HHSC Psychiatric Executive Formulary Committee Minutes

The HHSC Psychiatric Executive Formulary Committee (PEFC) convened on April 30, 2021 via MS Teams. The meeting was called to order by Dr. Moron, Interim Chair at 9:39 a.m.

Members

Member Names	Attendance	Member Names	Attendance
Yekini Adeyemi, RN	Present	Vicky Litton, MD	Present
Angela Babin, RPh	Present	Jeffery Matthews, MD	Present
Jean Baemayr, PharmD- Secretary	Present	David Moron, MD- Chair	Present
John Bennett, MD	Present	Leah Nunez, PharmD	Present
Giovanna Betancourt, PharmD	Present	Kenda Pittman, PharmD	Present
Rakesh Chadalavada, MD	Present	Rishi Sawhney, MD	Present
German Corso, MD	Present	Glenn Shipley, DO	Present
Brad Fitzwater, MD	Present	Lesia Trickett, MD	Present
Catherine Hall, PharmD	Present	Ashton Wickramasinghe, MD	Present
Dana Hopkins, RN	Present		

Guests Present: Tonya Barrios, State Hospitals Central Administration; Lisa Mican, PharmD, Austin State Hospital; Brittany Parmentier, PharmD, UT Health East Texas; Katie Tuck, PGY2 Resident, San Antonio State Hospital.

Opening

Introduction and Other Information

Dr. Jeana Heidel and Dr. Bonnie Burroughs have stepped down from the committee after many years of service. Dr. Leah Nunez, Rio Grande State Center, will replace Dr. Heidel on the committee as the state hospital pharmacist representative and Dr. Giovanna Betancourt, El Paso State Supported Living Center, will replace Dr. Burroughs on the committee as the state supported living center pharmacist representative.

Dr. Vicky Litton, Kerrville State Hospital and Dr. Rakesh Chadalavada, Terrell State Hospital, have been selected as state hospital physician representatives.

Conflict of Interest Disclosures

The committee members present did not disclose any new conflicts of interest.

Review of Minutes

The minutes from the January 29, 2021 meeting were approved as previously distributed.

Unfinished Business

TAC Title 26, Part 1, Chapter 306, Subchapter G (April 2017)

The revised rules went into effect on February 24, 2021. New selection letters for each committee member have been distributed.

New Business

Committee Membership

The committee approved the addition of an academic partner to the committee membership. An academic partner would be someone practicing in a relevant field (psychiatry, pharmacy, medical) that has an association with an institution of higher learning.

Adverse Drug Reaction Reports

The committee discussed five adverse drug reaction reports that were received from the field. These adverse events were reported to the FDA's MedWatch program.

ADR: risperidone/hyponatremia

A 53-year-old African American male diagnosed with schizoaffective disorder, bipolar type and a history of suspected hypertension was admitted to a state hospital on a forensic commitment. Upon admission, the patient exhibited symptoms of agitation, aggression, and hostility with tangential and loose thought processes. His baseline labs showed elevated LDL and total cholesterol, unremarkable complete blood count (CBC) and comprehensive metabolic panel (CMP); of note his sodium was 140 mmol/L (reference range 134-146). He was started on olanzapine the day after his admission at a dose of 10 mg daily, which was then increased to 20 mg daily four days later. About three weeks into the admission, valproic acid (VPA) solution was initiated at a dose of 500 mg twice daily (12.5 mg/kg, level was 42 mcg/ml 8 days later). He started refusing medications, leading to decompensation where he was displaying disorganized, hyperactive, impulsive, and bizarre symptoms. Court ordered medications were applied for and granted about four weeks into the admission, and olanzapine 20mg daily was restarted along with VPA solution 1500 mg daily (19 mg/kg, level was 68.9 mcg/ml 6 days later). VPA was then titrated to 2000 mg daily (25 mg/kg, level was 89.4 mcg/ml when checked almost 9 weeks later).

