

# Pramlintide Acetate

(Symlin® - Amylin Pharmaceuticals)

by Heather Swartz

Column Editor: Lee Vermeulen, MS, RPh, Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

**R**esults of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that improvement in glycemic control results in a significant reduction in risk for long-term microvascular complications in patients with type 1 or type 2 diabetes.<sup>6,7</sup> Yet despite the clear benefits of maintaining euglycemia and advances in insulin therapy, only a small portion of patients with type 1 or type 2 diabetes are meeting glycemic targets. A study following patients with type 1 and type 2 diabetes found that despite an increase in the number of patients using insulin three or more times daily, the average A1C values at the 10-year follow-up were  $10.0\% \pm 1.7\%$  and  $9.5\% \pm 1.9\%$  for type 1 and type 2 patients, respectively.<sup>8</sup> These values far exceed the recommended A1C goal of  $<7\%$  established by the American Diabetes Association (ADA).<sup>9</sup>

Several clinical barriers have been identified which limit the effectiveness of insulin therapy in achieving glycemic targets in patients with type 1 and type 2 diabetes.<sup>10</sup> Although there have been advances in insulin delivery methods in recent years and rapid-acting insulin products are now available, insulin therapy still does not parallel physiological insulin kinetics and release in the postprandial period.<sup>10</sup> The inability of insulin therapy in diabetic patients to mimic the activity of the hormone in non-diabetic patients results in fluctuations in postprandial blood glucose and subsequent excessive diurnal glycemic fluctuations in insulin-using patients with diabetes.<sup>10,11</sup> Both the DCCT and the UKPDS found that while intensive insulin therapy can improve glycemic control and reduce risks of long-term complications, it also significantly increases patients' risk of severe hypoglycemia.<sup>6,7</sup> The narrow therapeutic window for insulin may in part explain this risk for hypoglycemia, as patients must carefully adjust insulin doses based on meal size, composition, and duration, as well as their level of physical activity.<sup>10</sup> The DCCT and the UKPDS also found a connection between insulin therapy and weight gain, with patients on intensive insulin regimens gaining an average of 4.0–4.6 kg.<sup>6,7</sup> The weight gain associated with insulin use represents not only a cosmetic issue, but also puts patients at increased risk for cardiovascular disease.<sup>10</sup>

The problems and limitations of insulin therapy have led to the search for new agents that will allow patients to achieve their glycemic goals. The discovery of amylin, a peptide that reduces postprandial glucose and is deficient in patients with type 1 diabetes and late-stage type 2 diabetes, elicited attention as a possible new approach to diabetes therapy.<sup>12</sup> Pramlintide, the first-in-class amylin analog, received Food and Drug Administration (FDA) approval on March 16, 2005.<sup>13</sup>

## Summary

**Indications.** Pramlintide is indicated as adjunctive therapy in patients with type 1 diabetes who have not achieved adequate glycemic control despite optimal mealtime insulin therapy.<sup>1</sup> Pramlintide is also indicated as adjunctive treatment in patients with type 2 diabetes who use mealtime insulin, with or without a concurrent sulfonylurea agent and/or metformin, and have not achieved adequate glycemic control despite optimal insulin therapy.

**Monitoring Parameters.** Improvement in glycemic control should be monitored by following patient blood glucose and glycosylated hemoglobin (A1C) values. Because pramlintide treatment has been associated with weight loss in patients with type 1 and type 2 diabetes, body weight is another therapeutic monitoring parameter. While pramlintide itself does not cause hypoglycemia, the pramlintide prescribing information includes a boxed warning indicating that co-administration of this agent with mealtime insulin therapy can place patients at increased risk for insulin-induced severe hypoglycemia. Patients should therefore be carefully monitored for blood glucose concentrations and signs and symptoms of hypoglycemia. The most common adverse event reported with pramlintide therapy has been nausea. The nausea is usually mild to moderate, primarily occurs during the first few weeks of therapy, and subsequently dissipates over time.<sup>1</sup>

