



Department of Vermont Health Access

Therapeutic Class Review Amylinomimetics

Overview/Summary

Pramlintide (Symlin[®]), the only amylin analog available in the United States, is Food and Drug Administration (FDA)-approved as an adjunct treatment with insulin in patients with type 1 or type 2 diabetes who have failed to achieve desired glucose control despite optimal insulin therapy.^{1,2} Pramlintide is currently only available as a branded product.³ Type 1 diabetes typically results in an absolute, or near total insulin deficiency, while type 2 diabetes is a complex disorder characterized by insulin deficiency, insulin resistance, inflammation and gut neurohormonal imbalances.⁴ Concentrations of amylin and insulin in plasma show parallel peak and trough concentrations during fasting conditions and with meal intake.^{1,4} The amylin response to meal intake is absent in type 1 diabetes, exaggerated in obesity and impaired or diminished in type 2 diabetes.⁵

Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic beta cells, that contributes to glucose control during the postprandial period.⁴ As an amylinomimetic, pramlintide slows gastric emptying without altering nutrient absorption, decreases postprandial glucagon secretion and regulates food intake by centrally-mediated modulation of appetite. By slowing gastric-emptying, pramlintide reduces the rate that food is released from the stomach to the small intestine, diminishing the initial postprandial elevation in plasma glucose.^{1,2,4} Pramlintide decreases postprandial glucagon secretion in patients with diabetes, which has been shown to be abnormally elevated and contribute to postprandial hyperglycemia.⁴ Compared to newer agents indicated for type 2 diabetes such as the incretin mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors, pramlintide does not stimulate pancreatic insulin release, which makes it a useful treatment option for patients with type 1 or type 2 diabetes.^{1,2,4}

Pramlintide is administered subcutaneously prior to meals. The recommended dose varies depending on whether the patient has type 1 or type 2 diabetes; however, a 50% reduction in insulin dose by is required for all patients initiating therapy with pramlintide, to reduce the risk of insulin-induced hypoglycemia. Though pramlintide itself does not cause hypoglycemia, the likelihood of experiencing hypoglycemia with this treatment is increased due to coadministration with insulin therapy. Nausea and vomiting are the most frequently reported adverse events associated with pramlintide treatment.^{1,2} Patients typically initiate treatment with a lower strength and are titrated to targeted doses every three to seven days when no clinically significant nausea is apparent.¹ Pramlintide monotherapy can result in a glycosylated hemoglobin (HbA_{1c}) decrease of 0.5% to 1%.⁶ In clinical studies, treatment with pramlintide prior to meals has been shown to significantly reduce HbA_{1c}, postprandial glucose (PPG) and body weight compared to placebo, when given in conjunction with insulin. In addition, a greater percentage of patients were able to achieve an HbA_{1c} <7% while being treated with pramlintide.⁷⁻²⁰

The current consensus guideline by the American College of Clinical Endocrinologists recommends the use of pramlintide in patients with persistent postprandial hyperglycemia despite insulin treatment.²¹ In addition, the American Diabetes Association does not include the amylinomimetics in the two tiers of preferred agents in their algorithm for glycemic control, due to the lower or equivalent overall glucose-lowering effectiveness compared to the first- and second-tier agents, and/or due to limited clinical data or relative expense.²²

Medications

Table 1. Medications Included Within Class Review

| Generic Name (Trade name) | Medication Class | Generic Availability |
|------------------------------------|------------------|----------------------|
| Pramlintide (Symlin [®]) | Amylinomimetic | - |

Indications

Table 2. Food and Drug Administration Approved Indications^{1,2}

| Generic Name | Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy | Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy |
|--------------|---|---|
| Pramlintide | ✓ * | ✓ † |

* Indicated for patients who have failed to achieve desired glucose control despite optimal insulin therapy.

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

Pramlintide has been used off-label in the management of weight loss, as well as for the treatment of diabetes for patients who are not receiving concurrent insulin therapy.²

Pharmacokinetics

Table 3. Pharmacokinetics^{1,2}

| Generic Name | Bioavailability (%) | Absorption (%) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (minutes) |
|--------------|---------------------|----------------|---------------------|---------------------|---------------------------|
| Pramlintide | 30 to 40 | 30 to 40 | 80 to 85 | Des-lys pramlintide | ~48 |

Clinical Trials

The safety and efficacy of pramlintide in patients with type 1 diabetes has been established in randomized, controlled studies when administered in addition to patient's existing insulin regimens.⁷⁻⁹ A recent meta-analysis of three studies reported that the average glycosylated hemoglobin (HbA_{1c}) reduction from baseline with pramlintide was -0.3% and a weight loss of -1.8 kg compared to patients treated with placebo ($P < 0.0009$ for both).¹⁰

In a 52-week, double-blind, placebo-controlled, multicenter study by Whitehouse et al, 480 patients with type 1 diabetes were randomized to receive pramlintide 30 µg or placebo four times daily in addition to their existing insulin regimens. At 52 weeks, pramlintide significantly reduced HbA_{1c} from baseline compared to placebo (-0.39 vs -0.12%; $P = 0.0071$). Pramlintide treatment was also associated with a significant weight loss compared to placebo (approximately -1.0 vs -0.2 kg; $P < 0.001$). There was a greater incidence of nausea (46.5 vs 21.9%; P value not reported) and anorexia (17.2 vs 2.1%; P value not reported) reported with pramlintide compared to placebo.⁷

A second 52-week study was completed by Ratner et al (N=651) in patients with type 1 diabetes who did not have glycemic control despite their existing insulin regimens. Patients received pramlintide 60 µg three times daily, pramlintide 60 µg four times daily or placebo. Compared to placebo, patients experienced a significant reduction in HbA_{1c} at 26 weeks when receiving pramlintide 60 µg three times daily (-0.41 vs -0.18%; $P = 0.012$) and pramlintide 60 µg four times daily (-0.39 vs -0.18%; $P = 0.013$) at 26 weeks. Treatment with pramlintide three or four times daily continued to maintain reductions in HbA_{1c} at 52 weeks compared to treatment with placebo ($P = 0.011$ and $P = 0.001$ for the three- and four times daily dosing, respectively).⁸

Edelman et al evaluated pramlintide compared to placebo in patients with type 1 diabetes with an HbA_{1c} of 7.5 to 9.0% at baseline despite receiving treatment with insulin. Patients randomized to pramlintide were titrated to 60 µg with meals or 30 µg if the higher dose was not tolerated. The primary endpoint, the number of hypoglycemic events, occurred more frequently in the pramlintide group (0.57 events per patient-year) compared to placebo (0.30 events per patient-year; $P<0.05$).⁹ In a post-hoc patient satisfaction survey, patients favored pramlintide for glucose control, meal flexibility, weight control and appetite control ($P<0.05$ for all). No difference between pramlintide and placebo was reported in regard to patients' ability to avoid hypoglycemia, and patients' wanting to continue treatment with pramlintide ($P=NS$).¹¹

Pramlintide was evaluated in 656 patients with type 2 diabetes who had an HbA_{1c} of $\geq 8\%$ at baseline despite treatment with insulin (alone or in combination with sulfonylureas and/or metformin). Patients were randomized to receive mealtime doses of pramlintide (90 µg twice-daily, or 120 µg twice-daily). The change in HbA_{1c} at 26 weeks, the primary endpoint, was significantly reduced with pramlintide 120 µg compared to placebo (-0.68%; $P<0.05$). Notably, no difference in HbA_{1c} reduction was observed with pramlintide 90µg dose compared to placebo (-0.54%; P value not reported). Only the 120 µg dose maintained a significant improvement in HbA_{1c} throughout 52 weeks (-0.62%; $P<0.05$ compared to placebo). More patients treated with 90 µg or 120 µg of pramlintide achieved an HbA_{1c} $<7\%$ by the end of the study compared to placebo (9.4, and 12.2% vs 4.1%, respectively; P value not reported).¹²

