Sotagliflozin (INPEFA)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Sotagliflozin is an inhibitor of sodium-glucose cotransporters (SGLT) 1 and 2. According to the manufacturer's prescribing information, inhibiting SGLT2 reduces renal reabsorption of glucose and sodium which may lower both preload and afterload of the heart and downregulate sympathetic activity. Inhibiting SGLT1 reduces intestinal absorption of glucose and sodium which may contribute to diarrhea. The mechanism for cardiovascular (CV) benefit with sotagliflozin has not been established.

Indication(s) Under Review in This Document

- Sotagliflozin is an SGLT2 inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for heart failure (HF), and urgent heart failure visit in adults with:
    - heart failure or
    - type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and other CV risk factors

Dosage Form(s) Under Review

- Sotagliflozin is available as 200 mg and 400 mg tablets.
    - the recommended starting dose is 200 mg once daily, administered not more than one hour before the first meal of the day
    - after 2 weeks, the dose may be titrated to 400 mg once daily, as tolerated
    - assess volume status, correct volume depletion if indicated, before starting sotagliflozin; assess renal function prior to initiation and as clinically indicated; in patients with decompensated HF, dosing may begin when the patient is hemodynamically stable
    - if possible, sotagliflozin should be withheld for at least three days prior to major surgery or procedures associated with prolonged fasting

Clinical Evidence Summary[1-3]

Efficacy Considerations[1-3]

SOLOIST-WHF: Approval of sotagliflozin in patients with HF were based on data from a phase 3 multicenter randomized double-blind trial of 1222 patients with T2DM who were recently hospitalized for worsening HF and randomized to treatment with sotagliflozin or placebo. Patients were followed for a median of 9 months.

- Inclusion and exclusion criteria:
    - Main inclusion criteria were patients who had been hospitalized with signs or symptoms of HF and treated with intravenous (IV) diuretic therapy and had a diagnosis of T2DM or laboratory evidence to support a diagnosis of T2DM during hospital admission.
    - Among the exclusion criteria were patients with end-stage HF, recent acute coronary syndrome, stroke, percutaneous coronary intervention or coronary artery bypass surgery, or an estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2.

  - Prior to randomization, patients were also required to be clinically stable which included: no need for oxygen therapy, systolic blood pressure (SBP) ≥ 100 mm Hg, no need for IV inotropic or vasodilator therapy (excluding nitrates) and having transitioned from IV to oral diuretic therapy.
  - Patients were randomization to receive sotagliflozin or placebo, either before or within 3 days after being discharged from the hospital.
- The original primary end point of first occurrence of death from CV causes or HF hospitalization was changed to the total number of deaths from CV causes and hospitalizations and urgent visits for HF (to increase the power of the trial after enrollment was closed early due to loss of funding from the sponsor). Investigator reported events were analyzed (rather than adjudication of events due to loss of funding).
- Revised secondary end points included the total number of hospitalizations and urgent visits for HF; incidence of death from CV causes; incidence of death from any cause; total number of deaths from CV causes, hospitalizations for HF, nonfatal myocardial infarction (MI), and nonfatal strokes; total number of deaths from CV causes, hospitalizations and urgent visits for HF, and events of HF during hospitalization; as well as quality of life measures and change in eGFR.
- Primary and secondary end point results with a statistically significant benefit with sotagliflozin compared to placebo in SOLOIST-WHF in patients with T2DM recently hospitalized for HF are included in Table 1 below.

Table 1: Primary and Secondary End Point Results (SOLOIST-WHF)[2]

Patients with T2DM and recent worsening HF	Sotagliflozin (N=608)	Placebo (N=614)
Primary End Point		
Deaths from CV causes and hospitalizations and urgent visits for HF Number of events (Rate[a])	245 (51.0)	355 (76.3)
Hazard Ratio (HR) (95% CI)	0.67 (0.52 to 0.85)[b]	
Secondary End Points[c]		
Hospitalizations and urgent visits for HF Number of events (Rate[a])	194 (40.4)	297 (63.9)
HR (95% CI)	0.64 (0.49 to 0.83)[b]	

[a] Calculated as number of events per 100 person-years of follow-up
[b] P<0.001
[c] By hierarchical testing