**Dosing and Administration.** In patients with type 1 diabetes, pramlintide dosing should be initiated at 15 mcg subcutaneously and titrated in 15 mcg increments to a maintenance dose of 30 mcg or 60 mcg as tolerated. In insulin-using patients with type 2 diabetes, pramlintide should be started at a dose of 60 mcg subcutaneously and increased to 120 mcg as tolerated. For all patients beginning pramlintide therapy, pre-prandial rapid-acting or short-acting insulin dosages, including fixed-mix insulins (70/30), should be reduced by 50% and adjusted to optimize glycemic control once the target dose of pramlintide has been achieved. Pramlintide and insulin dose adjustments should be made under the direction of a health care professional. All pramlintide doses should be administered subcutaneously into the abdomen or thigh immediately prior to major meals ( $\geq 250$  calories or containing  $\geq 30$  g of carbohydrate), with injection sites being rotated. The manufacturer recommends that pramlintide be administered using a U-100 insulin syringe (preferably a 0.3 mL syringe) and instructs that pramlintide and insulin should not be mixed and should always be administered with separate injections. A recent study found that mixing pramlintide with short- or long-acting insulin in the same syringe prior to injection did not affect the pharmacodynamics of glucose or the pharmacokinetics of

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## Summary *continued* . . .

insulin or pramlintide in a clinically significant manner.<sup>2</sup> However, the authors urged caution in the interpretation of these results, as not all available insulin products or doses were tested.

**Pediatrics.** Pramlintide has not been evaluated in the pediatric population.<sup>1</sup> Pramlintide was administered in doses of 30–45 mcg to eight patients with type 1 diabetes between the ages of 12 and 18 and was found to acutely reduce postprandial hyperglycemia.<sup>3</sup>

**Geriatrics.** Although no pharmacokinetic studies have been carried out for pramlintide in the geriatric population, no consistent age-related differences in pramlintide activity were observed in the 539 patients 65 years of age or older included in clinical trials.<sup>1</sup>

**Renal Insufficiency.** Compared with subjects with normal renal function, patients with moderate or severe renal impairment (CrCl >20 to ≤50 mL/min) did not show increased exposure to pramlintide or reduced clearance of the drug.

**Hepatic Insufficiency.** While no pharmacokinetic studies have been performed in patients with hepatic impairment, pramlintide is largely metabolized by the kidney, and hepatic dysfunction is therefore not expected to change the blood concentrations of pramlintide.

**Pregnancy.** Category C. There have been no adequate and well-controlled studies in pregnant women. Ex vivo studies using perfused human placenta show that pramlintide negligibly passes the placental barrier.<sup>4</sup> Studies in rats show increased incidence of congenital abnormalities (neural tube defect, cleft palate, exencephaly) at pramlintide doses of 0.3 and 1.0 mg/kg/day (10 and 47 times the exposure represented by the maximum recommended human dose based on AUC, respectively).<sup>1</sup> In pregnant rabbits, doses of up to 0.3 mg/kg/day of pramlintide had no adverse effects on embryofetal development. Because animal reproduction studies are not always predictive of human response, and due to the lack of data in humans, pramlintide should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

**Breastfeeding.** The excretion of pramlintide in human milk has not been studied. However, many drugs, including peptide drugs, are excreted in human milk. Pramlintide should therefore be used in nursing women only when the potential benefit outweighs the risk to the infant.<sup>1</sup>

**Stability and Storage.** Unopened vials of pramlintide should be refrigerated in controlled temperatures between 36°F and 46°F (2°C to 8°C) and protected from light. Pramlintide should not be frozen, and frozen or overheated vials should be discarded. Unopened vials should not be used beyond the expiration date on the vial. Opened vials can be refrigerated or kept at room temperature for up to 28 days as long as the temperature does not exceed 77°F (25°C). Opened vials should be disposed of after 28 days.<sup>1</sup>

**Cost, How Supplied.** The AWP of pramlintide is \$95.40 per 5 mL vial.<sup>5</sup> Pramlintide is supplied as a sterile injection in 5 mL vials containing 0.6 mg/mL pramlintide as an acetate.

## PHARMACOLOGY/PHARMACOKINETICS/ PHARMACODYNAMICS

Amylin is a 37–amino acid peptide that is structurally unrelated to insulin.<sup>10</sup> This peptide is packaged with insulin in secretory granules and is co-secreted with insulin from pancreatic beta cells in response to food intake.<sup>10</sup> Amylin acts as a neuroendocrine hormone and binds receptors in the central nervous system to reduce the postprandial rise in blood glucose by modulating the flow of glucose into the circulation following meals.<sup>10,12</sup> It exerts this effect by suppressing glucagon secretion (and thereby limiting hepatic glucose output) and slowing the rate of gastric emptying, a vagally mediated effect.<sup>10</sup> Amylin also appears to play a role in signaling postprandial satiety, and thus regulates feeding behavior and body weight.

