Dapagliflozin: A new class of drug in the treatment of Type 2 diabetes

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Abstract:
Sodium-glucose co-transporter (SGLT) inhibitors are a new group of oral medications used for treating type 2 diabetes. Dapagliflozin was approved in January 8th, 2014 and is the second selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2) to be marketed in the US. It is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 Diabetes Mellitus (T2DM). It is available 5mg and 10 mg in film coated tablets. It acts by inhibiting SGLT2 decreases plasma glucose by increasing urinary glucose excretion. The common adverse reactions are genital mycotic infection, nasopharyngitis, urinary tract infections, back pain, urination increase, nausea, influenza. It is contraindicated in hypertension, renal impairment, hypoglycemia, genital mycotic infections and bladder cancer.

INTRODUCTION:

SGLT Inhibitors
- Sodium-glucose co-transporter (SGLT) inhibitors are a new group of oral medications used for treating type 2 diabetes.
- The following drugs belong to the SGLT inhibitors class:

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>TRADE NAME</th>
<th>COMPANY</th>
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<tbody>
<tr>
<td>DAPAGLIFLOZIN</td>
<td>Forxiga</td>
<td>Bristol-Myers Squibb Company and Astrazeneca</td>
</tr>
<tr>
<td>CANAGLIFLOZIN</td>
<td>Invokana</td>
<td>Johnson and Johnson</td>
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<tr>
<td>EMPAGLIFLOZIN</td>
<td>Jardiance</td>
<td>Boehringer</td>
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DAPAGLIFLOZIN
- Dapagliflozin was approved by USFDA on January 8th, 2014 and is the second selective inhibitor of the sodium-glucose co-transporter 2 (SGLT2) to be marketed in the US.
- It is manufactured and marketed by Bristol-Myers Squibb Company and Astrazeneca.

Indications and usage
- It is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 Diabetes (T2DM).

Dosage and administration
- The recommended starting dose is 5mg taken once daily in the morning with or without food.
- Assessment of renal function is recommended prior to initiation of dapagliflozin and periodically thereafter.

- Do not initiate dapagliflozin in patients with eGFR < 60mL/min/1.73m2.
- If additional glycemic control is needed, the dose may be increased to 10mg once daily in patients who have an estimated GFR (eGFR) of ≥ 60mL/min/1.73m2.
- Discontinue dapagliflozin if eGFR is persistently < 60mL/min/1.73m2.

Dosage forms and strengths
- It is available 5mg and 10 mg in film coated tablets.

Contraindications
- It is contraindicated in severe renal impairment, end stage renal disease, or patients on dialysis.
- History of hypersensitivity reactions.
Surendra et al., Dapagliflozin treatment for diabetes

Mechanism of action
- The kidney plays a major role in glucose homeostasis through glomerular filtration and reabsorption of glucose.
- Renal reabsorption of glucose is mediated by SGLT1 and SGLT2 within the proximal tubule.
- SGLT2 is expressed almost exclusively in the kidney and is responsible for the majority of glucose reabsorption.
- SGLT1 is primarily expressed along the brush border of the small intestine and is also located in the proximal tubule; it is mainly responsible for glucose absorption in the GI tract, but also accounts for approximately 10% of glucose reabsorption at the proximal renal tubule.
- Inhibiting SGLT2 decreases plasma glucose by increasing urinary glucose excretion.

Pharmacokinetics
- Absorption: The absolute oral bioavailability of this drug is 78%.
- Distribution: protein binding 91%
- Metabolism: liver; CYP450: minimal; UGT (Uridine 5'-diphospho-glucuronosyltransferase) : 1A9 substrate
- Excretion: urine 75% (<2% unchanged), feces 21% (15% unchanged);
- Half-life: 12.9hrs

Side effects
Serious Reactions
- Hypersensitivity reaction
- Anaphylaxis
- Renal impairment
- Orthostatic Hypotension
- Bladder cancer risk

Common Reactions
- Genital mycotic infection
- Nasopharyngitis
- UTI
- Back pain
- Urtication increase
- Nausea
- Influenza
- Cholesterol increase
- Constipation
- Urinary discomfort
- Extremity pain
- Creatinine increase
- Orthostatic Hypotension

Warnings and Precautions

Hypotension
- Dapagliflozin causes intravascular volume contraction.
- Symptomatic hypotension may occur after initiation of dapagliflozin particularly in patients with eGFR<60mL/min/1.73m2, elderly patients, those taking loop diuretics Volume status should be assessed and corrected before initiating dapagliflozin in patients with these characteristics.
- Monitor for signs and symptoms after initiating therapy.

Impairment in renal function
- Dapagliflozin increases serum creatinine and decreases eGFR.
- Elderly patients and patients with impaired renal function may be more susceptible to these changes.
- Evaluate renal function prior to initiating dapagliflozin and periodically thereafter.

Hypoglycemia
- The risk of hypoglycemia can be increased when dapagliflozin is combined with insulin or insulin secretagogues (e.g., sulfonylureas).
- A lower dose of insulin or insulin secretagogue may be needed to minimize the risk.

Genital mycotic infections
- Dapagliflozin increases the risk of genital mycotic infections.
- Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections.

Bladder Cancer
- There are insufficient data to determine if dapagliflozin has an effect on pre-existing bladder tumors.
- Dapagliflozin should not be used in patients with active bladder cancer.
- In those with a prior history of bladder cancer, the product labeling states that risk versus benefit be considered.

Pregnancy and Nursing
- Pregnancy Category C
- In rat studies, dapagliflozin may affect renal development and maturation.
- The timing of these effects corresponds to 2nd and 3rd trimester of human development; therefore consider alternate therapy during pregnancy especially during the 2nd and 3rd trimester.
- Dapagliflozin is secreted in milk of lactating rats.
- It is not known if dapagliflozin is excreted in human milk.
- Because of the potential for serious adverse reactions to the nursing infant, a decision should be made to discontinue dapagliflozin or nursing taking into account the importance of the drug to the mother.

Storage
Store at room temperature in between 20 to 25 degree centigrade.

References
2. Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial


