Acentra HEALTH

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2023 Quarter 3 Newsletter

FDA APPROVAL SPOTLIGHT

Inpefa (sotagliflozin) was approved on May 26, 2023 for risk reduction of cardiovascular mortality, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure and in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors. This effect is thought to be caused by the combined inhibition of sodium-glucose co-transporters (SGLT) 1 and 2. The SGLT1 protein is found in the mucosa of the small intestine, as well as the proximal tubule of nephrons, and is mostly responsible for the intestinal reabsorption of both sodium ions and glucose. The SGLT2 protein is found primarily in the proximal tubule of nephrons and is mostly responsible for the renal reabsorption of sodium ions and glucose. This mechanism is thought to reduce cardiac preload, cardiac afterload, and sympathetic activity. Previously, similar therapies to Inpefa only targeted the inhibition of SGLT2 and have been found to have benefit in type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and heart failure (HF).

A noted benefit to Inpefa is its dosing regimen. Inpefa is initially dosed as a single 200 mg tablet by mouth daily, given less than one hour prior to the first meal of the day, and titrated to 400 mg by mouth daily as tolerated after at least 2 weeks. There are no dose adjustments required for renal or hepatic dysfunction.
SOLOIST-WHF is a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial studying Inpefa in patients (N=1,222) with T2DM admitted inpatient for worsening heart failure. The primary composite endpoint was for cardiovascular (CV) death, hospitalization for HF, and urgent outpatient visit for HF. The study found a relative risk reduction (RRR) of 33% with a hazard ratio (HR) of 0.67 (95% CI 0.53-0.85, p<0.001) for the primary composite endpoint when Inpefa was initiated while inpatient up to 2 days post-discharge (see Fig. 1 below). The number needed to treat (NNT) was a surprisingly low number of 4. The researchers also conducted a post-hoc analysis in patients initiated on Inpefa on or before discharge and found a 51% RRR with a HR of 0.49 (95% CI 0.27-0.91) for readmission for HF-related events or CV death within 30 days (see Fig. 2 below). The most common adverse drug reactions (ADRs) are listed in Table 1 and show higher rates of urinary tract infection (UTI), volume depletion, diarrhea, hypoglycemia, and dizziness compared to placebo, as expected.

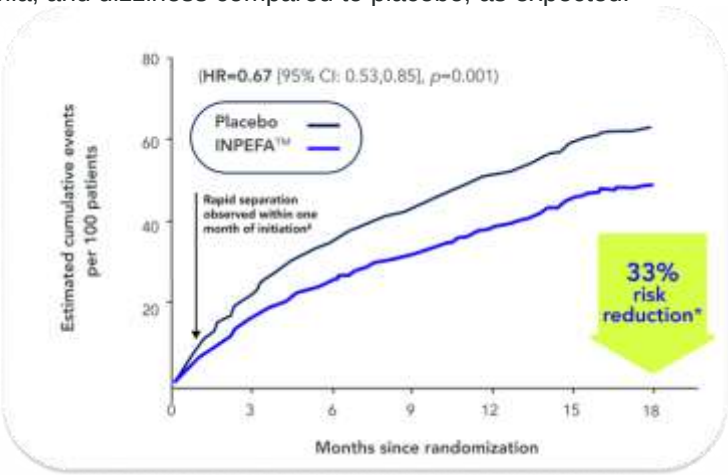

Figure 1: Primary composite endpoint for SOLOIST-WHF

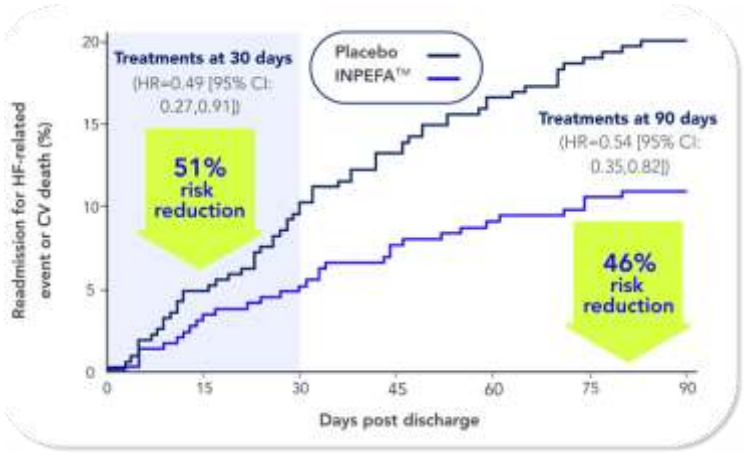

Figure 2: Post-hoc Analysis for SOLOIST-WHF

Table 1: ADRs from SOLOIST-WHF

ADR	Inpefa (N=605)	Placebo (N=611)
UTI	8.6%	7.2%
Volume depletion	9.3%	8.8%
Diarrhea	6.9%	4.1%
Hypoglycemia	4.3%	2.8%
Dizziness	2.8%	2.5%