Amylin itself is not a candidate for a pharmaceutical product because it self-aggregates; adheres to surfaces, including infusion apparatuses; forms  $\beta$ -pleated sheets, amyloid fibrils, and amyloid plaques; and is insoluble in pharmaceutical diluents.<sup>2,12</sup> Because these characteristics limit amylin's use as a therapeutic agent, pramlintide, the synthetic peptide analog of human amylin, was developed by selectively substituting prolines for positions 25 (alanine), 28 (serine), and 29 (serine).<sup>1</sup> Pramlintide has demonstrated the same full range of physiological effects as amylin with potency at least equal to its natural analog.<sup>10</sup> As an amylinomimetic agent, pramlintide slows the rate of gastric emptying without altering nutrient absorption, prevents the rise in plasma glucagon following meals, and centrally mediates satiety to reduce food intake and promote weight loss.<sup>1,10</sup>

A single subcutaneous dose of pramlintide has an absolute bioavailability of 30% to 40%.<sup>1</sup> Higher exposure with greater variability occurs after pramlintide injections in the arm, compared with abdominal or thigh injections. Skin fold thickness and degree of adiposity have not been found to strongly correlate with relative bioavailability. The time-to-peak concentration for a subcutaneous pramlintide injection is 27 minutes.<sup>14</sup> Because pramlintide does not extensively bind to blood cells or albumin (with approximately 40% being unbound in the plasma), pramlintide pharmacokinetics should not be affected by changes in binding sites.<sup>1</sup> The volume of distribution of pramlintide is 56 liters.<sup>14</sup> Pramlintide is primarily metabolized by the kidneys and has a half-life of approximately 48 minutes in healthy subjects.<sup>1</sup> Pramlintide's primary metabolite, Des-lys<sup>1</sup> pramlintide, has a similar half-life and is active both in vitro and in rats. No increased pramlintide exposure has been seen in patients with moderate to severe renal impairment (CrCl >20 to ≤50 mL/min), and no dosage adjustments are currently recommended for patients with renal or hepatic dysfunction. Because of its wide therapeutic window, pramlintide, unlike insulin, does not require mealtime dose adjustments based on meal size, carbohydrate content, or blood glucose levels.<sup>15</sup>

## CLINICAL TRIALS

### *Type 1 Diabetes*

Three randomized, long-term, double-blind, placebo-controlled, multicenter trials have been conducted using pramlintide in patients with type 1 diabetes.<sup>16–18</sup> An evidence table summarizing

these trials can be found in Appendix A. Enrollment for all three trials totaled 1717 patients, with two of the trials lasting for 52 weeks and the other for 26 weeks. Doses studied ranged from pramlintide 30 mcg four times daily to pramlintide 90 mcg three times daily. The mean change in A1C values achieved with pramlintide treatment ranged from +0.1% to -0.39% at the studies' final time points. Weight loss with pramlintide therapy ranged from 0.4 kg to 1.6 kg at final study endpoints, compared with an average weight gain seen in placebo groups. The most common adverse events reported in the trials were nausea, anorexia and vomiting. Two trials reported increased rates of severe hypoglycemia in patients using pramlintide in addition to their usual insulin regimens.

### *Type 2 Diabetes*

Three randomized, long-term, double-blind, placebo-controlled, multicenter trials have also been conducted using pramlintide in patients with type 2 diabetes.<sup>19-21</sup> The results of these trials are summarized in the evidence table located in Appendix B. Enrollment for all three trials totaled 1693 patients, with two trials lasting for 52 weeks and the other for 26 weeks. Doses studied ranged from pramlintide 30 mcg three times daily to pramlintide 150 mcg three times daily. The mean reduction in A1C seen with pramlintide therapy ranged from -0.3% to -0.62% at the studies' conclusions. Weight loss with pramlintide treatment ranged from -0.5 kg to -1.4 kg at final study endpoints, compared with a weight gain seen in placebo groups. The most common adverse events reported in the trials involving type 2 diabetic patients were nausea and headache. One trial reported an increased rate of severe hypoglycemia in pramlintide-treated patients during the first 4 weeks of treatment.