In a large 52-week study by Ratner et al (N=538), a significantly greater reduction in HbA_{1c} was observed in patients receiving pramlintide 75 µg three times daily compared to placebo (-0.9%; $P=0.0004$) after 13 weeks. With the 75 µg dose, HbA_{1c} was significantly reduced for the majority of the study periods with the exception of week 52. Significantly greater reductions in HbA_{1c} were noted with 150 µg pramlintide three times daily compared to placebo (-1.0%; $P=0.0002$). The reduction in HbA_{1c} remained significantly lower throughout the study (-0.6%; $P=0.0068$). There was no significant reduction in HbA_{1c} for patients who received the 30 µg pramlintide dose. In all pramlintide treatment groups, there were significant reductions in body weight throughout the study when compared to placebo ($P<0.05$). In addition the proportions of patients achieving HbA_{1c} $<7\%$ were 12.7% in the 30 µg pramlintide group, 13.4% in the 75 µg pramlintide group, 19.2% in the 150 µg pramlintide group, and 11.1% in the placebo group (P values not reported).¹³

Riddle et al evaluated the effect of adding pramlintide 60 µg two or three times daily (titrated to 120 µg) to insulin glargine in patients with type 2 diabetes. At baseline, patients were required to have a baseline HbA_{1c} of $>7\%$ to $\leq 10.5\%$, body mass index (BMI) of 25 to 45 kg/m² who were not taking mealtime insulin. At 16 weeks, there was a greater reduction in HbA_{1c} in patients receiving pramlintide compared to placebo (-0.70 vs -0.36%; $P<0.05$). More pramlintide-treated patients also met the composite endpoint (HbA_{1c} $\leq 7\%$ or an HbA_{1c} reduction from baseline $\geq 0.5\%$, mean daily postprandial glucose increments ≤ 40 mg/dl, no weight gain, and no severe hypoglycemia compared to placebo (25 vs 7%; $P<0.001$).¹⁴

An open-label study by Riddle et al compared pramlintide 120 µg to rapid acting insulin analogs in patients with type 2 diabetes who had a baseline HbA_{1c} of $>7\%$ to $\leq 10\%$ with or without oral antidiabetic agents. The primary endpoint was the proportion of patients achieving the composite endpoint of HbA_{1c} $\leq 7.0\%$, no weight gain from baseline, and no severe hypoglycemia at 24 weeks. A significantly greater proportion of patients achieved the composite endpoint at week-24 in the pramlintide treatment group compared to patients receiving treatment with a rapid acting insulin analog (30 vs 11%; $P=0.018$).¹⁵ A second open-label study lasting 12 months (data analysis reported at month-six) reported that patients who received treatment with pramlintide 120 µg three time daily with meals (in addition to their existing insulin regimen) had significant improvements in HbA_{1c} after three and six months of treatment (-0.66 and -.56%; $P<0.05$) compared to placebo. In addition, of patients with an HbA_{1c} of $>7\%$ at baseline, 28.1% were able to lower their HbA_{1c} to $<7\%$ with six months of pramlintide treatment (P value not reported). Significant reductions in weight were also noted at three and six months (-2.3 kg and -2.8 kg, respectively; $P<0.05$).¹⁶

Post-hoc analyses of these studies lasted up to 52 weeks and generally showed sustained improvements in HbA_{1c}, weight loss, and the proportion of patients who were able to achieve an HbA_{1c} <7%.¹⁷⁻¹⁹ In addition, a meta-analysis by Singh-Franco et al (N=1,616) found that that treatment with pramlintide (120 to 150 µg with meals) was associated with a -0.33% reduction in HbA_{1c} ($P=0.0004$), and these patients were more likely to achieve an HbA_{1c} ≤7% compared to placebo (odds ratio [OR], 1.52; 95% confidence interval [CI], 0.83 to 2.78; $P=0.18$), although this difference was not significant.²⁰

Table 4. Clinical Trials

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|--|--|--------------------------------|---|---|
| Ratner et al ¹⁰ Pramlintide (in addition to patients' existing insulin regimens) vs placebo (in addition to patients' existing insulin regimens) | MA Pooled analysis from 3 trials of patients with Type 1 diabetes and an HbA _{1c} of 7.0% to 8.5% | N=477 26 weeks | Primary: Change from baseline in HbA _{1c} , body weight and adverse events (hypoglycemia) Secondary: Not reported | Primary: Significant reductions in HbA _{1c} (-0.3%) and body weight (-1.8 kg) from baseline to end point were noted in the pramlintide treatment group ($P<0.0009$ for both). The risk of severe hypoglycemia was 1.40 in the pramlintide group compared to 1.86 in the placebo group. Secondary: Not reported |
| Whitehouse et al ⁷ Pramlintide 30 µg SC four times daily (in addition to their existing insulin regimens); after 20 weeks, patients receiving pramlintide who did not achieve an HbA _{1c} reduction of ≥1% were randomized again to receive 30 µg or 60 µg four times daily vs placebo (in addition to patients' existing insulin regimens) | DB, PC, RCT Type 1 diabetic patients; mean baseline HbA _{1c} was 8.9% in the placebo treatment arm and 8.7% in the pramlintide treatment arm | N=480 52 weeks | Primary: Effect on HbA _{1c} from baseline to week 52 Secondary: Effect on HbA _{1c} and body weight from baseline to weeks 13, 26, and 52 | Primary: Significantly greater reductions in HbA _{1c} were observed with pramlintide (-0.39%) vs placebo (-0.12%; $P=0.0071$) at 52 weeks. Secondary: A significantly greater reduction in HbA _{1c} with pramlintide was demonstrated at week 13 (-0.67 vs -0.16%; $P<0.0001$), week 26 (-0.58 vs -0.18%; $P=0.0001$), and week 52 (-0.39 vs -0.12%; $P=0.0071$). The pramlintide group had sustained reduction in body weight that was significantly different from placebo ($P<0.001$) from week 13 onward. (Note: weight reduction was reported in graph format and precise weight reduction values were not reported.) The most commonly reported side effects with pramlintide were nausea (46.5 vs 21.9% in placebo; no P values reported) and anorexia (17.7 vs 2.1% in placebo; no P values reported). Withdrawal due to adverse event(s) occurred in 31 (12.8%) of pramlintide patients and 19 (8.0%) placebo patients. |
| Ratner et al ⁸ Pramlintide 60 µg SC three | DB, PC, RCT Type 1 diabetic | N=651 52 weeks | Primary: Effect on HbA _{1c} from baseline to | Primary: Significantly greater reductions in HbA _{1c} were reported with 60 µg pramlintide three times daily vs placebo (-0.41 vs -0.18%; $P=0.012$) |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|--------------------------------|--|---|
| <p>times daily, 60 µg SC four times daily, or 90 µg SC three times daily (in addition to patients' existing insulin regimens)</p> <p>vs</p> <p>placebo (in addition to patients' existing insulin regimens)</p> | <p>patients, baseline HbA_{1c} was 9.0% in the placebo treatment arm and 8.9% in the pramlintide treatment arms</p> | | <p>week 26</p> <p>Secondary: Effect on HbA_{1c} from baseline to weeks 26 and 52 and percentage of patients achieving HbA_{1c}<7%</p> | <p>after 26 weeks.</p> <p>Significantly greater reductions in HbA_{1c} were noted with 60 µg pramlintide four times daily vs placebo (-0.39 vs -0.18%; <i>P</i>=0.013) after 26 weeks.</p> <p>Secondary: Significantly greater reductions in HbA_{1c} were observed with 60 µg pramlintide three times daily vs placebo (-0.29 vs -0.04%; <i>P</i>=0.011) after 52 weeks.</p> <p>Significantly greater reductions in HbA_{1c} were reported with 60 µg pramlintide four times daily vs placebo (-0.34 vs -0.04%; <i>P</i>=0.001) after 52 weeks.</p> <p>A threefold greater proportion of pramlintide-treated subjects reached HbA_{1c} <7% compared to placebo. (Note: results were reported in graph format and precise values were not available and <i>P</i> value not reported).</p> <p>The 90 µg pramlintide study arm was excluded from the analysis when results from a separate study indicated this dose had an adverse tolerability profile. Subjects assigned to this study arm continued to receive the 90 µg dose to preserve the study design.</p> <p>During the first four weeks of therapy, pramlintide-treated subjects had a four-fold increase in severe hypoglycemic event rate compared to placebo-treated subjects (3.78 vs 0.87 events/year; <i>P</i> value not reported).</p> <p>The most commonly reported side effect with pramlintide was nausea. Withdrawal due to adverse event(s) occurred in 38 (22.1%) of the 90 µg pramlintide three times daily patients, 22 (13.7%) of the 60 µg pramlintide four times daily patients, 32 (19.5%) of the 60 µg pramlintide three times daily and 6 (3.9%) placebo patients.</p> |
| Edelman et al ⁹ | DB, MC, PC, R | N=296 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|--|--|
| <p>Pramlintide 15 µg SC with meals, doses were titrated to 60 µg SC with meals; patients unable to achieve the 60 µg dose received 30 µg with meals (in addition to their existing insulin regimens)</p> <p>vs</p> <p>placebo (in addition to patients' existing insulin regimens)</p> | <p>Type 1 diabetic patients <18 years of age with an HbA_{1c} of 7.5% to 9.0%, intensely or continuously treated with insulin for the past year, and with no severe hypoglycemic event over the preceding 6 months</p> | <p>29 weeks</p> | <p>Safety</p> <p>Secondary: Change from baseline in HbA_{1c}, postprandial glucose concentrations, and body weight</p> | <p>Both treatment groups experienced a similar number of nonsevere hypoglycemic events. The event rate per patient years was 0.57 in the treatment group compared to 0.30 in the placebo group (<i>P</i><0.05).</p> <p>Reduced appetite, vomiting, and sinusitis occurred twice as frequently in the pramlintide group compared to the placebo group (<i>P</i><0.01).</p> <p>Secondary: Between weeks 0 and 29 the reduction in body weight was significant in the pramlintide-treated patients compared to placebo (-1.3 kg vs 1.2 kg; <i>P</i><0.0001).</p> <p>Among the pramlintide-treated patients, a greater number were able to achieve a PPG concentration of 9.9 mmol/L at breakfast (68 vs 51%), lunch (71 vs 61%), and dinner (70 vs 58%; <i>P</i><0.0001 for each meal).</p> <p>At 29 weeks the total insulin dose in the pramlintide group decreased by 12% compared to an increase of 1% in the placebo group.</p> |
| <p>Marrero et al¹¹</p> <p>Pramlintide 15 µg SC with meals, doses were titrated to 60 µg SC with meals; patients unable to achieve the 60 µg dose received the 30 µg with meals (in addition to their existing insulin regimens)</p> <p>vs</p> <p>placebo (in addition to their existing insulin regimen)</p> | <p>Post hoc analysis</p> <p>Type 1 diabetic patients who completed a 29-week double blind, noninferiority pramlintide dose-titration trial, who were intensely or continuously treated with insulin</p> | <p>N=266</p> <p>Surveys completed at end of 29-week trial</p> | <p>Primary: Patient response to satisfaction questionnaire</p> <p>Secondary: Not reported</p> | <p>Primary: For the following topics the survey ratings favored the pramlintide treatment: Study medication (1) "made my blood glucose control more even or predictable," (2) "provided me with more flexibility in what I can eat," (3) "made it easier to control my weight," and (4) "made it easier to control my appetite" (<i>P</i><0.05 for all).</p> <p>There was no significant difference between treatment groups in the response to the following statements: Study medication (1) "made it easier to avoid low blood sugar reactions (hypoglycemia)," and (2) "I would like to continue taking the study medication" (<i>P</i>=NS for both).</p> <p>Secondary: Not reported</p> |

