SYMLIN® (pramlintide acetate) injection for subcutaneous use

Initial U.S. Approval: 2005

SYMLIN dosage differs depending on whether the patient has type 1 or type 2 diabetes

2.1

Type 1 Diabetes: Start at 15 mcg subcutaneously before major meals. Increase in 15 mcg increments to a maximum premeal dose of 30 or 60 mcg; if not tolerated, reduce to 30 mcg, as tolerated (2.2).

Type 2 Diabetes: Start at 60 mcg subcutaneously before major meals then increase to 120 mcg before meals, as tolerated (2.2).

Wait at least 3 days between dose titrations to minimize nausea (2.1).

When initiating SYMLIN, reduce mealtime insulin doses, including premixed insulins, by 50% to reduce the risk of hypoglycemia.

To reduce the risk of nausea, wait at least 3 days before titrating SYMLIN to the next dose increment.

Monitor blood glucose frequently, including pre- and post-meals and at bedtime, particularly when initiating SYMLIN or increasing the SYMLIN dose. After the initial 50% reduction in mealtime insulin dose, individualize insulin dose adjustments based on glycemic control and tolerability (e.g., if nausea occurs it may affect the dose of insulin required). An increased frequency of mild-to-moderate hypoglycemia should be viewed as a warning sign of increased risk for severe hypoglycemia.

If SYMLIN therapy is discontinued for any reason (e.g., surgery or illnesses), the same initiation protocol should be followed when SYMLIN therapy is reinstituted [see Dosage and Administration (2.2)].

2.2

Patients with Type 2 Diabetes Using Mealtime Insulin

Reduce mealtime insulin doses (including premixed insulins) by 50%, then initiate SYMLIN at 60 mcg subcutaneously, injecting immediately prior to each major meal.

Increase the SYMLIN dose from 60 to 120 mcg prior to each major meal when no clinically significant nausea has occurred for at least 3 days.

If significant nausea persists at the 120 mcg dose, the SYMLIN dose should be decreased to 60 mcg.
2.3 Patients with Type 1 Diabetes
Reduce mealtime insulin doses by 50%, then initiate SYMLIN at 15 mcg subcutaneously, injecting immediately prior to each major meal. Increase the SYMLIN dose to the next increment (30, 45, or 60 mcg) when no clinically significant hypoglycemia has occurred for at least 3 days. If significant hypoglycemia 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.

2.4 Administration
SYMLIN should be administered subcutaneously immediately prior to each major meal (±250 kcal or containing ≥30 grams of carbohydrate).

SYMLIN should be at room temperature before injecting to reduce 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.

2.5 Discontinuation of Therapy
SYMLIN therapy should be discontinued if there is:
- 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 provider contacts or recommended clinic visits.

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

3 DOSAGES FORMS AND STRENGTHS
SYMLIN is supplied as a sterile injection in the following dosage forms:
- 1.5 mL disposable multidose SymlinPen® 60 pen-injector containing 1000 mcg/mL pramlintide (as acetate).
- 2.7 mL disposable multidose SymlinPen® 120 pen-injector containing 1000 mcg/mL pramlintide (as acetate).

4 CONTRAINDICATIONS
SYMLIN is contraindicated in patients with any of the following:
- serious hypersensitivity reaction to SYMLIN or to any of its product components.
- hypoglycemia unresponsive.
- confirmed gastroparesis.

5 WARNINGS AND PRECAUTIONS

5.1 Patient Selection
Proper patient selection is critical to the safe and effective use of SYMLIN. Before initiating SYMLIN, the patient’s HbA1c, current insulin regimen, and body weight should be reviewed. SYMLIN therapy should only be considered in patients with type 1 diabetes or patients with type 2 diabetes using mealtime insulin who fulfill the following criteria:
- have failed to achieve adequate glycemic control despite individualized insulin management.
- are receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educator(s).

Patients meeting any of the following criteria should NOT be considered for SYMLIN therapy:
- poor compliance with current insulin regimen.
- poor compliance with prescribed self blood glucose monitoring.
- have a HbA1c >9%.
- recurrent hypoglycemia requiring assistance during the past 6 months.
- complications that impair the patient’s ability to tolerate SYMLIN.
- need for insulin dose adjustments or changes of ≥30 units.

5.2 Hypoglycemia
SYMLIN alone does not cause hypoglycemia. However, SYMLIN is indicated to be coadministered with mealtime insulin therapy, and in this setting there is an increased risk of severe hypoglycemia, particularly in patients with type 1 diabetes. If severe hypoglycemia associated with SYMLIN occurs, it is usually seen within the first 2 to 3 hours following a SYMLIN injection. If severe hypoglycemia occurs while operating a motor vehicle, heavy machinery, or while engaging in other high-risk activities, serious injuries or death may occur. Therefore, when introducing SYMLIN therapy, appropriate precautions need to be taken to avoid increasing the risk for severe hypoglycemia. These precautions include:

- adequate carbohydrate intake (≥50 kcal or containing ≥30 grams of carbohydrate)
- frequent monitoring of blood glucose.
- discontinuation of SYMLIN if the next meal is delayed or skipped.
- prescription of oral medication if needed.
- discontinuation of SYMLIN if persistent hypoglycemia occurs.
- discontinuation of SYMLIN if the patient experiences recurrent hypoglycemia.

5.3 Never Share a SymlinPen Between Patients
SymlinPen must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.4 Never Mix SYMLIN and Insulin
Mixing SYMLIN and insulin can alter the pharmacokinetics of both products which may result in inadequate glucose control or hypoglycemia. Therefore, SYMLIN and insulin must always be administered as separate injections and should never be mixed (see Drug Interactions (7.1) and Clinical Pharmacology (12.3)).

