

Wyoming Drug Utilization Review

New Oral Medications for the Treatment of Type 2 Diabetes

Stevan Squires, PharmD

Type 2 diabetes mellitus (T2DM) accounts for up to 90% of diagnosed cases of diabetes.¹ T2DM is characterized by an increasing resistance to endogenous insulin production, and/or poor insulin secretion from the beta pancreatic cells. T2DM normally worsens over time as beta cell function continues to decline.¹ Two oral antidiabetic drug classes have come onto the market in

recent years. The first are the dipeptidyl peptidase 4 (DPP-4) inhibitors: Januvia™ (sitagliptin), Onglyza™ (saxagliptin), Nesina™ (alogliptin) and Tradjenta™ (linagliptin). The second are the sodium-glucose co-transporter 2 (SGLT-2) inhibitors: Invokana™ (canagliflozin), Jardiance™ (empagliflozin) and Farxiga™ (dapagliflozin).

Initial treatment of T2DM is usually directed towards lifestyle modifications that include weight loss, low carbohydrate diet and exercise.² If lifestyle modifications are insufficient for the control of blood glucose levels, then oral antidiabetic medications are initiated, typically with the biguanide, metformin. Metformin is known as an “insulin sensitizer”; it increases glycogen storage in skeletal muscles, and reduces gluconeogenesis in the liver.² Metformin has a low risk of hypoglycemia,

promotes weight loss and is usually continued as part of a dual therapy approach if monotherapy fails to produce satisfactory results.³ The need to add additional agents to metformin is usually determined following a 3 month trial of metformin alone. If results are unsatisfactory, an additional agent from another drug class is added to therapy.³

The mechanism of action of DPP-4 inhibitors is to block the enzyme activity that is responsible for the breakdown of glucagon-like peptide (GLP-1) and insulinotropic polypeptide (GIP).² Increasing GLP-1 and GIP levels causes an increase in insulin synthesis and release from the pancreatic beta cells and a more normal, physiologic insulin response following a meal.² DPP-4 inhibitors can be expected to lower A1C by 0.5 to 0.9%.³ Common adverse effects include hypoglycemia, nasopharyngitis, upper respiratory tract infection and headache.⁴ Post-marketing reports of hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria and Stevens-Johnson syndrome have been reported. DPP-4 inhibitors are only for use in T2DM, as the patient must still have the ability to produce endogenous insulin. Dose adjustments are recommended for patients with moderate to severe renal insufficiency for patients taking sitagliptin, saxagliptin or alogliptin. Linagliptin dosing does not need to be adjusted for renal function. Monitor all patients for signs and symptoms of hypoglycemia and for the possibility of developing pancreatitis. Any history of hypersensitivity to the members of this drug class such as angioedema or anaphylaxis is an absolute contraindication for their use. DPP-4 inhibitors should be used as an add-on to therapy with metformin but may also be used as monotherapy in patients who are intolerant to metformin.⁴ For Wyoming Medicaid patients; failure following 90 days of therapy with metformin is required before a DPP-4 inhibitor (sitagliptin or saxagliptin) will be approved. If treatment failure occurs with either of these two then either alogliptin or linagliptin may be used.

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P & T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on August 13, 2015. Highlights of this meeting include:

The responses to the PBM Services RFP are being reviewed. A decision is expected mid-September with a new contract starting in October of 2016.

Vyvanse will be allowed for patients aged 18 years and older with a diagnosis of binge eating disorder. Approvals will be given in 12 week increments.

Xenazine will be limited to the indication of chorea associated with Huntington's Disease. All other uses will require prior authorization.

Immunomodulators will be limited to 120% of labeled maximum dosages.

Corlanor will be approved for patients with congestive heart failure.

There is no evidence of improved efficacy or safety of Stiolto versus existing combination drugs for COPD. The Department of Health will conduct a cost analysis and determine PDL placement.

Entresto will be allowed for those with congestive heart failure. Due to the ARB component, duplicate therapy with ACE inhibitors or ARBs will not be allowed.

Orkambi will be approved for patients 12 years and older with cystic fibrosis as a result of homozygous F508 del genetic mutation.

There are two openings for physicians on the P&T Committee. If you are interested in this position, please contact Aimee Lewis at alewis13@uwyo.edu or by phone at (307) 766-6750.

The proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments for prior authorization criteria should be received prior to September 30, 2015.