## **CLINICAL TRIALS FOR UNAPPROVED INDICATIONS**

### *Obesity in Patients without Diabetes*

Chapman et al conducted a randomized, double-blind, placebo-controlled crossover trial in which 11 insulin-treated men with type 2 diabetes and 15 non-diabetic obese men underwent two standardized meal tests.<sup>22</sup> Subjects were between the ages of 18 and 70, were euthyroid, had stable weight, and were unrestrained eaters as determined by the Three-Factor Eating Questionnaire. Patients fasted overnight, then reported to the study center to receive either a 120-mcg injection of pramlintide or placebo, followed by a preload meal. Patients were offered an ad libitum buffet meal after 1 hour, and energy intake, meal duration, and hunger and fullness ratings were measured. Blood samples were also collected, and plasma cholecystokinin, glucagon-like peptide-1, and peptide YY concentrations over time were measured. In both patients with type 2 diabetes and obese patients, total energy intake at the buffet meal was significantly reduced following pramlintide injection when compared with placebo (-202 ± 64 kcal, or -23% ± 8%, for patients with diabetes [ $P < 0.01$ ] and -170 ± 68 kcal, or -16% ± 6%, for obese patients [ $P < 0.02$ ]). Decreases in hunger ratings following the preload and buffet meals and increases in fullness in response to the buffet meal were comparable between the placebo and pramlintide groups, suggesting that around 20% less energy intake was required following pramlintide injection to achieve the same levels of hunger

reduction and fullness compared with placebo. Measurement of anorexigenic gut hormones revealed that none of these factors appears to account for the reduction in food intake associated with pramlintide, indicating that pramlintide exerts its satiating effect independent of these hormones. This trial provides evidence that pramlintide may enhance satiety in patients with and without diabetes, and the drug is currently in clinical development as a potential obesity treatment for non-diabetic patients.

### *Glycemic Control in Patients With Type 2 Diabetes Not Treated with Insulin*

Pramlintide is currently FDA-approved only for insulin-treated patients with type 2 diabetes. A few studies examining the acute effects of pramlintide have included patients with type 2 diabetes not using insulin. Thompson et al conducted a single-blind, randomized, cross-over study of 24 patients with type 2 diabetes, 12 of whom were not using insulin and were managing their disease with diet and/or oral hypoglycemic agents.<sup>23</sup> During the study, patients received an infusion of pramlintide or placebo. One hour following the start of the infusion, patients consumed a Sustacal test meal. Patients repeated this process on the next day with the alternate injection. Blood samples were collected for the four-hour period following the test meal to measure concentrations of glucose, insulin, C-peptide, and lactate.

In the insulin-treated patients, significant reductions were seen in all measured values, with mean plasma glucose concentrations for the 4-hour period being reduced to  $10.2 \pm 0.8$  mmol<sup>-1</sup> during the pramlintide infusion compared with  $13.7 \pm 0.9$  mmol<sup>-1</sup> for placebo ( $P = 0.0031$ ). There were also significant reductions in mean plasma insulin, C-peptide, and lactate concentrations for patients treated with just diet and/or oral antidiabetic agents, but pramlintide did not significantly reduce mean glucose concentrations ( $9.5 \pm 0.9$  mmol<sup>-1</sup> during the pramlintide infusion compared with  $10.2 \pm 1.1$  mmol<sup>-1</sup> during the placebo infusion,  $P = 0.15$ ). Reduction in postprandial glucose concentrations was correlated with A1C values among patients not using insulin, with the five patients with A1C values higher than 8.0% showing a statistically significant reduction in incremental glucose AUC for the 4 hours following the standard meal ( $P = 0.032$ ).

A separate publication by Fineman et al on the same study indicated that pramlintide infusion significantly reduced postprandial glucagon response in patients with or without concurrent insulin treatment.<sup>24</sup> Pramlintide treatment reduced the glucagon AUC to  $8096 \pm 581$  pg x min/mL versus  $9200 \pm 580$  pg x min/mL for placebo ( $P = 0.005$ ) in the insulin-treated group, while also reducing the glucagon AUC in the non-insulin-treated group to  $7450 \pm 429$  pg x min/mL compared with  $8483 \pm 487$  pg x min/mL for placebo ( $P = 0.01$ ). These studies suggest that pramlintide may offer improved glycemic control for patients with type 2 diabetes not using insulin if their disease is poorly controlled with diet and/or oral agents.