- Results of the following additional secondary end points were also reported: deaths from CV causes (HR 0.84 95% CI 0.58 to 1.22, P=0.36); deaths from CV causes, hospitalizations for HF, nonfatal MI, and nonfatal strokes (HR 0.72 95% CI 0.56 to 0.92); deaths from CV causes, hospitalizations and urgent visits for HF, and events of HF during hospitalization (HR 0.68 95% CI 0.54 to 0.86); deaths from any cause (HR 0.82 95% CI 0.59 to 1.14). As per hierarchical testing, analysis of statistical significance was stopped after deaths from CV causes was found not to be statistically significant.
- At baseline, the median age was 70 years, 66% male, and 93% white; 79% had a left ventricular ejection fraction (LVEF) < 50%, mean eGFR was 49.7 ml/min/1.73m2, median glycated hemoglobin (HgA1c) 7.1%, and median N-terminal pro-B-type natriuretic peptide (NT-proBNP) 1799.7 pg/ml. Approximately 91% of patients were receiving any renin-angiotensin-aldosterone system (RAAS) inhibitor, 92% were treated with a beta-blocker, and 85% were on any glucose lowering medication.
- The first dose of sotagliflozin was administered as an inpatient in 48.8% of patients. Early discontinuation other than death or early termination of the trial occurred in 13% of patients in the sotagliflozin group compared to 15% in the placebo group. The most common adverse events reported more frequently in the sotagliflozin group were hypotension and diarrhea.
- In SOLOIST-WHF, treatment with sotagliflozin was found to decrease the risk of death from CV causes and hospitalizations and urgent visits for HF compared to placebo in patients with T2DM and recent worsening HF.

SCORED: In another multicenter, phase 3, double-blind trial supporting FDA approval of sotagliflozin, 10,584 patients with T2DM, CKD, and risks for CV disease were randomized to treatment with sotagliflozin or placebo. Patients were followed for a median of 16 months.

- Inclusion and exclusion criteria:
  - Main inclusion criteria were patients with T2DM and Hgb A1c 7% or higher, CKD with eGFR 25 to 60 ml/min/1.73m2, and additional CV risk factors (i.e., at least one major CV risk factor in patients 18 years of age or older, or at least one major CV risk factor in patients 55 years of age or older) as noted below.
    - Major CV risk factors: HF hospitalization in previous 2 years; ejection fraction (EF) ≤ 40% documented within the past year; left ventricular hypertrophy; coronary artery calcium (CAC) score ≥ 300; NT-proBNP ≥ 400 pg/mL; high-sensitivity troponin T > 15.0 pg/ml for men and > 10.0 pg/ml for women; high-sensitivity C-reactive protein > 3 mg/l; urinary albumin-to-creatinine ratio (UACR) ≥ 300 mg/g.
    - Minor CV risk factors: Body mass index (BMI) ≥ 35 kg/m2; dyslipidemia despite maximally-tolerated statin therapy, LDL > 130 mg/dl or HDL < 40 mg/dl for men or < 50 mg/dl for women; currently smoking tobacco; CAC score > 100 and < 300; UACR ≥ 30 mg/g and < 300 mg/g; SBP > 140 mmHg and diastolic blood pressure (DBP) > 90 mmHg despite antihypertensive therapy; family history of premature coronary heart disease (MI or coronary revascularization procedure) in a first-degree male relative < 55 years or first degree female relative < 65 years who had been hospitalized with signs or symptoms of HF and treated with IV diuretic therapy and had a diagnosis of T2DM or laboratory evidence to support a diagnosis of T2DM during hospital admission.
  - Several exclusion criteria were also listed (refer to publication Appendix).
- The original coprimary end points of first occurrence of a major CV event (MACE, defined as death from CV causes, non-fatal MI, or nonfatal stroke) and first occurrence of death from CV causes or HF hospitalization was changed to the total number of deaths from CV causes and hospitalizations and urgent visits for HF (to increase the power of the trial after enrollment was closed early due to loss of funding from the sponsor). Investigator reported events were analyzed (rather than adjudication of events due to loss of funding).
- Revised secondary end points included the total number of hospitalizations and urgent visits for HF; deaths from CV causes; total number of deaths from CV causes, hospitalizations for HF, nonfatal MI, and nonfatal strokes; total number of deaths from CV causes, hospitalizations and urgent visits for HF, and events of HF during hospitalization; first occurrence of the composite of a sustained decrease of at least 50% in the eGFR from baseline for at least 30 days, long-term dialysis, renal transplantation, or a sustained eGFR of < 15 ml/min/1.73 m2 for at least 30 days; deaths from any cause; and total number of deaths from CV causes, nonfatal MI, and nonfatal strokes. Total MI and total stroke were evaluated post hoc.
- Primary and secondary end point results with a statistically significant benefit with sotagliflozin compared to placebo in SCORED in patients with T2DM, CKD, and risk factors for CV disease are included in Table 2 below.

