National PBM Drug Monograph
Pramlintide (Symlin®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

EXECUTIVE SUMMARY

- Pramlintide is a synthetic analog of the neuroendocrine hormone amylin. Amylin works in concert with insulin in maintaining glucose homeostasis. Amylin suppresses postprandial glucagon and slows the rate of gastric emptying.

- Pramlintide is administered with insulin, not in place of insulin.

- Pramlintide is contraindicated in patients with gastroparesis.

- Pramlintide is approved for use in adults with type 1 and type 2 diabetes as adjunctive treatment to mealtime insulin therapy in patients who have been unable to achieve desired glucose control despite optimal insulin therapy (with or without concurrent sulfonylurea or metformin therapy for type 2 diabetes).

- Pramlintide has been studied in patients with type 1 and type 2 diabetes. There are two 26-week and four 52-week pivotal trials. In type 1 diabetes, the mean change in HbA1c ranged from -0.1 to -0.39% with pramlintide compared to -0.12 to +0.09% in the placebo group. In type 2 diabetes, the mean change in HbA1c ranged from -0.3 to -0.62% with pramlintide versus -0.15 to -0.25% with placebo.

- In type 1 diabetes, mean weight loss with pramlintide ranged from -1.0 to -2.3kg in the 26-week trial compared to a weight gain of 0.3kg with placebo. However, patients tended to regain weight as seen in the 52-week trials where mean weight change with pramlintide was -0.3 to -0.5kg and +0.8 to 1.0kg with placebo. A similar pattern is seen in type 2 diabetes. Mean weight change in the 26-week trial for pramlintide and placebo was -0.9 to -1.7kg and 0kg respectively. For the 52-week trials the changes were -0.4 to -1.3kg versus +0.75 to +1.1kg respectively.

- Nausea, vomiting and anorexia are the most commonly reported adverse events and tend to abate over time. Severe hypoglycemia, defined as requiring either third party assistance, administration of glucagon, or IV glucose, occurred more frequently in the pramlintide groups. Severe hypoglycemia occurred more often in type 1 than in type 2 diabetes. Severe hypoglycemia occurred most often during the first 4 weeks of therapy.

- Pramlintide carries the following **black box warning** for insulin-induced severe hypoglycemia: Hypoglycemic risk in higher in patients with type 1 diabetes, and usually occurs within 3 hours of injection. The black box also warns against the risk of hypoglycemia during driving or operating heavy machinery.

- The manufacturer recommends that pramlintide and insulin NOT be mixed in the same syringe. Pramlintide should be injected into a site different from where insulin is injected.

- Pramlintide is administered immediately prior to each major meal containing $\geq$ 250kcal or containing $\geq$ 30 grams of carbohydrate.

- The modest decrease in HbA1c and weight must be balanced by adverse drug reactions, inconvenient administration, potential for drug errors, and cost. It is recommended that pramlintide not be added to the national or VISN formularies at this time.

INTRODUCTION

Several hormones and peptides are involved in maintaining glucose homeostasis. One such hormone is amylin, which has been shown to suppress postprandial glucagon, slow the rate of gastric emptying, and regulate satiety. In non-diabetic subjects, fasting amylin concentrations range between 4-11 pmol/l and increase 2- to 3-fold in response to a meal. In type 1 diabetes, amylin concentrations are nearly undetectable and do not increase with meals. In type 2 diabetes, amylin follows a fate similar to insulin where levels are elevated early on in the disease and diminish over time. Pramlintide, a synthetic analog of the neuroendocrine hormone amylin is reviewed.

PHARMACOLOGY

Pramlintide differs from human amylin by 3 amino acid residues, replacing ^{25}Ala, ^{28}Ser, and ^{29}Ser with prolines. Amylin works in concert with insulin in maintaining glucose homeostasis. Both amylin and insulin are co-secreted from the pancreatic β-cell and are packaged in the same secretory granule. Amylin and insulin circulate in plasma in a molar ratio of ~1:20.

The neuroendocrine effects of amylin are thought to be orchestrated via the central nervous system. While the exact mechanism of how amylin/pramlintide is not fully known, animal studies have shown that amylin binds to specific amylin binding sites in the area postrema (part of the dorsal vagal complex), nucleus accumbens, and dorsal raphe. The area postrema lacks a blood-brain barrier so it is exposed to glucose, insulin, and amylin. Animal and clinical trials have shown that the effects of pramlintide are physiologically similar to amylin.

PHARMACOKINETICS

The following pharmacokinetic parameters were derived from healthy subjects receiving a single subcutaneous dose (30, 60, 90, 120mcg) of pramlintide into the abdomen or thigh.

Table 1: Pharmacokinetic parameters of pramlintide

Absolute bioavailability	30-40%
Cmax	ranged from 39-147pmol/L in a dose-proportionate manner
Tmax	approximately 20 minutes
T 1/2	approximately 50 minutes
Distribution	Approximately 40% bound to albumin; does not extensively bind to blood cells
Metabolism	Primarily in the kidneys to the active metabolite des-lys pramlintide
Elimination	Primarily renal

Data obtained from product package insert

Weyer et al showed that the needle length used to inject pramlintide (6mm vs. 12.4mm) and body mass index ($\leq$ 27kg/m^2 vs. 30-45kg/m^2) did not affect the AUC_{0-4} for plasma pramlintide concentration. Site of injection (abdomen, arm, and thigh) was also evaluated. There was more variability after injection into the arm than with the abdomen or thigh.[1]

FDA INDICATIONS

Pramlintide was approved in March 2005 for adults with type 1 and type 2 diabetes as adjunctive treatment to mealtime insulin therapy in patients who have been unable to achieve desired glucose control despite optimal insulin therapy (with or without concurrent sulfonylurea or metformin therapy for type 2 diabetes).