5.5 Concomitantly Administered Oral Medications
SYMLIN slows gastric emptying, which may delay the absorption of concomitantly administered oral medications. Administer the concomitant oral medication at least 1 hour prior to SYMLIN injection or 2 hours after SYMLIN injection if the rapid onset or threshold concentration of the concomitant medication is a critical determinant of its effectiveness (such as with anaglycines, antibiotics, and oral contraceptives) (see Drug Interactions (7.2) and Clinical Pharmacology (12.3)).

5.6 Medications that Affect Gastrointestinal Motility
SYMLIN slows gastric emptying. SYMLIN is not recommended for patients taking other medications that alter gastrointestinal motility (see Drug Interactions (7.3)).

5.7 Allergy

Local Allergy
Patients may experience urthema, edema, or pruritus at the site of injection. These minor reactions usually resolve in a few days to a few weeks. In some instances, these reactions may be related to factors other than SYMLIN, such as irritants in a skin cleansing agent or improper injection technique.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trial Experience

Adverse Reactions (Excluding Hypoglycemia)

Adverse reactions (excluding hypoglycemia, which is discussed separately below) commonly associated with SYMLIN when coadministered with a fixed dose of insulin in the 26- to 52-week, placebo-controlled trials in patients with type 1 diabetes and patients with type 2 diabetes on mealtime insulin are presented in Table 1 and Table 2, respectively.

Table 1: Patients with Type 1 Diabetes: Common Adverse Reactions (Incidence ≥5%) and Greater Incidence with SYMLIN Compared to Placebo in 3 Pooled Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SYMLIN 30 or 60 mcg 3 Times Daily + Insulin (N=716)</th>
<th>Placebo + Insulin (N=538)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>Anorexia</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Inflicted Injury</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

1 Examples of inflicted injury included among others, abrasions, bruises, burns, fractures, lacerations, and muscle strains.
Table 2: Patients with Type 2 Diabetes on Insulin: Common Adverse Reactions (Incidence ≥5% and Greater Incidence with SYMLIN Compared to Placebo) in 2 Pooled Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SYMLIN + Insulin (N=292)</th>
<th>Placebo + Insulin (N=284)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>28%</td>
<td>12%</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Cough</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 3: Incidence and Event Rate of Severe Hypoglycemia in Six-Month, Placebo-Controlled Trials and Dose Titration Trial in Patients with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Severe Hypoglycemia</th>
<th>Long-Term, Placebo-Controlled Studies</th>
<th>Placebo-Controlled Dose Titration Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>(No Insulin Dose-Reduction During Initiation)</td>
<td>SYMLIN + Insulin</td>
<td>Placebo + Insulin</td>
</tr>
<tr>
<td>0 to 3 Months (n=716)</td>
<td>&gt;3 to 6 Months (n=576)</td>
<td>0 to 3 Months (n=358)</td>
</tr>
<tr>
<td>Patient-Ascertained</td>
<td>1.55</td>
<td>0.82</td>
</tr>
<tr>
<td>Event Rate (events/patient-year)</td>
<td>16.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Subject Incidence</td>
<td>7.3</td>
<td>5.2</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SYMLIN. Because these reactions 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.

- Injection site reactions
- Pancreatitis

7 DRUG INTERACTIONS

7.1 Insulin

The pharmacokinetic parameters of pramlintide are altered when SYMLIN is mixed in the same syringe with regular, NPH, and 70/30 premixed formulations of recombinant human insulin. SYMLIN and insulin must not be mixed and must be administered as separate injections [see Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)].

7.2 Oral Medications

SYMLIN has the potential to delay the absorption of concomitantly administered oral medications. When the rapid onset or threshold concentration of a concomitantly administered medication is a critical determinant of effectiveness (such as with analgesics, antibiotics, and oral contraceptives), the medication should be administered at least 1 hour prior to SYMLIN injection or 2 hours after SYMLIN injection [see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)].

7.3 Drugs Affecting Gastrointestinal Motility

Due to its effects on gastric emptying, SYMLIN should not be considered for patients taking medications that alter gastrointestinal motility (e.g., anticholinergic agents such as atropine) or medications that slow the intestinal absorption of nutrients (e.g., alpha-glucosidase inhibitors). Patients using these medications have not been studied in SYMLIN clinical trials [see Warnings and Precautions (5.6)].

7.4 Drugs Affecting Glucose Metabolism

The following are examples of medications that may increase the susceptibility to hypoglycemia when administered with SYMLIN: anti-diabetic products, angiotensin converting enzyme (ACE) inhibitors, diisopyramide, lactates, floxetine, monoamine oxidase inhibitors, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics. SYMLIN and these drugs should be coadministered with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a small number of reports in the manufacturer’s safety database on SYMLIN use in pregnant women are not sufficient to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations).

Ex-vivo studies using term perfused human, rabbit, and rat placenta indicate that SYMLIN has low potential to cross the maternal/fetal placental barrier. In animal reproduction studies, congenital abnormalities were observed in fetuses of pregnant rats but not in fetuses of pregnant rabbits exposed during organogenesis to pramlintide at 10 times the clinical dose of 360 mcg/day, based on exposure (see Data).

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

- Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.
SYMLIN® (pramlintide acetate) injection for subcutaneous use

Data

Animal Data
Developmental and reproductive toxicity studies with SYMLIN were performed in pregnant rats and rabbits. Increases in congenital abnormalities (neural tube defect, cleft palate, exencephaly) were observed in fetuses of pregnant rats administered pramlintide subcutaneously during organogenesis at 0.3 and 1 mg/kg/day (10 and 47 times the human dose of 360 mcg/day based on AUC, respectively), but not at 3 mg/kg/day. Administration of pramlintide to pregnant rabbits during organogenesis resulted in maternal toxicity but did not increase fetal malformations at doses up to 0.3 mg/kg/day (9 times the human dose of 360 mcg/day based on AUC).

