Therapeutic Class Overview
Amylinomimetics

Therapeutic Class

- **Overview/Summary:** Pramlintide (Symlin®, SymlinPen®) is the only amylinomimetic in the medication class, and is Food and Drug Administration-approved as adjunct to treatment with insulin in patients with type 1 and 2 diabetes who have failed to achieve desired glucose control despite optimal insulin therapy.[1] Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β cells that contributes to glucose control during the post-prandial period. The actions of pramlintide include the slowing of gastric emptying, without altering nutrient absorption, decreasing post-prandial glucagon section, and regulation of food intake by centrally-mediated modulation of appetite.[1-3] Pramlintide is available as a subcutaneous injection and the specific dose administered will vary depending on whether the patient has type 1 or 2 diabetes.[1] Currently, pramlintide is only available as the branded products Symlin® and SymlinPen®.

Table 1. Current Medications Available in Therapeutic Class[1]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Pramlintide (Symlin®, SymlinPen®)	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, 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	Multi-dose Pen: 1,000 µg/mL* Vial: 600 µg/mL (5 mL)	-

*Available in two sizes. The SymlinPen® 60 (1.5 mL) should be used for doses of 15, 30, 45 and 60 µg. The SymlinPen® 120 (2.7 mL) should be used for doses of 60 and 120 µg.

Evidence-based Medicine

- In general, due to the approved indication of pramlintide, the agent has been evaluated as add-on therapy in type 1 and 2 diabetics already receiving insulin therapy.[1,4-17]
- Overall, data demonstrate that treatment with pramlintide achieves significantly greater baseline reductions in glycosylated hemoglobin (HbA_{1c}), post-prandial glucose levels, and body weight compared to placebo. In addition, greater proportions of patients are able to achieve an HbA_{1c} <7.0% with pramlintide compared to placebo.[4-17]
- Treatment with pramlintide is well tolerated.[4-17] The most commonly reported adverse events in clinical trials associated with pramlintide included nausea and anorexia.[5,6,9,13,15] In addition, though pramlintide itself does not cause hypoglycemia, increases in the incidence of hypoglycemic events with pramlintide compared to placebo were reported in some clinical trials, while others reported no difference between the two treatments when added to insulin therapy.[6-9,14,15]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Type 2 diabetes:[18-22]
        - Metformin remains the cornerstone to most antidiabetic treatment regimens.[18-22]
        - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.[18-22]
        - In general, current clinical guidelines do not support the use of amylinomimetics in the management of type 2 diabetes.[18,19]
            - However, it is noted that non-preferred or less well validated agents still may be appropriate choices in individual patients to achieve glycemic goals.[18]

  - Type 1 diabetes:[18,22-24]
    - The initiation of individualized insulin therapy is recommended at the time of diagnosis.[18,22-24]
    - Among type 1 diabetics, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management.[22]
- Other Key Facts:
  - Pramlintide is the only amylinomimetic in the medication class, and is only available as the branded products Symlin® and SymlinPen®.

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Therapeutic Class Review
Amylinomimetics

Overview/Summary

Pramlintide (Symlin®, SymlinPen®) is the only amylin analog, or amylinomimetic, in the class, and is Food and Drug Administration (FDA)-approved as an adjunct treatment with insulin in patients with type 1 or 2 diabetes who have failed to achieve desired glucose control despite optimal insulin therapy.[1] 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.[3] Concentrations of amylin and insulin in plasma show parallel peak and trough concentrations during fasting conditions and with meal intake.[1,3] The amylin response to meal intake is absent in type 1 diabetes, exaggerated in obesity, and impaired or diminished in type 2 diabetes.[4]

Specifically, pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β cells that contributes to glucose control during the post-prandial period.[3] As an amylinomimetic, pramlintide slows gastric emptying, without altering nutrient absorption, decreases post-prandial 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 post-prandial elevation in plasma glucose.[1-3] In patients with diabetes; this action is beneficial as post-prandial glucagon secretion has been shown to be abnormally elevated in such patients and contributes to post-prandial hyperglycemia.[3] Compared to newer antidiabetic agents used in the management of type 2 diabetes, such as the incretin mimetics and dipeptidyl peptidase-4 inhibitors, pramlintide does not stimulate pancreatic insulin release which makes it a useful treatment option for patients with type 1 or 2 diabetes.[1-3]

Pramlintide is available as a brand only subcutaneous injection that is administered prior to meals. The recommended dose of pramlintide varies depending on whether the patient has type 1 or 2 diabetes. Of note, a 50% reduction in insulin dose 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 is increased with combination therapy.[1,2] Treatment with pramlintide is typically initiated with a lower dose and then titrated to targeted doses every three to seven days when no clinically significant nausea is apparent.[1] Pramlintide monotherapy can result in a reduction of glycosylated hemoglobin (HbA_{1c}) of 0.5 to 1.0%.[5] In clinical trials, treatment with pramlintide achieved significantly greater baseline reductions in HbA_{1c}, post-prandial glucose, and body weight compared to placebo when given in combination with insulin. In addition, greater proportions of patients were able to achieve an HbA_{1c} <7.0% with pramlintide compared to placebo.[6-19]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone to most antidiabetic treatment regimens. Additionally, patients with high HbA_{1c} will most likely require combination or triple therapy in order to achieve glycemic goals.[5,20-23] According to the American Diabetes Association/European Association for the Study of Diabetes treatment algorithm specifically, amylinomimetics are not included as well-validated or preferred treatment options due to their lower or equivalent overall glucose-lowering effectiveness compared to first- and second-line agents, and/or due to limited clinical data, or relative expense.[5] However, it is noted that agents not included in the algorithm still may be appropriate choices in individual patients to achieve glycemic goals.[20] For the management of type 1 diabetes, current clinical guidelines recommend the initiation of individualized insulin therapy at the time of diagnosis.[20,23-25] Among type 1 diabetics, the addition of pramlintide to insulin therapy may be considered to enhance glycemic control and to assist with weight management.[23]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability

Generic Name (Trade name)	Medication Class	Generic Availability
Pramlintide (Symlin®, SymlinPen®)	Amylinomimetics	-

Indications

Table 2. Food and Drug Administration-Approved Indications[1]