VA FORMULARY ALTERNATIVES

None

DOSAGE AND ADMINISTRATION

Type 2 DM

- Initial dose is 60mcg given subcutaneously immediately prior to major meals ($\geq$ 250kcal or containing $\geq$ 30 g of carbohydrate).
- Reduce the dose of preprandial rapid-acting or short-acting insulin (including premixed 70/30 or 75/25 preparations) by 50%
- It is recommended that blood glucose be monitored more frequently, including pre- and postprandial , and bedtime testing

- If no clinically significant nausea has occurred for 3-7 days, increase the dose to 120mcg prior to major meals. If the 120mcg dose is not tolerated due to nausea, reduce the dose to 60mcg
- Once a stable dose of pramlintide has been reached (nausea subsided), the dose of insulin may be adjusted to optimize glycemic control, as directed by a healthcare practitioner

Type 1 DM

- Initial dose 15mcg subcutaneously immediately prior to major meals (≥250kcal or containing ≥ 30 g of carbohydrate).
- Reduce the dose of preprandial rapid-acting or short-acting insulin (including premixed 70/30 or 75/25 preparations) by 50%
- It is recommended that blood glucose be monitored more frequently, including pre- and postprandial , and bedtime testing
- The dose is titrated in 15mcg increments to 30, 45, or 60mcg. If no clinically significant nausea has occurred for at least 3 days, increase the dose to the next increment. If the 30mcg dose is not tolerated, consider discontinuing pramlintide
- Once a stable dose of pramlintide has been reached (nausea subsided), the dose of insulin may be adjusted to optimize glycemic control, as directed by a healthcare practitioner

The manufacturer recommends that pramlintide be injected subcutaneously into the abdomen or thigh at a site that is different from where insulin is injected. Injection sites should be rotated. Pramlintide and insulin should NOT be mixed in the same syringe. The pH of pramlintide is 4.0 and is not compatible with insulin which has a pH of approximately 7.8; therefore, separate syringes must be used when administering each drug. However, a single-dose trial has shown that the pharmacokinetics and pharmacodynamics of an older formulation of pramlintide at the 30mcg dose is not significantly altered when mixed with insulin (within 5 minutes of administration) and injected into the abdomen. Data on file with the manufacturer, using the currently marketed pramlintide formulation, reportedly shows that pharmacokinetics and pharmacodynamics of the 60mcg dose are not significantly altered when mixed with insulin. Other doses have not been tested.[24]

If a dose of pramlintide is missed, do not give an additional injection.

A U-100 insulin syringe is used to administer pramlintide; however, it is necessary to convert the microgram dosage to insulin syringe unit increments (table 2).

Table 2: Conversion of pramlintide dose to insulin unit equivalents

Pramlintide dose (mcg)	Increment using a U-100 syringe (units)	Volume (mL)
15	2.5	0.025
30	5.0	0.05
45	7.5	0.075
60	10	0.1
120	20	0.2

From pramlintide product package insert

Dosage adjustment is not necessary in patients with moderate to severe renal impairment (CrCl >20 to ≤ 50mL/min). No studies have been done in patients with CrCl < 20 or on dialysis.

No studies have been done in patients with hepatic impairment; however, pramlintide disposition is not likely to be effected.

Pramlintide is available in 5mL vials containing 0.6mg/mL. Unopened vials should be refrigerated and protected from light. Once opened, the vial can be kept in the refrigerator or at room temperature (not to exceed 77°F) for up to 28 days. Discard open vials after 28 days.

EFFICACY

Small Short term trials

Several short-term studies in type 1 and type 2 diabetes have shown that pramlintide decreases post-meal plasma glucagon levels [7, 8, 10, 13] and postprandial glucose compared to placebo. [2-8, 10-12, 14] Three small studies in patients with diabetes showed that pramlintide decreases the rate of gastric emptying compared to placebo.[5, 6, 9]

Type 1 diabetes (see appendix 1 for study details)

There is one 26-week and two 52-weeks randomized, double-blind, placebo-controlled trials.[15-17] In all trials, pramlintide was administered subcutaneously within 15 minutes prior to meals at a site different from the insulin injection using a separate syringe. Details for a large 4-week trial are provided in the appendix; however, is excluded from the discussion below.[18] The results of the 26-week trial have not been published (data obtained from FDA web site).[15]

In study 117, patients were randomized to pramlintide 90mcg bid (breakfast and dinner), 60mcg tid, 90mcg tid, or placebo for 26 weeks. Patients were maintained on their usual insulin regimen.[15]

Whitehouse et al., randomized patients to either pramlintide 30mcg qid or placebo. At week 20, those randomized to pramlintide whose HbA1c decreased by <1% from baseline were re-randomized to either pramlintide 30mcg or 60mcg qid. Adjustments to the patient's existing insulin dose were allowed. Because there was no difference in efficacy or safety in the 30 and 60mcg groups (weeks 20-52), the data were pooled. The evaluable population was used for efficacy analysis (those completing 52 weeks) and the intent-to-treat (ITT) population was used for the safety analysis. Those completing 52-weeks of treatment were eligible to enroll in a 52-week open-label extension study where everyone received pramlintide 30mcg qid. The primary endpoint was change in HbA1c at 52-weeks.[16]

Ratner et al., randomized patients to pramlintide 60mcg tid, 60mcg qid, 90mcg tid, or placebo. The 90mcg tid (n=158) group was excluded from the efficacy analysis because results from another study became available indicating that this dose had an adverse tolerability profile; however it was included in the safety analysis. This study differed from Whitehouse in several respects; the primary endpoint was change in HbA1c at 26weeks (although this was a 52-week trial), patients were to maintain baseline insulin dose, and investigators were allowed to temporarily reduce the dose of pramlintide by 50% for up to 2 weeks if the patient experienced nausea within the first 2 weeks of the study.[17]

The 30mcg and 60mcg qid doses of pramlintide in the 52-week trials resulted in the greatest decrease in HbA1c compared to placebo; however, that decrease was modest at best (-0.39%, -0.34%). All doses of pramlintide resulted in a mean weight loss of 0.3-0.5kg compared to a weight gain of 0.8-1kg in the placebo group.

Table 3: Mean change in HbA1c and weight in type 1 diabetes clinical trials

	Study 117 (26-weeks)				Whitehouse et al. (52-weeks)		Ratner et al (52-weeks)		
	90bid	**60tid**	**90tid**	**Placebo**	**30 qid**	**Placebo**	**60 tid**	**60 qid**	**Placebo**
HbA1c	-0.15%	-0.23%	-0.10%	+0.09%	-0.39%	-0.12%	-0.29%	-0.34%	-0.04%
HbA1c < 7%	-				25%	11.3%	11%	12.5%	3%
Weight	-1.0 to -2.3kg			+0.3kg	-0.5kg	+1kg	-0.3kg	-0.3kg	+0.8kg

The HbA1c remained reduced in those patients continuing open-label pramlintide in the extension study; however, patients regained the weight lost (see Appendix 1). Those who switched from placebo to open-label pramlintide had results similar to those who had been randomized to pramlintide at the beginning of the double-blind study.[16]

Type 2 diabetes (See appendix2 for study details)

There is one 26-week and two 52-weeks randomized, double-blind, placebo-controlled trials.[19-21] In all trials, pramlintide was administered subcutaneously within 15 minutes prior to meals at a site different from the insulin injection using a separate syringe. Details for a large 4-week trial are provided in the appendix; however, is excluded from the discussion below.[22] The results of the 26-week trial have not been published (data obtained from FDA web site).