8.2 Lactation

Risk Summary
There is no data on the presence of pramlintide in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for SYMLIN and any potential adverse effects on the breastfed child from SYMLIN or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

SYMLIN has been studied in patients ranging in age from 15 to 84 years of age, including 769 patients ≥65 to 75 years of age and 87 patients ≥75 years of age. No consistent differences in the efficacy and safety of SYMLIN have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out. As recommended for all patients, SYMLIN and insulin regimens should be carefully managed to minimize the risk of severe hypoglycemia.

8.6 Renal Impairment

The dosing requirements for SYMLIN are not altered in patients with mild (creatinine clearance (Clcr) 60-89 mL/min), moderate (Clcr 30-59 mL/min) or severe renal impairment (Clcr ≤ 29 mL/min). SYMLIN has not been studied in patients with end-stage renal disease [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

SYMLIN use has not been studied in patients with hepatic impairment [see Clinical Pharmacology (12.3)].

8.8 Gender

No consistent differences in the efficacy and safety of SYMLIN have been observed between men and women in SYMLIN clinical trials (n=2799 for male and n=2085 for female).

8.9 Race/Ethnicity

No consistent differences in the efficacy and safety of SYMLIN have been observed among patients of differing race/ethnicity in SYMLIN clinical trials (n=4257 for Caucasian, n=229 for black, n=337 for Hispanic or Latino, and n=61 for Asian and one or more races) although the smaller sample sizes for non-Caucasians, particularly Asians, limit conclusions.

10 OVERDOSAGE

Single 10 mg doses of SYMLIN (83 times the maximum recommended dose of 120 mcg for patients with type 2 diabetes) were administered to 3 healthy volunteers. All 3 individuals reported severe nausea associated with vomiting, diarrhea, vasodilatation, and dizziness. No hypoglycemia was reported. Pramlintide has a short half-life (approximately 48 minutes in healthy individuals). Initiate supportive measures in the case of overdose.

11 DESCRIPTION

SYMLIN® (pramlintide acetate) injection is an anti-diabetic medication for use in patients with diabetes treated with insulin. Pramlintide is a synthetic analog of human amylin, a naturally occurring neuropeptide hormone synthesized by pancreatic beta cells that contributes to glucose control during the postprandial period. Pramlintide is provided as an acetate salt of the synthetic 37-amino acid polypeptide, which differs in amino acid sequence from human amylin by replacement with proline at positions 25 (alanine), 28 (serine), and 29 (serine). The structural formula of pramlintide acetate is shown below:

\[
\text{Lys-Cys-Aa-Thr-Ala-Thr-Cys-Aa-Thr-Glu-Arg-Leu-Ala-Aas-Phe-Leu-Val-His-Ser-Ser-Asn-Aaa-Phe-Gly-Pro-Leu-Leu-Pro-Pro-Thr-Aaa-Val-Gly-Ser-Aaa-Thr-Tyr-NEt}_2\text{ acetate}
\]

(salt) with a disulfide bridge between the two Cys residues.

Pramlintide acetate is a white powder that has a molecular formula of C_{555}H_{916}N_{114}O_{236}S\times\text{CH}_2\text{O}_2\text{(NEt}_2)_2\text{acetate} = 3849.4. Pramlintide acetate is soluble in water.

SYMLIN is formulated as a clear, isotonic, sterile solution for subcutaneous administration. The disposable multidose SymlinPen® pen-injector contains 1000 mcg/mL of pramlintide (as acetate). The formulation contains 2.25 mg/mL of metacresol as a preservative, D-mannitol as a tonicity modifier, acetic acid, sodium acetate as pH modifiers, and water for injection.

SYMLIN has a pH of approximately 4.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pramlintide is an analog of human amylin. Amylin is colocated with insulin in secretory granules and cosecreted 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).
While SYMLIN reduces postprandial glucose, clinical studies employing a controlled hypoglycemic challenge have demonstrated that SYMLIN does not alter the counter-regulatory hormonal response to insulin-induced hypoglycemia. Likewise, in SYMLIN-treated patients, the perception of hypoglycemic symptoms was not altered with plasma glucose concentrations as low as 45 mg/dL. In a separate clinical trial pramlintide also reduced the 24-hour glucose fluctuations based on 24-hour glucose monitoring.

Reduced Food Intake
A single, subcutaneous dose of 30 mcg of SYMLIN to patients with type 1 diabetes and 120 mcg of SYMLIN to patients with type 2 diabetes administered 1 hour prior to an unlimited buffet meal was associated with reductions in total caloric intake (placebo-subtracted mean changes of −21% and 23%, respectively), which occurred without decreases in meal duration.

12.3 Pharmacokinetics
Absorption
The absolute bioavailability of pramlintide following a single subcutaneous dose of SYMLIN is approximately 30% to 40%. Subcutaneous administration of different doses of SYMLIN into the abdominal area or thigh of healthy individuals showed a linear, dose-dependent increase in maximum plasma concentrations (C\text{max}) and overall exposure (AUC) (Table 5).

