Wyoming Drug Utilization Review

Type-2 Diabetes Mellitus: Dipeptidyl Peptidase 4 (DPP-4) inhibitors

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Dipeptidyl peptidase-4 (DPP-4) inhibitors are a second-line agent in the American Diabetes Association(1) treatment algorithm for the treatment of type-2 diabetes mellitus, and lower blood glucose by slowing the inactivation of incretin hormones. These incretin hormones include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are involved in the physiologic regulation of glucose homeostasis.(2) DPP-4 inhibitors increase active GLP-1 and GIP levels approximately 2-3 fold following a meal. All currently FDA-approved DPP-4 inhibitors appear to, on average, lower HbA1c by 0.5-0.8%. Limited head-to-head data between DPP-4 inhibitors currently suggests similar efficacy in reducing HbA1c.(3)

DPP-4 inhibitors have a neutral effect on weight due to the relatively limited increase in GLP-1 activity compared to GLP-1 agonists. Due to DPP-4 inhibitors primarily GLP-1 driven mechanism of action, there is a limited risk of hypoglycemia.(3) However, a meta-analysis observed an increased risk of both acute pancreatitis and hypoglycemia with the use of DPP-4 inhibitors.(4)

Caution should be taken when prescribing DPP-4 inhibitors to patients with heart failure due to mixed safety results.(5,6) However, in a meta-analysis of 114 studies of DDP-4 inhibitors by Savarese et al.(5), when compared to placebo, no significant effect was found on all-cause and cardiovascular mortality. No significant effect was noted on risk of myocardial infarction, stroke, and heart failure.(5) Due to the mixed safety results available at this time, caution should be taken when prescribing DPP-4 inhibitors in patients with heart failure or at risk of developing heart failure.

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Preferred agent:
Sitagliptin (Januvia) is the current Medicaid preferred DPP-4 agent when clinical criteria are met.(8) The clinical criteria required for sitagliptin are: trial and failure of metformin greater than or equal to a 90-day supply in the last 12 months.(8) The main adverse reactions for sitagliptin are diarrhea (4%), constipation (3%), nausea (2%), hypoglycemia, osteoarthritis, pharyngitis (1%), nasopharyngitis (5%), and peripheral edema (2%).(4) There have been postmarketing reports of patients receiving sitagliptin monotherapy and in combination with metformin developing acute pancreatitis.(4) Saxagliptin + metformin and sitagliptin + metformin were found to be non-inferior to one another in a head-to-head trial.(7)

Non-preferred agents:
Alogliptin (Nesina) is available as a generic medication and in combination with metformin under the trade name of Kazano or as a generic.(4,8) The main adverse events for alogliptin are increased serum ALT (more than 3 times ULN: 1%), nasopharyngitis (4%), upper respiratory tract infection (4%), and headache (4%).(4) The evidence for the efficacy of the combination of alogliptin + metformin at reducing HbA1C, while statistically significant, had a very wide confidence interval.(7)

Saxagliptin is available under the brand name of Onglyza and in combination with metformin under the trade name of Komboglyze.(4,8) The main adverse events for saxagliptin are abdominal distress (2%), vomiting (2%), headache (7%), hypersensitivity reaction (2%), hypoglycemia (6% or less; incidence increased in conjunction with insulin secretagogues: 15% or less), sinusitis (3%), gastroenteritis (2%), lymphocytopenia (2% or less; dose related), peripheral edema (≤ 4%), and urinary tract infection (7%).(4) In the SAVOR trial(6) there was a higher risk for heart failure hospitalization in the saxagliptin group (3.5%) when compared to the placebo group (2.8%) (HR 1.27, 95% CI 1.07 to 1.51; p = 0.007).(6) An important note from these results is that the SAVOR trial was not designed to assess heart failure risk.(6)

Linagliptin is available under the brand name of Tradjenta and in combination with metformin under the trade name of Jentadueto.(4,8) The main adverse events to note for linagliptin are increased uric acid (3%), constipation (2%, in combination therapy), arthralgia (8%, in combination therapy), back pain (9%, in combination therapy), limb pain (5%, in combination therapy), cough (2-6%), nasopharyngitis (7%), headache (6%, in combination therapy), urinary tract infection (3%, in combination therapy), hypoglycemia (combination therapy in renal function impairment 63%, combined with metformin and sulfonylurea 23%, monotherapy 4% to 7%), severe hypoglycemia (combination therapy in renal function impairment [life-threatening or requiring hospitalization] 3%, with insulin 2%, with insulin [life-threatening] 1%); hypertriglyceridemia (combination therapy 2%), weight gain (combination therapy 2%).(4)

The current Wyoming Medicaid preferred DPP-4 with clinical criteria, sitagliptin, is similarly efficacious when compared to the other available, non-preferred, DPP-4 agents. Sitagliptin also has a similar adverse reaction profile and as such is an appropriate DPP-4 inhibitor agent for the treatment of type-2 diabetes mellitus.

References:

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7. Craddy P, Palin HJ, Johnson, KI. Comparative effectiveness of dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and mixed treatment comparison. Diabetes Ther. 2014;5:1–41.
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The P&T Committee met for its quarterly business meeting on February 10, 2022.

Highlights of this meeting include:
Teri Green, Wyoming Medicaid Director, has retired. She was the longest standing Medicaid Director in the nation. Jan Stall has been named Interim Director during the hiring process.

Albuterol inhalers will require prior authorization after a total of 12 inhalers per year. Inhalers are currently limited to two per month. This update brings policy closer in line with current asthma guidelines.

Livmarli, Voxzogo, Livtencity, Paxlovid and Zavesca will be limited to indication. Due to safety concerns, the Committee recommended that Elyxyb and molnupravir be non-preferred. Qulipta, Skytrofa, Tyrvaya, and Vuity were referred to the Department of Health for cost analysis and PDL placement.

Medicare announced that under a proposed rule, Aduhelm would only be covered for patients currently enrolled in a clinical trial. Additional discussion regarding how Medicaid will handle dual eligible clients will occur in May after Medicare finalizes their rule.

Proposed criteria are open for public comment. Comments can be sent by email to alewis13@uwyo.edu. All comments should be received by April 1, 2022. The next P&T Committee meeting will be held May 10, 2022 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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