Despite treatment with olanzapine and VPA, documentation indicated that the patient's psychiatric symptoms had not significantly changed other than some

increase in ability to participate in conversation. Changing antipsychotics was reportedly discussed with the patient, but he was not in agreement. Documentation indicates that the patient verbally reported that he had an allergy to risperidone but could not remember the reaction. The provider noted that a record review was completed and no documentation of allergy to risperidone was found (only haloperidol, although the patient had received haloperidol during other state hospital admissions with no issue). Roughly 10 weeks into the admission, when he had been on court ordered olanzapine 20 mg daily for about 7 weeks and VPA 2000 mg/day for about 6 weeks, a decision was made to transition from olanzapine to risperidone. A test dose of risperidone 1 mg was given with no adverse effect. Risperidone was initiated at 1 mg/day and titrated to 6mg/day in 1 mg per day increments. Olanzapine was tapered down to 10mg daily three days into risperidone treatment, then down to 5 mg four days later. During this cross titration, it was noted by staff that the patient was "slightly decompensating" with "more loose/tangential" thoughts and pressured speech.

Six days after this cross titration began, when the patient was on risperidone 3 mg twice daily and olanzapine 5 mg daily along with VPA 1000 mg twice daily, a CMP was drawn. The results indicated hyponatremia with sodium 122 mmol/ L (reference range 134-146); note that there was no documentation of polydipsia or increased urination. He was transferred to and admitted to a medical facility for hyponatremia, where he was placed on a fluid restriction of 1.5 liters. Medications were continued as they were ordered at the state hospital. Sodium was reportedly 124 mmol/L while admitted. Urinalysis and antidiuretic hormone were not checked or not reported. When the patient returned to the state hospital from the medical hospital two days later, a follow-up sodium level was 125 mmol/L. Because it was thought to be the possible cause of hyponatremia, olanzapine was not restarted upon return to the state hospital, and the patient was continued on fluid restriction for about two weeks and started on sodium chloride 1000 mg tablets daily for two days which was then increased to 1000 mg twice daily. The sodium level after five days off of olanzapine and on sodium tablet treatment remained at 125 mmol/L. Sodium chloride was increased to 1000 mg three times daily; a repeat sodium five days later was 129 mmol/L. Considering the only minimum improvement in sodium despite discontinuation of olanzapine and addition of sodium tablets, and after discussion with clinical pharmacists regarding other agents that might be of risk, valproic acid was decreased from 1000 mg twice daily (2000 mg/ day) to 500 mg in the morning and 750 mg at night (1250 mg/day). Risperidone was increased to 4 mg twice daily (8 mg/day) at the same time to address potential risk of decompensation.

Repeat sodium three days later was 128 mmol/L, a slight decrease. The clinical pharmacist suggested that risperidone could also cause hyponatremia, so a transition from risperidone to aripiprazole was initiated. Risperidone was decreased to 6mg/day, and a repeat sodium was 132 mmol/L three days later.

Risperidone was completely tapered off over the next few days and sodium increased to 135 mmol/L, within normal limits (wnl) seven days after the risperidone was completely discontinued. Sodium was tapered down to 1000 mg twice daily then 1000 mg daily with no drop in sodium. The patient remains on aripiprazole 20 mg daily and valproic acid 1250 mg daily.

ADR: aripiprazole/rash

An 18-year-old African American female with a diagnosis of schizoaffective bipolar disorder and a long history of multiple psychiatric hospital admissions since adolescence was admitted to a state hospital on a forensic commitment. Upon admission, the patient exhibited verbal aggression, irritability, disorganized thought process, was seen responding to internal stimuli, and voiced bizarre and persecutory delusions. Baseline labs and physical exam were unremarkable. She was initiated on risperidone the day she was admitted, but she was frequently refusing medication, so court ordered medications were applied for and granted about three weeks into her admission. Risperidone was restarted and titrated up to 3 mg twice daily over about two weeks.

She showed improvement on risperidone, with a more stable mood, a reduction in reports of responding to internal stimuli, and documentation of more organized, although still occasionally delusional, thought process. She complained of some back pain, so topical methyl salicylate/menthol was initiated once daily at bedtime.

Due to some breast pain with discharge along with elevated prolactin 181 ng/ml (reference range 2.8-29.2), the decision was made to begin to taper risperidone and transition to aripiprazole. Aripiprazole was initiated at 10 mg per day. About six days later (and seven days after initiation of methyl salicylate menthol), the patient reported a rash and pruritis, indicating the rash had begun the day before on her legs and then spread to her trunk and arms. The medical provider described the rash as fine macular with excoriation and coalescence. The provider documented no other signs of swelling (tongue normal in size), the patient appeared in no distress upon examination.