<table>
<thead>
<tr>
<th>Subcutaneous Dose (mcg)</th>
<th>C_{\text{max}} (pmol/L)</th>
<th>T_{\text{max}} (min)</th>
<th>Elimination t_{1/2} (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3750</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td>60</td>
<td>8778</td>
<td>79</td>
<td>20</td>
</tr>
<tr>
<td>90</td>
<td>8507</td>
<td>102</td>
<td>19</td>
</tr>
<tr>
<td>120</td>
<td>11970</td>
<td>147</td>
<td>21</td>
</tr>
</tbody>
</table>

Injection of SYMLIN into the arm in obese patients with type 1 or type 2 diabetes showed higher overall exposure (20%-36%) with greater variability (% CV for AUC: 73%-106%), compared with exposure after injection of SYMLIN into the abdominal area or thigh. Relative bioavailability of pramlintide was not significantly different between obese and non-obese patients and based on BMI or skin fold thickness. Injections administered with 6.0-mm and 12.7-mm needles yielded similar bioavailability.

Distribution
SYMLIN does not extensively bind to red blood cells or albumin (approximately 40% of the drug is unbound in plasma).

Metabolism and Elimination
In healthy individuals, the half-life of pramlintide is approximately 48 minutes. The primary metabolite, Des-lys1 pramlintide (2-37 pramlintide), is biologically active in vitro. Overall exposure (AUC) to pramlintide is relatively constant with repeat dosing of SYMLIN, indicating no bioaccumulation.

Specific Populations
Renal Impairment
No studies have been conducted in patients with end-stage renal disease. In a single-dose pharmacokinetic study in patients with type 1 diabetes, 60 mcg of SYMLIN was administered to 4 patients with normal renal function (C\text{cr} >90 mL/min), 9 patients with mild renal impairment (C\text{cr} 60-89 mL/min), 5 patients with moderate renal impairment (C\text{cr} 30-59 mL/min) and 3 patients with severe renal impairment (C\text{cr} 15-29 mL/min). No statistically significant differences were noted in total (AUC\text{∞}) and peak (C\text{max}) exposure of pramlintide for mild, moderate, and severe renal impairment categories in comparison to patients with normal renal function; although, inter-patient variability in pharmacokinetic parameters was high.

Hepatic Impairment
Pharmacokinetic studies have not been conducted in patients with hepatic impairment.

Geriatric
Pharmacokinetic studies have not been conducted in the geriatric population [see Use in Specific Populations (8.5)].

Pediatric
The efficacy and safety of SYMLIN have not been established in the pediatric population. The use of SYMLIN is not recommended in pediatric patients due to the risk of severe hypoglycemia [see Warnings and Precautions (5.1, 5.2)].

Gender
No study has been conducted to evaluate the effect of gender on pramlintide pharmacokinetics.

Race/Ethnicity
No study has been conducted to evaluate the effect of ethnicity on pramlintide pharmacokinetics.

13 NONCLINICAL TOXICOLOGY
13.1 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 pramlintide (32, 67, and 159 times the exposure resulting from the human dose of 360 mcg/day 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 pramlintide (3, 9, and 25 times the exposure resulting from the human dose of 360 mcg/day based on AUC, respectively). No drug-induced tumors were observed in any organ.

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

Impairment of Fertility
Administration of 0.3, 1, or 3 mg/kg/day of pramlintide (up to 140 times the human dose of 360 mcg/day based on exposure) prior to and during mating 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 maternal toxicity and significant decreases in serum calcium levels.

14 CLINICAL STUDIES
A total of 2333 patients with type 1 diabetes and 1852 patients with type 2 diabetes received SYMLIN in controlled clinical trials.

14.1 Type 1 Diabetes
The efficacy and safety of SYMLIN were evaluated in 3 (26-52-week), randomized, double-blind, placebo-controlled trials in patients with type 1 diabetes. In these studies, insulin adjustments were minimized in order to isolate the SYMLIN effect with insulin adjustments allowed, at the investigator’s discretion, when excessive hypoglycemia was encountered. Patients participating in these 3 trials had a mean age of 40 years, a mean duration of diabetes of 17 years, and a mean body mass index of 25.9 kg/m2. Table 6 summarizes the 6-month results for those patients assigned to the 30 or 60 mcg dose of SYMLIN or placebo.
In the dose titration study, from a mean baseline body weight of 73.3 kg, 76.6 kg, respectively, after randomization there were corresponding mean reductions of –1.4 kg, and –1.6 kg in the SYMLIN treatment group compared to mean increases of +0.3 kg, and +0.1 kg in the placebo treatment group.

11 HOW SUPPLIED/STORAGE AND HANDLING
SYMLIN Injection is available in the following package sizes:
- SymlinPen® 60 pen-injector, containing 1000 mcg/mL pramlintide (as acetate)
- 2.7 mL disposable multidose pen-injectors (NDC 0310-6627-02)
- SymlinPen® 120 pen-injector, containing 1000 mcg/mL pramlintide (as acetate)
- 2.7 mL disposable multidose pen-injectors (NDC 0310-6625-02)

Storage and Handling
SYMLIN pen-injectors not in use: Refrigerate (2°C to 8°C; 36°F to 46°F), 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 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

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Unopened (not in use)</th>
<th>Refrigerated or Temperature up to 86°F (30°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7 mL pen-injector</td>
<td>Until Expiration Date</td>
<td>Use Within 30 Days</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Hypoglycemia
Discuss the risk and consequences of hypoglycemia and approaches to minimize its occurrence. Inform patients about the importance of self-management practices including glucose monitoring and timing of dosing. In addition, reinforce the importance of adherence to meal planning, physical activity, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications.

Never Share a SymlinPen Between Patients
Advise patients that they must never share a SymlinPen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Never Mix SYMLIN and Insulin
Inform patients that SYMLIN and insulin should always be administered as separate injections and never be mixed.