The SCORED trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial studying Inpefa in patients (N=10,584) with T2DM, CKD, and additional CV risk factors. The primary composite endpoint was CV death, hospitalization for HF, and urgent HF outpatient visits. The study found a 25% RRR for Inpefa compared to placebo with a HR of 0.75 (95% CI 0.63-0.88, p<0001) (see Fig. 4 below). A secondary endpoint of a 3-point major adverse cardiovascular event (MACE) calculation showed a 21% RRR with a HR of 0.79 (95% CI, 0.67-0.93). The most common ADRs (see Table 2) were similar to the SOLOIST-WHF trial, with the addition of genital mycotic infection, which was also more common in Inpefa compared to placebo.

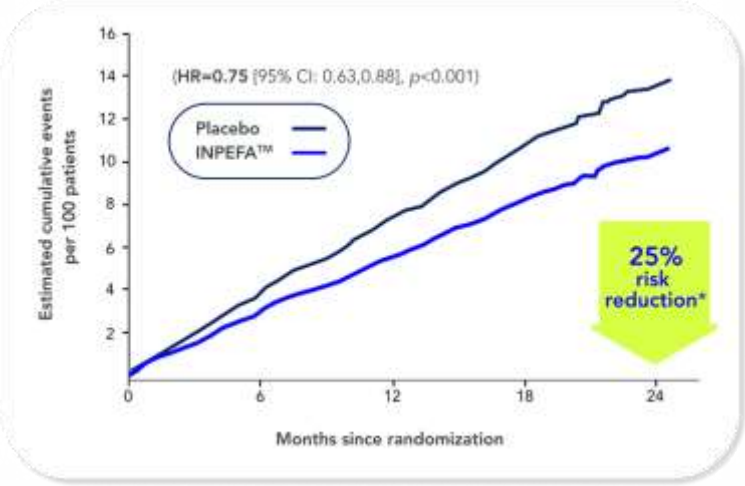

Figure 3: Primary composite endpoint for SCORED

Table 2: ADRs from SCORED

ADR	Inpefa (N=605)	Placebo (N=611)
UTI	11.5%	11.0%
Volume depletion	5.2%	4.0%
Diarrhea	8.4%	6.0%
Hypoglycemia	7.7%	7.9%
Dizziness	3.3%	2.8%
Genital mycotic infection	2.4%	0.9%

Although there is still research to be done to fully elucidate Inpefa's current place in the treatment of T2DM, CKD, and HF, especially compared to other SGLT2 inhibitors, the well-powered clinical trials of Inpefa with their large sample sizes have promising results. The two SGLT2 inhibitors that have the same three indications as Inpefa are Farxiga (dapagliflozin) and Jardiance (empagliflozin). A 2023 meta-analysis (Iyer et al.) comparing Farxiga and Inpefa efficacy in HF noted that Inpefa seems to be most effective when initiated immediately following and acute HF decompensation, while Farxiga seems to be most effective overall in patients with greater symptom burden. There is no data directly comparing Inpefa with SGLT2 inhibitors in humans. However, there is one 2023 study (Kim et al.) comparing Inpefa and Jardiance in a zebrafish model for the treatment of DM and heart failure reduced ejection fraction (HFrEF), which demonstrated that both have a significant cardioprotective effects but that Inpefa might be slightly less cardioprotective. There is also ongoing to determine Inpefa's role, if any, in the treatment of inadequately controlled type 1 diabetes mellitus (T1DM).

Due to the lack of comparative studies but the promising results of Inpefa's clinical trials, its current place in treatment can be considered similar to current SGLT2 therapies. The AHA 2022 guidelines for the treatment of HF newly recommend SGLT2 inhibitors as a first-line therapy for HFrEF and HFpEF to reduce hospitalization and CV mortality. The KDIGO 2022 guideline update for diabetes management in CKD includes SGLT-2 inhibitors in combination with metformin as first-line therapy for this patient population. Until more comparative studies are published and further guidelines updates are released, it is expected that Inpefa will be utilized under the current SGLT2 recommendations.

