Long-Term Care Updates

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Another SGLT2 Inhibitor? Sotagliflozin in Review

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Introduction

Sotagliflozin (Impefa) was FDA-approved in May 2023, making it the 6th sodium-glucose cotransporter 2 (SGLT2) inhibitor to come to the US market. What sets sotagliflozin apart, however, is its unique indications, ability to inhibit sodium-glucose cotransporter 1 (SGLT1), and lack of an indication for improving glycemic control in adults with type 2 diabetes. This article will review relevant prescribing information and clinical research on the use of sotaglilfozin, noting specific details that prevent sotagliflozin from being considered a "me too" medication.

Indications

Sotagliflozin is FDA-approved to reduce the risk of cardiovascular death, heart failure-related hospitalization, and urgent heart failure visits in adults with:[1]

1.) Heart failure or

2.) Type 2 diabetes, chronic kidney disease (CKD), and other cardiovascular risk factors

Dapagliflozin carries a similar indication, among many others; however, dapagliflozin's use in patients with heart failure was approved based on studies in patients with heart failure *with or without* diabetes.[2] All patients in the phase III clinical trials for sotagliflozin had diabetes. It is unclear how patients with heart failure *without* diabetes will respond to sotagliflozin therapy. Beyond this, sotagliflozin is the only SGLT2 inhibitor that does not carry a labeled indication to improve glycemic control in patients with type 2 diabetes.

Mechanism of Action

Sotagliflozin is an inhibitor of both SGLT1 and SGLT2. Inhibition of SGLT1 reduces the absorption of glucose and sodium in the intestine. This is thought to explain the higher rates of diarrhea reported with sotagliflozin. Inhibition of SGLT2 reduces reabsorption of glucose and sodium in the kidneys. From a glycemic control perspective, this lowers the renal threshold for glucose and increases urinary glucose excretion, thereby decreasing glucose levels in the plasma. And while the precise mechanism of sotagliflozin's cardiovascular effects is unclear, inhibition of SGLT2 is also thought to reduce pre- and afterload of the heart and downregulate sympathetic activity, which may contribute to its cardiovascular benefits.[1]

Place in Therapy

In 2022, the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of American (HFSA) published updated guidelines for the management of heart failure, which included recommendations related to the use of SGLT2 inhibitors.[3] However, the guidelines offer no preference for a specific SGLT2 inhibitor. Key SGLT2 inhibitor-related recommendations follow:

- Recommend SGLT2 inhibitors for patients with type 2 diabetes and increased cardiovascular risk to prevent hospitalizations for heart failure (strong recommendation).
- Recommend SGLT2 inhibitors in patients with heart failure and type 2 diabetes to reduce heart failure-related morbidity and mortality and improve glycemic control (strong recommendation).
- For patients with heart failure with moderately reduced ejection fraction or preserved ejection fraction, SGLT2 inhibitors may be used to reduce heart failure-related hospitalization and cardiovascular mortality (moderate recommendation).
- Recommend SGLT2 inhibitors for patients with symptomatic heart failure with reduced ejection fraction to reduce heart failure-related hospitalization and cardiovascular mortality regardless of diabetes status (strong recommendation).[3]

Due to the publication date of these guidelines with respect to sotagliflozin's approval, sotagliflozin's place in therapy is not specifically addressed. However, given that its safety and efficacy in patients with heart failure *without* diabetes has not been addressed, it is possible that dapagliflozin may be preferred over sotaglilfozin for this purpose.

Clinical Research

Sotagliflozin was FDA-approved on the basis of two phase III clinical trials, which enrolled nearly 12,000 patients with heart failure and type 2 diabetes (SOLOIST trial) or type 2 diabetes, CKD, and other cardiovascular risk factors (SCORED trial). Collectively, the studies compared sotagliflozin once daily to placebo for a median of 9 months (SOLOIST) or 16 months (SCORED).[4,5]

The primary outcome for each trial was the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure, reported as the number of events per 100 patient-years. Compared with placebo, the event rate was reduced by 33% in patients with heart failure and diabetes and 26% in patients with type 2 diabetes, CKD, and additional cardiovascular risk factors. The rate of hospitalizations and urgent visits for heart failure was also significantly reduced with sotagliflozin over placebo in both trials. No significant difference between sotagliflozin and placebo was reported for the rate of death from cardiovascular causes. However, the studies were not adequately powered to detect differences between groups for this outcome. Further, both trials ended early due to a loss of funding from the trial sponsor.[4,5]