Show patients how to administer SYMLIN using the pen-injector. Advise patients to use a new needle for each injection.

Instructions
Instruct patients on the proper injection technique and proper storage of SYMLIN. Refer patients to the SYMLIN Medication Guide and Patient Instructions for Use for additional information. Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850 SYMLIN and SymlinPen are registered trademarks of the AstraZeneca group of companies. Rev. 12/19 US-36084 01/20
MEDICATION GUIDE
SYMLIN® (SIM-lin) (pramlintide acetate) injection for subcutaneous use

Read this Medication Guide and Instructions for Use that come with your SYMLIN 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 healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMLIN?
SYMLIN can cause serious side effects, including:
• severe low blood sugar (hypoglycemia). 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 severe low blood sugar (hypoglycemia) happens, it is seen within 3 hours after a SYMLIN injection. Symptoms of severe low blood sugar and low blood sugar include:
  o lightheadedness
  o dizziness
  o shakiness
  o sweating
  o hunger
  o fast heartbeat
  o trouble concentrating or confusion
  o change in vision
  o headache
  o irritability
  o drowsiness

People who have severely low blood sugar have had injuries while driving their car, operating heavy machinery or doing other dangerous activities. You and your healthcare provider 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 for injection with you at all times. Call your healthcare provider if you have severe low blood sugar or if you have low blood sugar more often than normal.

You have a higher chance of getting severe low blood sugar if you:
  o do not follow your healthcare provider’s instructions to reduce your insulin use before meals
  o use more SYMLIN or insulin than prescribed by your healthcare provider
  o change your insulin dose without checking your blood sugar
  o eat less food than your usual meal
  o are sick and cannot eat
  o are more active than usual
  o have a low blood sugar level before eating
  o drink alcohol

SYMLIN is used with insulin to lower blood sugar, especially high blood sugar that happens after meals.
SYMLIN is taken at mealtimes. The use of SYMLIN does not replace your daily insulin but may lower the amount of insulin you need, especially before meals.

Do not share your SymlinPen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is SYMLIN?
SYMLIN is an injectable prescription medicine used to treat adults with type 1 and type 2 diabetes to control blood sugar. SYMLIN is used when your mealtime insulin dose has not controlled your blood sugar well enough.

It is not known if SYMLIN is safe and effective in children.

Who should not use SYMLIN?
Do not use SYMLIN if you:
• are allergic to SYMLIN or any ingredients in SYMLIN. See the end of this Medication Guide for a complete list of ingredients in SYMLIN.
• 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.

What should I tell my healthcare provider before using SYMLIN?
Before you use SYMLIN, tell your healthcare provider about all of your medical conditions, including if you:
• are pregnant or plan to become pregnant. It is not known if SYMLIN will harm your unborn baby. You and your healthcare provider should decide how to best control your blood sugar levels during pregnancy.
• are breastfeeding or plan to breastfeed. It is not known if SYMLIN passes into your breast milk. You and your healthcare provider should decide about the best way to feed your baby if you are using SYMLIN.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SYMLIN slows stomach emptying and can affect medicines that need to pass through the stomach quickly.

How should I use SYMLIN?
• Read the “Instructions for Use” and the Medication Guide and that come with your SYMLIN for information about the right way to use SYMLIN.
• Use SYMLIN exactly as your healthcare provider tells you to use it.
• Your healthcare provider will tell you how much SYMLIN to use and when to use it.
• Your healthcare provider may change your dose if needed.
• If you stop taking SYMLIN for any reason, such as surgery or illness, talk to your healthcare provider about how to re-start SYMLIN.
• To reduce the risk of hypoglycemia, it is important that you plan your meals and physical activity every day while you use SYMLIN. Plan for what you will eat and when you will eat your meals.
• The amount of SYMLIN you use will depend on whether you have type 1 or type 2 diabetes.
• The way you inject SYMLIN is similar to the way you inject insulin. Inject SYMLIN under the skin 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. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.
• Never mix SYMLIN and insulin. Insulin can affect SYMLIN when they 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 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 healthcare provider 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.
• Do not share your SymlinPen with other people, even if the needle is changed. You may give other people a serious infection or get a serious infection from them.

Using SYMLIN and insulin with type 1 diabetes:
• When starting SYMLIN, you will need to reduce your dose of mealtime insulin. Your healthcare provider will tell you how to reduce your dose of mealtime insulin the right way.
• You must check your blood sugar as often as your healthcare provider advises you to, which may include before and after every meal and at bedtime.
• The usual starting dose of SYMLIN for people who have type 1 diabetes is 15 micrograms (mcg) injected under your skin.
• Inject SYMLIN under your skin (subcutaneously) just before a major meal. A major meal must have at least 250 calories or 30 grams of carbohydrate.
• If you have not had any nausea for 3 days or more after your dose of SYMLIN is changed, your healthcare provider may tell you to increase your dose of SYMLIN. Do not increase your dose of SYMLIN unless your healthcare provider tells you to.
• Tell your healthcare provider right away if you have nausea or low blood sugar after your dose of SYMLIN is changed. Your healthcare provider will tell you what to do.
• Your healthcare provider may make changes to your insulin dose to better control your blood sugar. Your healthcare provider should tell you what the right dose of insulin is for you.

