**Invokamet and Xigduo XR — Two New Combinations for Type 2 Diabetes**

The FDA has approved fixed-dose combinations of metformin with either canagliflozin (Invokamet) or dapagliflozin (Xigduo XR) for treatment of patients with type 2 diabetes not adequately controlled with any one of these drugs, or in those already being treated with both metformin and either canagliflozin or dapagliflozin.

**Pronunciation Key**

Canagliflozin: kan' a gli floe' zin  
Invokamet: in voe' ka met  
Dapagliflozin: dap' a gli floe' zin  
Xigduo: zig doo oh

**MECHANISMS OF ACTION** — Metformin decreases hepatic glucose production and, to a lesser extent, increases peripheral glucose uptake. Canagliflozin and dapagliflozin inhibit SGLT2 (sodium-glucose co-transporter 2); they decrease renal glucose reabsorption, thereby increasing urinary glucose excretion.

**STANDARD TREATMENT** — Metformin is generally the preferred first-line treatment for type 2 diabetes, but most patients eventually require multi-drug therapy, which may include insulin, to achieve glycemic control. There is no consensus agreement on which drug should be added to metformin, which is already available in fixed-dose combinations with many other antihyperglycemic drugs.\(^1\)

**CLINICAL STUDIES** — No new clinical trials were required for approval of the combination products, but both have been shown to be bioequivalent to the individual tablets of metformin and either canagliflozin or dapagliflozin taken together. In randomized, double-blind trials with the individual drugs in patients who had not achieved glycemic goals with metformin alone, addition of either canagliflozin or dapagliflozin lowered A1C by 0.4-0.9%. Direct comparisons are lacking, but A1C reductions with either canagliflozin or dapagliflozin appear to be similar. Both canagliflozin and dapagliflozin reduce body weight by 2-3 kg and lower systolic blood pressure by 3-5 mm Hg.\(^2,3\)

**ADVERSE EFFECTS** — Metformin commonly causes gastrointestinal adverse effects (metallic taste, nausea, diarrhea, abdominal pain), which can be minimized by starting with a low dose, titrating slowly, dividing doses, and taking the drug with food. Lactic acidosis is a rare, but potentially fatal, complication that can occur with accumulation of metformin. Decreases in vitamin B12 serum concentrations have occurred in patients taking metformin long-term and have rarely been associated with anemia.

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**Table 1. Canagliflozin, Dapagliflozin and Combinations with Metformin**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Usual Daily Dosage</th>
<th>Cost(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin – Invokana (Janssen)</td>
<td>100, 300 mg tabs</td>
<td>100-300 mg PO once/d(^2,3)</td>
<td>$312.00</td>
</tr>
<tr>
<td>Canagliflozin/metformin – Invokamet (Janssen)</td>
<td>50/500, 50/1000, 150/500, 150/1000 mg tabs</td>
<td>50/500-150/500 mg PO bid(^2,3)</td>
<td>$312.00</td>
</tr>
<tr>
<td>Dapagliflozin – Farxiga (AstraZeneca)</td>
<td>5, 10 mg tabs</td>
<td>5-10 mg PO once/d(^2,3)</td>
<td>$312.10</td>
</tr>
<tr>
<td>Dapagliflozin/metformin – Xigduo XR (AstraZeneca)</td>
<td>5/500, 5/1000, 10/500, 10/1000 mg tabs</td>
<td>5/500-10/1000 mg PO once/d(^2,3)</td>
<td>$312.10</td>
</tr>
</tbody>
</table>

ER = extended-release

1. Approximate WAC for 30 days’ treatment at the lowest usual daily dosage. WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. November 5, 2014. Reprinted with permission by First Databank, Inc. All rights reserved. ©2014. www.fdbhealth.com/policies/drug-pricing-policy.
2. Once-daily dose should be taken with breakfast or first meal of the day.
3. Maximum dose of canagliflozin is 100 mg in patients with moderate renal impairment (eGFR 45-59 mL/min/1.73m\(^2\)). It should not be given to patients with an eGFR <45 mL/min/1.73m\(^2\).
4. Should be taken with meals.
5. Maximum daily dose is 300 mg/2000 mg in patients with an eGFR <60 mL/min/1.73m\(^2\).
6. Taken in the morning with or without food.
7. Should not be used in patients with an eGFR <60 mL/min/1.73m\(^2\) or in those with active bladder cancer.
Canagliflozin and dapagliflozin can cause genital mycotic infections and urinary tract infections in both men and women. Both drugs have a diuretic effect, which can lead to dehydration, hypovolemia, and hypotension, particularly in elderly patients with renal dysfunction and in those taking loop diuretics. Increased serum creatinine levels, decreased estimated glomerular filtration rate (eGFR), hyperkalemia, hypermagnesemia, hyperphosphatemia, and increased LDL-cholesterol can occur. An increased incidence of fracture has been reported with both drugs; the risk may be greater in patients with renal impairment.

In clinical trials, patients treated with dapagliflozin had a higher incidence of bladder cancer (10/6045; 0.17%) than those taking placebo (1/3512; 0.03%). When patients treated for less than one year before diagnosis were excluded, there were 4 cases of bladder cancer with dapagliflozin and none with placebo. Canagliflozin has not been associated with an increase in the incidence of bladder cancer.

**CONCLUSION** — The fixed-dose combinations of metformin and canagliflozin (Invokamet) and metformin plus dapagliflozin (Xigduo XR) should be more convenient than taking the drugs separately. Neither canagliflozin nor dapagliflozin offers any advantage in glycemic efficacy over other second-line drugs for type 2 diabetes, but both cause weight loss rather than weight gain and do not cause hypoglycemia.