## **DRUG INTERACTIONS**

Because pramlintide slows the rate of gastric emptying, it should not be used in patients taking drugs that change gastric motility, such as anticholinergic agents, and medications that slow intestinal nutrient absorption, including alpha-glucosidase inhibi-

tors.<sup>1</sup> Pramlintide's effect on gastric emptying may also delay the absorption of concomitantly administered oral agents. If rapid onset is important for the effectiveness of the oral agent, such as with pain medications, the oral product should be taken at least 1 hour before or 2 hours after pramlintide injection. No formal interaction studies have been conducted to examine the effects of pramlintide on oral antidiabetic agents, although concurrent use of sulfonylureas or biguanides did not alter the rate of adverse events in clinical trials.

### ADVERSE EFFECTS

Although pramlintide by itself does not cause hypoglycemia, it can increase the risk of severe hypoglycemia when co-administered with insulin, particularly in patients with type 1 diabetes.<sup>1</sup> Severe hypoglycemic events usually occur within 3 hours of the pramlintide injection. During the first 3 months of therapy in long-term, placebo-controlled trials in patients with type 1 diabetes, 16.8% of the pramlintide-treated patients had self-ascertained severe hypoglycemia compared with 10.8% of patients receiving placebo. Medical assistance for severe hypoglycemia was required by 7.3% and 3.3% of pramlintide- and placebo-treated patients, respectively. In patients with type 2 diabetes, 8.2% of patients treated with pramlintide had self-ascertained severe hypoglycemia during the first 3 months of treatment during clinical studies, compared with 2.1% of subjects receiving placebo. The incidence of hypoglycemic events requiring medical assistance was 1.7% for pramlintide-treated patients and 0.7% for patients receiving placebo. The boxed warning regarding hypoglycemia in the pramlintide prescribing information notes that because severe hypoglycemia could lead to major injuries if it occurs while a patient is operating a motor vehicle or engaged

in other high-risk activities, prescribers are urged to carefully select patients for treatment with this drug, to thoroughly instruct patients on its use, and to appropriately adjust patients' insulin doses.

Adverse events other than hypoglycemia are presented in the following tables. Table 1 lists adverse events occurring with greater incidence in pramlintide-treated patients compared with placebo in long-term, placebo-controlled studies of patients with type 1 diabetes. Adverse events occurring with greater incidence with pramlintide than with placebo in long-term, placebo-controlled trials of patients with type 2 diabetes are contained in Table 2. The incidence of nausea in patients treated with pramlintide was higher at the beginning of pramlintide treatment and dissipated over time. Gradual titration of pramlintide dosing can reduce the incidence and severity of nausea.<sup>1</sup>

### MEDICATION SAFETY

Several potential risks for dosing and administration errors have been identified that may interfere with the safe use of pramlintide. One major concern is that while pramlintide is dosed in micrograms, the manufacturer recommends that the medication be administered with U-100 insulin syringes. Administering pramlintide with insulin syringes requires the conversion of micrograms to insulin unit equivalents for each pramlintide dose. Some practitioners fear that patients may inadvertently confuse units with micrograms and administer overdoses which could cause serious harm. In addition, the patient Medication Guide does not provide information regarding volume of pramlintide doses, which means that patients may be unable to measure doses if their prescribers recommend the use of tuberculin syringes with pramlintide to reduce confusion with insulin dosing. Because insulin and pramlintide will be administered at approximately the same time, by the same route, and using the same type of syringe, patients could also confuse their insulin and pramlintide doses. Patient education will be vital for all patients started on pramlintide therapy. Because instruction for titration of pramlintide doses and adjustments in insulin doses will not fit on pharmacy labels, it will be critical for prescribers to provide detailed written instructions to patients and for pharmacists to check that patients have received this material. Patients will also need guidance on monitoring their response to pramlintide therapy and should be instructed to record blood sugar values and pramlintide and insulin doses. The Institute for Safe Medication Practices has recommended that a unique dosing device be provided for pramlintide, or, alternatively, that pramlintide be formulated to be less concentrated so that tuberculin syringes can easily be used to measure the product.<sup>25</sup>

**TABLE 1: ADVERSE EVENTS IN TYPE 1 DIABETES TRIALS<sup>1</sup>**

Adverse Event	Pramlintide	Placebo
Nausea	48%	17%
Anorexia	17%	2%
Inflicted Injury	14%	10%
Vomiting	11%	7%
Arthralgia	7%	5%
Fatigue	7%	4%
Allergic Reaction	6%	5%
Dizziness	5%	4%

**TABLE 2: ADVERSE EVENTS IN TYPE 2 DIABETES TRIALS<sup>1</sup>**

Adverse Event	Pramlintide	Placebo
Nausea	28%	12%
Headache	13%	7%
Anorexia	9%	2%
Vomiting	8%	4%
Abdominal Pain	8%	7%
Fatigue	7%	4%
Dizziness	6%	4%
Coughing	6%	4%
Pharyngitis	5%	2%

### COST, DOSE, AND HOW SUPPLIED

The AWP of a pramlintide 0.6 mg/mL 5 mL vial is \$95.40.

