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Indiana Medicaid Drug Utilization Review Board Newsletter

New Injectable Therapeutic Options for the Treatment of Diabetes

The FDA has recently approved two new antidiabetic medications that represent two new therapeutic classes: Symlin® (pramlintide), which is an amylin analog and Byetta® (exenatide), which is an incretin mimetic.

Amylin Analog: Symlin (Pramlintide)

Pramlintide is a medication that is used as an adjunct to insulin therapy in patients with type 1 or type 2 diabetes mellitus. Pramlintide is a synthetic analog of human amylin, a neuroendocrine hormone secreted by pancreatic beta cells. Amylin works in concert with insulin to regulate postprandial glucose concentrations. Amylin is normally stored with insulin in secretory granules and is secreted along with insulin.¹

Amylin secretion is absent in patients with type 1 diabetes mellitus and is decreased in patients with type 2 diabetes mellitus. Decreased or absent amylin concentrations contribute to inadequacies of insulin therapy in patients with persistent postprandial hyperglycemia. Amylin replacement therapy complements insulin's effects in achieving optimal glycemic control.¹

Amylin affects glucose concentrations by three different mechanisms: (1) slowing gastric emptying without altering the overall absorption of nutrients, (2) suppressing postprandial glucagon

secretion, and (3) modulating appetite via the central nervous system. When used in combination with insulin, pramlintide reduces glycosylated hemoglobin concentrations and helps patients achieve current practice guidelines. Unlike the weight gain that is experienced with insulin monotherapy, modest weight reductions were observed with pramlintide and insulin combination therapy. Both of these effects have been maintained in clinical trials lasting 12 months.¹

Pramlintide is indicated for the adjunct treatment of type 1 diabetes in patients who use mealtime insulin therapy and have failed to achieve desired glucose control. Additionally, pramlintide is indicated for the adjunct treatment of type 2 diabetes in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without concurrent sulfonylurea and/or metformin therapy. Pramlintide is self-administered and is given subcutaneously immediately prior to each major meal (≥250 kcal or 30 g of carbohydrates). In type 1 diabetics, pramlintide should be initiated at a dose of 15 mcg and titrated at 15 mcg increments to a maintenance dose of 30 mcg or 60 mcg as tolerated. Type 2 diabetics should be initiated at a dose of 60 mcg and increased to a dose of 120 mcg as tolerated. In clinical studies, pramlintide reduced the amount of required short-acting insulin.²

The two most common adverse effects of pramlintide are hypoglycemia and nausea. Severe hypoglycemia is more common

during the initiation of therapy but can be minimized by a dose reduction in mealtime insulin and close monitoring of blood glucose levels. Nausea is typically reported as mild to moderate and tends to resolve with continued therapy. Nausea can be minimized by gradual dose titration.¹

Due to the effects on gastric emptying, pramlintide has the potential to interact with other medications. It should not be considered for patients taking drugs that alter gastrointestinal motility (e.g., anticholinergic agents) and agents that slow intestinal absorption (e.g., alpha-glucosidase inhibitors). When rapid onset of a concomitant orally administered agent is a critical determinant of effectiveness (such as analgesics), the agent should be administered at least 1 hour prior to or 2 hours after pramlintide injection. In clinical trials, the concomitant use of sulfonylureas or biguanides did not alter the adverse event profile of pramlintide. However, the risk of hypoglycemia may be increased when pramlintide is administered with other diabetic medications. In addition, pramlintide and insulin should be as separate injectins.²

Incretin Mimetics: Byetta (Exenatide)

Exenatide is the first in a new class of agents called incretin mimetics. Endogenous human incretins, such as glucagon-like peptide-1 (GLP-1), enhance insulin secretion after release from the gut into the systemic circulation. Occupation of the GLP-1 receptor site by exenatide results in an increase in both glucose-dependent synthesis of insulin and insulin secretion³

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes. Exenatide leads to a release of insulin only in the presence of elevated glucose concentrations. As euglycemia occurs, insulin secretion subsides. First-phase

insulin response is lost in patients with type 2 diabetes. Exenatide has been shown to significantly improve first- and second-phase insulin secretion over placebo in patients with type 2 diabetes. In patients with type 2 diabetes, exenatide moderates glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia. Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation. Exenatide has also been shown to reduce food intake in both animals and humans, which may help to control weight.³

Several clinical trials have demonstrated the effectiveness of exenatide either with metformin or in combination with metformin and a sulfonylurea. Exenatide, whether administered alone or in combination, significantly reduces glycosylated hemoglobin concentrations and helps patients achieve ADA recommended goals.