Indication(s)	Pramlintide
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	✔
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	✔

Pharmacokinetics

Table 3. Pharmacokinetics[26]

Generic Name	Bioavailability (%)	Renal Elimination (%)	Active Metabolites	Serum Half-Life (hours)
Pramlintide	30 to 40	Not reported	Des-lys(1) pramlintide (2-37 pramlintide)	0.50 to 0.83

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the amylinomimetics in Food and Drug Administration-approved indications are outlined in Table 4.[6-19] In general, due to the approved indication of pramlintide, the agent has been evaluated as add-on therapy in type 1 and 2 diabetics already receiving insulin therapy.[1,6-19]

With regards to the treatment of type 1 diabetes, results of a small meta-analysis (three trials) demonstrated that pramlintide was associated with an average baseline reduction in glycosylated hemoglobin (HbA_{1c}) of -0.3% and weight loss of -1.8 kg compared to placebo (P<0.0009 for both).[10] These findings were supported by a one year, double-blind, placebo-controlled, multicenter trial in which type 1 diabetics were randomized to receive pramlintide 30 µg or placebo four-times daily (N=480). At trial end, pramlintide again was associated with a significant baseline reduction in both HbA_{1c} (-0.39 vs -0.12%; P=0.0071) and body weight (-1.0 vs -0.2 kg; P<0.001) compared to placebo. In this trial, greater incidences of nausea (46.5 vs 21.9%; P value not reported) and anorexia (17.2 vs 2.1%; P value not reported) were reported with pramlintide.[7] A second one year trial (N=651) demonstrated similar results with regards to baseline reductions in HbA_{1c}; however, in this trial doses of pramlintide 60 µg three-times daily and four-times daily demonstrated "superiority" over placebo (26 weeks; P=0.012 and P=0.13, 52 weeks; P=0.011 and P=0.001, respectively).[8] As mentioned previously, pramlintide itself does not cause hypoglycemia, but when administered in combination with insulin, the incidence of hypoglycemic events increases.[1] In a 29 week trial, the primary endpoint of the incidence of hypoglycemic events was significantly greater with pramlintide compared to placebo (0.57 vs 0.30 events per patient-year; P<0.05).[6] In a post-hoc analysis of patient response to a satisfaction survey, treatment with pramlintide was favored for questions relating to glucose control, meal flexibility, weight control, and appetite control (P<0.05 for all). No difference between pramlintide and placebo was observed with questions relating to patients' ability to avoid hypoglycemia and patients' wanting to continue treatment with pramlintide (P value not significant).[9]

Data from clinical trials demonstrate that pramlintide is also associated with significant baseline reductions in HbA_{1c} in type 2 diabetics. Results from a meta-analysis of eight trials (four trials with type 2 diabetic patients and four trials with obese patients without diabetes) demonstrate that pramlintide (120 to 150 µg) was associated with a -0.33% reduction in baseline HbA_{1c} (P=0.0004); however, no difference was observed between pramlintide and placebo in the likely hood of achieving an HbA_{1c} ≤7.0% (odds ratio, 1.52; 95% confidence interval, 0.83 to 2.78; P=0.18).[12] In general, these findings were again supported by individual clinical trials. In a one year trial (N=656) in which patients were randomized to

either pramlintide 90 or 120 µg or placebo twice-daily, after 26 weeks of treatment a significant baseline reduction in HbA_{1c} was achieved with pramlintide 120 µg compared to placebo (-0.68%; *P*<0.05). Furthermore, only pramlintide 120 µg maintained a significant improvement in HbA_{1c} throughout one year of treatment (-0.62%; *P*<0.05). However, a greater proportion of patients receiving pramlintide 90 or 120 µg achieved an HbA_{1c} <7.0% by trial end (9.4 and 12.2 vs 4.1%, respectively; *P* values not reported).[14] In another one year trial (N=538), a significantly greater reduction in baseline HbA_{1c} was achieved in patients receiving pramlintide 75 or 150 µg three-times daily compared to patients receiving placebo (-0.9%; *P*=0.0004 and -1.0%; *P*=0.0002) after 13 weeks of treatment, and only pramlintide 150 µg maintained "superiority" throughout one year (-0.6%; *P*=0.0068). In this trial, treatment with pramlintide was also associated with a significant baseline reduction in weight compared to placebo (*P*<0.05), and greater proportions of patients receiving pramlintide achieved an HbA_{1c} <7.0% (75 µg, 13.4%; 150 µg, 19.2%; placebo, 11.1%; *P* values not reported).[15] In a third, 16 week trial, in addition to a significant baseline reduction in HbA_{1c} (-0.70 vs -0.36%; *P*<0.05), a significantly greater proportion of patients receiving pramlintide achieved the composite endpoint of HbA_{1c} ≤7.0% or an HbA_{1c} reduction from baseline ≥0.5%, mean daily post-prandial glucose increments ≤40 mg/dL, no weight gain, and no severe hypoglycemia compared to patients receiving placebo (25 vs 7%; *P*<0.001).[13] Post-hoc analyses of these trials lasted up to one year and generally demonstrated sustained improvements in HbA_{1c}, weight loss, and the proportion of patients able to achieve an HbA_{1c} <7.0% with pramlintide.[16-18]

