following package sizes:

- SymLinPen<sup>®</sup> 60 pen-injector, containing 1000 mcg/mL pramlintide (as acetate) 2 X 1.5 mL disposable multidose pen-injector (NDC 66780-115-02)
- SymLinPen<sup>®</sup> 120 pen-injector, containing 1000 mcg/mL pramlintide (as acetate) 2 X 2.7 mL disposable multidose pen-injector (NDC 66780-121-02)
- 5 mL vial, containing 600 mcg/mL pramlintide (as acetate), for use with an insulin syringe (NDC 66780-110-01)

## STORAGE

**SYMLIN pen-injectors and vials not in use:** Refrigerate (36°F to 46°F; 2°C to 8°C), and protect from light. Do not freeze. Do not use if product has been frozen. Unused SYMLIN (opened or unopened) should not be used after the expiration (EXP) date printed on the carton and the label.

**SYMLIN pen-injectors and vials in use:** After first use, refrigerate or keep at a temperature not greater than 86°F (30°C) for 30 days. Use within 30 days, whether or not refrigerated.

Storage conditions are summarized in **Table 9**.

Table 9: Storage Conditions	Dosage Form	Unopened (not in use) Refrigerated	Open (in use) Refrigerated or Temperature Up To 86°F (30°C)
	1.5 mL pen-injector 2.7 mL pen-injector 5 mL vial	Until Expiration Date	Use Within 30 Days

The SymLinPen<sup>®</sup> pen-injectors and SYMLIN vials are manufactured for: Amlyn Pharmaceuticals, Inc. San Diego, CA 92121 USA 1-800-349-8919 <http://www.SYMLIN.com>

## Rx only

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