WEST VIRGINIA Department of Health & Human Resources
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DUR Capsules

News and Information for West Virginia Providers from the West Virginia Bureau for Medical Services (WVBMS)

Incretin-Based Therapies in the Management of Type 2 Diabetes
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Introduction

Diabetes is a chronic illness which can lead to both micro and macrovascular complications. Currently it affects over 25.8 million people in the United States, 90-95% of which have type 2 diabetes (T2DM).[1] With improved glycemic control, rates of microvascular complications can be decreased. However in order to achieve a goal A1C of < 7%, as recommended by the American Diabetes Association (ADA), patients often need multiple medications to target the different pathophysiologic defects leading to hyperglycemia.[2] This newsletter will review pertinent information about a new group of antidiabetic agents as it relates to their use in clinical practice in the management of T2DM.

Pharmacology

These new drug therapies aim at restoring the "incretin effect" which is diminished in patients with T2DM.[3] The incretin effect describes the phenomenon where orally ingested glucose leads to a larger insulin release compared to when the same glucose load is administered intravenously.[4,5] This was subsequently determined to be the result of intestinal secretion of hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which contributes to approximately 50-70% of the insulin secretion in response to meals.[4,5] GLP-1 also decreases plasma glucagon levels, slows gastric emptying, and promotes feelings of satiety.[3,5] The enzyme dipeptidyl peptidase-4 (DPP-4) rapidly degrades GLP-1 endogenously decreasing its plasma half-life to 1-2 minutes.[5] By restoring this natural effect, through increased GLP-1 concentrations or prevention of degradation by DPP-4, patients with T2DM can obtain an adequate insulin response to a glucose load.

GLP-1 agonists enhance glucose-dependent insulin secretion from pancreatic β cells, suppress inappropriately elevated glucagon secretion, and slow gastric emptying.[3,4] Currently two GLP-1 agonists are available, exenatide (immediate and extended-release formulation) and liraglutide. Both are full GLP-1 receptor agonists that are resistant to DPP-4 degradation.[3,4] Exenatide is the synthetic form of exendin-4 with 53% amino acid sequence similarity to human GLP-1, while liraglutide is a human GLP-1 analogue with 97% homogenicity to human GLP-1.[5] Liraglutide has a longer half-life compared to the immediate release exenatide (approximately 13.5 hours versus 3.5 hours) allowing for once verses twice daily dosing.[4] Exenatide extended-release (ER) contains exenatide encapsulated into a suspended release microsphere formulation which, after an initial release of surface bound exenatide, gradually releases drug over approximately 10 weeks. Unlike the other GLP-1 agonists, it is administered weekly.[4,6] Because exenatide is primarily cleared by the kidney, it is not recommended for use in patients with severe renal impairment or end-stage renal disease.[6]

The DPP-4 inhibitors inhibit the enzyme DPP-4 from breaking down endogenous GLP-1, thereby enhancing glucose-dependent secretion from pancreatic β cells.[7] At therapeutic doses, they reduce plasma DPP-4 activity by 70-90% allowing for approximately a 1.5- to 4-fold increase in endogenous GLP-1 levels.[7] The half-life of the currently available agents allows for once daily administration. With the exception of linagliptin, all of the DPP-4 inhibitors undergo significant renal excretion and require dose adjustment in patients with renal impairment (see table 1).