Treatment with pramlintide has also been evaluated head-to-head with insulin. Specifically, an open-label trial compared the addition of pramlintide 120 µg and rapid acting insulin analogs as add-on therapies to basal insulin in type 2 diabetics (N=113). Of note, patients enrolled in this trial may or may not have also been managed with oral antidiabetic agents. The primary endpoint of the proportion of patients achieving the composite of HbA_{1c} ≤7.0%, no weight gain from baseline, and no severe hypoglycemia after 24 weeks was significantly greater with pramlintide (30 vs 11%; *P*=0.018).[19]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Type 1 Diabetes				
Edelman et al[6] Pramlintide 15 µg/meal SC, titrated to 60 µg/meal vs placebo All patients also received existing insulin regimens.	DB, MC, PC, RCT 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	N=296 29 weeks	Primary: Safety Secondary: Change from baseline in HbA_{1c}, postprandial glucose concentrations, insulin, and weight; tolerability	Primary: Both treatments resulted in a similar number of nonsevere hypoglycemic events. The event rate per patient years was 0.57 with pramlintide compared to 0.30 with placebo (*P*<0.05). Secondary: Baseline HbA_{1c} was 8.1% with both treatments and at week 29 had decreased comparably (-0.50; 95% CI, -0.61 to -0.33 vs -0.50%; 95% CI, -0.63 to -0.35; *P* value not reported). Among pramlintide-treated patients, a significantly greater number were able to achieve a postprandial glucose concentration of 9.9 mmol/L at breakfast (68 vs 51%), lunch (71 vs 61%), and dinner (70 vs 58%; *P*<0.0001 for each meal). At week 29 the total insulin dose with pramlintide decreased by -12% compared to an increase of 1% with placebo. Between weeks 0 through 29, the reduction in body weight was significant with pramlintide compared to placebo (-1.3 vs 1.2 kg; *P*<0.0001). Reduced appetite, vomiting, and sinusitis occurred at twice the level with pramlintide compared to placebo (*P*<0.01).
Whitehouse et al[7] Pramlintide 30 µg SC QID; after 20 weeks, patients receiving pramlintide who did not achieve an HbA_{1c} reduction of ≥1.0% were re-randomized to either 30 or 60 µg SC QID vs	DB, PC, RCT Type 1 diabetic patients	N=480 52 weeks	Primary: Change from baseline HbA_{1c} Secondary: Change from baseline HbA_{1c} and body weight at weeks 13, 26, and 52	Primary: Significantly greater reductions in HbA_{1c} were observed with pramlintide (-0.39%) compared to placebo (-0.12%; *P*=0.0071) at 52 weeks. Secondary: Significantly greater reductions in HbA_{1c} with pramlintide were achieved at weeks 13 (-0.67 vs -0.16%; *P*<0.0001), 26 (-0.58 vs -0.18%; *P*=0.0001), and 52 (-0.39 vs -0.12%; *P*=0.0071). Pramlintide-treated patients had sustained reductions in body weight that were significantly different compared to placebo (*P*<0.001) from week 13 onward (data reported in graphical form only).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients also received existing insulin regimens.				The most commonly reported side effects with pramlintide were nausea (46.5 vs 21.9%; *P* values not reported) and anorexia (17.7 vs 2.1%; *P* values not reported). Withdrawal due to adverse event(s) occurred in 31 (12.8%) and 19 (8.0%) pramlintide- and placebo-treated patients.
Ratner et al[8] Pramlintide 60 µg SC TID or QID, or 90 µg SC TID vs placebo All patients also received existing insulin regimens.	DB, PC, RCT Type 1 diabetics	N=651 52 weeks	Primary: Change from baseline HbA_{1c} at week 26 Secondary: Change from baseline HbA_{1c} at week 52, proportion of patients achieving HbA_{1c}<7.0%, safety	Primary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg TID compared to placebo (-0.41 vs -0.18%; *P*=0.012) after 26 weeks. In addition, significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg QID compared to placebo (-0.39 vs -0.18%; *P*=0.013). Secondary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg TID compared to placebo (-0.29 vs -0.04%; *P*=0.011) after 52 weeks. In addition, significantly greater reductions in HbA_{1c} were achieved with pramlintide 60 µg QID compared to placebo (-0.34 vs -0.04%; *P*=0.001). A threefold greater proportion of pramlintide-treated patients achieved HbA_{1c} <7.0% compared to placebo Treated patients (*P* value not reported; data was reported in graphical form only). Pramlintide 90 µg was excluded from the analysis when results from a separate trial indicated the dose had an adverse tolerability profile. Patients originally randomized to this treatment continued to receive 90 µg to preserve the trial design. During the first four weeks of therapy, pramlintide-treated patients had a fourfold increase in severe hypoglycemic event rate compared to placebo-treated subjects (3.78 events/year vs 0.87 events/year; no *P* value reported). The most commonly reported adverse event with pramlintide was nausea. Withdrawal due to adverse event(s) occurred in 38 (22.1%) patients receiving pramlintide 90 µg TID, 22 (13.7%) patients receiving 60 µg QID, 32 (19.5%) patients receiving 60 µg TID, and six (3.9%) patients receiving placebo.
Marrero et al[9] Pramlintide 15 µg SC with meals, titrated to 60	Post hoc analysis Type 1 diabetic patients who	N=266 29 weeks	Primary: Patient response to satisfaction questionnaire	Primary: For the following topics the survey ratings favored pramlintide: 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,”