| Type 2 Diabetes | | | | |
|---|---|-------------------------------|---|---|
| <p>Hollander et al¹²</p> <p>Pramlintide 60 µg SC twice-daily (data not reported), Pramlintide 90 µg SC twice-daily, pramlintide 120 µg SC twice-daily (in addition to patients' existing insulin regimens)</p> <p>vs</p> <p>placebo (in addition to patients' existing insulin regimens)</p> | <p>DB, MC, PC, PG, RCT</p> <p>Patients >18 years of age with type 2 diabetes requiring insulin treatment for ≥ 6 months prior to study initiation with an HbA_{1c} ≥8% without hypoglycemia in the 2 weeks preceding the study</p> | <p>N=656</p> <p>12 months</p> | <p>Primary: Change from baseline in HbA_{1c} at week-26</p> <p>Secondary: Absolute changes in HbA_{1c} at other time points, changes in body weight from baseline to weeks 26 and 52, and the percentage of patients who achieved American Diabetes Association recommended glucose control targets of HbA_{1c} <7 or <8%, respectively</p> | <p>Primary: After 26 weeks, patients receiving treatment with pramlintide 120 µg experienced a significant reduction in HbA_{1c} compared to placebo (-0.68; <i>P</i><0.05), but no difference in HbA_{1c} was reported between the 90 µg group and placebo (-0.54%; <i>P</i> value not reported).</p> <p>Secondary: After 52 weeks, patients receiving treatment with pramlintide 120 µg experienced a significant reduction in HbA_{1c} compared to placebo (-0.62; <i>P</i><0.05), but there was no difference in HbA_{1c} associated with the 90 µg group (-0.35%; <i>P</i> value not reported).</p> <p>More patients treated with 90 µg or 120 µg of pramlintide achieved an HbA_{1c} of <7% compared to placebo 9.4 and 12.2 vs 4.1%, respectively; <i>P</i> value not reported). Similarly, 42.4%, 45.7% and 27.6% of patients receiving pramlintide 90 µg, 120 µg and placebo, respectively, achieved an HbA_{1c} of less than 8% (<i>P</i> value not reported).</p> |
| <p>Ratner et al¹³</p> <p>Pramlintide 30 SC µg three times daily, pramlintide 75 µg SC three times daily, or pramlintide 150 SC µg three times daily (in addition to patients' existing insulin regimens)</p> <p>vs</p> | <p>DB, PC, RCT</p> <p>Type 2 diabetic patients; baseline HbA_{1c} was 9.2% for placebo, 9.0% for 30 µg pramlintide, 9.3% for 75 µg pramlintide, and</p> | <p>N=538</p> <p>52 weeks</p> | <p>Primary: Change in HbA_{1c} and body weight from baseline to weeks 13, 26 and 52</p> <p>Secondary: Percentage of patients achieving</p> | <p>Primary: Significantly greater reductions in HbA_{1c} were observed with 75 µg pramlintide three times daily vs placebo (-0.9%; <i>P</i>=0.0004) after 13 weeks. HbA_{1c} was significantly lower for the majority of the study periods with the exception of week 52.</p> <p>Significantly greater reductions in HbA_{1c} were noted with 150 µg pramlintide three times daily vs placebo (-1.0%; <i>P</i>=0.0002). After 13 weeks, HbA_{1c} remained significantly lower for the rest of the study (-0.6%; <i>P</i>=0.0068).</p> |

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| <p>placebo (in addition to patients' existing insulin regimens)</p> | <p>9.2% for 150 µg pramlintide</p> | | <p>HbA_{1c}<7% or 8% and relative change of insulin use</p> | <p>The reduction in HbA_{1c} in the 30 µg pramlintide three times daily group was not significant at any point during the study when compared to placebo.</p> <p>Significant (<i>P</i><0.05) reductions in body weight were noted for all pramlintide groups throughout the study when compared to placebo.</p> <p>Secondary: The proportions of patients achieving HbA_{1c}<7% were 12.7% in the 30 µg pramlintide group, 13.4% in the 75 µg pramlintide group, 19.2% in the 150 µg pramlintide group and 11.1% in the placebo group (<i>P</i> values not reported).</p> <p>The proportions of patients achieving HbA_{1c}<8% were 45.1% in the 30 µg pramlintide group, 46.4% in the 75 µg pramlintide group, 54.0% in the 150 µg pramlintide group (<i>P</i> value not reported) and 37.6% in the placebo group (<i>P</i> value not reported).</p> <p>Insulin use increased in all study groups: for the pramlintide groups insulin use increased by 7.9 to 10.9%, while insulin use increased 15.4% in the placebo group (<i>P</i> values not reported).</p> <p>The most commonly reported side effect with pramlintide was nausea.</p> |
| <p>Riddle et al¹⁴</p> <p>Pramlintide 60 µg SC at meals (two or three times daily) titrate to 120 µg SC (in addition to patients' existing basal insulin regimen titrated to fasting glucose of ≥70 to <100 mg/dl)</p> <p>vs</p> <p>placebo (in addition to patients' existing basal</p> | <p>DB, MC, PC, RCT</p> <p>Patients 25 to 75 years of age with type 2 diabetes who were not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with or without oral antidiabetic</p> | <p>N=212</p> <p>16 weeks</p> | <p>Primary: Change from baseline HbA_{1c} at week-16, proportion of patients meeting all of the following prespecified criteria at week 16: HbA_{1c} ≤7% or an HbA_{1c} reduction from baseline ≥0.5%, mean</p> | <p>Primary: Patients treated with pramlintide experienced greater reductions in HbA_{1c} at week 16 compared to patients receiving placebo (-0.70 vs -0.36%; <i>P</i><0.05).</p> <p>At week 16, significantly more pramlintide-treated patients achieved the composite end point compared to placebo-treated patients (25 vs 7%; <i>P</i><0.001).</p> <p>Secondary: The percentage of patients who achieved an HbA_{1c} of ≤7% or had a reduction in HbA_{1c} of ≥0.5% was not significantly different between pramlintide and placebo (54 vs 45%; <i>P</i> value not reported).</p> <p>Significantly more pramlintide treated patients achieved mean PPG</p> |