Efficacy

Use of these incretin-based therapies results in improved glycemic control by reducing both fasting and postprandial blood glucose levels.[3,4,7] In clinical trials, GLP-1 agonists reduced A1C levels by 0.8-1.1%.[4] In addition to improvements in glycemic control, patients also experienced weight loss (on average 0.5-3.0 kg).[4] They have been studied as monotherapy or in combination with metformin, a sulfonylurea, a thiazolidinedione, or in combinations including metformin.[3,4] Liraglutide has also been studied in combination with insulin detemir.[3,4] In a 26-week open-labeled trial, 464 patients with T2DM inadequately controlled on metformin, sulfonylurea or both, were randomized to liraglutide 1.8 mg daily or exenatide 10 mcg twice daily to assess the change in A1C. Liraglutide decreased the mean change in A1C more than exenatide (-1.12% vs. -0.79%; -0.33 [95% CI 0.47-0.18] p<0.0001).[7]

DPP-4 inhibitors have been studied as monotherapy and in combination with metformin, thiazolidinediones, sulfonlyureas, and insulin. Unlike many of the other oral antidiabetics, these agents are typically weight neutral (mean changes in weight <1 kg).[7] In clinical trials, DPP-4 inhibitors reduced A1C levels by 0.4-0.1% (as monotherapy), however an additive effect in A1C lowering occurs when used in combination with other antidiabetic agents.[3,7] In trials with patients taking concomitant metformin therapy, GLP-1 agonists produced a statistically greater reduction in A1C and postprandial blood glucose levels as compared to DPP-4 inhibitors.[3,7]

Adverse Effects

The most common adverse effects with the GLP-1 agonists are gastrointestinal, especially fullness and nausea. The incidence in clinical trials ranged from 3% to 50%, and they were the most common reason for treatment discontinuation.[3,4] Nausea is generally mild to moderate in nature, occurring during the first weeks of therapy, with improvement and/or cessation as therapy continues.[4] These symptoms are lessened when the drug is titrated up from a lower dose. Cases of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, have also been reported.[3,4] If pancreatitis is suspected, therapy should be discontinued. If pancreatitis is confirmed, the GLP -1 agonist should not be restarted.[4,6] Since GLP-1 agonists stimulate the release of insulin and inihibit the release of glucagon in a glucose dependent manner, they do not cause hypoglycemia when used as monotherapy.[4] However, hypoglycemia can occur when used in combination with sulfonylureas and potentially with other insulin secretagogues. The development of antibodies to GLP-1 agonists can also occur, and in some cases can result in an attenuated glycemic response.[4-6] These antibodies do not cross react to endogenous GLP-1. Both liraglutide and exenatide ER carry a black box warning regarding the development of thyroid C-cell tumors in rodents exposed to these drugs at clinically relevant exposures.[6] At this time it is unknown whether this occurs in humans.

Conversely, DPP-4 inhibitors are well tolerated and have rates of adverse effects similar to placebo.[3,7] There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, therapy should be discontinued.[6,7]

Table 1. Dosing[6]

	Dosing	Renal Impairment	Hepatic Impairment
GLP-1 Agonists			
Exenatide (Byetta®)	5 mcg sc bid within 60 min prior to meals (2 main meals of the day). Increase to 10 mcg SC bid after 1 month	Should not be used in patients with CrCl < 30 ml/min or ESRD	No information on use in patients with hepatic impairment
Exenatide extended release (Bydureon™)	2 mg SC once a week	Should not be used in patients with CrCl < 30 ml/min or ESRD	No information on use in patients with hepatic impairment
Liraglutide* (Victoza®)	0.6 mg sc qd for one week. Increase to 1.2 mg SC qd. Can increase dose to 1.8 mg based on clinical response	Limited experience, use with caution in patients with any degree of renal impairment	Limited experience, use with caution