In patients with type 1 diabetes, pramlintide therapy should be initiated at 15 mcg subcutaneously immediately prior to major meals and titrated in 15-mcg increments to a maintenance dose of 30 mcg or 60 mcg as tolerated. Pre-prandial rapid-acting or short-acting insulin doses (including fixed-mix insulins [70/30]) should be reduced by 50% and adjusted to optimize

glycemic control once the target dose of pramlintide has been achieved. Patients should monitor blood glucose frequently (pre- and post-meals and at bedtime). Pramlintide and insulin dose adjustments should be made under the direction of a health care professional. Pramlintide doses should be administered subcutaneously into the abdomen or thigh immediately prior to major meals ( $\geq 250$  calories or containing  $\geq 30$  g of carbohydrate), with injection sites being rotated. The manufacturer recommends that pramlintide be administered using a U-100 insulin syringe (preferably a 0.3 mL size) and instructs that pramlintide and insulin should not be mixed and should always be administered with separate injections.

In insulin-using patients with type 2 diabetes, pramlintide should be started at a dose of 60 mcg subcutaneously immediately prior to major meals and increased to 120 mcg as tolerated. Patients beginning pramlintide therapy should reduce pre-prandial rapid-acting or short-acting insulin doses (including fixed-mix insulins [70/30]) by 50%, then adjust insulin doses to optimize glycemic control once the target dose of pramlintide has been achieved. Patients should monitor blood glucose frequently (pre- and post-meals and at bedtime). Pramlintide and insulin dose adjustments should be made under the direction of a health care professional. Pramlintide doses should be administered subcutaneously into the abdomen or thigh immediately prior to major meals ( $\geq 250$  calories or containing  $\geq 30$  g of carbohydrate), with injection sites being rotated. The manufacturer recommends that pramlintide be administered using a U-100 insulin syringe (preferably a 0.3 mL size) and instructs that pramlintide and insulin should not be mixed and should always be administered with separate injections.

The manufacturer provides the following pramlintide dose conversion table for health care providers<sup>1</sup>:

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

## CONCLUSION

The UWHC Pharmacy and Therapeutics Committee denied pramlintide formulary status at this time. Endocrinologists consulted indicated that they will likely prescribe pramlintide for a small number of patients on insulin with inadequate glycemic control and weight problems. Physicians have expressed concern about the use of pramlintide in hospitalized patients, as it may delay the effects of oral medications due to its effect on gastric emptying, as well as increase the risk of hypoglycemia in patients who may already have blood glucose control issues secondary to illness, concurrent medications and intravenous fluids. In the ambulatory patient population, careful patient selection and thorough instruction will be critical for the safe use of pramlintide, given the dosing and administration risks discussed above. The relatively small improvements in A1C and weight achieved

with pramlintide, along with various medication safety issues, suggest that pramlintide will be used in a limited number of patients with diabetes who have not achieved adequate glycemic control with insulin +/- oral medications. ●

Heather Swartz is a fourth-year PharmD student at the UW School of Pharmacy and developed this paper while on rotation at the Center for Drug Policy, University of Wisconsin Hospital and Clinics, Department of Pharmacy.