Table 2: Primary and Secondary End Point Results (SCORED)[3]

Patients with T2DM, CKD, and CV risk	Sotagliflozin (N=5292)	Placebo (N=5292)
Primary End Point		
Deaths from CV causes and hospitalizations and urgent visits for HF Number of events (Rate[a])	400 (5.6)	530 (7.5)
HR (95% CI)	0.74 (0.63 to 0.88)[b]	
Secondary End Points[c]		
Hospitalizations and urgent visits for HF Number of events (Rate[a])	245 (3.5)	360 (5.1)
HR (95% CI)	0.67 (0.55 to 0.82)[b]	

[a] Calculated as number of events per 100 person-years of follow-up
[b] P<0.001
[c] By hierarchical testing

- Results of the following additional secondary end points were also reported: deaths from CV causes (HR 0.90 95% CI 0.73 to 1.12, P=0.35); total deaths from CV causes, hospitalizations for HF, nonfatal MI, and nonfatal strokes (HR

0.72 95% CI 0.63 to 0.83); total deaths from CV causes, hospitalizations and urgent visits for HF, and events of HF during hospitalization (HR 0.76 95% CI 0.65 to 0.89); first occurrence of a sustained decrease of at least 50% in the eGFR from baseline for at least 30 days, long-term dialysis, renal transplantation, or a sustained eGFR of < 15 ml/min/1.73 m2 for at least 30 days (HR 0.71 95% CI 0.46 to 1.08); deaths from any cause (HR 0.99 95% CI 0.83 to 1.18); total deaths from CV causes, nonfatal MI, and nonfatal strokes (HR 0.72 95% CI 0.63 to 0.83). As per hierarchical testing, analysis of statistical significance was stopped after deaths from CV causes was found not to be statistically significant.

- At baseline, the median age was 69 years, 55% male, and 83% white; 20% had an ejection fraction ≤ 40%, median eGFR was 45 ml/min/1.73m2, HgA1c 8.3%, and median UACR ≥ 300 in 31% of patients. Approximately 89% of patients were receiving any RAAS inhibitor, and 97% were on any glucose lowering medication.
- Early discontinuation other than death or early termination of the trial occurred in 10.9% of patients in the sotagliflozin group compared to 11.3% in the placebo group. There was a statistically significant increase in diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis with sotagliflozin compared to placebo.
- In SCORED, treatment with sotagliflozin was found to decrease the risk of death from CV causes and hospitalizations and urgent visits for HF compared to placebo in patients with T2DM, CKD, and risks for CV disease.

Safety Results from Clinical Trials[1-3]

- Per the prescribing information, the most common adverse reactions with sotagliflozin were urinary tract infection, volume depletion, diarrhea, and hypoglycemia.
- Adverse reactions reported in ≥ 2% of patients receiving sotagliflozin and greater than placebo in either of the pivotal clinical trials (SOLOIST-WHF, SCORED) are included in Table 3 below.

Table 3: Adverse Reactions as Noted per the Prescribing Information (SOLOIST, SCORED)[1-3]

Adverse Reaction	SOLOIST		SCORED	
	Sotagliflozin N=605 (%)	Placebo N=611 (%)	Sotagliflozin N=5,291 (%)	Placebo N=5,286 (%)
Urinary tract infection	8.6	7.2	11.5	11.0
Volume depletion	9.3	8.8	5.2	4.0
Diarrhea	6.9	4.1	8.4	6.0
Hypoglycemia	4.3	2.8	7.7	7.9
Dizziness	2.6	2.5	3.3	2.8
Genital mycotic infection	0.8	0.2	2.4	0.9

Safety Considerations[1]

- **Boxed Warning:** None
- **Contraindications:**
  - History of serious hypersensitivity reaction to sotagliflozin.
- **Warnings / Precautions**:
  - Diabetic Ketoacidosis (DKA) in Patients with Type 1 Diabetes Mellitus (T1DM) and Other Ketoacidosis: sotagliflozin significantly increases the risk of DKA in patients with T1DM; the risk may be greater with higher doses. It is noted that sotagliflozin is not indicated for glycemic control. Consider ketone monitoring in patients with T1DM as well as in other patients at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose and discontinue sotagliflozin if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before sotagliflozin is restarted.