	Dosing	Renal Impairment	Hepatic Impairment
DPP-4 Inhibitors			
Saxagliptin (Onglyza®)	2.5 or 5 mg po qd	CrCl ≤ 50 ml/min: 2.5 mg PO qd	
Saxagliptin/metformin† (Kombiglyze™ XR)	Metformin naïve patients: 5 mg saxagliptin/ 500 mg metformin PO qd with evening meal	Contraindicated: Males: SCr ≥ 1.5 mg/dl Females: SCr ≥ 1.4 mg/dl	Not recommended in patients with hepatic impairment
Sitagliptin (Januvia®)	100 mg po qd	CrCl > 30 ml/min to < 50 ml/min: 50 mg PO qd CrCl < 30 ml/min or ESRD: 25 mg PO qd	No information on use in patients with severe hepatic impairment
Sitaglipin/metformin‡ (Janumet®)	Metformin naïve patients: 50 mg sitagliptin/500 mg metformin po bid with meals	Contraindicated: Males: SCr ≥ 1.5 mg/dl Females: SCr ≥ 1.4 mg/dl	Not recommended in patients with hepatic impairment
Sitaglipin/metformin‡ Janumet® XR	Metformin naïve patients: 100 sitagliptin/1000 mg metformin po qd with evening meal	Contraindicated: Males: SCr ≥ 1.5 mg/dl Females: SCr ≥ 1.4 mg/dl	Not recommended in patients with hepatic impairment
Linagliptin (Tradjenta®)	5 mg po qd	No adjustment needed	No adjustment needed
Linagliptin/metformin± (Jentadueto™)	Metformin naïve patients: 2.5 mg linagliptin/500 mg metformin po bid with meals	Contraindicated: Males: SCr ≥ 1.5 mg/dl Females: SCr ≥ 1.4 mg/dl	Not recommended in patients with hepatic impairment

sc: subcutaneous; bid: twice daily; ESRD: end-stage renal disease; po: by mouth; CrCl: creatinine clearance; qd: once daily; SCr: serum creatinine; * Reinitiate with the 0.6 mg dose if more than 3 days have elapsed since the last dose; † Dose should be individualized. Do not exceed a daily dose of 5 mg saxagliptin/2000 mg metformin; ‡ Dose should be individualized. Do not exceed a daily dose of 100 mg sitagliptin/2000 mg metformin; ± Dose should be individualized. Do not exceed a daily dose of 100 mg linagliptin/2000 mg metformin

Drug Interactions

GLP-1 agonists delay gastric emptying which can alter the absorption of oral medications, however the clinical significance of this effect is uncertain.[6] When given with sulfonlyureas, hypoglycemia can occur. As a result, it is recommended that the sulfonylurea dose be reduced with concomitant therapy.[6] DPP-4 inhibitors can also, when used in combination with insulin secretagogues or insulin, increase the risk of hypoglycemia. Strong inducers of P-glycoprotein or the cytochrome (CYP) P450 3A4 pathway (e.g., rifampin) can decrease the effectiveness of linagliptin.[6] In contrast, strong inhibitors of the CYP450 3A4 pathway can increase the effect of saxagliptin. As a result, 2.5 mg daily of saxiglipitin should be used with these agents (e.g., itraconazole, ketoconazole, clarithromycin, ritonavir).[6]

Contraindications

In addition to use in patients that develop a severe hypersensitivity reaction during use with either a GLP-1 agonists or DPP-4 inhibitors, both exenatide ER and liraglutide are contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2.[6] DPP-4 inhibitor combination products that contain metformin are contraindicated for use in patients with impaired renal function (Scr ≥ 1.5 mg/dl in males, ≥ 1.4 mg/dl in females) or with abnormal creatinine clearance resulting from an acute condition, acute/chronic metabolic acidosis .[6]

Indications and place in therapy

Both GLP-1 agonists and DPP-4 inhibitors are indicated for use in adult patients with T2DM as an adjunct to diet and exercise.[6] Neither of these agents should be used in patients with type 1 diabetes or for treatment of ketoacidosis. GLP-1 agonists should not be used as a substitute for insulin, or with prandial insulin since this has not been evaluated.[6] The recently updated ADA and European Association for the Study of Diabetes treatment guidelines recommend metformin and lifestyle modifications as first line therapy for the treatment of newly diagnosed T2DM.[2,9] Additionally, they recommend individualized treatment since there is not a

consensus on which therapy should be added to metformin.[2,9] Factors such as cost, concomitant conditions, and drug therapy, and lifestyle should be taken into consideration.