Documentation indicated that there were no recent changes in detergents or other body products, so after discussion between the medical provider, psychiatric provider, and clinical pharmacist it was decided that the probable cause was the recently initiated aripiprazole, which was discontinued. Topical methyl salicylate/menthol was also discontinued (of note, she had refused several doses but had received a total of four doses).

The patient was given a STAT dose of loratadine and started on a methylprednisolone dose pack. That afternoon, the patient reported an improvement in itchiness. The rash did not spread further. On the last day of the methylprednisolone treatment, the

rash was documented to be resolved. There was no further documentation of rash. The aripiprazole was not restarted, and olanzapine was initiated.

ADR: aspirin/anemia, gastritis, esophagitis

A 57-year-old female was admitted to a state hospital in November of 2019 with diagnoses of schizoaffective disorder bipolar type, polysubstance abuse, hyperammonemia, obesity and hypothyroidism. Due to a positive COVID-19 PCR test in late November 2020 she was placed on several COVID protocol medications including a 2-week regimen of famotidine, melatonin, vitamin D3, zinc sulfate and ascorbic acid for supportive therapy. In addition, low dose aspirin 81 mg daily was prescribed per the COVID protocol for a 90-day duration of therapy. Of note, the complete blood count (CBC) in October was wnl with red blood cells (RBC) 4.26 10^6/mcL, hemoglobin (Hgb) 12.1 g/dL, hematocrit (Hct) 37.2%, and platelets 196 10^9/L with slight increase in red cell distribution width (RDW) 15.2%. The November CBC prior to aspirin therapy showed some changes with RBC 3.83 10^6/mcL, Hgb 10.9 g/dL, Hct 33.2%, and platelets 207 10^9/L with RDW 15.8%. Two and a half months later, the CBCs the day prior to medical hospital admission and the day of hospital admission showed significant changes with RBC 3.05 10^6/mcL and 3.06 10^6/mcL, Hgb 7.3 g/dL and 6.8 g/dL, Hct 23.3% and 24.1%, and platelets 224 10^9/L and 234 10^9/L with RDW 18.3% and 16.9% respectively. RBC morphology noted microcytes and hypochromia. A urine analysis (UA) in February also showed evidence of a urinary tract infection (UTI) without RBC present in sample, fecal blood hemoccult was positive, iron level low <10 ug/dL (reference range 35-140), ferritin low 3.9 (reference range 11-306.8) and total iron-binding capacity (TIBC) elevated 514 mcg/dL (reference range 245-400). Medications prescribed at that time were aspirin 81 mg daily, vitamin D3 4,000 units daily, simvastatin 20 mg daily, quetiapine 150 mg in the morning and 400 mg at bedtime with an addition 50 mg every 8 hours as needed, melatonin 10 mg at 7 pm, levothyroxine 117 mcg daily, lamotrigine 200 mg twice daily, clonazepam 1 mg in the morning and 2 mg at bedtime and lorazepam 2 mg every 6 hours as needed. Ferrous sulfate 325 mg twice daily and ascorbic acid 1000 mg twice daily were initiated the day before medical hospital admission. Aspirin 81 mg was discontinued after the morning dose on the day of medical hospital admission. The client was asymptomatic aside from reporting feeling "tired all the time."

At the medical hospital the patient was administered 1 unit of packed red blood cells, Bactrim DS 3-day course for UTI and pantoprazole 40 mg twice daily for gastroesophageal reflux disease (GERD). Endoscopy and colonoscopy were performed, and she was found to have a 5 cm hiatal hernia, erosive gastritis, and grade C erosive esophagitis in addition to iron deficiency anemia. The clients CBC indices improved over her hospital stay prior to her return to the psychiatric hospital. Aspirin therapy was not restarted.