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg SC with meals vs placebo All patients also received existing insulin regimens.	completed a 29 week DB, noninferiority, dose-finding pramlintide trial		Secondary: Not reported	and (4) "made it easier to control my appetite" (P<0.05 for all). There was no difference between treatments 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" (P value not significant). Secondary: Not reported
Ratner et al[10] Pramlintide vs placebo All patients also received existing insulin regimens.	MA (3 trials) Type 1 diabetic patients with HbA_{1c} of 7.0 to 8.5%	N=477 26 weeks	Primary: Change from baseline in HbA_{1c} and body weight, adverse events (hypoglycemia) Secondary: Not reported	Primary: Significant baseline reductions in HbA_{1c} (-0.3%) and body weight (-1.8 kg) at end point were achieved with pramlintide (P<0.0009 for both). The risk of severe hypoglycemia was 1.40 with pramlintide compared to 1.86 with placebo. Secondary: Not reported
Type 2 Diabetes				
Karl et al[11] Pramlintide 120 µg SC with meals (either TID or BID) All patients also received existing insulin regimens.	MC, OL Type 2 diabetics >18 years of age currently receiving insulin therapy with or without oral antidiabetics, and HbA_{1c} >7.0 to <11.0%	N=166 12 months (all results reported at 6 months)	Primary: Change from baseline in HbA_{1c}, fasting glucose, postprandial glucose, body weight, and insulin; safety Secondary: Not reported	Primary: Pramlintide resulted in significant HbA_{1c} reductions at months three and six (-0.66 and -0.56%; P<0.05). At some point during the initial six months after initiating therapy, 28.1% of the patients who had a baseline HbA_{1c}>7.0% achieved an HbA_{1c}<7.0%. Compared to baseline, both fasting and postprandial glucose concentrations were significantly reduced (P<0.05). Significant baseline reductions in weight were noted at months three and six (-2.3 and -2.8 kg; P<0.05). At months three and six, mealtime and total insulin doses remained significantly lower compared to baseline (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Nausea (29.5%), vomiting (7.2%), and diarrhea (5.4%) were the most commonly reported adverse events. There was an overall incidence of 12% for hypoglycemia, with two patients experiencing severe hypoglycemia during the six month treatment period. Secondary: Not reported
Singh-Franco et al[12] Pramlintide 120 to 150 µg SC BID or TID with meals	MA (8 trials) Type 2 diabetic patients (4 trials) and obese patients without diabetes (4 trials)	N=1,616 6 to 52 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Likelihood of achieving HbA_{1c} ≤7.0%; change from baseline in FPG, PPG, and weight	Primary: Pooled analysis revealed that compared to placebo, pramlintide was associated with a baseline reduction in HbA_{1c} of -0.33% (*P*=0.0004). Secondary: After 52 weeks, pramlintide-treated patients were 1.52 times (95% CI, 0.83 to 2.78) more likely to achieve an HbA_{1c} ≤7.0% compared to placebo treated patients; however, this difference was not significant (*P*=0.18). 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 (*P*=0.50). 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 (*P*=0.67). Pramlintide was associated with a significant change in body weight in patients with type 2 diabetes compared to placebo (-2.21 kg; *P*<0.000001).
Riddle et al[13] Pramlintide 60 µg SC BID or TID with meals, titrated to 120 µg SC vs placebo	DB, MC, PC, RCT Type 2 diabetics 25 to 75 years of age not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with or	N=212 16 weeks	Primary: Change from baseline HbA_{1c} at week 16, proportion of patients meeting all of the following prespecified criteria at week	Primary: Pramlintide-treated patients experienced significantly greater baseline reductions in HbA_{1c} at week 16 compared to placebo –treated patients (-0.70 vs -0.36%; *P*<0.05). At week 16, significantly more pramlintide-treated patients achieved the composite end point compared to placebo-treated patients (25 vs 7%; *P*<0.001). Secondary: The proportion of patients who achieved an HbA_{1c} ≤7.0% or who had a reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients also received existing insulin regimens.	without oral antidiabetic therapy, and an HbA_{1c} >7.0 to 10.5% and BMI 25 to 45 kg/m^2		16: HbA_{1c} ≤7.0% or an HbA_{1c} baseline reduction ≥0.5%, mean daily PPG increments ≤40 mg/dL, no weight gain, and no severe hypoglycemia Secondary: Individual components of the composite endpoint; proportion of patients achieving HbA_{1c} ≤7.0 or ≤6.5%; changes from baseline to each time point in HbA_{1c}, seven-point glucose profiles, PPG increments, FPG, weight, and insulin glargine dose	in HbA_{1c} ≥0.5% was not different between pramlintide and placebo (54 vs 45%; *P* value not reported). Significantly more pramlintide-treated patients achieved mean PPG increments ≤40 mg/dL (*P*<0.0001) and did not experience weight gain (*P*<0.0001) compared to placebo-treated patients. Compared to placebo-treated patients, 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). The proportion of patients achieving an HbA_{1c} ≤7.0 or ≤6.5% was 23 and 11% with pramlintide compared to 13 and 4% with placebo, respectively (*P* values not reported). The insulin glargine dosage increased steadily throughout the trial. The mean increase in insulin glargine dosage at week 16 was 11.7±1.9 and 13.1±1.6 units with pramlintide and placebo, respectively (*P* value not reported). The average change from baseline in FPG was -28.3 and -12.0 mg/dL at week 16 with pramlintide and placebo, respectively (*P* value not reported). At Week 16, PPG was significantly decreased from baseline in pramlintide compared to placebo (-24.4 vs -0.4 mg/dL; *P*<0.0001). By week 16, pramlintide was associated with weight loss compared to weight gain with placebo (-1.6 vs 0.7 kg; *P*<0.0001) By the end of treatment, 68% of pramlintide-treated patients had lost weight compared to approximately 35% of placebo-treated patients (*P*<0.0001).
Hollander et al[14] Pramlintide 60, 90, or 120 µg SC BID	DB, MC, PC, PG, RCT Type 2 diabetics >18 years of age	N=656 12 months	Primary: Change from baseline in HbA_{1c} at week 26	Primary: After 26 weeks, pramlintide 120 µg was associated with a significant reduction in HbA_{1c} compared to placebo (-0.68; *P*<0.05), but no difference in the baseline reduction of HbA_{1c} was reported between the pramlintide 90 µg and placebo (-0.54%; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients also received existing insulin regimens. Data for patients randomized to pramlintide 60 µg SC BID are not reported.	requiring insulin therapy for ≥ 6 months prior to trial initiation with an HbA_{1c} ≥8.0%, and without hypoglycemia in the 2 weeks preceding the trial		Secondary: Absolute change in HbA_{1c} at other time points, proportion of patients who achieved an HbA_{1c} <7.0 or <8.0%	Secondary: After 52 weeks, pramlintide 120 µg was associated with a significant baseline reduction in HbA_{1c} compared to placebo (-0.62; *P*<0.05), but no difference in the baseline reduction of HbA_{1c} was reported between pramlintide 90 µg and (-0.35%; *P* value not reported). More patients receiving pramlintide (either dose) achieved an HbA_{1c} <7.0% compared to patients receiving placebo (9.4 and 12.2 vs 4.1%, respectively; *P* value not reported). Similarly, 42.4, 45.7, and 27.6% of patients receiving pramlintide 90 µg, pramlintide 120 µg, and placebo, respectively, achieved an HbA_{1c} <8.0% (*P* value not reported).