Both the GLP-1 agonists and DPP-4 inhibitors have additive efficacy when added to metformin, and offer many advantages over existing diabetes therapies. These include: a unique mechanism of action, lack of hypoglycemia as monotherapy, weight neutral or weight lowering effects, and tolerability (DPP-4 inhibitors). In addition, DPP-4 inhibitors can be dosed once daily, and are available in combination products with metformin and simvastatin, while extenatide ER can be administered weekly. Disadvantages include cost, modest A1C lowering effect, unknown risks of pancreatitis, and lack of long-term data. Specifically, the GLP-1 agonists have an injectable route of administration, gastrointestinal adverse effects, and unknown risks of thyroid cancer which warrants further investigation.

Conclusion

These new incretin-based therapies represent a new therapeutic approach to the management of T2DM and offer another option to help patients achieve their glycemic goals. Even though they are not first line therapies for most patients with T2DM, they offer unique advantages to current available antidiabetic therapy. Long-term outcome studies are currently underway with these agents which will help to better classify their use in relation to other therapies and to provide more data for some of the unanswered questions on safety. Additionally, more clinical experience is needed with these drugs to help determine which patient populations would benefit most from their use.

The hypoglycemic, incretin mimetics/enhancer class is managed on the West Virginia Medicaid Preferred Drug List. Preferred and non-preferred agents and prior authorization criteria are listed in the following table:

HYPOGLYCEMICS, INCRETIN MIMETICS/ENHANCERS

Preferred	Non-Preferred	PA Criteria
	Injectable	
	BYDUREON (exenatide) BYETTA (exenatide) SYMLIN (pramlintide) VICTOZA (liraglutide)	Byetta, Bydureon and Victoza will be authorized for 6-month intervals if each of the following criteria are met: 1. Diagnosis of Type 2 Diabetes 2. Previous history of a 30-day trial of metformin 3. No history of pancreatitis 4. For concurrent therapy with insulin, treatment with a basal insulin is required. Approval will be given for 6-month intervals. For re-authorization, A1C levels must be </= 7. Current laboratory values must be submitted. Symlin will be approved with a history of bolus insulin utilization in the past 90 days with no gaps in insulin therapy greater than 30 days.
	Oral	
JANUMET (sitagliptin/metformin) JANUVIA (sitagliptin) JUVISYNC (sitagliptin/simvastatin) KOMBIGLYZE XR (saxagliptin/metformin) ONGLYZA (saxagliptin) TRADJENTA (linagliptin)	JANUMET XR (sitagliptin/metformin) JENTADUETO (linagliptin/metformin)	Januvia/Janumet/Juvisync, Onglyza/Kombiglyze XR and Tradjenta will be subject to the following edits: 1. Previous history of a 30-day trial of metformin, sulfonylurea, or TZD. 2. Tradjenta will not be approved for concurrent use with insulin. 3. Januvia /Janumet /Juvisync, Onglyza/Kombiglyze XR will be approved for concurrent use with insulin for 6-month intervals. For re-authorization, A1C levels must be </= 7. Current laboratory values must be submitted. Jentajueto and Janumet XR will be approved after 30-day trials of the preferred combination agents, Janumet and Kombiglyze XR.

References

1. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
2. American Diabetes Association. Position Statement: Standards of Medical Care in Diabetes-2012. Diabetes Care 2012;35(Suppl 1):S11-S63.
3. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. Am J Med 2011;124:S3-18.
4. Gallwitz B. GLP analogues in type 2 diabetes. Drugs 2011;71(13):1675-1688
5. Sisson EM. Liraglutide: Clinical pharmacology and considerations for therapy. Pharmacotherapy 2011;31(9):896-911.
6. U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed October 10, 2012.
7. Baetta R and Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors. Similarities and differences. Drugs 2011;71(11):1441-1467.
8. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.
9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2012;35:1364-1379.

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