Although the presence of hiatal hernia can contribute to GERD and gastritis, the abrupt decline in CBC indices occurred within the 2.5 months after initiation of aspirin. Injury to the esophagus has been reported with aspirin use and is not thought to be related to the dose of the medication. Upper and lower GI bleeding and gastritis have also been reported with greater risk in older individuals and those prescribed regimens for longer than 3 weeks in duration. One study in 112 elderly patients also found a higher incidence of iron deficiency anemia with no definite medical cause in those prescribed aspirin 24% vs. those not prescribed aspirin 11% (MicroMedex). The antiplatelet effects of aspirin may last 7-10 days after drug discontinuation due to the time needed for platelet turn over. At this time, the Infectious Diseases Society of America (IDSA) and National Institutes of Health (NIH) COVID-19 guidelines do not have a recommendation regarding aspirin therapy for prophylaxis or treatment of SARs-CoV-2. Due to risk:benefit it may be worthwhile to consider reducing the duration of therapy for aspirin in the facility COVID-19 supportive therapy protocol.

ADR: amlodipine/gingival hyperplasia

A 46-year-old African American female was transferred to one state hospital after a 6-month admission at another state hospital. The following medications were continued upon admission: amlodipine 5 mg twice daily, enalapril 10 mg twice daily, hydralazine 50 mg twice daily, potassium chloride 20 meq once daily, ziprasidone 60 mg twice daily with meals, paroxetine 40 mg once daily in the morning, and hydroxyzine 25mg every 8 hours as needed for anxiety.

Over the first weeks of hospitalization, a few changes were made in her medications to address some psychotic and mood symptoms, including increasing the ziprasidone dose and adding valproic acid. The enalapril dose was titrated due to her elevated blood pressure.

A little over a month after she was admitted, she was referred to the dentist due to dental pain and gum swelling that had begun three months prior, per the patient. The dentist documented that she had "hypertrophic gingivia as if she had been on Dilantin for a long time, but she denied ever taking Dilantin; bulbous heavily stippled gingival tissue covering almost all of her teeth." The excess tissue was deflected and gross debridement of calc with Cavitron (ultrasonic scaling system used to clean teeth) was performed that day, then periodontal prophylactic treatment (teeth cleaning) was completed at a second visit five days later. The patient reported improvement in pain at that time, but the dentist recorded that although the tissue was less inflamed, there was still swelling. Additionally, the patient went to the medical provider for evaluation of her blood pressure regimen, where the patient reported feeling that enalapril made her sleepy. Enalapril was discontinued both due to the patient's request as well as the dentist reporting suspicion that enalapril was related to the gingival hyperplasia. A few days later, after consultation with

pharmacy on potential drug induced causes of gingival overgrowth, amlodipine was discontinued.

A Pubmed search for literature potentially associating gingival overgrowth/hyperplasia with all medications the patient was taking at the time was completed; Lexicomp was also reviewed. There were no published association/reports for the following agents that the patient was taking: ziprasidone, paroxetine, hydroxyzine, potassium chloride, or hydralazine. Enalapril was included in at least one case report, but in that report, it was felt that the amlodipine the patient was taking was the cause because there was rapid improvement in gingival overgrowth after reduction of amlodipine (Clin Adv Periodontics. 2017 Feb;7(1):25-29). Both amlodipine and valproic acid have been shown to be associated with gingival hyperplasia. Although the incidence of gingival hyperplasia with nifedipine is noted to be higher (around 10% according to Lexicomp), there are several published case reports of this drug-induced reaction with amlodipine. An article reviewing spontaneous reports of adverse effects noted the time of onset of drug induced gingival hyperplasia with calcium channel blockers was on average 262 days (nearly 9 months) with the 25th percentile at about 75 days and 75th percentile at nearly 450 days (Journal of Pharmaceutical Health Care and Sciences. 2017;3:19).

The reviewing pharmacist contacted the pharmacist at the transferring state hospital for more information regarding the patient's medication regimen. Per that pharmacist, the patient had never received phenytoin while at their facility. Amlodipine had been started at the time of admission at a dose of 5 mg daily, titrated up to 10 mg daily about two weeks later, then divided into twice dosing four months later. This would align with the onset of action reported in the article mentioned above. Enalapril was initiated at 10 mg daily about a month after amlodipine was initiated (about 6 months prior to report of dental pain/gum swelling) then titrated to 20 mg daily about a month later, then converted to 10 mg twice daily two months later. The patient had taken valproic acid for about 12 days about 5 months before transfer to the current hospital, where it was reinitiated about four weeks prior to the patient's complaint of dental pain and report that gum swelling had started three months prior. Because the gum swelling began prior to initiation of valproic acid, it is most likely that this case of gingival overgrowth occurred secondary to treatment with amlodipine, which has considerable published data linking it to this particular adverse effect.