- Volume Depletion: sotagliflozin can cause intravascular volume depletion which may result in symptomatic hypotension or acute transient changes in creatinine. It is noted that patients with impaired renal function (eGFR < 60 ml/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. If considering sotagliflozin in these patients, it is recommended to assess volume status and renal function before initiating therapy, and to monitor for signs and symptoms of hypotension and renal function after starting therapy.
- Urosepsis and Pyelonephritis: treatment with an SGLT2 inhibitor, including sotagliflozin, increases the risk for urinary tract infections. Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported. It is recommended to evaluate patients for signs and symptoms of urinary tract infections during therapy and treat promptly, if indicated.
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: sotagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with sotagliflozin.
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): reports of this rare but serious and life-threatening infection (requiring urgent surgical intervention) have been identified in postmarketing surveillance in patients with diabetes receiving SGLT2 inhibitors. Serious outcomes have included hospitalization, multiple surgeries, and death. It is recommended that patients treated with sotagliflozin who present with pain, tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, treatment should be started immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue sotagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for heart failure.
- Genital Mycotic Infections: sotagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. It is recommended to monitor and treat as appropriate.

Other Considerations[1,4]

- Unlike other available SGLT2 inhibitors, sotagliflozin is not FDA approved for glycemic control in patients with T2DM.
- Sotagliflozin was submitted for FDA approval as add-on therapy to insulin in T1DM but was rejected in 2019 due to safety concerns of an increased risk of DKA.
- Sotagliflozin received approval (April 2019) in the European Union (EU) as an adjunct to insulin therapy to improve glycemic control in adults with T1DM with a BMI ≥ 27 kg/m2, who have failed to achieve adequate glycemic control despite optimal insulin therapy. In March 2022, the European Commission withdrew the marketing authorization for sotagliflozin in the EU at the request of the marketing authorization holder for commercial reasons.
- Drug interactions include: digoxin - monitor digoxin levels; uridine 5'-diphospho-glucuronosyltransferase inducers (e.g., rifampin) - sotagliflozin exposure is reduced, consider monitoring clinical status; lithium - monitor serum lithium concentrations.
- Pregnancy and Lactation: per the prescribing information, sotagliflozin is not recommended during the second and third trimesters of pregnancy. Sotagliflozin is not recommended when breastfeeding.

Other Therapeutic Options[1,5-13]

A comparison of the SGLT2 inhibitors is provided in Table 4 below.

Table 4: Comparison of the SGLT2 Inhibitors [1,5-13]

Drug	Formulary status	FDA Indications
sotagliflozin	NF	• To reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF or with T2DM, CKD, and other CV risk factors
empagliflozin	VANF	• To reduce the risk of CV death and hospitalization for HF in adults with HF • To reduce the risk of CV death in adults with T2DM and established CV disease • As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with T2DM
canagliflozin	NF	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM • To reduce the risk of major adverse CV events (CV death, nonfatal MI and nonfatal stroke) in adults with T2DM and established CV disease • To reduce the risk of end-stage kidney disease (ESKD), doubling of sCr, CV death, and hospitalization for HF in adults with T2DM and diabetic nephropathy with albuminuria greater than 300 mg/day
dapagliflozin	NF	• To reduce the risk of sustained eGFR decline, ESKD, CV death, and hospitalization for HF in adults with CKD at risk of progression • To reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults with HF • To reduce the risk of hospitalization for HF in adults with T2DM and either established CV disease or multiple CV risk factors • As an adjunct to diet and exercise to improve glycemic control in adults with T2DM
ertugliflozin	NF	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM
bexagliflozin	NF	• As an adjunct to diet and exercise to improve glycemic control in adults with T2DM

Clinical Practice Guideline Recommendations (refer to respective guidelines for definitions of grading recommendations/evidence)

ACC/AHA/HFSA HF (2022):[10]

- In patients with symptomatic chronic HFrEF, **SGLT2 inhibitors** are recommended to reduce hospitalization for HF and CV mortality, irrespective of the presence of T2DM (IA)
- In patients with HFmrEF, **SGLT2 inhibitors** can be beneficial in decreasing HF hospitalizations and CV mortality (2aBR)
- In patients with HFpEF, **SGLT2 inhibitors** can be beneficial in decreasing HF hospitalizations and CV mortality (2aBR)
- In patients with HF and T2DM, the use of **SGLT2 inhibitors** is recommended for the management of hyperglycemia and to reduce HF related morbidity and mortality (IA)

ESC HF (2021):[11]

- **Dapagliflozin** or **empagliflozin** are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death (IA)
- **SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin)** are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations (IA)
- **SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin)** are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death (IA)
- **SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin)** are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death (IA)

ADA DM (2023);[12] ADA DM CKD (2022):[13]