Ratner et al[15] Pramlintide 30, 75, or 150 µg TID vs placebo All patients also received existing insulin regimens.	DB, PC, RCT Type 2 diabetic patients	N=538 52 weeks	Primary: Change in baseline HbA_{1c} and body weight at weeks 13, 26, and 52 Secondary: Proportion of patients achieving HbA_{1c}<7.0 or 8.0%, relative change of insulin use, safety	Primary: Significantly greater reductions in HbA_{1c} were achieved with pramlintide 75 µg compared to placebo (-0.9%; *P*=0.0004) after 13 weeks. In addition, HbA_{1c} was significantly lower for the majority of the study periods with the exception of week 52 (*P* value not reported). Significantly greater reductions in HbA_{1c} were achieved with pramlintide 150 µg compared to placebo (-1.0%; *P*=0.0002). After 13 weeks, HbA_{1c} remained significantly lower for the rest of the trial (-0.6%; *P*=0.0068). Reductions in HbA_{1c} with pramlintide 30 µg were not different compared to placebo at any point during the trial. Significant baseline reductions (*P*<0.05) in body weight were achieved with all pramlintide doses throughout the trial when compared to placebo. Secondary: The proportions of patients achieving an HbA_{1c}<7.0% were 12.7, 13.4, and 19.2% in patients receiving pramlintide 30, 75, and 150 µg compared to 11.1% in patients receiving placebo (*P* values not reported). The proportions of patients achieving an HbA_{1c}<8.0% were 45.1, 46.4, and 54.0% in patients receiving pramlintide 30, 75, and 150 µg compared to 37.6% in patients receiving placebo (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Insulin use increased with all treatments. With pramlintide, insulin use increased by 7.9 to 10.9%, while insulin use increased by 15.4% with placebo (*P* values not reported). The most commonly reported side effect with pramlintide was nausea.
Hollander et al[16] Pramlintide 120 µg SC BID vs placebo All patients also received existing insulin regimens.	Post hoc analysis Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT	N=186 26 and 52 weeks	Primary: Change in baseline HbA_{1c}, body weight, insulin use, and the rate of severe hypoglycemia at week 26; safety Secondary: Not reported	Primary: At week 26, the difference in HbA_{1c} baseline reduction with pramlintide compared to placebo was- 0.43% (*P*<0.0009). The proportion of patients who achieved an HbA_{1c}<7.0% at week 26 was 14% in the pramlintide group compared to 2% in the placebo group (*P* value was not reported). At week 26, the difference in weight baseline reduction with pramlintide compared to placebo was 2 kg (*P*<0.0003). No significant change in insulin dose or the number of insulin injections was noted between the treatments (*P* value not reported). At week 26, no significant difference was noted between the treatments in rates of severe hypoglycemia as reported in event rate per subject year (0.13 vs 0.19; *P* value not reported). No serious adverse events were reported with either treatment. Secondary: Not reported
Maggs et al[17] Pramlintide 120 µg SC BID or 150 µg SC TID vs placebo All patients also	Post hoc analysis Type 2 diabetic patients who completed a 52 week, DB, PC, RCT	N=410 52 weeks	Primary: Change in baseline in HbA_{1c} and weight at week 52, safety Secondary: Not reported	Primary: A significantly greater baseline reduction in HbA_{1c} was achieved with pramlintide compared to placebo at week 52 (*P*<0.0001). This result was seen across the following ethnic groups: African Americans (-0.7%), Caucasians (-0.5%), and Hispanics (-0.3%). A significant baseline reduction in body weight was achieved with pramlintide compared to placebo at week 52 (-2.6 kg; *P*<0.0001). Nausea was more common with pramlintide, and hypoglycemia was reported to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
received existing insulin regimens.				a similar extent with both treatments. Secondary: Not reported
Hollander et al[18] Pramlintide 120 µg BID vs placebo All patients also received existing insulin regimens.	Post hoc analysis Type 2 diabetic patients who completed a 26 or 52 week, DB, PC, RCT	N=498 26 and 52 weeks	Primary: Change in baseline HbA_{1c}, insulin dose, and body weight Secondary: Not reported	Primary: At Week 26, mean baseline reductions in HbA_{1c} with pramlintide compared to placebo (-0.59 vs -0.18%; *P*<0.0001). There was no difference in the change in total daily insulin requirements between the two treatments. At week 26, pramlintide-treated patients achieved a significant baseline reduction in weight compared to placebo (-1.5 vs 0.3 kg; *P*<0.0001). Secondary: Not reported
Riddle et al[19] Pramlintide 120 µg SC with meals plus basal insulin titrated twice weekly to achieve a FPG ≥70 to <100 mg/dL vs rapid acting insulin analogs SC (lispro, aspart, glulisine) plus basal insulin titrated twice weekly to achieve a FPG ≥70 to <100 mg/dL Rapid acting insulin analogs were initiated	MC, OL, RCT Type 2 diabetics 18 to 75 years of age with an HbA_{1c} >7.0 to ≤10.0%, who were pramlintide naïve, and either insulin naive or had used <50 units/day of basal insulin for <6 months with or without other oral antidiabetic agents	N=113 24 weeks	Primary: Proportion of patients achieving the following prespecified criteria at Week 24: HbA_{1c} ≤7.0%, no baseline weight gain, and no severe hypoglycemia Secondary: Change in baseline HbA_{1c}, proportion of patients achieving an HbA_{1c} ≤6.5%,	Primary: After 24 weeks, a significantly higher proportion of pramlintide-treated patients achieved the composite endpoint compared to rapid acting insulin analog-treated patients (30 vs 11%; *P*=0.018). Secondary: The mean reduction in baseline HbA_{1c} was -1.1% with pramlintide compared to -1.3% with rapid acting insulin analogs (*P*=0.46). There was no difference in the proportion of patients achieving an HbA_{1c} ≤6.5% after 24 weeks between the two treatments (29 vs 34%, respectively; *P*=0.68). The change from baseline 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 patients compared to 27% of rapid acting insulin analog-treated patients (*P*=0.83). At 24 weeks, there was no change in weight with pramlintide compared to a gain of 4.7 kg with rapid acting insulin analogs (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
with 5 units before each meal. Mealtime insulin doses were adjusted with investigator guidance by 1 to 2 units every 3 to 7 days with the aim of maintaining glucose concentrations ≥70 and <100 mg/dL before the subsequent meal or (for the dinnertime dose) at bedtime.			weight, waist circumference, hypoglycemia, nausea, basal insulin dose	The change in waist circumference was significantly greater with pramlintide compared to rapid acting insulin analogs (-0.6 vs 2.2 cm; *P*=0.016). There were no episodes of severe hypoglycemia reported, but mild or moderate hypoglycemia occurred more frequently than nausea with both treatments and was observed more with rapid acting insulin analogs (82%) compared to pramlintide (55%; *P* value not reported). At 24 weeks, the average daily dose of insulin glargine was 57 units with rapid acting insulin analogs compared to 52 units with pramlintide (*P* value not reported).