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ADR: canagliflozin/acute kidney injury

A 58-year-old Hispanic male with neurocognitive disorder, unspecified psychosis, depression, focal seizures, hyperlipidemia, hypertension, anemia, constipation, hearing loss, UTI, cerebrovascular accident, aphasia, proteinuria, chronic dehydration with elevated blood urea nitrogen (BUN), and diabetes mellitus was treated with canagliflozin 100 mg titrated to 200 mg daily from May 2020 to December 2020. From May to September, his serum creatinine ranged from 0.7 to 1.1 mg/dL. On December 2, his serum creatinine was 1.5 mg/dL. Canagliflozin was discontinued due to risk of acute kidney injury and insulin was started.

Other medications:

- Lisinopril 10 mg twice daily (discontinued December 3)
- Omeprazole 40 mg twice daily (started October 30 for hiatal hernia, discontinued December 3)
- Rosuvastatin
- Senna-docusate

- Zinc sulfate
- Zonisamide
- Ciprofloxacin (started December 4 due to UA results showing signs of infection)

On December 20, canagliflozin was restarted at 100 mg daily and on March 15, losartan 25 mg daily was started on the recommendation of the nephrologist due to macroalbuminuria. Omeprazole 40 mg twice daily was restarted on March 8 due to vomiting unresponsive to carafate, pantoprazole, and famotidine.

Labs:

Date	BUN mg/dL	Creatinine mg/dL	Urine albumin-creatinine ratio mg/g (normal range 30 to 300)	A1C %	UA
09/03/2020	17	0.86			
12/02/2020	27	1.5		7.9	
12/04/2020	28	1.24			● 25-50 wbc/hpf (0-5) ● + eosinophils ● specific gravity 1.008 (1.000-1.030) ● >100,000 cfu/ml klebsiella pneumoniae, resistant to ampicillin/sulbactam, nitrofurantoin, intermediate resistance to piperacillin/tazobactam
12/05/2020	23	1.11			
12/06/2020	20	1.03			
12/20/2020			3159		
03/15/2021			4000		
03/23/2021	14	0.83			

Midazolam Nasal Spray – System Usage Review

Midazolam nasal spray (Nayzilam®) was newly added to the formulary in April 2020. As this product had been on the market for less than one year at the time it was added to the formulary, state hospital and state supported living center midazolam

nasal spray usage from April 1, 2020 through March 31, 2021 was reviewed. Total purchase cost was $6,635 for the state hospitals (one facility) and $24,498 for the state supported living centers (3 facilities). No adverse drug reactions or medication errors related to the use of midazolam nasal spray were reported.

Psychotropic Medication Utilization Parameters for Children and Youth in Texas Behavioral Health

Dr. Matthews and Dr. Sawhney have begun the process of updating these guidelines by meeting with several of the agencies that use this document as a reference. The PEFC will support this project by reviewing drafts as requested and by posting the final document on the HHS PEFC website.

Quarterly Non-Formulary Drug Justification Report

For the second quarter of fiscal year 2021 (December 2020 through February 2021), only the state hospitals reported use of non-formulary agents. The state supported living centers (SSLCs) currently do not have the capability to obtain non-formulary drug usage reports from their computer system but are working with the vendor to make this reporting possible. The following were the top five non-formulary agents, by number of orders, that were prescribed in the state hospitals during the second quarter of fiscal year 2021:

- Quercetin (plant flavonoid dietary supplement)
- Zinc gluconate
- Acetaminophen/caffeine/pyrilamine (Midol Menstrual Complete)
- Promethazine injection
- Listerine Zero

New Drug Applications

Canagliflozin (Invokana®)

Presented by Dr. Hall. Please refer to Appendix A for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of canagliflozin to the formulary in the Miscellaneous Antidiabetic Agents section.

The formulary check list was completed and no issues were detected.

Empagliflozin (Jardiance®)

Presented by Dr. Hall. Please refer to Appendix B for the monograph that was considered when determining action by the committee.

After discussion of the monograph, the committee approved the addition of empagliflozin to the formulary in the Miscellaneous Antidiabetic Agents section.

The formulary check list was completed and no issues were detected.