In study 123, patients were randomized to pramlintide 90mcg bid (breakfast and dinner), 12mcg bid (breakfast and dinner), 90mcg tid, or placebo for 26 weeks. Patients were maintained on their usual insulin regimen.[15]

While Hollander et al. was a 52-week trial, the primary endpoint was change in HbA1c at 26weeks.[20] Change in HbA1c at 52-weeks was the primary endpoint in Ratner et al.[21] In both 52-week studies, patients were encouraged to maintain existing insulin, oral hypoglycemic agents, diet, and exercise routines. Dosing of pramlintide varied from study to study. In Hollander et al., patients were randomized to pramlintide 60mcg tid, 90mcg bid, 120mcg bid, or placebo. The 60mcg tid (n=158) group was excluded from the efficacy analysis because results from another study became available indicating that this dose was not as effective. In Ratner, patients were randomized to 30, 75, or 150mcg tid or placebo.

Reduction in HbA1c and weight was seen with all doses of pramlintide, but was greatest with 120mcg bid and 150mcg tid groups.

Table 4: Mean change in HbA1c and weight in type 2 diabetes clinical trials

	Study 123 (26-weeks)*				Hollander et al. (52-weeks)			Ratner et al. (52-weeks)			
	90 bid	120 bid	90 tid	Placebo	90 bid	120 bid	Placebo	30 tid	75 tid	150 tid	Placebo
HbA1c	-0.31%	-0.36%	-0.26%		-0.35%	-0.62%	-0.25%	-0.3%	-0.47%	-0.6%	-0.15%
Weight	-0.9kg	-1.7kg	-1.4kg	0kg	-0.5kg	-1.2kg	+0.75kg	-0.5kg	-0.4kg	-1.3kg	+1.1kg

*Values for HbA1c from study 123 are shown as difference from placebo

A pooled post hoc subgroup analysis of African Americans (n=47) and Hispanics (n=48) from the two 52-week trials in type 2 diabetes was conducted.[22] Data were pooled from the pramlintide 120mcg bid and 150mcg tid arms from each study. The percentage of patients using insulin, oral hypoglycemic agents and insulin dose remained constant throughout the study. The greatest decrease in HbA1c and weight was seen among African Americans (table 5).

Table 5: Subgroup analysis of results by race (at 52-weeks)

	African American	Hispanic	Caucasian
Change in HbA1c (difference vs. placebo)	-0.7%	-0.3%	-0.5%
Change in weight (difference vs. placebo)	-4.1kg	-2.3kg	-2.4kg
Incidence of nausea (pramlintide vs. placebo)	23% vs. 14%	23% vs. 12%	26% vs. 17%
Incidence of hypoglycemia (pramlintide vs. placebo)	31% vs. 33%	23% vs. 27%	48% vs. 43%

Another post hoc subgroup analysis in overweight and obese patients (BMI > 25kg/m^2) with type 2 diabetes was conducted.[23] Data from the 52-week and the unpublished 26-week study were pooled.[19, 20] Only the pramlintide 120mcg and placebo groups were compared in this analysis. Results at 26-weeks are presented in table 6.

Mean baseline weight, BMI, and HbA1c were approximately 95kg, 35kg/m^2, and 9.3% respectively. Greater weight and HbA1c reduction was seen with pramlintide. No correlation was found between change in body weight and change in HbA1c. Weight reduction was slightly greater for those taking concomitant metformin (~12% of the study population). The placebo-corrected weight reduction was -2.5kg and -1.6kg for metformin and no metformin respectively.

Table 6: Results of subgroup analysis in overweight and obese patients with diabetes

	Pramlintide 120mcg (n=254)	Placebo (n= 244)
Mean change in HbA1c (%)	-0.59*	-0.18
Mean weight change (kg)	-1.5*	+0.3
% patients gaining weight	23.6%	44.6%
% patients with 2.5-5% weight reduction^	17.5%*	8.8%
% patients with 5.0-7.5% weight reduction^	8.5%*	1.5%
% patients with 7.5-10% weight reduction^	2%	1.1%
% patients with ≥10%% weight reduction^	2%	0
Avg. weight loss in those with baseline BMI >25-30 (kg)^	-1.1*	+0.05
Avg. weight loss in those with baseline BMI 30-35 (kg)^	-0.75*	+0.5
Avg. weight loss in those with baseline	-2.2*	+0.2

BMI >35-40 (kg)^		
Avg. weight loss in those with baseline BMI >40 (kg)^	-2.3*	+0.9

*significant vs. placebo
^values estimated from graph

ADVERSE EVENTS (SAFETY DATA)
There was no evidence of cardiovascular, hepatic, pulmonary, or renal adverse effects associated with pramlintide. Additionally, there were no changes in laboratory test including lipids, electrocardiogram, or vital signs.

The overall withdrawal rate in the type 1 diabetes trials was higher in the pramlintide groups (except in Whitehouse et. al.); however, withdrawal due to adverse events was consistently higher in the pramlintide groups.[15-17] The pooled withdrawal rate for all reasons was 34% and 25% for pramlintide and placebo respectively. Withdrawals due to adverse events were 18% and 6% respectively.[15]

The overall withdrawal rates in the type 2 studies were fairly similar between pramlintide (with the exception of the pramlintide 150mcg tid arm) and placebo. Withdrawals due to adverse events were reported by Ratner et al., which found the rates to be similar between pramlintide (excluding the high-dose pramlintide arm) and placebo.[21] The pooled withdrawal rate for all reasons was 24% for both pramlintide and placebo. Withdrawals due to adverse events were 9% and 7% respectively.[15]

Nausea
Nausea was the most commonly reported adverse event and appears to be dose-related (table 7). The majority of cases were mild to moderate and most often occurred during the first 4 weeks of therapy. Among those with type 1 diabetes who had nausea in the first 4 weeks (92%), recurrence rates were 70% (weeks >4-13), 54% (weeks 13-20), 53% (weeks 26-39), and 49% (weeks 39-52). The overall rate of withdrawal due to nausea was 12% with pramlintide and 1% with placebo.[15]

Among those with type 2 diabetes who had nausea in the first 4 weeks (73%), recurrence rates were 60.5% (weeks >4-13), 44% (weeks >13-20), 40% (weeks >26-39), and 36% (weeks 39-52). The overall rate of withdrawal due to nausea was 3% with pramlintide and 2% with placebo.[15]