Adverse Reactions:

Pooled adverse reaction data from the two phase III placebo-controlled trials evaluating sotagliflozin are presented in the Table below. Discontinuation due to adverse effects was reported in 5.6% and 5.0% of patients receiving sotagliflozin in the SOLOIST and SCORED trials, respectively. Rates of discontinuation due to adverse effects in patients receiving placebo in these trials were 5.4% and 4.5%, respectively.[1] While a statistical analysis of the adverse event data was not provided in the SOLOIST trial, a significantly greater risk of diarrhea (NNH=40), genital mycotic infections (NNH=66), volume depletion (NNH=76), and diabetic ketoacidosis (NNH=333) was reported with sotagliflozin vs. placebo in the SCORED trial.[5]

Table: Adverse reactions reported in ≥2% of sotagliflozin-treated patients at a rate greater than placebo[1]

	Sotagliflozin (n = 5896)	Placebo (n = 5897)
Diarrhea	8.2%	5.8%
Dizziness	3.2%	2.8%
Genital Mycotic Infection	2.2%	0.8%
Urinary Tract Infection	11.2%	10.6%
Volume Depletion	5.6%	4.5%

Contraindications, Warnings, and Precautions

Sotagliflozin carries a labelled contraindication for hypersensitivity and warnings/precautions related to genital mycotic infections, hypoglycemia, ketoacidosis, necrotizing fasciitis of the perineum, urosepsis, pyelonephritis, and volume depletion. [1]

Because cases of ketoacidosis, urosepsis, pyelonephritis, and necrotizing fasciitis of the perineum (Fournier's Gangrene) have been reported with SGLT2 inhibitors, patients taking sotagliflozin should be monitored for signs and symptoms of these conditions. If these conditions are suspected, sotagliflozin should be discontinued and appropriate treatment should be initiated.[1]

Higher rates of volume depletion-related adverse effects and genital mycotic infections have been reported with sotagliflozin. Before initiating sotagliflozin, volume status should be corrected in patients at risk for volume depletion-related adverse effects, including elderly patients and those with impaired renal function or low blood pressure.[1]

Drug Interactions

Pharmacokinetic drug interactions with sotagliflozin are relatively limited. Co-administration with UGT enzyme inducers may decrease exposure to sotagliflozin and therefore reduce its efficacy. Additionally, concomitant use with insulin or insulin secretagogues may increase the risk of hypoglycemia. Sotagliflozin also has the potential to decrease serum lithium concentrations and increase digoxin exposure.[1]

Geriatric/Nursing Considerations

In the clinical efficacy trials of sotagliflozin, around 70% of patients were aged ≥65 years, and around 25% were aged ≥75 years. In general, no differences in safety or efficacy were seen in younger versus older adult patients. However, the rate of volume depletion-related adverse reactions was higher in patients aged ≥65 years.[1]

Sotagliflozin should be taken not more than one hour before the first meal of the day. The tablets should not be cut, crushed, or chewed.[1]

Sotagliflozin should be held for at least 3 days, if possible, before major surgery or procedures requiring prolonged fasting.[1]

Dosing and Availability[1]

Sotagliflozin is available as 200mg and 400mg oral tablets.

Usual Adult Dosage: 200mg once daily; if tolerated, dose should be titrated up to 400mg after at least 2 weeks.

Renal Dosing:

- ❑ Mild or moderate renal impairment (eGFR 30-89mL/min/1.73m^2): No adjustment needed
- ❑ Severe renal impairment (eGFR <30mL/min/1.73m^2): Safety and efficacy not established.
  - ✓ Patients with eGFR <25mL/min/1.73m^2 or on dialysis were not enrolled in clinical trials.
  - ✓ In clinical trials, therapy was discontinued if eGFR fell below 15mL/min/1.73m^2.

Hepatic Dosing:

- ❑ Mild hepatic impairment (Child-Pugh class A): No adjustment needed
- ❑ Moderate hepatic impairment (Child-Pugh class B): Use not recommended
- ❑ Severe hepatic impairment (Child-Pugh class C): Use not recommended

References:

1. Inpefa [package insert]. The Woodlands, TX: Lexicon Pharmaceuticals, Inc.; May 2023.
2. Farxiga [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2023.
3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e876-e894.
4. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117-128.
5. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med.* 2021;384(2):129-139.