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|--|--|------------------------------|--|---|
| <p>insulin regimen titrated to fasting glucose of ≥ 70 to < 100 mg/dl)</p> | <p>therapy, and an HbA_{1c} of $> 7\%$ to 10.5% and BMI of 25 to 45 kg/m²</p> | | <p>daily PPG increments ≤ 40 mg/dl, no weight gain and no severe hypoglycemia.</p> <p>Secondary: components of the composite end point, the proportion of patients achieving HbA_{1c} ≤ 7.0 or $\leq 6.5\%$ and changes from baseline to each time point in HbA_{1c}, seven-point glucose profiles, PPG increments, FPG, weight, and insulin glargine dose.</p> | <p>increments ≤ 40 mg/dl ($P < 0.0001$) and did not experience weight gain compared to ($P < 0.0001$).</p> <p>Compared with placebo, more pramlintide treated patients achieved both HbA_{1c} and PPG components ($P < 0.005$), more reached the HbA_{1c} goal without weight gain ($P < 0.0001$), and more had well controlled PPG without weight gain ($P < 0.0001$).</p> <p>The proportion of patients achieving an HbA_{1c} ≤ 7.0 or $\leq 6.5\%$ was 23% and 11% with pramlintide and 13 and 4% with placebo, respectively (P value not reported).</p> <p>The insulin glargine dosage increased steadily throughout the study. The mean increase in insulin glargine dosage at week 16 was 11.7 ± 1.9 units and 13.1 ± 1.6 units, for pramlintide- and placebo-treated patients respectively (P value not reported).</p> <p>The average change from baseline of in FPG was -28.3 mg/dl and -12.0 mg/dl at week 16 for patients treated with pramlintide and placebo, respectively (P value not reported).</p> <p>At week 16, PPG was significantly decreased from baseline in pramlintide- treated patients compared to placebo (-24.4 vs -0.4; $P < 0.0001$).</p> <p>By week 16, pramlintide treatment was associated with weight loss, compared to weight gain observed in the placebo group (-1.6 kg vs 0.7; $P < 0.0001$) By the end of treatment, 68% of pramlintide treated patients had lost weight compared with approximately 35% of placebo-treated patients ($P < 0.0001$).</p> |
| <p>Riddle et al¹⁵</p> <p>Pramlintide 120 SC μg prior to major meals plus basal insulin titrated twice-weekly to achieve a FPG of ≥ 70 to < 100 mg/dl</p> | <p>MC, OL, RCT</p> <p>Patients aged 18 to 75 years of age with a diagnosis of type 2 diabetes, and an</p> | <p>N=113</p> <p>24 weeks</p> | <p>Primary: Proportion of patients achieving the following prespecified criteria at week 24: HbA_{1c} $\leq 7.0\%$,</p> | <p>Primary: After 24 weeks of treatment, a higher percentage of patients treated with pramlintide achieved the composite endpoint compared to patients receiving rapid acting insulin analogs (30 vs 11%; $P = 0.018$).</p> <p>Secondary: The mean reduction in HbA_{1c} from baseline was -1.1% for pramlintide and -1.3% for rapid acting insulin analogs ($P = 0.46$).</p> |

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| <p>vs</p> <p>rapid acting insulin analogs SC (lispro, aspart, glulisine) plus basal insulin titrated twice-weekly to achieve a FPG of ≥ 70 to < 100 mg/dl</p> <p>Rapid acting insulin analogs were started with five units before each meal. Mealtime insulin doses were adjusted with investigator guidance by one to two units every three to seven days with the aim of maintaining glucose concentrations at ≥ 70 and < 100 mg/dl before the subsequent meal or (for the dinnertime dose) at bedtime.</p> | <p>HbA_{1c} $> 7\%$ to $\leq 10\%$ who were pramlintide naive and either insulin naive or had used < 50 units/day of basal insulin for < 6 months with or without other OADs</p> | | <p>no weight gain from baseline and no severe hypoglycemia.</p> <p>Secondary: Changes from baseline in HbA_{1c}, proportion of patients with an HbA_{1c} $\leq 6.5\%$, weight, waist circumference, hypoglycemia, nausea and basal insulin dose</p> | <p>There was no difference in the proportion of patients achieving an HbA_{1c} of $\leq 6.5\%$ at 24 weeks between treatment with pramlintide and the rapid acting insulin analogs (29 vs 34%, respectively; $P=0.68$).</p> <p>The change from baseline in FPG was -31 mg/dl with pramlintide compared to -34 mg/dl with the rapid acting insulin analogs ($P=0.65$). In addition a FPG concentration < 100 mg/dl was achieved at week 24 by 30% of pramlintide-treated and 27% of patients treated with a rapid acting insulin analog ($P=0.83$).</p> <p>At 24 weeks, there was no change in weight for patients treated with pramlintide compared to the 4.7 kg weight gain reported in patients treated with rapid acting insulin analogs ($P<0.0001$).</p> <p>The change in waist circumference was greater with pramlintide treatment compared to the rapid acting insulin analogs (-0.6 vs 2.2 cm,; $P=0.016$).</p> <p>There were no episodes of severe hypoglycemia reported, but mild or moderate hypoglycemia occurred more frequently than nausea in both treatment groups and was observed in more patients treated with the rapid acting insulin analogs (82%) compared to pramlintide (55%; P value not reported).</p> <p>At 24 weeks, the average daily dose of insulin glargine was 57 units in the treatment group using rapid acting insulin analogs compared to 52 units in patients treated with pramlintide (P value not reported).</p> |
| <p>Karl et al¹⁶</p> <p>Pramlintide 120 μg SC immediately prior to major meals (two or three times daily depending on eating habits and in addition to patients' existing insulin regimens)</p> | <p>MC, OL</p> <p>Men and women > 18 years of age with type 2 diabetes who were currently taking insulin therapy with or without oral</p> | <p>N=166</p> <p>12 months (all results reported at 6 months)</p> | <p>Primary: Change in HbA_{1c}, fasting and postprandial glucose, body weight and insulin doses from baseline, safety</p> | <p>Primary: Pramlintide resulted in significant HbA_{1c} reductions at three and six months (-0.66 and -0.56%; $P<0.05$).</p> <p>At some point during the initial six months after initiating therapy, 28.1% of the patients who originally had an HbA_{1c} $> 7\%$ achieved an HbA_{1c} $< 7\%$.</p> <p>Compared to baseline, both FPG and PPG concentrations were significantly reduced ($P<0.05$).</p> |