Drug regimen abbreviations: BID=twice-daily, QID=four times daily, SC=subcutaneous, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
Miscellaneous abbreviation: BMI=body mass index, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin A_{1c}, PPG=post-prandial glucose

Special Populations

Table 5. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pramlintide	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[1]

Adverse Event	Pramlintide*
Central Nervous System	
Dizziness	2 to 6
Fatigue	3 to 7
Headache	5 to 13
Gastrointestinal	
Abdominal pain	2 to 8
Anorexia	0 to 17
Nausea	28 to 48
Vomiting	7 to 11
Respiratory	
Coughing	2 to 6
Pharyngitis	3 to 5
Other	
Allergic reaction	<1 to 6
Arthralgia	2 to 7
Inflicted injury	8 to 14
Severe hypoglycemia (medically assisted)	0.4 to 7.3
Severe hypoglycemia (patient-ascertained)	0.6 to 16.8

*In combination with insulin therapy.

Contraindications/Precautions

Pramlintide is contraindicated with a known hypersensitivity to the agent or any component of the formulation, a diagnosis of gastroparesis, and hypoglycemia unawareness.[1]

Proper patient selection is critical to safe and effective use of pramlintide. Before initiation of pramlintide, the patient's glycosylated hemoglobin (HbA_{1c}), recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight should be reviewed. Pramlintide should only be considered in patients with type 1 or 2 diabetes receiving insulin therapy who fulfills the following criteria: have failed to achieve adequate glycemic control despite individualized insulin management, and receiving ongoing care under the guidance of a healthcare professional skilled in the use of insulin and supported by the services of diabetes educators. Furthermore, patients meeting any of the following criteria should not be considered for treatment with pramlintide: poor compliance with current insulin regimen, poor compliance with prescribed self-blood glucose monitoring, have a HbA_{1c} >9.0%, 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 gastrointestinal motility, and pediatric patients.[1]

When pramlintide is used in combination with insulin therapy, the risk of insulin-induced severe hypoglycemia can be increased, particularly in type 1 diabetics. Severe hypoglycemia associated with pramlintide, when added on to insulin therapy, occurs within the first three hours following administration. Therefore, when initiating pramlintide, appropriate precautions need to be taken to avoid increasing the risk for insulin-induced severe hypoglycemia. These precautions include frequent pre- and post-meal glucose monitoring combined with an initial 50% reduction in pre-meal doses of short-acting insulin.[1]

Pramlintide should be prescribed with caution to patients with visual or dexterity impairment. Patients should be instructed on the handling of special situations such as intercurrent conditions (e.g., illness, stress), an adequate or omitted insulin dose, inadvertent administration of increased insulin of pramlintide dose, inadequate food intake, or missed meals. Pramlintide and insulin should always be administered as separate injections and never be mixed.[1]

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warnings outlined below.

Black Box Warning for Symlin®, SymlinPen® (pramlintide)[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 three 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

There are no significant drug interactions associated with the amylinomimetics.[2]

Dosage and Administration

Table 7. Dosing and Administration[1]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Pramlintide	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: Multi-dose pen, vial: initial, 15 µg SC immediately prior to major meals; maintenance, 30 to 60 µg SC immediately prior to major meals 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: Multi-dose pen, vial: Initial, 60 µg SC immediately prior to major meals; maintenance, 60 to 120 µg SC immediately prior to major meals	Safety and efficacy in children have not been established.	Multi-dose Pen: 1,000 µg/mL* Vial: 600 µg/mL (5 mL)

*Available in two sizes. The SymlinPen® 60 (1.5 mL) should be used for doses of 15, 30, 45 and 60 µg. The SymlinPen® 120 (2.7 mL) should be used for doses of 60 and 120 µg.
SC=subcutaneous

Clinical Guidelines

Current clinical guidelines are summarized in Table 8. Please note that guidelines addressing the treatment of type 1 and 2 diabetes are presented globally, addressing the role of various medication classes.

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2011)**[20]	Current criteria for the diagnosis of diabetes • 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 with a random plasma glucose ≥200 mg/dL. Prevention/delay of type 2 diabetes • 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, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • 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} ≥6.0%) despite lifestyle interventions. Glycemic goals in adults • A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • 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. Pharmacologic and overall approaches to treatment-type 1 diabetes • Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. o Matching of pre-prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For many patients, use of insulin analogs. Pharmacologic and overall approaches to treatment-type 2 diabetes • The treatment algorithm outlined below from the American Diabetes Association/European Association for the Study of Diabetes is recommended.[5] • Highlights of the algorithm include the following: o Intervention at the time of diagnosis with metformin in combination with lifestyle changes. o Continuing timely augmentation of therapy with additional agents

Clinical Guideline	Recommendations
	(including early initiation of insulin therapy) as a means of achieving and maintaining recommended glycemic goals. o As glycemic goals are not achieved, treatment intensification is based on the addition of another agent from a different class. o The overall objective is to achieve and maintain glycemic control and to change interventions when therapeutic goals are not being met. o The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets safely. o Medications not included in the algorithm still may be appropriate choices in individual patients to achieve glycemic goals. o Initiation of insulin at the time of diagnosis is recommended for patients presenting with weight loss or other severe hyperglycemia symptoms or signs.
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)**[5]	• The goal of the recommended algorithm is to achieve and maintain HbA_{1c} levels <7.0% 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, dipeptidyl peptidase-4 (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. Tier 1: well-validated core therapies • 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. Tier 2: less well-validated therapies • 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 (<8.0%), then exenatide may be an option (at the time of publication only exenatide had Food and Drug Administration [FDA] approval). • If these interventions do not effectively achieve glycemic goals or if they