Table 7: Treatment emergent effects from long-term placebo-controlled trials

	Type 1 DM		Type 2 DM	
	Pramlintide 30 or 60mcg + insulin (n=716)	**Placebo + insulin (n=538)**	**Pramlintide 120mcg + insulin (n=292)**	**Placebo + insulin (n=284)**
Nausea	48%	17%	28%	12%
Anorexia	17%	2%	9%	2%
Vomiting	11%	7%	8%	4%
Abdominal pain	-	-	8%	7%
Headache	-	-	13%	7%
Fatigue	7%	4%	7%	4%
Dizziness	5%	4%	6%	4%
Allergic reaction	6%	5%	-	-
Arthralgia	7%	5%	-	-
Coughing	-	-	6%	4%
Pharyngitis	-	-	5%	2%

Adapted from pramlintide product package insert

Hypoglycemia
Severe hypoglycemia, defined as requiring either third party assistance, administration of glucagon, or IV glucose, occurred more frequently in the pramlintide groups (seen in all clinical trials except Whitehouse et al.). It is unknown if the lower rate in this study can be attributed to the lower dose of pramlintide used or because the study protocol allowed adjustments to insulin as appropriate. It should be noted that Whitehouse et al., was the only pivotal trial allowing adjustments to insulin as appropriate. Attempts were made to maintain baseline insulin doses in the other trials. The rate of severe hypoglycemia was highest during the first 4 weeks of therapy. Severe hypoglycemia was more common in type 1 than in type 2 diabetes. See table 8 for combined values from studies using approved dosing and Appendices 1 and 2 for values from individual trials.

Withdrawal from the study due to hypoglycemia in type 1 diabetes was 3% with pramlintide and 1% with placebo. For type 2 diabetes, the rates were <1% and 0 respectively. [15]

Table 8: Incidence and event rate of severe hypoglycemia in long-term placebo controlled trials

	Type 1 DM				Type 2 DM			
	Pramlintide 30 or 60mcg + insulin		Placebo + insulin		Pramlintide 120mcg + insulin		Placebo + insulin	
	0-3mos	>3-6mos	0-3mos	>3-6mos	0-3mos	>3-6mos	0-3mos	>3-6mos
Incidence ¶	16.8%	11.1%	10.8%	8.7%	8.2%	4.7%	2.1%	2.4%
Event rate/patient year	1.55	0.82	1.33	1.06	0.45	0.39	0.24	0.13
Incidence §	7.3%	5.2%	3.3%	4.3%	1.7%	0.4%	0.7%	1.2%
Event rate/patient year	0.50	0.27	0.19	0.24	0.05	0.03	0.06	0.07

Adapted from pramlintide product package insert
¶ requiring aid from another individual for ingestion of oral carbohydrate and/or administration of glucagon injection
§Requiring glucagon, IV glucose, hospitalization, paramedic assistance, ER visit, and/or assessed as a SAE by the investigator

***Black Boxed Warning*:** Pramlintide carries a black box warning for insulin-induced severe hypoglycemia. Hypoglycemic risk in higher in patients with type 1 diabetes, and usually occurs within 3 hours of injection. The black box also warns against the risk of hypoglycemia during driving or operating heavy machinery.

Deaths

There were 17 deaths in all the pramlintide trials combined, including uncontrolled trials. Two deaths possibly related to hypoglycemia occurred in the type 1 diabetes studies (pramlintide 30mcg qid and pramlintide 90mcg tid).

Table 9: Number of deaths during all pramlintide trials

	Type 1 DM		Type 2 DM	
	Pramlintide	Placebo	Pramlintide	Placebo
Controlled short-term trials (n)	0	0	1	0
Controlled long-term trials (n)	3	2	3	5
Uncontrolled trials (n)	2		1	

Data obtained from medical review safety at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b1.htm

CONTRAINDICATIONS

- Hypersensitivity to pramlintide, metacresol, D-mannitol, acetic acid, or sodium acetate
- A confirmed diagnosis of gastroparesis
- Hypoglycemia unawareness

LOOK-ALIKE/SOUND-ALIKE DRUGS

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name pramlintide: Prandin

Both pramlintide and Prandin (repaglinide) are used to treat diabetes and are dosed prior to meals. However, Prandin is an oral agent; therefore, errors should be unlikely.

LA/SA for trade name Symlin: insulin

Both Symlin and insulin are injectable, are stored in the refrigerator, are used to treat diabetes, have similar instructions for use (e.g. prior to meals), and have potentially similar volumes for injection. While insulin is dosed in units and pramlintide in micrograms, pramlintide which can be dosed at 15, 30, 45, or 60 is numerically similar to some insulin doses.

DRUG INTERACTIONS

Because of the effects of pramlintide on gastric emptying, it should not be used in patients taking drugs that alter GI motility or who use the α-glucosidase inhibitors (acarbose, miglitol).

The absorption of concomitantly administered oral agents may be potentially delayed. Those agents where a rapid onset is important (e.g. analgesics) should be administered at least 1 hour prior to or 2 hours after pramlintide.

Concurrent use with other diabetic medications can increase the risk of hypoglycemia, due to increased blood-glucose lowering effect. Practitioners should be aware of other agents that can increase the risk of hypoglycemia, including ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, and sulfonamide antibiotics.

PHARMACOECONOMICS

There are no published pharmacoeconomics studies at this time.

COST

The FSS cost for pramlintide (5mL vial containing 0.6mg/mLor 3000mcg/vial) is $57.07. Monthly cost will depend on the dosage prescribed.

Table 10: Cost for commonly used doses for type 2 diabetes

Dosage	Total dose/month	Number of doses/vial	Number of vials/month	FSS cost/month
60mcg tid meals	5400mcg/month	16 doses/vial	1.8 vials/month	$102.73
120mcg tid meals	10,800mcg/month	8 doses/vial	3.6 vials/month	$205.45
60mcg bid meals	3600mcg/month	25 doses/vial	1.2 vials/month	$68.48
120mcg bid meals	7200mcg/month	12 doses/vial	2.4 vials/month	$136.97

RECOMMENDATIONS

The modest decrease in HbA1c and weight must be balanced by adverse drug reactions, inconvenient administration, potential for drug errors, and cost. Use of this agent will be limited to very highly motivated patients who are willing to accept the burden of additional injections of pramlintide along with insulin. Extensive patient education will be required outlining the need for separate syringes/needles and injection site for pramlintide, and how to convert the pramlintide dose to insulin syringe units. The patient must also be willing to perform more frequent self-monitoring of blood glucose.

Prescribing of pramlintide should be limited to physicians who specialize in diabetes management and are supported by diabetes care teams.

It is recommended that pramlintide not be added to the national and VISN formularies at this time.