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| | antidiabetics and an HbA _{1c} >7% and <11% | | Secondary: Not reported | <p>Significant reductions in weight were noted at six and six months (-2.3 kg and -2.8 kg; <i>P</i><0.05).</p> <p>At both three and six months, mealtime and total insulin doses remained significantly lower compared to baseline (<i>P</i><0.05).</p> <p>Nausea (29.5%), vomiting (7.2%), and diarrhea (5.4%) were the most common adverse events reported.</p> <p>There was an overall incidence of 12% for hypoglycemia, with two patients experiencing severe hypoglycemia during the 6-month treatment period.</p> <p>Secondary: Not reported</p> |
| <p>Hollander et al¹⁷</p> <p>Pramlintide 120 µg SC twice daily (in addition to patients' existing insulin regimen)</p> <p>vs</p> <p>placebo (in addition to patients' existing insulin regimen)</p> | <p>Post hoc analysis</p> <p>Type 2 diabetic patients who completed a 26-week or 52-week double-blind, randomized, placebo-controlled trial; baseline HbA_{1c} was 7.0% to 8.5%</p> | <p>N=186</p> <p>26 weeks and 52 weeks</p> | <p>Primary: Change from baseline to week 26 in HbA_{1c}, body weight, insulin use, and the rate of severe hypoglycemia</p> <p>Secondary: Not reported</p> | <p>Primary: The proportion of patients who achieved an HbA_{1c}<7.0% at week 26 was 14% in the pramlintide-treated group compared to 2% in the placebo group (<i>P</i> value was not reported).</p> <p>At week 26, the difference in HbA_{1c} decrease in the pramlintide group compared to the placebo group was -0.43% (<i>P</i><0.0009).</p> <p>At week 26, the difference in weight loss in the pramlintide group compared to the placebo group was -2.0 kg (<i>P</i><0.0003).</p> <p>No significant change in insulin dose or number of daily insulin injections was noted between the treatment groups.</p> <p>At week 26, no significant difference was noted between the treatment groups in rates of severe hypoglycemia as reported in event rate per subject-year (0.13 for pramlintide to 0.19 for placebo).</p> <p>No serious adverse events were reported in either treatment group.</p> <p>Secondary: Not reported</p> |

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| <p>Maggs et al¹⁸</p> <p>Pramlintide 120 µg SC twice daily, or pramlintide 150 SC µg three times daily (in addition to patients' existing insulin regimen)</p> <p>vs</p> <p>placebo (in addition to patients' existing insulin regimen)</p> | <p>Post hoc analysis</p> <p>Type 2 diabetic patients who completed a 52-week double-blind, randomized, placebo-controlled trial</p> | <p>N=410</p> <p>52 weeks</p> | <p>Primary: Change from baseline to week 52 in HbA_{1c} and weight, safety</p> <p>Secondary: Not reported</p> | <p>Primary: A significantly greater reduction from baseline in HbA_{1c} was seen in the pramlintide group compared to placebo ($P<0.0001$). This result was seen across different ethnic groups: African Americans (-0.7%), Caucasians (-0.5%), and Hispanics (-0.3%).</p> <p>A significant reduction from baseline in body weight was seen in the pramlintide group compared to the placebo group at week 52 (-2.6 kg; $P<0.0001$).</p> <p>Nausea was more common in the pramlintide group and hypoglycemia was reported to a similar extent between the two treatment groups.</p> <p>Secondary: Not reported</p> |
| <p>Hollander et al¹⁹</p> <p>Pramlintide 120 µg SC twice daily (in addition to patients' existing insulin regimen)</p> <p>vs</p> <p>placebo (in addition to patients' existing insulin regimen)</p> | <p>Post hoc analysis</p> <p>Type 2 diabetic patients who completed a 26-week or 52-week double-blind, randomized, placebo-controlled trial</p> | <p>N=498</p> <p>26 weeks and 52 weeks</p> | <p>Primary: Body weight, total daily insulin use, change in HbA_{1c} from baseline</p> <p>Secondary: Not reported</p> | <p>Primary: From baseline to week 26, pramlintide-treated patients achieved a significantly greater reduction in HbA_{1c} compared with placebo-treated patients (-0.59 vs -0.18%; $P<0.0001$).</p> <p>No significant difference in total daily insulin requirements was reported between the two treatment groups.</p> <p>From baseline to week 26, pramlintide-treated patients achieved a significant weight reduction compared with placebo-treated patients (-1.5 vs 0.3 kg; $P<0.0001$).</p> <p>Secondary: Not reported</p> |
| <p>Singh-Franco et al²⁰</p> <p>Pramlintide 120 to 150 µg SC two or three times daily before major meals</p> | <p>MA (eight studies)</p> | <p>N=1,616</p> <p>6 to 52 weeks</p> | <p>Primary: The change in HbA_{1c} from baseline to study endpoint</p> <p>Secondary: Likelihood of achieving an</p> | <p>Primary: The endpoint data combined from all studies showed that compared to placebo, pramlintide was associated with a reduction in HbA_{1c} of -0.33% ($P=0.0004$).</p> <p>Secondary: Patients treated with pramlintide for 52 weeks were 1.52 (95% CI, 0.83 to 2.78) times more likely to achieve an HbA_{1c} of $\leq 7\%$ compared to placebo; however, this difference was not significant ($P=0.18$)</p> |

| | | | | |
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| | | | <p>HbA_{1c} of ≤7%, change in FPG, PPG and weight</p> | <p>Treatment with pramlintide was associated with a reduction from baseline in FPG of -6.34 mg/dl (95% CI, -24.96 to 12.28) over 24 weeks of treatment, but the difference was not significant (<i>P</i>=0.50).</p> <p>Treatment with pramlintide was associated with a reduction from baseline in PPG of -7.20 mg/dl (95% CI, -40.12 to 25.75) over 24 weeks of treatment, but the difference was not significant (<i>P</i>=0.67).</p> <p>Pramlintide treatment was associated with a significant change in body weight in patients with type 2 diabetes compared to placebo (-2.21 kg; <i>P</i><0.000001).</p> |
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*Agent not available in the United States

†Trial is registered on ClinicalTrials.gov

Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, R=randomized, RCT=randomized controlled trial,

Miscellaneous abbreviations: BMI=body mass index, FPG=fasting plasma glucose, HbA_{1c}= glycosylated hemoglobin, OAD=oral antidiabetic agent, PPG=postprandial glucose

Special Populations[#]**Table 5. Special Populations^{1,2}**

| Generic Name | Population and Precaution | | | | |
|--------------|---|--------------------------------|-------------------------------------|-----------------------|----------------------------|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Pramlintide | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established. | No dosage adjustment required. | Not studied in hepatic dysfunction. | C | Unknown |

Adverse Drug Events

The most common adverse events associated with pramlintide are typically gastrointestinal in nature. The adverse events occurring in $\geq 5\%$ of patients and more frequently with pramlintide compared to placebo are listed in Table 5. In postmarketing studies of pramlintide, the occurrence of injection site reactions has been reported. Patients may experience redness, swelling or itching at the site of injection. These reactions generally resolve within a few days to weeks. In some instances, these reactions may be related to factors other than pramlintide, such as irritants in a skin-cleansing agent or improper injection technique.^{1,2}

Table 6. Adverse Drug Events[#]

| Adverse Event | Pramlintide (%) |
|-------------------------------|-----------------|
| Central Nervous System | |
| Dizziness | 5 to 6 |
| Fatigue | 7 |
| Headache | 13 |
| Gastrointestinal | |
| Abdominal pain | 8 |
| Anorexia | 9 to 17 |
| Nausea | 28 to 48 |
| Vomiting | 8 to 11 |
| Respiratory | |
| Coughing | 6 |
| Pharyngitis | 5 |
| Other | |
| Allergic reaction | 6 |
| Arthralgia | 7 |
| Inflicted injury | 14 |

Contraindications / Precautions

Pramlintide is contraindicated in any patient with a known hypersensitivity to pramlintide or any of its components. Pramlintide is also contraindicated in patients with gastroparesis due to additive effects on slowed gastric motility. This may further delay the release of food from the stomach, potentially causing severe postprandial hypoglycemia. In addition, pramlintide should not be used in patients with hypoglycemic unawareness.^{1,2} Proper patient selection is critical to safe and effective use of pramlintide. Do not consider patients meeting any of the following criteria for pramlintide therapy: poor compliance with current insulin regimen, poor compliance with prescribed self-blood glucose monitoring, an HbA_{1c} greater than 9%, recurrent severe hypoglycemia requiring assistance during the past six months, presence of hypoglycemia unawareness, confirmed diagnosis of gastroparesis, require the use of drugs that stimulate GI motility or pediatric patients.^{1,2}

Pramlintide alone does not cause hypoglycemia. However, pramlintide is indicated to be coadministered with insulin therapy, and in this setting, pramlintide increases the risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Pramlintide carries a black box warning which highlights the risks of hypoglycemia following administration of pramlintide and is outlined below.