Using SYMLIN and insulin with type 2 diabetes:
• When starting SYMLIN, you will need to reduce your dose of mealtime insulin. Your healthcare provider will tell you how to reduce your dose of mealtime insulin the right way.
• You must check your blood sugar as often as your healthcare provider advises you to, which may include before and after every meal and at bedtime.
• The usual starting dose of SYMLIN for people who have type 2 diabetes is 60 micrograms (mcg) injected under your skin.
• Inject SYMLIN under your skin (subcutaneously) just before a major meal. A major meal must have at least 250 calories or 30 grams of carbohydrate.
• If you have not had any nausea for 3 days or more after your dose of SYMLIN is changed, your healthcare provider may tell you to increase your dose of SYMLIN. Do not increase your dose of SYMLIN unless your healthcare provider tells you to.
• Tell your healthcare provider right away if you have nausea or low blood sugar after your dose of SYMLIN is changed. Your healthcare provider will tell you what to do.
• Your healthcare provider may make changes to your insulin dose to better control your blood sugar. Your healthcare provider should tell you what the right dose of insulin is for you.

What should I avoid while taking SYMLIN?
• See “What is the most important information I should know about SYMLIN?”
• Do not drive, operate machinery, or do other dangerous activities until you know how SYMLIN affects you. Talk to your healthcare provider about the activities you should avoid.
• Alcohol. Drinking alcohol may increase your chances of getting severe low blood sugar.

What are the possible side effects of SYMLIN?
SYMLIN may cause serious side effects, including:
• See “What is the most important information I should know about SYMLIN?”
• injection site reactions. SYMLIN may cause bruising, swelling, or itching at the injection site.

The most common side effects of SYMLIN include:
• nausea
• vomiting
• decreased appetite
• stomach pain
• headache

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of SYMLIN. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store SYMLIN?

Unopened SYMLIN:
- Keep SYMLIN in the refrigerator between 36°F to 46°F (2°C to 8°C), until you are ready to use it.
- Do not freeze. Do not use SYMLIN if it has been frozen.
- Keep unopened SYMLIN out of the light.

Opened SYMLIN:
- Keep SYMLIN either in the refrigerator or at room temperature between 36°F to 86°F (2°C to 30°C) for up to 30 days.
- Throw away used SYMLIN after 30 days of use, even if the pen still has medicine in it.
- Do not use SYMLIN (opened or unopened) after the expiration (EXP) date printed on the carton and the label.

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. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYMLIN that is written for health professionals.

More information, go to www.SYMLIN.com or call 1-800-236-9933.

What are the ingredients in SYMLIN?
Active ingredient: pramlintide acetate
Inactive ingredients: metacresol, D-mannitol, acetic acid, and sodium acetate

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Distributed by: AstraZeneca Pharmaceuticals LP Wilmington, DE 19850
Revised: February 2015 US-36084 1/20
Read the Medication Guide and these Instructions for Use before you start using SYMLIN and each time you get a refill. There may be new information.

Do not share your SymlinPen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Important:
- Ask your healthcare provider about your dose of SYMLIN and how to inject SYMLIN the right way before you inject it for the first time.
- Use a new needle for each SYMLIN injection. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.
- This SymlinPen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of this SymlinPen.
- Check SYMLIN before you use it. SYMLIN should be clear and colorless. Do not use SYMLIN if the liquid looks cloudy or colored or has lumps or particles in it.
- Your SymlinPen may look empty because SYMLIN is a clear and colorless liquid.
- Small bubbles will not hurt you or affect your dose of SYMLIN.
- Do not transfer SYMLIN from your SymlinPen into a syringe.
- Do not inject your dose of SYMLIN if you:
  - have low blood sugar (hypoglycemia)
  - do not plan to eat. Do not inject SYMLIN if you skip a meal. Wait until the next meal and take your usual dose of SYMLIN at that meal.
  - plan to eat a meal with less than 250 calories or 30 grams of carbohydrate
  - are sick and cannot eat your usual meal
  - are having surgery or a medical test where you cannot eat
- If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and 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 healthcare provider for guidance.

Supplies you will need to give each injection of SYMLIN:
- SymlinPen® 120 Pen-Injector (Pen) (See Figure A)
- a new SymlinPen compatible needle (See Figure B). Pen needles are not included. Use 29, 30, or 31 gauge disposable pen needles. Ask your healthcare provider which needle gauge and length is best for you.
- alcohol swab
- 1 sharps container for throwing away used SymlinPens and needles. See “Disposing of used SymlinPens and needles” at the end of these Instructions for Use.
Preparing your SymlinPen:
- Wash your hands with soap and water.
- Check the SymlinPen label before each use to make sure you have the right SymlinPen.
- Check the expiration date (EXP) on the SymlinPen label (See Figure A). Do not use the SymlinPen past the expiration date printed on the label.
- Check the liquid in your SymlinPen to make sure you have enough SYMLIN left in your SymlinPen to load your correct dose.
  - The lines on the cartridge show about how much SYMLIN is left in your SymlinPen. When the top of the plunger is at the thickest line on the cartridge, your SymlinPen is almost empty (See Figure C).

Attaching a Needle:

Step 1:
- Pull the pen cap straight off the SymlinPen and wipe the rubber seal with an alcohol swab.

Step 2:
- Get a new needle
- Peel off the paper tab and throw it away.

Step 3:
- Push the capped needle straight onto the end of the SymlinPen and twist the needle clockwise until it is tight.

Step 4:
- Pull off the outer needle cover. Do not throw it away.
- Pull off the inner needle cover and throw it away.

New Pen Setup - Priming your SymlinPen:
Note:
- Steps 5 through 7 are only required if you are using your SymlinPen for the first time. Do not repeat Step 1 through 4 before each dose.
- If you have already primed your SymlinPen, go to Step 8 for instructions about giving your scheduled dose.