References:

- Lexicon Pharmaceuticals, Inc. Inpefa [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216203s000lbl.pdf. Revised May 2023. Accessed October 18, 2023.
- Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B; SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021 Jan 14;384(2):117-128. doi: 10.1056/NEJMoa2030183. Epub 2020 Nov 16. PMID: 33200892.
- Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZI, Dwyer JP, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG; SCORED Investigators. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021 Jan 14;384(2):129-139. doi: 10.1056/NEJMoa2030186. Epub 2020 Nov 16. PMID: 33200891.
- Iyer N, Hussein S, Singareddy S, et al. (September 19, 2023) Sotagliflozin vs Dapagliflozin: A Systematic Review Comparing Cardiovascular Mortality. Cureus 15(9): e45525. doi:10.7759/cureus.45525
- Kim I, Cho HJ, Lim S, Seok SH, Lee HY. Comparison of the effects of empagliflozin and sotagliflozin on a zebrafish model of diabetic heart failure with reduced ejection fraction. Exp Mol Med. 2023 Jun;55(6):1174-1181. doi: 10.1038/s12276-023-01002-3. Epub 2023 Jun 1. PMID: 37258583; PMCID: PMC10318005.

- Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895-e1032. doi: 10.1161/CIR.0000000000001063. Epub 2022 Apr 1. Erratum in: Circulation. 2022 May 3;145(18):e1033. Erratum in: Circulation. 2022 Sep 27;146(13):e185. Erratum in: Circulation. 2023 Apr 4;147(14):e674. PMID: 35363499.
- Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022 Nov;102(5S):S1-S127. doi: 10.1016/j.kint.2022.06.008. PMID: 36272764.

2023 GUIDELINE UPDATES

In June of 2023, a multidisciplinary panel from the American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG) published clinical practice guidelines for the pharmacological management of chronic idiopathic constipation (CIC) in adults. Previously, the most robust set of guidelines was published by the American Journal in Managed Care in 2019, focusing on better definition and diagnostic criteria for CIC. Prior to this point, the AGA had published in 2016 an overview for the diagnosis and treatment of bowel disorders generally. However, since both of these guidelines have been published, the diagnostic criteria for CIC have been refined, and more research has been performed on treatments in this patient population, necessitating more robust and up-to-date treatment guidelines.

As CIC has a high prevalence of 8-12% in the United States, initial and follow-up access to medical care and treatments may be limited. Therefore, the guidelines emphasize the importance of both pharmacologic and non-pharmacologic approaches, as well as the use of both over-the-counter (OTC) and prescription medication therapies. The guidelines consist of 10 main recommendations for the treatment of CIC and include appropriate dosing, duration, and cost for the selected therapies. A summary of this information can be found in Table 1.

Table 1: 2023 AGA/ACG CIC Treatment Guideline Recommendation Summary

Recommendation	***Dose***	***Strength/Certainty***
Fiber supplementation with psyllium as first-line therapy with adequate hydration	TDD of fiber 20-30 g/day OR 14 g/1000 kcal intake/day	Conditional/Low
Long-term use (up to 6 months as needed) of polyethylene glycol (PEG) with or without fiber supplementation for mild constipation	17 g daily	Strong/Moderate

Magnesium oxide for 4 weeks or longer in patients without renal insufficiency	400-500 mg daily	Conditional/Very low
Lactulose in patients who fail or are intolerant to OTC therapies	15 g daily	Conditional/Very low
Bisacodyl or sodium picosulfate for short-term use (≤4 weeks) or as rescue therapy in combination with other agents	5-10 mg daily	Strong/Moderate
Senna for at least 4 weeks	8.6-17.2 mg daily	Conditional/Low
Lubiprostone instead of or in combination with OTC agents for at least 4 weeks in patients non-responsive to OTC agents alone	24 µg BID	Conditional/Low
Linaclotide, plecanatide, or prucalopride instead of or in combination with OTC agents for at least 12 weeks in patients non-responsive to OTC agents alone	Linaclotide: 72-145 µg daily Plecanatide: 3 mg daily Prucalopride: 1-2 mg daily	Strong/Moderate

To summarize, the 2023 AGA/ACG guidelines for the treatment of CIC focus primarily on initial therapy with OTC treatments, such as psyllium, PEG, and magnesium oxide, followed by a trial of lactulose, bisacodyl, and/or a sennoside. If trials of these OTC therapies are ineffective, a trial of lubiprostone or a serotonin (5-HT4) receptor agonist may be used in combination with OTC treatments or as a monotherapy, 5-HT4 receptor agonist having more robust evidence to support use in this patient population. Most of these are recommended for a duration of at least 4 weeks to see full effect.

As newer therapies are released on the market, further updates to the guidelines will be required. Additionally, further research will likely be conducted comparing the prescription therapies to each other, as several have only been compared to placebo or standard OTC therapies. This is the reason that none are recommended preferentially over the others in these guidelines. Currently, these recommendations are the most robust and up-to-date collection of data for the CIC patient population and will likely assist greatly in supporting current practices in the treatment of CIC.