The symptoms of hypoglycemia may include hunger, headache, sweating, tremor, irritability or difficulty concentrating. Rapid reductions in blood glucose concentrations may induce such symptoms regardless of glucose values. More severe symptoms of hypoglycemia include loss of consciousness, coma or seizure. The early warning symptoms of hypoglycemia are highly variable and may be different under certain conditions, such as duration of diabetes, diabetic nerve disease, the use of certain medications including (e.g., beta-blockers, clonidine, guanethidine, or reserpine) or intensified diabetes control. The addition of any antihyperglycemic agent such as pramlintide to an existing regimen of one or more antihyperglycemic agents (e.g., insulin or sulfonylurea), or other agents potentially causing hypoglycemia may necessitate further insulin dose adjustments and particularly close monitoring of blood glucose.^{1,2}

Patients may experience redness, swelling, or itching at the site of injection. These minor reactions usually resolve within a few days to a few weeks. In some instances, these reactions may be related to factors other than pramlintide, such as irritants in a skin-cleansing agent or improper injection technique.^{1,2}

Black Box Warning for Symlin® (pramlintide)^{1,2}

WARNING

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

Drug Interactions

No specific serious drug interactions with pramlintide have been reported by the manufacturers or documented in the literature.^{1,2,4} Due to its slowing effect on gastric emptying pramlintide may delay the absorption of oral medications administered concomitantly. The manufacturer recommends that caution be used for oral medications that require rapid gastrointestinal absorption or require threshold concentrations for efficacy (e.g., oral contraceptives and antibiotics). The manufacturer also recommends that pramlintide should not be considered for patients concomitantly taking agents that alter gastrointestinal motility as it may result in a synergistic effect (e.g., anticholinergics).²

Dosage and Administration

Pramlintide should be administered subcutaneously into the thigh or abdomen immediately prior to each major meal. The injection site selected should also be separate from the site chosen for any concomitant insulin injection.^{1,2} Pramlintide should always be administered as a separate injection and should not be mixed with any type of insulin.

Pramlintide has the potential to delay the absorption of coadministered oral medications. When the rapid onset of an orally coadministered agent is a critical determinant of effectiveness (e.g., analgesics), administer the agent at least one hour prior to or two hours after pramlintide injection.^{1,2}

When initiating therapy with pramlintide, an initial insulin dose reduction of 50% is required in all patients (both type 2 and type 1 diabetes) taking rapid-acting or short-acting insulins (including fixed-mixed insulins) in order to reduce the risk of insulin-induced hypoglycemia.^{1,2}

In patients with type 1 diabetes, the dose of pramlintide should be titrated to the next increment when no clinically significant nausea has occurred for at least three days. If significant nausea persists at the 45 or 60 µg dose level, the pramlintide dose should be decreased to 30 µg. If the 30 µg dose is not tolerated, discontinuation of pramlintide therapy should be considered.^{1,2}

In patients with type 2 diabetes, the dose of pramlintide should be titrated to the next increment when no clinically significant nausea has occurred for three to seven days. If significant nausea persists at the 120 µg dose, the pramlintide dose should be decreased to 60 µg.^{1,2}

Table 8. Dosing and Administration^{1,2}

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|-------------------------------|--|--|--|
| Single Entity Products | | | |
| Pramlintide | <p><u>Type 1 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy:</u> Initial: 15 µg administered SC immediately prior to major meals; maintenance, 30 to 60 µg administered SC immediately prior to major meals</p> <p><u>Type 2 diabetes, as an adjunct treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin:</u> Initial: 60 µg administered SC immediately prior to major meals; maintenance, 120 µg administered SC immediately prior to major meals</p> | Safety and efficacy in children have not been established. | <p>Injection (pre-filled multi-dose pen): 60 µg/0.06 mL 120 µg/0.12 mL</p> <p>Vial: 600 µg/mL</p> <p>This injectable medication is self-administered</p> |

Drug regimen abbreviations: SC=subcutaneously

Clinical Guidelines

Table 10. Clinical Guidelines

| Clinical Guideline | Recommendations |
|---|---|
| American Association of Clinical Endocrinologists/ American College of | <p><u>Principles underlying the algorithm</u></p> <ul style="list-style-type: none"> Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes. Achieving an HbA_{1c} 6.5% is recommended as the primary goal; however, |

| Clinical Guideline | Recommendations |
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| <p>Endocrinology: Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel of Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (2009)²¹</p> | <p>the goal must be customized for individual patients.</p> <ul style="list-style-type: none"> • If glycemic goals are not achieved, dosages of medications can be titrated, regimens can be changed (add or discontinue medications), or, in certain instances, glycemic goals can be reconsidered and revised. • When using combination therapy it is important to have medications that have complementary mechanisms of action. • Effectiveness of therapy must be re-evaluated frequently, typically every two to three months. <p><u>Stratification by current HbA_{1c}</u></p> <ul style="list-style-type: none"> • Patients with an HbA_{1c} ≤7.5% may be able to achieve a goal of 6.5% with monotherapy; however, if monotherapy fails to achieve this goal, the usual progression is to combination therapy, and then to triple therapy. Insulin therapy, with or without additional agents, should be initiated if goals still fail to be achieved. • Patients with an HbA_{1c} of 7.6 to 9.0% should be initiated on combination therapy as monotherapy in these patients is likely not to achieve glycemic goals. If combination therapy fails, triple therapy and then insulin therapy, with or without additional oral agents, should be administered. • Patients with an HbA_{1c} >9.0% have a small possibility of achieving glycemic goals, even with combination therapy. In these patients, if they are asymptomatic triple therapy based on a combination of metformin and an incretin mimetic or a dipeptidyl peptidase-4 (DPP-4) inhibitor combined with either a sulfonylurea or a thiazolidinedione (TZD) should be initiated. If patients are symptomatic or if they have failed therapy with similar agents, insulin therapy with or without additional oral agents should be initiated. <p><u>Management of patients with a HbA_{1c} of 6.5 to 7.5%</u></p> <ul style="list-style-type: none"> • In these patients monotherapy with metformin, an α-glucosidase inhibitor, a DPP-4 inhibitor or a TZD are recommended. Because of the established safety and efficacy of metformin, it is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy. • If monotherapy, even after appropriate dosage titration, is unsuccessful in achieving glycemic goals combination therapy should be initiated. • Because of the established safety and efficacy of metformin, it is considered the cornerstone of combination therapy for most patients. When contraindicated, a TZD may be used as the foundation for combination therapy options. • Due to the mechanism of action (insulin sensitizer) of metformin and TZDs, it is recommended that the second agent in combination therapy be an incretin mimetic, DPP-4 inhibitor or a secretagogue (glinide or sulfonylurea). • The glucagon-like-peptide-1 (GLP-1) receptor agonists (incretin mimetics) and DPP-4 inhibitors are associated with less hypoglycemia compared to the secretagogues. • Despite the gastrointestinal side effects, dosing frequency and injection-based therapy, the GLP-1 agonists are preferred due to its greater effectiveness in reducing postprandial glucose excursions (relative to the DPP-4 inhibitors) and the potential for weight loss. • Combination metformin and TZD therapy is efficacious but carries risks of adverse events associated with both agents. The combination is recommended with a higher priority than a secretagogue because of a |