Step 5:
- Turn the dial to select 60 mcg.
  - You should see the number 60 in the window.
Step 7:
• Hold your SymlinPen with the needle pointing up. Push the knob all the way in until it stops. You should hear a “clicking” sound while you are pushing the knob in.
  ▪ A stream of liquid should be seen from the needle.
    ▪ If you do not see a stream of liquid, repeat Step 6 and Step 7 (you may repeat up to 3 times).
    ▪ If you still do not see a stream of liquid after 3 attempts, change the needle and repeat Step 6 and Step 7. If you still do not see a stream of liquid, call Information Support.

Figure J

Step 10:
• Turn the knob forward or backward until you see the correct dose you need to inject.
• Check that you see the line to make sure you have loaded your full dose. You should see a line, arrow, and the number of your dose.
  ▪ If you do not see a line, arrow, and the number of your dose, do not inject the dose. Point the needle away from you, push the knob all the way in until it stops, then repeat Step 8 to Step 10.
  ▪ Once the knob has been pulled out, the dial will not move and you cannot reset your dose. If correct dose was not selected, push in the knob to discard the dose and repeat the instructions. If the knob is pushed in all the way, and you cannot turn the dial, call Information Support.

Figure M

Selecting your routine dose:

Step 8:
• Turn the dial to select the correct dose you need to inject.

Figure K

Step 9:
• Pull the knob straight out as far as it will go. You should hear a “clicking” sound while you are pulling the knob out.

Figure L

Giving your SYMLIN injection:

• Inject your SYMLIN exactly as your doctor has shown you.
• Change (rotate) injection sites for SYMLIN. 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, let SYMLIN come to room temperature before you inject it.

Figure N

Step 11:
• Choose your injection site.
• SYMLIN is injected under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh).
• Wipe the skin with an alcohol swab, and let the injection site dry before you inject your dose.

Figure O
### Step 12:
- Insert the needle into your skin.

**Figure P**

### Step 13:
- Put your thumb on the knob and push the knob all the way in until it stops. You should hear the “clicking” as you push and hold the knob in and **slowly count to 10** to give your full dose.

**Figure Q**

### Step 14:
- Pull the needle out of your skin.
- If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.
  - A drop or 2 of liquid on the needle tip is normal. It will not affect your dose.
  - If you see more than 2 drops, you may not have received your full dose. **Do not** inject another dose. Talk to your doctor for help.

**Figure R**

### Step 15:
- Carefully replace the outer needle cover by pushing straight onto the end of the SymlinPen.

**Figure S**

### Step 16:
- Unscrew the capped needle counterclockwise with the outer needle cover on it and throw it away.
- **Do not** store the SymlinPen with the needle attached or with the knob pulled out to prevent air bubbles.

**Figure T**

### Step 17:
- Replace the pen cap.

**Figure U**

### After your injection:
- Put your used needles and SymlinPen in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.
  - If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic,
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
    - upright and stable during use,
    - leak-resistant, and
    - properly labeled to warn of hazardous waste inside the container.
  - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and SymlinPen. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: [http://www.fda.gov/safesharpsdisposal](http://www.fda.gov/safesharpsdisposal)
  - **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

### How should I store my SymlinPen?

**Unused SymlinPens:**
- Keep SYMLIN in the refrigerator between 36°F to 46°F (2°C to 8°C), until you are ready to use it.
- **Do not** freeze. **Do not** use SYMLIN if it has been frozen.
- Keep unopened SYMLIN out of the light.
Used SymlinPens:

- Store SymlinPens in the refrigerator or at room temperature between 36°F to 86°F (2°C to 30°C) for up to 30 days.
- Throw away used SymlinPens after 30 days of use, even if a used SymlinPen still has medicine in it.
- **Do not** use SymlinPens (opened or unopened) after the expiration (EXP) date printed on the carton and the label.

General information about the safe and effective use of SymlinPens.

- If you drop your SymlinPen, you should prime it before you use it to make sure your SymlinPen works.
- **Do not** use your SymlinPen if any part looks broken or damaged.
- **Keep SYMLIN and all medicines out of the reach of children.**
- It is not known if SYMLIN is safe and effective in children.

If you are having problems using your SymlinPen, go to www.SYMLIN.com or call Information Support at 1-800-236-9933.

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

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Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Revised: March 2015 US-36084 1/20
Instructions for Use

**SymlinPen® (SIM-lınPen) 60**  
(pramlintide acetate)  
Pen-Injector

Read the Medication Guide and these Instructions for Use before you start using SYMLIN and each time you get a refill. There may be new information.

**Do not share your SymlinPen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.**

**Important:**

- Ask your healthcare provider about your dose of SYMLIN and how to inject SYMLIN the right way before you inject it for the first time.
- Use a new needle for each SYMLIN injection. **Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.**
- This SymlinPen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of this SymlinPen.
- Check SYMLIN before you use it. SYMLIN should be clear and colorless. **Do not** use SYMLIN if the liquid looks cloudy or colored or has lumps or particles in it.
- Your SymlinPen may look empty because SYMLIN is a clear and colorless liquid.
- Small bubbles will not hurt you or affect your dose of SYMLIN.
- **Do not** transfer SYMLIN from your SymlinPen into a syringe.
- **Do not inject your dose of SYMLIN if you:**
  - have low blood sugar (hypoglycemia)
  - do not plan to eat. **Do not** inject SYMLIN if you skip a meal. Wait until the next meal and take your usual dose of SYMLIN at that meal.
  - plan to eat a meal with less than 250 calories or 30 grams of carbohydrate
  - are sick and cannot eat your usual meal
  - are having surgery or a medical test where you cannot eat
- If you take more than your prescribed dose of SYMLIN, you may get nauseous or vomit, and 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 healthcare provider for guidance.