- In adults with T2DM and established/high risk of atherosclerotic CV disease, HF, and/or CKD, the treatment regimen should include **agents that reduce cardiorenal risk** (A)
- In individuals with T2DM who have established atherosclerotic CV disease or indicators of high CV risk, established kidney disease, or HF, a **SGLT2 inhibitor** and/or GLP1 receptor agonist **with demonstrated CV disease benefit** is recommended as part of the glucose-lowering regimen and comprehensive CV risk reduction, independent of A1C and in consideration of person-specific factors (A)
- For patients with T2DM and diabetic kidney disease, use of a **SGLT2 inhibitor** in patients with an eGFR ≥ 25 ml/min/1.73 m2 and urinary albumin ≥ 300 mg/g creatinine is recommended to reduce CKD progression and CV events (A)
- In patients with T2DM and CKD, consider use of **SGLT2 inhibitors** additionally for CV reduction when eGFR and urinary albumin creatinine are ≥ 25 ml/min/1.73 m2 or ≥ 300 mg/g, respectively (A)

ACC=American College of Cardiology; ADA=American Diabetes Association; AHA=American Heart Association; ESC=European Society of Cardiology; HFmrEF=HF with mildly reduced ejection fraction; HFpEF=HF with preserved ejection fraction; HFSA=Heart Failure Society of America; NF=non-formulary; VANF=VA National Formulary; TBD=to be determined

Conclusions and Projected Place in Therapy[1-3,5-22]

- Several SGLT2 inhibitors are available and depending on the agent, FDA approved for indications including glycemic control in T2DM,[5-9] CV outcome benefit,[1,5-7] reduction in HF hospitalizations in various patient populations, [1,5-7] and kidney outcome benefit.[5,6] Based on meta-analyses including several long-term outcome trials, SGLT2 inhibitors were reported to reduce major adverse CV events, CV death, hospitalizations for HF, and kidney outcomes in patients with T2DM;[13] reduce all-cause mortality, CV mortality, hospitalization for HF, MI, and composite kidney outcomes in patients with T2DM, and in patients with HF and CKD, regardless of T2DM;[14] and reduce all-cause mortality, CV death, non-fatal MI, HF hospitalizations, and ESKD in a large meta-analyses of treatments for T2DM.[15] As noted in Table 4, the SGLT2 inhibitors are recommended in several clinical practice guidelines for use in patients with HF, HF and T2DM, T2DM and CV risk, and T2DM with CKD.[10-13] In general, guidelines include recommendations for the SGLT2 inhibitors as a class, with some making specific recommendations for agents within the class (e.g., empagliflozin or dapagliflozin in HFrEF)[11] or including discussion of data in a specific patient population (e.g., empagliflozin or dapagliflozin in HFrEF[17,18], empagliflozin in HFpEF[19]) with the respective references included as support for the recommendation.[10]
- Sotagliflozin is an inhibitor of SGLT2 and SGLT1, and is FDA approved to reduce the risk of CV death, HF hospitalization, and urgent HF visits in patients with HF, or with T2DM, CKD, and other CV risk factors.[1] Approval for these indications is based on data from clinical trials in a patient population with T2DM.[2,3] Unlike the other SGLT2 inhibitors, sotagliflozin is not FDA approved for the management of hyperglycemia in patients with T2DM.[5-9]
- In SOLOIST-WHF, treatment with sotagliflozin was found to decrease the risk of death from CV causes and hospitalizations and urgent visits for HF by 33% compared to placebo in patients with T2DM and recent worsening HF.[2] Data from SCORED demonstrated a reduction in the risk of death from CV causes and hospitalizations and urgent visits for HF of 26% with sotagliflozin compared to placebo in patients with T2DM, CKD, and risks for CV disease.[3] The most common adverse reactions reported with sotagliflozin included urinary tract infection, volume depletion, diarrhea, and hypoglycemia. The prescribing information for sotagliflozin includes similar warnings and precautions as with other SGLT2 inhibitors including risk for DKA, volume depletion, urosepsis and polynephritis, hypoglycemia with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections.[1]
- The SGLT2 inhibitor empagliflozin is available on the VA National Formulary with FDA approval for several indications and use supported by clinical trial outcome data and clinical practice guidelines.[7,10-17,19-22] Other SGLT2 inhibitors are available via the non-formulary process. Without direct comparison data of sotagliflozin and the other available SGLT2 inhibitors and given the established use and outcome data with the current formulary SGLT2 inhibitor, considerations for non-formulary use of an alternative SGLT2 inhibitor may be based on patient tolerability on a case-by-case basis.

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