Exenatide is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but have not achieved adequate glycemic control. Exenatide therapy is self-administered and should be initiated at 5 mcg per dose administered twice daily at any time within the 60-minute period before the morning and evening meals. Exenatide should not be administered after a meal. Based on clinical response, the dose of exenatide can be increased to 10 mcg twice daily after 1 month of therapy. Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.⁴

Adverse effects associated with exenatide may include

hypoglycemia and gastrointestinal adverse effects. The patient and clinician should monitor for hypoglycemia when exenatide treatment is initiated and continued. When exenatide is added to metformin therapy, the current dose of metformin can be continued, as it is unlikely that the dose of metformin will require adjustment due to hypoglycemia when used with exenatide. In clinical trials, the incidence of hypoglycemia was increased when exenatide was used in combination with a sulfonylurea. Although specific dose recommendations are not available, the clinician should consider a dose reduction of the sulfonylurea when used in combination with exenatide. The use of exenatide is commonly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea. The use of exenatide is not recommended in patients with severe gastrointestinal disease.³

Exenatide should be used with caution in patients receiving orally administered medications that require rapid gastrointestinal absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those medications at least 1 hour before exenatide injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when exenatide is not administered.⁴

In conclusion, these innovative therapies represent an exciting new advancement in the treatment of diabetes. They offer clinicians additional options when determining the best therapy for patients. While these agents do provide new options, the high cost of these medications will ultimately limit their use to those patients who are extremely difficult to manage with traditional antidiabetic medications.

Top 25 Drugs for First Quarter 2005

Top 25 Drugs 1st Quarter 2005 By Total Amount Paid		
Drug	Total Paid	Total Claims
Zyprexa	\$10,008,455	29,239
Risperdal	\$8,474,362	38,679
Seroquel	\$6,200,733	29,930
Abilify	\$4,210,356	12,813
Depakote	\$4,178,323	30,680
Novoseven	\$3,982,993	23
Lipitor	\$3,951,038	42,863
Zoloft	\$3,423,345	35,960
Plavix	\$2,936,591	23,909
Gabapentin	\$2,897,639	26,464
Protonix	\$2,832,210	24,809
Topamax	\$2,700,081	12,270
Zocor	\$2,483,596	18,868
Effexor	\$2,165,611	17,442
Oxycontin	\$2,155,135	8,963
Lexapro	\$2,132,016	31,051
Aricept	\$2,106,829	15,772
Advair	\$2,097,548	14,286
Duragesic	\$1,986,498	9,843
Geodon	\$1,934,165	7,418
Zithromax	\$1,796,682	40,809
Lamictal	\$1,730,736	7,773
Singulair	\$1,680,594	19,676
Trileptal	\$1,539,708	9,996
Norvasc	\$1,523,440	25,997

Top 25 Drugs 1st Quarter 2005 Ranked by Claims Paid		
Drug	Total Claims	Total Paid
Hydrocodone/APAP	99,759	\$859,976
Furosemide	59,089	\$306,464
Albuterol	53,818	\$580,256
Amoxicillin	45,473	\$421,223
Lipitor	42,863	\$3,951,038
Lisinopril	41,312	\$381,680
Zithromax	40,809	\$1,796,682
Ranitidine	40,744	\$588,372
Risperdal	38,679	\$8,474,362
Aspirin	36,136	\$24,933
Zoloft	35,960	\$3,423,345
Alprazolam	35,526	\$209,451
Lexapro	31,051	\$2,132,016
Docusate	30,868	\$62,622
Depakote	30,680	\$4,178,323
Seroquel	29,930	\$6,200,733
Potassium	29,660	\$392,177
Zyprexa	29,239	\$10,008,455
Loratadine	29,096	\$368,140
Levothyroxine	28,711	\$291,132
Propoxy. N/APAP	27,705	\$199,487
Gabapentin	26,464	\$2,897,639
Norvasc	25,997	\$1,523,440
Protonix	24,809	\$2,832,210
Toprol	24,141	\$808,595

Program Assistance

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

PDL Listing

The fee-for-service PDL listing may be found at the following website:

<http://www.indianapbm.com>

¹ Clinical Pharmacology 2005, Symlin® (pramlintide) Monograph [accessed 2005 May 16]. Available at <http://cpip.gsm.com/>

² Symlin® package insert. Amylin Pharmaceuticals, Inc. San Diego, CA. 2005 [accessed 2005 May 16]. Available at www.symmlin.com

³ Clinical Pharmacology 2005, Byetta® (exenatide) Monograph [accessed 2005 May 16]. Available at <http://cpip.gsm.com/>

⁴ Byetta® package insert. Amylin Pharmaceuticals, Inc. San Diego, CA 2005 [accessed 2005 May 16] Available at www.BYETTA.com