| Clinical Guideline | Recommendations |
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| | <p>lower risk of hypoglycemia and greater flexibility in timing of administration.</p> <ul style="list-style-type: none"> • The combination therapies of metformin and an α-glucosidase inhibitor and metformin and colesevelam are also included in the algorithm because of their safety and the ability of colesevelam to lower lipid profiles. • If combination therapy fails after each medication has been titrated to its maximally effective dose then triple therapy should be initiated. • The following triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 agonist + TZD. ○ Metformin + GLP-1 agonist + glinide. ○ Metformin + GLP-1 agonist + sulfonylurea. ○ Metformin + DPP-4 inhibitor + TZD. ○ Metformin + DPP-4 inhibitor + glinide. ○ Metformin + DPP-4 inhibitor + sulfonylurea. • Because of the established safety and efficacy of metformin, it is considered the cornerstone for triple therapy. • The GLP-1 agonist, exenatide, is the second preferred component of triple therapy because of its safety (low risk of hypoglycemia) and its potential for inducing weight loss. It also inhibits glucagon secretion in a glucose-dependent manner after consumption of means resulting in increased satiety and delayed gastric emptying. • The third component of triple therapy is recommended in order to minimize the risk of hypoglycemia. • The combination with metformin, especially when combined with an incretin mimetic, may counteract the weight gain often associated with glinides, sulfonylureas, and TZDs. • When triple therapy fails to achieve glycemic goals, insulin therapy is needed. <p><u>Management of patients with a HbA_{1c} of 7.6 to 9.0%</u></p> <ul style="list-style-type: none"> • The management of these patients is similar to that just described except patients can proceed directly to combination therapy because monotherapy is unlikely to be successful in these patients. • The following combination therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 agonist. ○ Metformin + DPP-4 inhibitor. ○ Metformin + TZD. ○ Metformin + sulfonylurea. ○ Metformin + glinide. • Metformin is again considered the cornerstone of combination therapy. • A GLP-1 agonist or a DPP-4 inhibitor is the preferred second component in view of the safety and efficacy of these agents in combination with metformin. Additionally, a GLP-1 agonist is given higher priority in view of its somewhat greater effect on reducing postprandial glucose excursions and its potential for inducing substantial weight loss. • TZDs are positioned lower due to the risks of weight gain, fluid retention, congestive heart failure and fractures associated with their use. • Glinides and sulfonylureas are relegated to the lowest position because the greater risk of inducing hypoglycemia. • When combination therapy fails to achieve glycemic goals, triple therapy should be started. • The following triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 agonist + TZD. |

| Clinical Guideline | Recommendations |
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| | <ul style="list-style-type: none"> ○ Metformin + DPP-4 inhibitor + TZD. ○ Metformin + GLP-1 agonist + sulfonylurea. ○ Metformin + DPP-4 inhibitor + sulfonylurea. ○ Metformin + TZD + sulfonylurea. <ul style="list-style-type: none"> ● Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy with either a GLP-1 agonist or a DPP-4 inhibitor. ● The preference for metformin and the GLP-1 agonist or DPP-4 inhibitor is based on the safety of these agents and minimal associated risks of hypoglycemia. ● TZDs are assigned a higher priority than a sulfonylurea because of their lower risk of hypoglycemia. ● A GLP-1 agonist is assigned a higher priority than a DPP-4 inhibitor because of its somewhat greater effect on reducing postprandial glucose excursions and the possibility that it might induce considerable weight loss. ● Metformin + TZD + sulfonylurea is relegated to the lowest priority due to an increased risk of weight gain and hypoglycemia. ● α-glucosidase inhibitors, colesevelam, and glinides are not considered as options in these patients due to their limited HbA_{1c}-lowering potential. ● The considerations for insulin therapy in these patients are similar to those used in patients with an HbA_{1c} of 6.5 to 7.5%. <p><u>Management of patients with a HbA_{1c} >9%</u></p> <ul style="list-style-type: none"> ● Patients who are drug-naïve with an HbA_{1c} >9% are unlikely to achieve glycemic goals with the use of one, two or even three agents (other than insulin). ● For patients who are asymptomatic, particularly with a relatively recent onset of diabetes, there is a good chance that some endogenous β-cell function exists; implying that combination or triple therapy may be sufficient. ● The following combination and triple therapy regimens are considered: <ul style="list-style-type: none"> ○ Metformin + GLP-1 agonist. ○ Metformin + GLP-1 agonist + sulfonylurea. ○ Metformin + DPP-4 inhibitor. ○ Metformin + DPP-4 inhibitor + sulfonylurea. ○ Metformin + TZD. ○ Metformin + TZD + sulfonylurea. ○ Metformin + GLP-1 agonist + TZD. ○ Metformin + DPP-4 inhibitor + TZD. ● Metformin again provides the foundation of treatment in these patients. ● An incretin-based therapy can be added with a GLP-1 agonist being preferred due to its greater effectiveness at controlling postprandial glycemia and its potential for inducing weight loss. However the DPP-4 inhibitors in combination with metformin have also demonstrated a robust benefit for drug-naïve patients in this HbA_{1c} range. ● A sulfonylurea or a TZD can also be added, with a sulfonylurea being preferred because of its somewhat greater efficacy and more rapid onset of action. ● If patients are symptomatic (polydipsia, polyuria and weight loss) or if they have already failed the aforementioned treatment regimens, insulin therapy should be initiated without delay. ● Insulin therapy for these patients follows the same principals as outlined |

| Clinical Guideline | Recommendations |
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| | <p>previously for patients with different HbA_{1c} levels.</p> <ul style="list-style-type: none"> • This algorithm favors the use of GLP-1 agonists (at the time of publication only exenatide had Food and Drug Administration [FDA] approval) and DPP-4 inhibitors with higher priority due to their effectiveness and overall safety profiles. Additionally, due to the increasing amount of literature indicating the serious risks of hypoglycemia, these agents are becoming preferred in most patients in place of secretagogues. • The algorithm moves sulfonylureas to a lower priority due to the risks of hypoglycemia and weight gain associated with their use, as well as the failure of these agents to provide improved glycemic control after use for a relatively short period. • A TZD is considered a “well-validated” effective agent due to demonstrated extended durability of action, but these agents have a lower priority for many patients in light of their potential side effects. • The three classes of medications; α-glucosidase inhibitors, colesevelam and glinides, are considered in relatively narrow, well-defined clinical situations, due to their limited efficacy. |
| <p>American Diabetes Association/European Association for the Study of Diabetes: Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy (2009)²²</p> | <ul style="list-style-type: none"> • The goal of the recommended algorithm is to achieve and maintain HbA_{1c} levels <7% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved. • The α-glucosidase inhibitors, amylin agonists, DPP-4 inhibitors and glinides are not included in the two tiers of preferred agents in the algorithm due to their lower or equivalent overall glucose-lowering effectiveness compared to the first- and second-tier agents, and/or due to limited clinical data or relative expense. These agents may be appropriate choices in selected patients. <p><u>Tier 1: well-validated core therapies</u></p> <ul style="list-style-type: none"> • These interventions represent the best established and most effective and cost-effective therapeutic strategies for achieving target glycemic goals, and are the preferred route of therapy for most type 2 diabetic patients. • Step 1: Lifestyle interventions and metformin should be initiated concurrently at diagnosis of type 2 diabetes. • Step 2: If lifestyle interventions and the maximal tolerated dose of metformin fail to achieve or sustain glycemic goals after two to three months, insulin or a sulfonylurea should be added. The choice between insulin or a sulfonylurea will be based on the HbA_{1c} levels, with consideration given to insulin (the more effective glycemia-lowering agent) for patients with an HbA_{1c} >8.5%. However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications. • Step 3: If lifestyle interventions, metformin and basal insulin or a sulfonylurea do not achieve glycemic goals, insulin therapy should be initiated or intensified. <p><u>Tier 2: less well-validated therapies</u></p> <ul style="list-style-type: none"> • In selected clinical settings, the tier 2 algorithm may be considered. • Specifically, when hypoglycemia is particularly undesirable, the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended. • Additionally, if a major consideration is weight loss and the HbA_{1c} level is close to target (<8%), then exenatide may be an option (at the time of publication only exenatide had FDA approval). |

| Clinical Guideline | Recommendations |
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| | <ul style="list-style-type: none"> If these interventions do not effectively achieve glycemic goals or if they are not tolerated, the addition of a sulfonylurea could be considered or the tier 2 interventions should be discontinued and basal insulin should be initiated. <p><u>Rationale for selecting specific combinations</u></p> <ul style="list-style-type: none"> Over time the majority of patients will require more than one medication. When selecting combination therapy, in general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. Combination insulin and metformin therapy is a particularly effective means of lowering glycemia with limited weight gain. <p><u>Special considerations/patients</u></p> <ul style="list-style-type: none"> In the setting of severely uncontrolled diabetes with catabolism combination insulin and lifestyle intervention therapy is the treatment of choice. |
| <p>American Diabetes Association: Standards of Medical Care in Diabetes (2011)²³</p> | <p><u>Current criteria for the diagnosis of diabetes</u></p> <ul style="list-style-type: none"> The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, OR a fasting plasma glucose (FPG) ≥126 mg/dL, OR a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test OR patients with classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). <p><u>Prevention/delay of type 2 diabetes</u></p> <ul style="list-style-type: none"> An ongoing support program for weight loss of 7% of body weight and an increase in physical activity, to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance or impaired fasting glucose. Metformin therapy for prevention of type 2 diabetes may be considered in patients at the highest risk for developing diabetes, such as those with multiple risk factors, especially if they demonstrate progression of hyperglycemia (e.g., HbA_{1c} ≥6%) despite lifestyle interventions. <p><u>Glycemic goals in adults</u></p> <ul style="list-style-type: none"> A reasonable HbA_{1c} goal for many nonpregnant adults is <7%. Based on data from randomized trials, it may be reasonable for providers to suggest more stringent HbA_{1c} goals for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy and no significant cardiovascular disease. Conversely, less stringent HbA_{1c} goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and those with longstanding diabetes in whom the general goal is difficult to attain. |