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Prepared 6/2005

Contact person: Deb Khachikian, PharmD

Appendix 1: Large clinical trials in type 1 diabetes

<table>
<tr>
<td>Thompson 1997[18]
R, DB, PC, PR

4 weeks
N=215</td>
<td>Type 1 DM
18-66 years old
HbA1c 6.9-13.1%
Basal C-peptide < 1.0ng/ml and/or history of DKA</td>
<td>Pramlintide 30mcg qid (breakfast, lunch, dinner, evening snack) vs. pramlintide 30mcg tid (breakfast, lunch, dinner) vs. 30mcg tid (breakfast, dinner, and evening snack) vs. pramlintide 60mcg bid (breakfast and dinner)

Doses administered subcutaneously within 15 minutes before meal given in addition to existing insulin therapy in a separate syringe and different injection site. Patients to maintain their usual diet, exercise, and insulin regimen, unless otherwise told</td>
<td>Data shown as pramlintide 30mcg qid / pramlintide 30mcg tid-1/ pramlintide 30mcg tid -2 / pramlintide 60mcg bid / placebo

Age (years): 36.1 ± 1.6 / 35 ± 1.6 / 34.8 ± 1.6 / 35.4 ± 1.6 / 35.6 ± 1.8
BMI: 25.2 ± 0.5 / 24.6 ± 0.6 / 24.7 ± 0.5 / 25.6 ± 0.6 / 25.2 ± 0.5
Duration of DM (years): 14.8 ± 1.17 / 15.2 ± 1.37 / 13.4 ± 1.3 / 15.4 ± 1.47 / 15 ± 1.41
Fructosamine (mmol/l): 401 ± 13 / 406 ± 9.9 / 403 ± 11.6 / 393 ± 7.5 / 398 ± 9.7
HbA1c (%): 8.9 ± 0.2 / 9.1 ± 0.2 / 9.1 ± 0.2 / 8.6 ± 0.2 / 9.3 ± 0.2

Mean ± SEM</td>
<td>
<table>
<tr><th></th><th>P30 qid</th><th>P30 tid-1</th><th>P30 tid-2</th><th>P-60 bid</th><th>Placebo</th></tr>
<tr><td>fructosamine (mmol/l)</td><td>-61.6*</td><td>-43.3</td><td>-46.9*</td><td>-46.3</td><td>-28.9</td></tr>
<tr><td>24-h glucose AUC*</td><td>-2080 ± 663*</td><td>-45 ± 780</td><td>-210 ± 547</td><td>-1261 ± 693</td><td>359 ± 715</td></tr>
<tr><td>Glucose C_{max} (mmol/l)</td><td>-1.2 ± 0.7</td><td>-0.3 ± 0.8</td><td>0.03 ± 0.8</td><td>-1.9 ± 0.6</td><td>0.4 ± 0.7</td></tr>
<tr><td>Glucose C_{min} (mmol/l)</td><td>-0.5 ± 0.5</td><td>0.2 ± 0.3</td><td>-0.2 ± 0.4</td><td>-1.5 ± 0.5</td><td>-0.5 ± 0.5</td></tr>
<tr><td>short-acting insulin dose</td><td colspan="3">-1.0 to 2.3 units</td><td></td><td>+3.6 units</td></tr>
</table>
Pramlintide 30mcg tid-1 (breakfast, lunch, dinner)
Pramlintide 30mcg tid-2 (breakfast, dinner, evening snack)
Units for glucose AUC mmol · min^{-1} · 1^{-1}
Mean ± SEM
*significant vs. placebo</td>
</tr>
<tr>
<td>Study 117[15]
R, DB, PC, PR
N=586
26-weeks

ITT</td>
<td>Type 1 DM
No adjustment in daily insulin dose by > ± 10% for at least 2 months
Stable weight ± 2.5kg for at least 2 months
HbA1c ≥ 8%</td>
<td>Pramlintide 90mcg bid (breakfast and dinner)
Pramlintide 60mcg tid
Pramlintide 90mcg tid
Placebo
Dose administered subcutaneously within 15 minutes of meal

Patients to maintain usual insulin dose, insulin regimen, diet, and exercise</td>
<td>% male: 49.7%
Age: 38 years
% Caucasian: 99.5%
Weight: 73kg
BMI: 25.2kg/m^2
HbA1c: 9.0%
Total daily insulin dose: 50.2 units
Duration of DM (years): 16

Mean values for ITT population</td>
<td>
<table>
<tr><th></th><th>P90 bid</th><th>P60 tid</th><th>P90 tid</th><th>Placebo</th></tr>
<tr><td>Withdrawals</td><td>33.3%</td><td>18.2%</td><td>32%</td><td>11.7%</td></tr>
<tr><td>HbA1c (%)</td><td>-0.15%</td><td>-0.23%*</td><td>-0.10%</td><td>+0.09</td></tr>
<tr><td>Insulin dose (units)</td><td>-1</td><td>-1</td><td>0</td><td>+0.5</td></tr>
<tr><td>Weight (kg)</td><td colspan="2">-0.7 to -1.6</td><td></td><td>+0.3</td></tr>
<tr><td>Severe hypoglycemia ^
weeks 0-4
Weeks 4-26</td><td></td><td>3.2
1</td><td></td><td>1.7
1</td></tr>
</table>
*significant vs. placebo
Mean values for insulin dose and weight
^event rate per patient year</td>
</tr>
<tr>
<td>Whitehouse 2002[16]
R, DB, PC, PR
52-weeks
and 52-week extension trial

Double-blind trial
Evaluable pop.
n=342

ITT population
n=480</td>
<td>Type 1 DM
16-70 years old
HbA1c 7-13%

No symptoms of severe hypo- or hyperglycemia for 2 weeks prior to screening

No adjustment in daily insulin dose by > ± 10% for 1 week prior to study

Exclusions: clinically significant IHD, HTN (BP > 150/95mmHg), GI disease,</td>
<td>30mcg pramlintide qid
Placebo qid

Doses administered subcutaneously within 15 minutes prior to breakfast, lunch, dinner and bedtime snack

Given in addition to existing insulin therapy in a separate syringe and different injection site

Adjustments to insulin may be made as appropriate</td>
<td>Demographics for the evaluable population (pramlintide/placebo)
Data not shown for ITT population