Drug Formulary Sectional Review

In reviewing the formulary drug listings for psychotropic and substance use agents, the following changes were approved:

- Benzodiazepine anxiolytics and hypnotics
  - Oxazepam- remove tablet dosage form
- Antipsychotics
  - Aripiprazole injection (immediate release)- remove from the formulary
- Stimulants
  - Dextroamphetamine- remove Dextrostat trade name
- Substance use treatments
  - Buprenorphine and Buprenorphine-naloxone- update to correct error in DEA schedule (change CII to CIII)

The updated formulary will be posted on the PEFC website.

Other Formulary Changes

The committee also approved the following changes to the formulary:

- Place methadone in the Analgesics-Opiate Agonist therapeutic classification table and develop Reserve Use Criteria.
- Add naltrexone oral dosage form to the Reserve Use Table with the guideline "not to be used for the treatment of opioid use disorders."

The updated formulary will be posted on the PEFC website.

Psychotropic Audit Criteria & Guidelines Review

The committee reviewed and approved recommended revisions to the following audit criteria documents, as presented by Dr. Tuck:

- Topiramate
- Acamprosate
- Buprenorphine; buprenorphine/naloxone
- Disulfiram
- Naltrexone

The updated documents will be posted to the PEFC website.

Issues from the Chief Medical Officer, State Hospitals

Dr. Matthews requested input from committee members regarding how the risk of QTc prolongation was being monitored in their practice settings. Were EKGs routinely performed? Were computer alerts sufficient to alert providers that one or more medications being prescribed had the potential to cause a prolonged QTc?

Issues from the Medical Services Coordinator, SSLCs

Dr. Shipley reported that Covid-19 vaccination of residents in the SSLCs is currently over 90%, and staff vaccinations are around 50%. One resident was recently treated with combination monoclonal antibody therapy and is doing well.

Drug Shortages, Recalls, and FDA Safety Communications

The FDA has issued the following safety communications and recalls that may impact our facilities:

Shortages

Loxapine: All strengths are currently available from the HSCS drug wholesaler.

Recalls

Spironolactone: Bryant Ranch Prepack is recalling 4 lots of spironolactone tablets because the products have been found to be mislabeled, displaying the incorrect strength. Prepackaged bottles labeled spironolactone 50 mg may contain spironolactone 25 mg tablets and prepackaged bottles of spironolactone 25 mg may contain spironolactone 50 mg tablets. As of 3/9/2021 Bryant Ranch Prepack has not received any reports of adverse events related to this recall.

Telmisartan: Alembic Pharmaceuticals Limited is recalling one lot of telmisartan 20 mg tablets packaged in 30-count bottles, Lot No. 1905005661. The product is being recalled due to a market complaint received which stated that one bottle labelled as 30-count telmisartan 20 mg tablets incorrectly contained 30 tablets of 40mg telmisartan tablets.

Safety-related Labeling Changes

Benzodiazepines (chlordiazepoxide, clobazam, clonazepam, diazepam, lorazepam, midazolam, temazepam): Revisions to Boxed Warning and Warning and Precautions sections.

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- The use of benzodiazepines exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.

- The continued use of benzodiazepines for several days to weeks may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose.

Tofacitinib (Xeljanz)
The U.S. Food and Drug Administration (FDA) is alerting the public that preliminary results from a safety clinical trial show an increased risk of serious heart-related problems and cancer with the arthritis and ulcerative colitis medicine tofacitinib compared to another type of medicine called tumor necrosis factor (TNF) inhibitors. FDA required the safety trial, which also investigated other potential risks including blood clots in the lungs and death. Those final results are not yet available.

Phenytoin (Dilantin)
Warnings and Precautions, Serious Dermatologic Reactions. Additions underlined:
…retrospective, case-control, genome-wide association studies in patients of southeast Asian ancestry have also identified an increased risk of SCARs in carriers of the decreased function CYP2C9*3 variant, which has also been associated with decreased clearance of phenytoin.