Clinical Guideline	Recommendations
	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. Rationale for selecting specific combinations • 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. Special considerations/patients • In the setting of severely uncontrolled diabetes with catabolism, combination insulin and lifestyle intervention therapy is the treatment of choice.
American College of Physicians: **Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)**[21]	• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia. • Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes. • It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
American Association of Clinical Endocrinologists/ American College of Endocrinology: **Statement by an American Association of Clinical Endocrinologists/ American College of Endocrinology Consensus Panel on Type 2 Diabetes Mellitus: An Algorithm for Glycemic Control (2009)**[22]	Principles underlying the algorithm • 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, the goal must be customized for individual patients. • 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. Stratification by current HbA_{1c} • 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} 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 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

Clinical Guideline	Recommendations
	therapy with or without additional oral agents should be initiated. Management of patients with a HbA_{1c} 6.5 to 7.5% • 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 lower risk of hypoglycemia and greater flexibility in timing of administration. • 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: o Metformin + GLP-1 agonist + TZD. o Metformin + GLP-1 agonist + glinide. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + TZD. o Metformin + DPP-4 inhibitor + glinide. o 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

Clinical Guideline	Recommendations
	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. Management of patients with a HbA_{1c} 7.6 to 9.0% • 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: o Metformin + GLP-1 agonist. o Metformin + DPP-4 inhibitor. o Metformin + TZD. o Metformin + sulfonylurea. o Metformin + glinide. • Metformin is again considered the cornerstone of combination therapy. • A GLP-1 agonist or 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 post-prandial glucose (PPG) 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: o Metformin + GLP-1 agonist + TZD. o Metformin + DPP-4 inhibitor + TZD. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD + sulfonylurea. • 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 PPG 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} 6.5 to 7.5%. Management of patients with a HbA_{1c} >9.0% • Patients who are drug-naïve with an HbA_{1c} >9.0% are unlikely to achieve

Clinical Guideline	Recommendations
	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: o Metformin + GLP-1 agonist. o Metformin + GLP-1 agonist + sulfonylurea. o Metformin + DPP-4 inhibitor. o Metformin + DPP-4 inhibitor + sulfonylurea. o Metformin + TZD. o Metformin + TZD + sulfonylurea. o Metformin + GLP-1 agonist + TZD. o 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 post-prandial 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, 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 previously for patients with different HbA_{1c} levels. • This algorithm favors the use of GLP-1 agonists (at the time of publication only exenatide had 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.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[23]	<u>Glycemic management-all patients with diabetes</u> • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: o $HbA_{1c} \leq 6.5\%$. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. • Refer patients for comprehensive, ongoing education in diabetes self-

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	management skills and nutrition therapy. • Initiate self-monitoring blood glucose levels. <u>Glycemic management-patients with type 1 diabetes</u> • Initiate intensive insulin therapy with one of the following regimens: o Basal-bolus therapy, using a long-acting insulin analog in combination with a rapid-acting insulin analog or inhaled insulin at meals. o Continuous SC insulin infusion with an insulin pump; insulin pump therapy indicated for: ▪ Patients unable to achieve control using a regimen of multiple daily injections. ▪ Patients with histories of frequent hypoglycemia and/or hypoglycemia unawareness. ▪ Patients who are pregnant. ▪ Patients with extreme insulin sensitivity (pump therapy facilitates better precision than SC injections). ▪ Patients with a history of dawn phenomenon (these patients can program a higher basal rate for the early morning hours to counteract the rise in blood glucose concentration). ▪ Patients who require more intensive diabetes management because of complications including neuropathy, nephropathy, and retinopathy. ▪ Patients taking multiple daily injections who have demonstrated willingness and ability to comply with prescribed diabetes self-care behavior including frequent glucose monitoring, carbohydrate counting, and insulin adjustment. • Consider adding pramlintide to intensive insulin therapy to enhance glycemic control and to assist with weight management. • Consider adding an insulin sensitizer to address insulin resistance as needed. Exercise caution because of the potential for increased fluid retention when TZDs are used with insulin. • Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. • Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. • Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. • Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. • Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <u>Glycemic management-patients with type 2 diabetes</u> • Aggressively implement all appropriate components of care at the time of diagnosis.

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	• Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous SC insulin infusion in insulin-treated patients. • Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. • Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. • Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients. • Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. • Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. • Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. • Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving.

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	• Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <u>Clinical support-clinical considerations in patients with type 1 diabetes</u> • Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. • Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. • Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. • Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. • Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. • Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia. • Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs. • Individualize insulin regimens to accommodate patient exercise patterns. • Treat hypoglycemic reactions with simple carbohydrates. <u>Clinical support-clinical considerations in patients with type 2 diabetes</u> • Combining therapeutic agents with different modes of action may be advantageous. • Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. • Insulin is the therapy of choice in patients with advanced chronic kidney disease. • Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. • The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. • Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target.

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	• Individualize treatment regimens to accommodate patient exercise patterns. • Administer basal insulin in the evening if fasting glucose is elevated. • Long-acting insulin analogs are associated with less hypoglycemia than neutral protamine Hagedorn (NPH) insulin.
National Institute for Clinical Excellence: **Managing Type 1 Diabetes in Adults (full guideline part 2) (2008)**[24]	Insulin regimens • Patients should have access to the types (preparation and species) of insulin they find allow them optimal well-being. • Cultural preferences need to be discussed and respected in agreeing on the insulin regimen for a patient. • Multiple insulin injection regimens, in patients who prefer them, should be used as part of an integrated package of which education, food, and skills training should be integral parts. • Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes. • Mealtime insulin injections should be provided by injection unmodified ('soluble') insulin or rapid-acting insulin analogs before main meals. • Rapid-acting insulin analogs should be used as an alternative to mealtime unmodified insulin where nocturnal or late inter-prandial hypoglycemia is a problem, and in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired. • Basal insulin therapy (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogs (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogs are given at mealtimes or the midday insulin dose is small or lacking, the need to give isophane (NPH) insulin twice-daily (or more often) should be considered. • Long-acting insulin analogs (insulin glargine) should be used when: o Nocturnal hypoglycemia is a problem on isophane (NPH) insulin. o Morning hypoglycemia or isophane (NPH) insulin results in difficult daytime blood glucose control. o Rapid-acting insulin analogues are used for mealtime blood glucose control. • Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life: o Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance. o Biphasic rapid-acting insulin analog pre-mixes may give an advantage to those prone to hypoglycemia at night. o Such twice-daily regimens may also help: ▪ Those who find adherence to their agreed lunchtime insulin injection difficult. ▪ Those with learning difficulties who may require assistance from others. • Patients whose nutritional and physical activity patterns vary considerably from day-to-day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations and consideration of unusual patterns and combinations. • For patients undergoing periods of fasting or sleep following eating (e.g., during religious feasts and fasts, after night-shift work), a rapid-acting insulin analog before the meal (provided the meal is not prolonged)