% male: 55% / 55%
% Caucasian: 96%/ 92%
Age (years): 40.3 ± 11.6 / 40.4 ± 12.1
Weight (kg): 75 ± 13.8 / 75.6 ± 13.3
BMI: 25.2 ± 3.3 / 25.8 ± 3.5
HbA1c (%): 8.7 ± 1.3 / 8.9 ± 1.5
Duration of DM (years): 16.5 ± 10/ 17.1 ± 10.5</td>
<td>Randomized (weeks 0-52)
<table>
<tr><th></th><th>Pramlintide</th><th>Placebo</th></tr>
<tr><td>Withdrawals</td><td>28.4%</td><td>29.1%</td></tr>
<tr><td>Withdrawals due to AE</td><td>12.8%</td><td>8.0%</td></tr>
<tr><td>HbA1c</td><td>-0.39%*</td><td>-0.12%</td></tr>
<tr><td>% achieving HbA1c <7%</td><td>25%*</td><td>11.3%</td></tr>
<tr><td>% achieving HbA1c <8%</td><td>58.6%*</td><td>35.1%</td></tr>
<tr><td>Change in insulin dose</td><td>+2.3%*</td><td>+10.3%</td></tr>
<tr><td>Change in weight ^</td><td>-0.5kg*</td><td>+1kg</td></tr>
<tr><td>Severe hypoglycemia¶
Weeks 0-4 / 4-26 / 26-52</td><td>2.12 ± 0.35
0.74 ± 0.09
0.43 ± 0.07</td><td>2 ± 0.34
1.37 ± 0.13
1.24 ± 0.12</td></tr>
</table></td>
</tr>
</table>

<table>
<tr>
<td>Extension trial
Evaluable pop.
n=161
ITT population
n= 236</td>
<td>renal disease, unstable diabetic retinopathy, drugs known to affect GI motility or glucose metabolism</td>
<td>At week 20, those randomized to pramlintide whose HbA1c decreased by <1% from baseline were re-randomized to either pramlintide 30mcg or 60mcg QID</td>
<td></td>
<td>*significant vs. placebo
^ estimated from graph
¶event rate per patient year; mean ± SEM

Open-label extension (weeks 52-104)
<table>
<tr><th></th><th>Continued pramlintide</th><th>Switched to pramlintide</th></tr>
<tr><td>HbA1c^</td><td>-0.36%</td><td>-0.36%</td></tr>
<tr><td>Change in weight^</td><td>+0.5kg</td><td>-0.9kg</td></tr>
<tr><td>Severe hypoglycemia¶</td><td>0.43</td><td>0.68</td></tr>
</table>
^ estimated from graph
¶event rate per patient year</td>
</tr>
<tr>
<td>Ratner 2004[17]
R, DB, PC, PR
52-weeks

ITT LOCF
N=479</td>
<td>Type 1 DM
16-76 years old
Required insulin for ≥ 1year
Stable insulin regimen ± 10% for at least 2 months prior to study
HbA1c ≥ 8%
C-peptide ≤ 1.0ng/ml or history of DKA or presence of islet cell antibodies
Stable body weight ± 2.5kg for at least 2 months prior to study
No severe hypo- or hyperglycemic symptoms for at least 2 weeks prior to screening

Exclusions: Clinically significant CV, pulmonary, CNS, renal, hematologic diseases, GI, eating disorders, drug/alcohol abuse, drugs known to affect GI motility or glucose metabolism</td>
<td>Pramlintide 60mcg tid
Pramlintide 60mcg qid
Pramlintide 90mcg tid
Placebo

Doses administered subcutaneously within 15 minutes prior to breakfast, lunch, dinner and bedtime snack (for qid regimen)

Given in addition to existing insulin therapy in a separate syringe and different injection site

Patients to maintain usual insulin dose, insulin regimen, diet, and exercise

Investigators were allowed to temporarily reduce the dose of pramlintide by 50% for up to 2 weeks if pt. experienced nausea within the first 2 weeks of the study</td>
<td>Demographics for the evaluable population. Data not shown for ITT population

% male: 51%
Age: 41 years old
% Caucasian: 90%
Duration of DM: 19 years
BMI: 26.5kg/m^2
HbA1c: 8.9%
Total daily insulin dose: 52 units</td>
<td>
<table>
<tr><th></th><th>P60 tid</th><th>P60 qid</th><th>Placebo</th></tr>
<tr><td>Withdrawals</td><td>42.1%</td><td>34.2%</td><td>33.1%</td></tr>
<tr><td>Withdrawal due to AE</td><td>19.5%</td><td>13%</td><td>3.9%</td></tr>
<tr><td>HbA1c (%)</td><td>-0.41*
-0.29*</td><td>-0.39*
-0.34*</td><td>-0.18
-0.04</td></tr>
<tr><td>% achieving HbA1c <7%</td><td>11%</td><td>12.5%</td><td>3%</td></tr>
<tr><td>insulin dose</td><td>-2.5%</td><td>-6.1%</td><td>-0.3%</td></tr>
<tr><td>Weight</td><td>-0.3kg*</td><td>-0.3kg*</td><td>+0.8kg</td></tr>
<tr><td>Severe hypoglycemia (%)</td><td>18.3%</td><td>17.4%</td><td>14.3%</td></tr>
<tr><td>Severe hypoglycemia event/pt-yr (mean ± SEM)</td><td></td><td></td><td></td></tr>
<tr><td>weeks 0-4</td><td>3.78 ±0.57</td><td>3.41 ± 0.55</td><td>0.87 ± 0.27</td></tr>
<tr><td>weeks 4-26</td><td>1.13 ± 0.15</td><td>0.98 ± 0.13</td><td>0.8 ± 0.12</td></tr>
<tr><td>weeks 26-52</td><td>0.74 0.12</td><td>0.79 ± 0.12</td><td>0.45± 0.09</td></tr>
</table>

The 90mcg tid (n=158) group was excluded from the efficacy analysis because results from another study became available indicating that this dose had an adverse tolerability profile. This arm was included in the safety analysis

Data for the evaluable (completed 26-weeks of tx) and completer (completed 52-weeks of tx) populations were similar to the ITT population

Patients whose insulin dose remained stable throughout the 52-weeks had a greater decrease in HbA1c (-0.59%, -0.57%, +0.13% pramlintide tid, qid, placebo)</td>
</tr>
</table>

AE=adverse event, AUC= area under the curve, BID= twice daily, BMI= body mass index, BP= blood pressure, CNS= central nervous system, CV= cardiovascular, DB= double-blind, DKA= diabetic ketoacidosis, DM= diabetes mellitus, GI= gastrointestinal, HTN= hypertension, IHD= ischemic heart disease, ITT= intent-to-treat, LOCF= last observation carried forward, PC= placebo-controlled, PR= parallel, QID= four times daily, R= randomized, TID= three times daily

Appendix 2: Large clinical trials in type 2 diabetes

<table>
<tr>
<td>Thompson 1998[21]
R, DB, PC, PR

4 weeks
N=203</td>
<td>Type 2 DM
25-78 years old
Using insulin for ≥ 6 months prior to study
HbA1c < 13%</td>
<td>Pramlintide 30mcg qid vs. Pramlintide 60mcg tid vs. pramlintide 60mcg qid vs. placebo qid

Doses administered subcutaneously within 15 minutes before breakfast, lunch, dinner and bedtime snack (the tid group received placebo at the bedtime snack)

Given in addition to existing insulin therapy in a separate syringe and different injection site.