Conclusions

Pramlintide (Symlin®) is an amylin analog that is Food and Drug Administration (FDA)-approved as an adjunctive therapy with mealtime insulin for the management of type 1 and type 2 diabetes.¹ Pramlintide acts via several mechanisms to improve glycosylated hemoglobin (HbA_{1c}) including the modulation of gastric emptying, prevention of postprandial glucagon secretion and satiety, leading to decreased caloric intake and potential weight loss.^{1,2,4} Unlike many agents that are FDA-approved for the treatment of

diabetes, pramlintide has no effect on insulin release, resulting in its use for both types of diabetes. Pramlintide is administered subcutaneously prior to major meals. When initiating pramlintide treatment, an insulin dose reduction of 50% is required in all patients in order to reduce the risk of hypoglycemia.^{1,2} Pramlintide carries a black box warning which highlights the risk of insulin-induced hypoglycemia within three hours following pramlintide injection. Pramlintide alone does not cause hypoglycemia; however, since it is indicated to be coadministered with insulin therapy, the risk of hypoglycemia is higher due the effect pramlintide has on postprandial plasma glucose.¹ Most adverse events associated with pramlintide are gastrointestinal in nature. The incidence of nausea and vomiting is typically higher at the beginning of treatment and has been shown to decrease with time and gradual dose titration.^{1,2,4}

In clinical trials, pramlintide has been shown to decrease HbA_{1c} compared to placebo in patients with type 1 or type 2 diabetes that are not achieving their glycemic goals despite treatment with mealtime insulin, in addition to reductions in body weight.⁷⁻²⁰ Pramlintide is also associated with a reduction in daily insulin dose, and body weight. Compared to treatment with rapid acting insulin analogs, a higher percentage of patients treated with pramlintide were able to achieve an HbA_{1c} of <7% with less weight gain and hypoglycemia over 24 weeks.¹⁵ When combined with insulin glargine, pramlintide has been associated with further improvements in HbA_{1c} and glycemic control compared with insulin glargine alone.¹⁴

The current consensus guideline by the American College of Clinical Endocrinologists, recommends the use of pramlintide in patients with persistent postprandial hyperglycemia despite insulin treatment and that pramlintide can be used effectively in the treatment of obese patients with type 2 diabetes who use before-meal insulin injections, with or without orally administered antidiabetic agents.²¹ The American Diabetes Association does not include pramlintide in the two tiers of preferred agents in their algorithm for glycemic control, due to the lower or equivalent overall glucose-lowering effectiveness compared to the first- and second-tier agents, and/or due to limited clinical data or relative expense.²²

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to September 30, 2011

| Medication | Unique utilizers | # of Rx's | Market Share (%) | Plan Cost \$ | Avg \$/Rx |
|---------------------|------------------|-----------|------------------|--------------------|-----------------|
| Symlin pen 120 | 5 | 12 | 63.16% | \$10,577.98 | \$881.50 |
| Symlin pen 60 | 2 | 4 | 21.05% | \$1,768.99 | \$442.25 |
| Symlin | 2 | 3 | 15.79% | \$1,333.00 | \$444.33 |
| Class Total: | 9 | 19 | 100% | \$13,679.97 | \$720.00 |

Recommendations

No changes to the current Department of Vermont Health Access (DVHA) approval criteria for Symlin[®] (below) are proposed.

Symlin:

- The patient has a diagnosis of diabetes mellitus.
AND
- The patient is at least 18 years of age.
AND
- The patient is on insulin.

References:

1. Symlin® [package insert]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2008 Jul.
2. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2011 [cited 2011 Nov]. Available from: <http://online.factsandcomparisons.com>.
3. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2011 [cited 2011 Nov 5]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
4. Younk LM, Mikeladze M, Davis SN. Pramlintide and the treatment of diabetes: a review of the data since its introduction. *Expert Opin Pharmacother*. 2011 Jun;12(9):1439-51.
5. Weyer C, Maggs DG, Young AA, Kolterman OG. Amylin replacement with pramlintide as an adjunct to insulin therapy in type 1 and type 2 diabetes mellitus: a physiological approach toward improved metabolic control. *Curr Pharm Des*. 2001 Sep;7(14):1353-73.
6. Nathan DM, Buse JB, Davidson MB. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.
7. Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care*. 2002;25(4):724-30.
8. Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med*. 2004; 21(11):1204-12.
9. Edelman S, Garg S, Frias J, Maggs D, Wang Y, Strobel S et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in Type 1 diabetes. *Diabetes Care*. 2006;29:2189-98.
10. Ratner R, Whitehouse F, Fineman S, Strobel S, Shen L, Maggs DG, et al. Adjunctive therapy with pramlintide lowers HbA_{1c} without concomitant weight gain and increased risk of severe hypoglycemia in patients with Type 1 diabetes approaching glycemic targets. *Exp Clin Endocrinol Diabetes*. 2005;113:199-204.
11. Marrero D, Crean J, Zhang B, Kellmeyer T, Gloster M, Herrmann K, et al. Effect of adjunctive pramlintide treatment on treatment satisfaction in patients with Type 1 diabetes. *Diabetes Care*. 2007;30:210-6.
12. Hollander PA, Levy P, Fineman MS, Maggs DG, Shen LZ, Strobel SA, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care*. 2003 Mar;26(3):784-90.
13. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol Ther*. 2002;4(1):51-61.
14. Riddle M, Frias J, Zhang B, Maier H, Brown C, Lutz K, Kolterman O. Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes Care*. 2007 Nov;30(11):2794-9.
15. Riddle M, Pencek R, Charenkavanich S, Lutz K, Wilhelm K, Porter L. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. *Diabetes Care*. 2009 Sep;32(9):1577-82.
16. Karl D, Philis-Tsimikas A, Darsow T, Lorenzi G, Kellmeyer T, Lutz K, et al. Pramlintide as an adjunct to insulin in patients with Type 2 Diabetes in a clinical practice setting reduced A1C, postprandial glucose excursions, and weight. *Diabetes Technol Ther*. 2007; 9(2):191-9.
17. Hollander P, Ratner R, Fineman M, Strobel S, Shen L, Maggs D, et al. Addition of pramlintide to insulin therapy lowers HbA_{1c} in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. *Diabetes Obes Metab*. 2003 Nov;5(6):408-14.
18. Maggs D, Shen L, Strobel S, Brown D, Kolterman O, Weyer C. Effect of pramlintide on A1c and body weight in insulin treated African Americans and Hispanics with type 2 diabetes: a pooled post hoc analysis. *Metabolism*. 2003;52(12):1638-42.

19. Hollander P, Maggs DG, Ruggles JA, Fineman M, Shen L, Kolterman OG, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obes Res*. 2004 Apr;12(4):661-8.
20. Singh-Franco D, Perez A, Harrington C. The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2011 Feb;13(2):169-80.
21. The American Diabetes Association (ADA). Executed Summary: Standards of medical care in diabetes-2010. *Diabetes Care*. 2010;33(Suppl 1):S4-10.
22. Rodboard HW, Jellinger PS, Davidson JA, Einhorn D, Garber AJ, Grunberger G et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An algorithm for glycemic control. *Endocr Pract*. 2009;15(6):541-59.
23. ADA and the European Association for the Study of Diabetes (EASD). Medical Management of Hyperglycemia in Type 2 Diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes care*. 2009 Jan;32(1):193-203.