**Supplies you will need to give each injection of SYMLIN:**

- SymlinPen® 60 Pen-Injector (Pen) (See Figure A)
- a new SymlinPen compatible needle (See Figure B). Pen needles are not included. Use 29, 30, or 31 gauge disposable pen needles. Ask your healthcare provider which needle gauge and length is best for you.
- alcohol swab
- 1 sharps container for throwing away used SymlinPens and needles. See “Disposing of used SymlinPens and needles” at the end of these Instructions for Use.
Pen Parts

- **Pen Cap**: Covers Pen when not in use
- **Pen Label**: EXP date on back
- **Dial**: Turn to dial dose
- **Knob**: Pull out to load dose. Spin to check dose. Push in to inject dose
- **Cartridge**: Clear colorless liquid
- **Window**: Shows dialed dose
- **Dose Check**: Look for line, arrow, and number

(Figure A)

Attach Pen Needle (needles not included)

- Remove paper tab from outer needle cover.
- Push needle straight onto Pen.
- Screw needle on until tight.
- Remove outer needle cover and save for needle removal.
- Remove inner needle cover and throw away

(Figure B)

Preparing your SymlinPen:

- Wash your hands with soap and water.
- Check the SymlinPen label before each use to make sure you have the right SymlinPen.
- Check the expiration date (EXP) on the SymlinPen label (See Figure A). Do not use the SymlinPen past the expiration date printed on the label.
- Check the liquid in your SymlinPen to make sure you have enough SYMLIN left in your SymlinPen to load your correct dose.
  - The lines on the cartridge show about how much SYMLIN is left in your SymlinPen. When the top of the plunger is at the thickest line on the cartridge, your SymlinPen is almost empty (See Figure C).

Attaching a Needle:

**Step 1:**
- Pull the pen cap straight off the SymlinPen and wipe the rubber seal with an alcohol swab.

(Figure D)

**Step 2:**
- Get a new needle
- Peel off the paper tab and throw it away.

(Figure E)
Step 3:
• Push the capped needle straight onto the end of the SymlinPen and twist the needle clockwise until it is tight.

Step 4:
• Pull off the outer needle cover. Do not throw it away.
• Pull off the inner needle cover and throw it away.

New Pen Setup - Priming your SymlinPen:
Note:
• Steps 5 through 7 are only required if you are using your SymlinPen for the first time. Do not repeat Step 1 through 4 before each dose.
• If you have already primed your SymlinPen, go to Step 8 for instructions about giving your scheduled dose.

Step 5:
• Turn the dial to select 15 mcg.
  ○ You should see the number 15 in the window.

Step 6:
• Pull the knob straight out as far as it will go. You should hear a “clicking” sound while you are pulling the knob out.

Step 7:
• Hold your SymlinPen with the needle pointing up. Push the knob all the way in until it stops. You should hear a “clicking” sound while you are pushing the knob in.
  ○ A stream of liquid should be seen from the needle.
    • If you do not see a stream of liquid, repeat Step 6 and Step 7 (you may repeat up to 6 times).
    • If you still do not see a stream of liquid after 6 attempts, change the needle and repeat Step 6 and Step 7. If you still do not see a stream of liquid, call Information Support.

Selecting your routine dose:
Step 8:
• Turn the dial to select the correct dose you need to inject.

Step 9:
• Pull the knob straight out as far as it will go. You should hear a “clicking” sound while you are pulling the knob out.
Step 10:
• Turn the knob forward or backward until you see the correct dose you need to inject.
• Check that you see the line to make sure you have loaded your full dose. You should see a line, arrow, and the number of your dose.
  ◦ If you do not see a line, arrow, and the number of your dose, **do not** inject the dose. Point the needle away from you, push the knob all the way in until it stops, then repeat Step 8 to Step 10.
  ◦ Once the knob has been pulled out, the dial will not move and you cannot reset your dose. If correct dose was not selected, push in the knob to discard the dose and repeat the instructions. If the knob is pushed in all the way, and you cannot turn the dial, call Information Support.

Giving your SYMLIN injection:
• Inject your SYMLIN exactly as your doctor has shown you.
• Change (rotate) injection sites for SYMLIN. 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, let SYMLIN come to room temperature before you inject it.

Step 11:
• Choose your injection site.
• SYMLIN is injected under the skin (subcutaneously) of your stomach area (abdomen) or upper leg (thigh).
• Wipe the skin with an alcohol swab, and let the injection site dry before you inject your dose.

Step 12:
• Insert the needle into your skin.

Step 13:
• Put your thumb on the knob and push the knob all the way in until it stops. You should hear the “clicking” as you push and hold the knob in and **slowly count to 10** to give your full dose.

Step 14:
• Pull the needle out of your skin.
• If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab.
  **Do not** rub the area.
  ◦ A drop or 2 of liquid on the needle tip is normal. It will not affect your dose.
  ◦ If you see more than 2 drops, you may not have received your full dose. **Do not** inject another dose. Talk to your doctor for help.

Step 15:
• Carefully replace the outer needle cover by pushing straight onto the end of the SymlinPen.
Step 16:
- Unscrew the capped needle counterclockwise with the outer needle cover on it and throw it away.
- Do not store the SymlinPen with the needle attached or with the knob pulled out to prevent air bubbles.

Step 17:
- Replace the pen cap.

How should I store my SymlinPen?

Unused SymlinPens:
- Keep SYMLIN in the refrigerator between 36°F to 46°F (2°C to 8°C), until you are ready to use it.
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- Keep unopened SYMLIN out of the light.

Used SymlinPens:
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- Keep SYMLIN and all medicines out of the reach of children.
- It is not known if SYMLIN is safe and effective in children.

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