Patients to maintain their usual diet, exercise, and insulin regimen, unless otherwise told</td>
<td>Data shown as pramlintide 30mcg / 60mcg tid / 60mcg qid / placebo

% males: 46-54%
Age (years): 60.2 ± 1.3 / 58.9 ± 1.5 / 58.9 ± 1.5 / 57.5 ± 1.5
BMI: 30.6 ± 0.7 / 29.8 ± 0.6 / 31.7 ± 0.8 / 30.5 ± 0.7
Weight (kg): 88.5 ± 2.6 / 86 ± 2.3 / 92.1 ± 2.4 / 87.2 ± 2.4
Duration of DM (years): 10.6 ± 1.1 / 8.4 ± 0.9 / 11.8 ± 1.1 / 11.3 ± 1.1
Duration of insulin therapy (years): 6.3 ± 0.8 / 4.4 ± 0.5 / 5.3 ± 0.7 / 7.5 ± 1.1
Baseline fructosamine (mmol/l): 320 / 328 / 323 / 330
Baseline HbA1c (%): 8.8 / 8.9 / 8.9 / 8.9
Baseline TC (mg/dl): 205 / 204 / 217 / 198
Baseline LDL (mg/dl): 130 / 131/ 132 / 121
Baseline HDL (mg/dl): 41/ 40 / 42 / 43
Baseline triglycerides (mg/dl): 178 / 200 / 250 / 164</td>
<td>
<table>
<tr><th></th><th>Pramlintide 30mcg qid</th><th>Pramlintide 60mcg tid</th><th>Pramlintide 60mcg qid</th><th>Placebo</th></tr>
<tr><td>Fructosamine (mmol/l)</td><td>-18*</td><td>-25*</td><td>-23*</td><td>-1</td></tr>
<tr><td>HbA1c (%)</td><td>-0.53*</td><td>-0.54*</td><td>-0.41*</td><td>-0.23</td></tr>
<tr><td>TC (mg/dl)</td><td>-4.73</td><td>-8.35</td><td>-10.46</td><td>1.19</td></tr>
<tr><td>LDL-C (mg/dl)</td><td>-4.41</td><td>-5.542</td><td>-7.50</td><td>-2.05</td></tr>
<tr><td>HDL-C (mg/dl)</td><td>-0.7</td><td>-0.86</td><td>-0.51</td><td>0.65</td></tr>
<tr><td>Triglycerides (mg/dl)</td><td>7.02</td><td>-8.95</td><td>-66.37</td><td>22.05</td></tr>
<tr><td>Weight (kg)</td><td>-0.36</td><td>-0.89^</td><td>-0.72^</td><td>-0.04</td></tr>
<tr><td>Insulin dose</td><td colspan="4">No significant changes from baseline- values not shown</td></tr>
</table>
*statistically significant versus placebo
^statistically significant within study group
Values for fructosamine and HbA1c estimated from graph
Mean values shown
</td>
</tr>
<tr>
<td>Study 123[15]
R, DB, PC, PR
26-weeks
N=499

ITT</td>
<td>Type 2 DM
No adjustment in daily insulin dose by > ± 10% for at least 2 months
Stable weight
HbA1c ≥ 8%</td>
<td>Pramlintide 90mcg bid
Pramlintide 120mcg bid
Pramlintide 90mcg tid
Placebo

Twice daily regimens were given at breakfast and dinner

Patients to maintain usual insulin dose, insulin regimen, diet, and exercise</td>
<td>% male: 47%
Age: 58 years old
% Caucasian: 98%
Duration of DM: 13.5 years
Weight: 85kg
BMI: 30.6kg/m^2
HbA1c: 9.4%
Total daily insulin dose: 55.5 units</td>
<td>
<table>
<tr><th></th><th>P90 bid</th><th>P120 bid</th><th>P90 tid</th><th>Placebo</th></tr>
<tr><td>HbA1c (difference from placebo)</td><td>-0.31</td><td>-0.36*</td><td>-0.26</td><td></td></tr>
<tr><td>Change in insulin dose (units)</td><td>+2%</td><td>-1%</td><td>0</td><td>+7%</td></tr>
<tr><td>Change in weight</td><td>-0.9kg*</td><td>-1.7kg*</td><td>-1.4kg*</td><td>0kg</td></tr>
<tr><td>Severe hypoglycemia Rate/patient-yr</td><td>5.8%
0.2*</td><td>7.9%
0.3*</td><td>3.9%
0.2*</td><td>1.6%
0.1</td></tr>
</table>
*significant vs. placebo
None of the lipid comparisons were significant
For pramlintide, the majority of hypoglycemia occurred during weeks 0-4
</td>
</tr>
<tr>
<td>Hollander 2003[19]
R, DB, PC, PR
52-week

ITT population for safety and efficacy analysis
N=498</td>
<td>Type 2 DM
Required insulin for ≥ 6 months prior to study
≥ 18years old
HbA1c ≥ 8%
No symptoms of severe hypo- or hyperglycemia for 2 weeks prior to screening
Stable insulin dose (± 10%) and stable weight (± 5%) for</td>
<td>Pramlintide 90mcg bid
Pramlintide 120mcg bid
Pramlintide 60mcg tid
Placebo tid

Given subcutaneously 15 minutes before breakfast and dinner (BID regimens) or breakfast, lunch and dinner (TID regimens)</td>
<td>Data shown as pramlintide 90 / pramlintide 120 / placebo

% male: 49 / 48 / 52
Age (years): 57 ± 10.2 / 56.9 ± 10.5/ 56.4 ± 10.2
% Caucasian: 77 / 73 / 75
Weight (kg): 97.1 ± 19.3 / 96.7 ± 23.2 / 96.8 ± 20.5
BMI: 33.8 ± 6.3 / 34.1 ± 7.5 / 33.7 ± 7.2</td>
<td>
<table>
<tr><th></th><th>Pramlintide 90mcg bid (n=171)</th><th>Pramlintide 120mcg bid (n=166)</th><th>Placebo tid (n=161)</th></tr>
<tr><td>Withdrawals</td><td>29%</td><td>32%</td><td>30%</td></tr>
<tr><td>HbA1c (week 26/52)</td><td>-0.57%
-0.37%</td><td>-0.73%*
-0.68%*</td><td>-0.25%</td></tr>
<tr><td>% achieving HbA1c <7% (vs. placebo)</td><td>9.4%</td><td>12.2%</td><td>4.1%</td></tr>
<tr><td>% achieving HbA1c</td><td>42.4%</td><td>45.7%</td><td>27.6%</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>at least 2 months prior to study
Exclusions: DKA, clinically significant CV, pulmonary, CNS, renal, GI, hematologic diseases, eating disorders, drug/alcohol abuse, drugs known to affect GI motility or glucose metabolism</td>
<td>Used separate syringe and injection site