References:

- Chang L, Chey WD, Imdad A, Almario CV, Bharucha AE, Diem S, Greer KB, Hanson B, Harris LA, Ko C, Murad MH, Patel A, Shah ED, Lembo AJ, Sultan S. American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. Gastroenterology. 2023 Jun;164(7):1086-1106. doi: 10.1053/j.gastro.2023.03.214. PMID: 37211380; PMCID: PMC10542656.
- Lacy BE. Update on the management of chronic idiopathic constipation. Am J Manag Care. 2019 Mar;25(4 Suppl):S55-S62. PMID: 31002489.
- Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology. 2016 Feb 18:S0016-5085(16)00222-5. doi: 10.1053/j.gastro.2016.02.031. Epub ahead of print. PMID: 27144627.
- Palsson OS, Whitehead W, Törnblom H, Sperber AD, Simren M. Prevalence of Rome IV Functional Bowel Disorders Among Adults in the United States, Canada, and the United Kingdom. Gastroenterology. 2020 Apr;158(5):1262-1273.e3. doi: 10.1053/j.gastro.2019.12.021. Epub 2020 Jan 7. PMID: 31917991.

LEGISLATIVE NEWS

Generally, the U.S. Drug Enforcement Administration (DEA) classifies any drug with an abuse potential and/or physical or psychological dependence as a controlled substance and groups them into one of five schedules. Particularly, Schedule I drugs are those with a high potential for abuse or harm and no currently accepted medical uses. These drugs include cannabis derivates like tetrahydrocannabinol (THC) and cannabimimetic agents.

On August 29, 2023, the U.S. Department of Health and Human Services (HHS) recommended to the DEA that cannabis be rescheduled to a Schedule III drug. Schedule III drugs are classified as those with an intermediate abuse potential. These can be obtained with a prescription which, unlike those for Schedule II drugs, may include refills. The implementation of this recommendation would greatly increase the public's access to cannabis and it's derivates within healthcare settings.

Currently in West Virginia, the possession of products containing THC or cannabidiol (CBD) is legal for medical purposes from a pre-specified facility, and selling any of these products with the intended use of human consumption requires registration, a certificate of analysis, and THC content less than or equal to 0.3% per product. On a federal level, the U.S. Food and Drug Administration (FDA) has approved several cannabinoids for medical uses (see Table 1 below for examples).

Table 1: Summary of Currently Approved Cannabinoids

Drug	***Dose***	***FDA-Approved Indication***
Epidiolex (cannabidiol)	5-20 mg/kg/day	Treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.
Marinol/Syndros (dronabinol)	2.1-10 mg PO BID	Anorexia in patients with AIDS
	2.5-15 mg/m^2 at 1-3 hr. prior to and every 2-4 hr. after chemotherapy	Refractory chemotherapy-induced nausea and vomiting
Nabilone	2-6 mg/day in 2-3 divided doses	Refractory chemotherapy-induced nausea and vomiting

With the current classification of cannabis as Schedule I, any research on potential medical uses and human benefit is extremely limited and regulated. A purported benefit of its rescheduling would be increased access to research, as there is already proven benefit for certain cannabis derivates, as listed above. However, rescheduling would also pose challenges, as there is limited research on the safety, efficacy, pharmacokinetics, and pharmacodynamics of many of its formulations. In addition, there are little to no regulations on current CBD products on the market. Therefore, prescribers and other healthcare professionals may be uncomfortable prescribing scheduled substances or even recommending currently available OTC products until more research is available.

For payers, it is unlikely that the coverage of any legalized or rescheduled medical cannabis products will be mandated in the near future. However, it is advisable that relevant policies, prior authorization criteria, and/or appeals processes be

developed to address purported uses and include available research of medical cannabis products. In this way, payers can be prepared for the likely event that cannabis will be rescheduled, whether now or in the future.

References:

- Schedules of Controlled Substances, 21 C.F.R. Sect. 1308.11-1308.15 (2023).
- Schedules of Controlled Substances, 21 C.F.R. Sect. 812. (2021).
- Medical Cannabis Program, 64 West Virginia Bureau for Public Health. Sect. 109.1-109.8 (2020).
- Epidiolex [package insert]. Carlsbad, CA: Greenwich Biosciences, Inc; 2018.
- Marinol [package insert]. North Chicago, IL: AbbVie Inc; 2017.
- Syndros [package insert]. Chandler, AZ: Benuvia Therapeutics Inc; 2021.
- Cesamet [package insert]. Costa Mesa, CA: Valeant Pharmaceuticals International; 2006.