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	should be considered. • For patient with erratic and unpredictable blood glucose control, rather than a change in a previously optimized insulin regimen, the following should be considered: o Re-suspension of insulin and injection technique. o Injection sites. o Self-monitoring skills. o Knowledge and self-management skills. o Nature of lifestyle. o Psychological and psychosocial difficulties. o Possible organic causes (e.g., gastroparesis). • Continuous SC insulin infusion is recommended as an option provided that: o Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and o Patients receiving the treatment have the commitment and competence to use the therapy effectively. • Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some mealtime insulin) should be considered for patients initiating insulin therapy, until such time as islet β-cell deficiency progresses further. • Clear guidelines and protocols should be given to all patients to assist them in adjusting insulin doses appropriate during intercurrent illness. • Oral glucose-lowering drugs should generally not be used in the management of type 1 diabetics. <u>Insulin delivery</u> • Patients who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen. • Patients who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing. • Insulin injection should be made into the deep SC fat. To achieve this, needles of a length appropriate to the individual should be made available. • Patients should be informed that the abdominal wall is the therapeutic choice for mealtime insulin injections. • Patients should be informed that extended-acting suspension insulin (e.g., isophane [NPH] insulin) may give a longer profile of action when injected into the SC tissue of the thigh rather than the arm or abdominal wall. • Patients should be recommended to use one anatomical area for the injections given at the same time of day, but to move the precise injection site around in the whole of the available skin within that area. • Patients should be provided with suitable containers for the collection of used needles. Arrangements should be available for the suitable disposal of these containers. • Injection site condition should be checked annually, and if new problems with blood glucose control occur.
National Institute for Clinical Excellence/National	<u>Insulin regimens</u> • Pre-school and primary school children should be offered the most appropriate individualized regimens to optimize glycemic control.

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Collaborating Center for Women's and Children's Health: **Diagnosis and Management of Type 1 Diabetes in Children and Young People (2004 and 2009 Update)**[25]	• Young people should be offered multiple daily injection regimens to help optimize glycemia control. • As it improves glycemic control, multiple daily injection regimens should be offered only as part of a package of care that involves continuing education; dietary management; instruction on the use of insulin delivery systems and blood glucose monitoring; emotional and behavioral support; and medical, nursing, and dietetic expertise in pediatric diabetes. • Children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycemia and short-term weight gain. • Children and young people and their families should be informed about strategies for the avoidance and management of hypoglycemia. • Young people who do not achieve satisfactory glycemic control with multiple daily injection regimens should be offered additional support and, if appropriate, alternative insulin therapy (once-, twice-, or three-times daily mixed insulin regimens or continuous SC insulin infusion using an insulin pump). • Young people who have difficulty adhering to the multiple daily injection regimens should be offered twice-daily injection regimens. • Continuous SC insulin infusion is recommended as an option for patients provided that: o Multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed, and; o Patients receiving the treatment have the commitment and competence to use the therapy effectively. • Continuous SC insulin infusion therapy should be initiated only by a trained specialist team. • All individuals beginning continuous SC insulin infusion therapy should be provided with specific training in its use. • Established users of continuous SC insulin infusion therapy should have their insulin management reviewed by their specialist team so that a decision can be made about whether a trial or a switch to multiple-dose insulin incorporating insulin glargine would be appropriate. <u>Insulin preparations</u> • Children and young people should be offered the most appropriate insulin preparations according to their individual needs with the aim of obtaining an HbA_{1c} <7.5% without frequent disabling hypoglycemia and maximizing quality of life. • Children and young people using multiple daily insulin regimens should be informed that injection of rapid-acting insulin analogs before eating (rather than after eating) reduces PPG levels thus helps to optimize blood glucose control. • For pre-school children it may be appropriate to use rapid-acting insulin analogs shortly after eating (rather than before eating) because food intake can be unpredictable. • Children and young people who use insulin preparations containing intermediate-acting insulin should be informed that these preparations should be mixed before use according to instructions provided in patient information leaflets. <u>Insulin delivery</u> • Children and young people should be offered a choice of insulin delivery

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	systems that takes account of their insulin requirements and personal preferences. • Children and young people using insulin injection regimens should be offered needles that are of an appropriate length for their body fat. Non-insulin agents (oral antidiabetic agents) • Children and young people should not be offered acarbose or sulfonylureas in combination with insulin because they may increase the risk of hypoglycemia without improving glycemic control. • Metformin in combination with insulin is suitable for use only within research trials because the effectiveness of this combination therapy in providing glycemic control is uncertain.

Conclusions

Pramlintide (Symlin®, SymlinPen®) is the only agent within the amylinomimetic medication class, and is Food and Drug Administration-approved as adjunctive therapy to mealtime insulin for the management of diabetes (type 1 and 2). Pramlintide is approved for use in combination with insulin therapy, specifically in patients unable to achieve desired glucose control despite optimal insulin therapy.[1] Data from clinical trials demonstrate that treatment with pramlintide is associated with significant baseline reductions in glycosylated hemoglobin compared to treatment with placebo in type 1 and 2 diabetics already receiving insulin. Furthermore, treatment with pramlintide is associated with significant baseline reductions in fasting plasma glucose levels, post-prandial glucose levels, insulin use, and body weight.[6-19] Although pramlintide itself does not cause hypoglycemia, when used in combination with insulin therapy, the risk of insulin-induced hypoglycemia can be increased.[1]

In general, current clinical guidelines do not support the use of amylinomimetics in the management of type 2 diabetes.[5,20-23] Among type 1 diabetic patients, the addition of pramlintide to first-line insulin therapy may be considered to enhance glycemic control and to assist with weight management.[23]

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