Patients were encouraged to maintain existing insulin, oral hypoglycemic agents, diet, and exercise routines</td>
<td>Duration of DM (years): 12 ± 6.6 / 12.1 ± 7.3 / 12.4 ± 7
HbA1c (%): 9.1± 1.1 / 9 ± 1.1 / 9.3 ± 1.3
Total daily insulin dose (units): 70 / 69 / 74
% using short- and long-acting insulin: 78 / 82 / 86
% using 2 injections/day: 73 / 72 / 68
% using 3+ injections/day: 20 / 19 / 23
% using oral agents: 26 / 23 / 27</td>
<td>
<table>
<tr><td><8% (vs. placebo)</td><td></td><td></td><td></td></tr>
<tr><td>Change in weight^</td><td>-0.5kg</td><td>-1.2kg*</td><td>+0.75kg</td></tr>
<tr><td>Total daily insulin dose (units)</td><td>72</td><td>70</td><td>76</td></tr>
<tr><td>% using short- and long-acting insulin</td><td>79</td><td>82</td><td>85</td></tr>
<tr><td>% using 2 injections/day</td><td>72</td><td>70</td><td>73</td></tr>
<tr><td>% using 3+ inject/day</td><td>22</td><td>22</td><td>22</td></tr>
<tr><td>% using oral agents</td><td>23</td><td>21</td><td>27</td></tr>
<tr><td>Severe hypoglycemia¶
Weeks 0-4 / 4-26 / 26-52</td><td>0.1± 0.08
0.2 ± 0.06
0.0 ± 0.02</td><td>0.9 ± 0.3
0.4 ± 0.09
0.1 ± 0.05</td><td>0.3 ± 0.2
0.3 ± 0.07
0.2 ± 0.06</td></tr>
</table>
*significant vs. placebo
^ estimated from graph
¶event rate per patient year; mean ± SD
The 60mcg tid (n=158) group was excluded from analysis because results from another study became available indicating that this dose was not as effective
</td>
</tr>
<tr>
<td>Ratner 2002[20]
R, DB, PC, PR
52-weeks
N=538

ITT population for safety and efficacy analysis (all randomized subjects receiving at least 1 dose of medication)</td>
<td>Type 2 DM
Required insulin for ≥ 6 months prior to study
26-76 years old
HbA1c 7.5% - 13%
Weight within ± 60% of desirable weight in Metropolitan life tables
Stable insulin ≤ ±10% deviation prior to randomization
No symptoms of severe hypo- or hyperglycemia for 2 weeks prior to screening

Exclusions: clinically significant IHD, HTN (BP > 150/95mmHg), GI disease, renal disease, unstable diabetic retinopathy, drugs known to affect GI motility or glucose metabolism</td>
<td>Pramlintide 30 tid
Pramlintide 75 mcg tid
Pramlintide 150mcg tid
Placebo tid

Dose given subcutaneously within 15 minutes prior to their breakfast, lunch, and dinner

Used separate syringe and injection site

Patients to maintain their usual diet, exercise, oral hypoglycemic agents, and insulin regimen, unless told otherwise</td>
<td>Data shown as pramlintide 30 / pramlintide 75 / pramlintide 150 / placebo

% male: 56 / 57 / 56 / 62
Age (years): 57.5 ± 10.8 / 56.5 ± 10.3 / 56.4 ± 8.9 / 55.5 ± 10.6
% Caucasian: 77 / 76 / 78 / 81
BMI: 31.1 ± 5.2 / 30.4 ± 5 / 31.1 ± 5.5 / 30.4 ± 4.7
HbA1c (%): 9.0 ± 1.1 / 9.3 ± 1.2 / 9.2 ± 1.2 / 9.2 ± 1.2
Duration of DM (years): 11.9 ± 7.0 / 11.3 ± 7.8 / 13.3 ± 7.4 / 11.8 ± 7.7
Total daily insulin dose (units): 55.1 ± 26.5 / 60.4 ± 31.1 / 60.6 ± 29.2 / 58.4 ± 29.1
% using oral agents: 19.7 / 12.5 / 13.2 / 19.1</td>
<td>
<table>
<tr><th></th><th>Pramlintide 30 tid (n=122)</th><th>Pramlintide 75 tid (n=136)</th><th>Pramlintide 150 tid (n=144)</th><th>Placebo tid (n=136)</th></tr>
<tr><td>Withdrawals</td><td>26.2%</td><td>25%</td><td>37.5%</td><td>27.2%</td></tr>
<tr><td>Withdrawals due to AE</td><td>7.4%</td><td>10.3%</td><td>18.1%</td><td>10.3%</td></tr>
<tr><td>HbA1c %^</td><td>-0.3%</td><td>-0.47%</td><td>-0.6%*</td><td>-0.15%</td></tr>
<tr><td>% achieving HbA1c <7%</td><td>12.7%</td><td>13.4%</td><td>19.2%</td><td>11.1%</td></tr>
<tr><td>% achieving HbA1c <8%</td><td>45.1%</td><td>46.4%</td><td>54%</td><td>37.6%</td></tr>
<tr><td>Change in weight (kg)^</td><td>-0.5</td><td>-0.4</td><td>-1.3</td><td>+1.1</td></tr>
<tr><td>Δ in total daily insulin dose</td><td>+10.9%*</td><td>+7.9%</td><td>+9.1%*</td><td>+15.4%</td></tr>
<tr><td>Hypoglycemia (Total/severe)</td><td>67.2%
4.1%</td><td>67.6%
2.2%</td><td>64.6%
2.8%</td><td>70.6%
1.5%</td></tr>
</table>
^values for HbA1c and weight are estimated from graph
*significant vs. placebo
</td>
</tr>
</table>

AE=adverse event, BID= twice daily, BMI= body mass index, CV= cardiovascular, DB= double-blind, DKA= diabetic ketoacidosis, DM= diabetes mellitus, GI= gastrointestinal, HDL-C= high density lipoprotein cholesterol, HTN= hypertension, IHD= ischemic heart disease, ITT= intent-to-treat, LDL-C= low density lipoprotein cholesterol, LOCF= last observation carried forward, PC= placebo-controlled, PR= parallel, QID= four times daily, R= randomized, TC= total cholesterol, TID= three times daily