The next P&T Committee meeting will be held November 12, 2015 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Chronic Pain Management Toolkit

The Chronic Pain Management Toolkit is now available from The Wyoming Rx Abuse Stakeholders (RAS). The toolkit provides official documentation about drug abuse in Wyoming and preventative actions and policies. An on-line version of the toolkit is available at

<http://www.wyrxabusestakeholders.com/#!health-care-providers/cksr>

RAS is comprised of representatives of the health care community, law enforcement, government and community members in Wyoming to prevent the increasing abuse of prescription medications while ensuring that they remain available for patients in need. We seek to help doctors, physician assistants, nurses, pharmacists, other health care professionals, law enforcement and the general public become more aware

of both the use and abuse of prescription medication. In addition, we seek to improve the regulatory framework to ensure that prescription medications are available to the patients who need them while preventing these drugs from becoming a source of harm or abuse.

It is the hope of the RAS that the information provided in this toolkit will assist Wyoming medical providers in the treatment of their chronic pain patients. It is not meant to be regulatory in nature. The presentation of this toolkit is purely to provide a resource to health care professionals on pain management. Your comments on how the toolkit can be improved to meet the needs of Wyoming practitioners and their patients are welcomed. Please direct all comments to the Rx Abuse Stakeholders at wyrxabusestakeholders@gmail.com.

SGLT-2 inhibitors are the newest class of oral antidiabetic medications that first came onto the market in March of 2013. SGLT-2 inhibitors work by blocking the reabsorption of glucose in the proximal renal tubules, thereby increasing the excretion of glucose from the body.² Urinary tract infections, yeast infections, increased urination, increased thirst, constipation and nausea are the most commonly reported adverse effects.⁴ A modest reduction in A1C of 0.7%-1.0% is typical of the medications found in this drug class. The SGLT-2 drug class is considered “non-preferred” at this time and will likely remain second or third-line options for patients who have failed other drug therapy regimens. Patients should be monitored for hypotensive episodes due to the change in volume status that the drug class produces. Administering a SGLT-2 inhibitor with a diuretic increases the risk of hypotension due to further volume depletion. Patients with renal function impairment will need to be monitored, and the medication dosage should be appropriately adjusted. SGLT-2 inhibitors have been shown to increase LDL-C levels, and patients should be advised to have routine lipid panels checked. Absolute contraindications to this drug class include a history of hypersensitivity to canagliflozin, empagliflozin or dapagliflozin and severe renal impairment, ESRD or dialysis. Rifampin, phenytoin, phenobarbital and ritonavir are contraindicated for use along with canagliflozin due to UDP glucuronosyltransferases (UGT) enzyme induction. This interaction can significantly decrease the effectiveness of canagliflozin, and the dose should be increased to 300 mg daily when taken in combination with these agents, if the eGFR is above 60 mL/min. Patients taking both canagliflozin and digoxin should be monitored closely as digoxin levels may increase. Patients taking any SGLT-2 inhibitor should be counseled that urine glucose tests will likely be positive while taking these medications due to the increase in urine glucose excretion.⁴ SGLT-2 inhibitors are an option for add-on therapy to metformin if a trial of metformin alone is unsuccessful after 90 days. Formulary requirements would then allow for dapagliflozin or canagliflozin to be used. A failure following 90 days of therapy with either of these two agents would then qualify the patient to receive empagliflozin. The 2014 Standards of Medical Care in Diabetes position

statement does not include SGLT-2 inhibitors in the recommended treatment algorithm.⁵

SGLT-2 inhibitors and DPP-4 inhibitors are new, novel drug classes that are available as add-on therapy to metformin, or as monotherapy after A1C goals have not been met while using other agents. The modest reduction in A1C of 0.7% to 1.0% and non-preferred formulary status makes these agents better suited as second or third options for patients with T2DM.

References

¹Triplitt CL, Repas T, Alvarez C. Diabetes mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: a Pathophysiologic Approach*, 9e. New York, (NY): McGraw-Hill; 2014. Available from: <http://accesspharmacy.com>. Accessed: January 30, 2015.

² Powers AC, D'Alessio D. Endocrine, pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In: Brunton LL, Chabner BA, Knollmann BC. eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 12e. New York, (NY): McGraw-Hill; 2011. Available from: <http://accesspharmacy.com>. Accessed: January 30, 2015.

³Garber A, Abrahamson M, Barzilay J, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocrine Practice*. 2013; 19:1-48.

⁴Januvia – sitagliptin phosphate tablet, film coated. Whitehouse Station (NJ): Merck Sharp & Dohme Corp.; 2014 February.

⁵Position statement: standards of medical care in diabetes-2014. *Diabetes Care*. 2014;37:S14-S79.

P & T Committee Openings

There are 2 physician openings on the P & T Committee. If you are interested, please contact Aimee Lewis at 307-766-6750 or alewis13@uwyo.edu. Time requirement includes 4 quarterly meetings per year in Cheyenne.

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Please contact WY-DUR at 307-766-6750 to have your name added or removed from our mailing list, or if you need to update your address. The WY-DUR newsletter is also available on-line at www.uwyo.edu/DUR/newsletters.