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## APPENDIX A

### Long-term Trials, Type 1 Diabetes

Reference	Patients	Design/Duration	Intervention	A1C Change	Body Weight Change	Comments
Whittemore (2002) <sup>16</sup>	430	R, DB, PC, MC 52 weeks	Praminide 30 mg QID Praminide 60 mg QID Placebo	-0.39% (P=0.0071) -0.12% (week 52)	-0.5 kg (P<0.001) +1.0 kg (week 52)	Seventy-one percent of study subjects completed 52 weeks of treatment (186 patients treated with placebo, 174 treated with praminide). The study also included a one-year open-label extension in which all 238 participants received praminide 30 or 60 mg QID. Subjects switched to praminide at the beginning of the open-label study saw similar reductions in A1C and weight as those receiving praminide during the double-blind trial. Patients in the open-label trial who were continued on praminide maintained lowered A1C values compared with baseline but tended to regain weight.
Katzev (2004) <sup>17</sup>	651	R, DB, PC, PG, MC 52 weeks	Praminide 60 mg TID Praminide 60 mg QID Praminide 60 mg TID Placebo	-0.29% (P=0.011) -0.24% (P=0.001) Excluded -0.04% (week 52)	-0.4 kg (P=0.027) -0.4 kg (P=0.040) Excluded +0.8 kg (week 52)	Data from the praminide 60 mg treatment arm were excluded from the efficacy analysis because information became available during the study that this regimen had an adverse tolerability profile compared with lower doses. After exclusion of the 60-mg praminide group, 479 patients remained available for evaluation. Sixty-three percent of the remaining patients completed 52 weeks of treatment (133 patients treated with placebo, 95 patients receiving praminide 60 mg TID, and 135 patients treated with praminide 60 mg QID).
Hindman (1998) <sup>18</sup> [abstract only]	690	R, DB, PC, MC 26 weeks	Praminide 60 mg TID Praminide 60 mg BID Praminide 60 mg TID Placebo	-0.2% (P=0.207) -0.1% (P=0.048) +0.1% (P=0.105) +0.1% (week 26)	-1.6 ± 0.27 kg -0.7 ± 0.35 kg -1.6 ± 0.27 kg +0.3 ± 0.36 kg (week 26)	Study available only as a meeting abstract.

R=randomized; DB=double-blind; PC=placebo-controlled; PG=parallel-group; MC=multicenter; NS=not statistically significant.

## APPENDIX B

### Long-term Trials, Type 2 Diabetes

Reference	Patients	Design/Duration	Intervention	A1C Change	Body Weight Change	Comments
Baker (2002) <sup>19</sup>	538	R, DB, PC, MC, dose-titration 52 weeks	Praminide 30 mg TID Praminide 75 mg TID Praminide 150 mg TID Placebo	-0.3% (NS) -0.5% (NS) -0.6% (P<0.01) -0.2% (week 52)	-0.5 kg (P<0.01) -0.6 kg (P<0.01) -1.3 kg (P<0.01) +1.0 kg (week 52)	Of the 538 subjects enrolled, 561 (71%) completed the 52-week study. The overall withdrawal rates in the 30 mg and 75 mg dose groups were similar to the placebo group. The 150 mg praminide dose group had a higher withdrawal rate, primarily due to adverse effects (especially nausea).
Hollander (2005) <sup>20</sup>	458	R, DB, PC, PG, MC 52 weeks	Praminide 60 mg TID Praminide 60 mg BID Praminide 120 mg BID Placebo	Excluded -0.35% (NS) -0.62% (P<0.05) -0.22% (week 52)	Excluded -0.5 kg (NS) -1.2 kg (P<0.05) +0.7 kg (week 52)	The praminide 60 mg TID group was excluded from the efficacy analysis because results from another trial became available during this study which indicated that this regimen was less effective. Of the remaining 438 patients, 113 (70%) placebo-treated patients, 122 (71%) patients in the praminide 60 mg BID group, and 113 (88%) patients receiving praminide 120 mg BID completed 52 weeks of treatment.
Gallardo (1995) <sup>21</sup> [abstract only]	439	R, DB, PC, MC 26 weeks	Praminide 60 mg BID Praminide 60 mg TID Praminide 120 mg BID Placebo	-0.3% (P=0.058) -0.4% (P=0.076) -0.4% (P=0.028) -0.1% (week 26)	-0.8 ± 0.3 kg -1.3 ± 0.3 kg -1.4 ± 0.3 kg +0.1 ± 0.3 kg (week 26)	Study available only as a meeting abstract.

R=randomized; DB=double-blind; PC=placebo-controlled; PG=parallel-group; MC=multicenter; NS=not statistically significant.

## Parasites Tighten Grip on Unwary Humans

The following paragraph introduced an article published in the *Wisconsin Pharmacist*, February 1969.

Permissiveness and promiscuity, venery and vice, love-ins and lice—these and related factors have quite suddenly come to the attention of medical editors as more and more physicians are called on to treat parasitic infections among their patients.

The article concluded,

With the foresight provided by these guidelines, we can look forward to a future in which lice and mites—like bacteria and fungi that attack the skin—will be literally routinely washed away.

125 years