The use of HLA-B*1502 or CYP2C9 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management.
Drug Interactions-Additions underlined: Phenytoin is extensively bound to plasma proteins and is prone to competitive displacement. Phenytoin is primarily metabolized by the hepatic cytochrome P450 enzyme CYP2C9 and to a lesser extent by CYP2C19 and is particularly susceptible to inhibitory drug interactions because it is subject to saturable metabolism.
Use in Specific Populations-Use in Patients with Decreased CYP2C9 Function New subsection added: Patients who are intermediate or poor metabolizers of CYP2C9 substrates (e.g., *1/*3, *2/*2, *3/*3) may exhibit increased phenytoin serum concentrations compared to patients who are normal metabolizers (e.g.,*1/*1). Thus, patients who are known to be intermediate or poor metabolizers may ultimately require lower doses of phenytoin to maintain similar steady-state concentrations compared to normal metabolizers. If early signs of dose-related central nervous system (CNS) toxicity develop, serum concentrations should be checked immediately.

Metronidazole (Flagyl)
Drug Interactions and Adverse Reactions-Additions underlined: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval. Flattening of the T-wave may be seen in electrocardiographic tracings.

Other FDA Safety Communications

Lamotrigine: At the October 2020 meeting, this committee discussed changes to lamotrigine prescribing information in which the FDA added information about a

potential increased risk of arrhythmias in patients with heart disease who are taking lamotrigine. The FDA is requiring that in vitro safety studies be conducted on other medications in the same drug class to see if they have similar effects on the heart. These medications include carbamazepine, lacosamide, oxcarbazepine, phenytoin, topiramate, and zonisamide, among others.

News Briefs

The following information was shared with the committee members:

Empagliflozin In Patients With HFrEF May Improve LV Volume, Mass, And Systolic Function

Cardiology Advisor (2/16, Stong) reports the "treatment of nondiabetic patients with heart failure with reduced ejection fraction (HFrEF) with empagliflozin was found to improve left ventricular (LV) volume, mass, and systolic function as well as functional capacity and quality of life, according to" research. In the "double-blind, placebo-controlled trial...84 nondiabetic patients with HFrEF (mean age, 62±12.1 years; 64% men; 50% Hispanic/Latino) were randomly assigned to receive the sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin – (10 mg daily) or placebo for 6 months." The findings were published in the Journal of the American College of Cardiology.

Joint Task Force Issues Advisory To Address Concerns Arising From FDA Warning Of Cardiac Risk In Patients Taking Lamotrigine

Medscape (2/22, Anderson, Subscription Publication) reports, "A joint task force of the American Epilepsy Society (AES) and International League Against Epilepsy (ILAE) has issued an advisory to address concerns arising from a Food and Drug Administration (FDA) warning of cardiac risk in patients taking" lamotrigine, an antiseizure medication. The joint "task force is concerned that the FDA warning is based on data not yet widely available, and that its sweeping nature has caused alarm" both among physicians and patients. In the advisory, the task force "addresses key issues, including which patients can safely take lamotrigine and when an ECG is warranted."

FDA Approves New Drug For Children With ADHD

The AP (4/5, Johnson) reports the FDA approved Supernus Pharmaceuticals' Qelbree (viloxazine) for the treatment of children with ADHD. Unlike most alternatives, "Qelbree is not a stimulant or a controlled substance, making it harder to abuse than older drugs," which has been an issue for other ADHD drugs. The AP adds that "viloxazine was sold as an antidepressant in Europe for several decades but was never approved by the FDA." The Hill (4/5, Choi) reports viloxazone is the first new drug approved by the FDA to treat children with ADHD in more than a decade.

Study Examines Long-Term Effects Of Cholinesterase Inhibitors On Patients With Alzheimer's Dementia

Healio (4/5, Marabito) reports, "Cholinesterase inhibitors provided moderate but persistent benefits in patients with Alzheimer's dementia, including a lower risk for death," investigators concluded, but galantamine was the only "cholinesterase inhibitor (ChEI) that demonstrated a significant reduction in the risk for severe dementia." Investigators arrived at these conclusions after comparing 11,652 patients with Alzheimer's "who were started on ChEIs within three months of their dementia diagnosis – either donepezil, rivastigmine or galantamine – and 5,836" patients with Alzheimer's "who did not take ChEIs." The findings were published online in the journal Neurology.

Open Forum

Dr. Sawhney shared that he is working to update the local mental health authority (LMHA) performance contract to add language in relation to the state hospital operating procedure on long-acting injections (LAIs). The updated language will include the expectation to coordinate with the state hospitals when a request to start treatment with a LAI is received from a state hospital, as well as a deadline for the expected response to the state hospital from the LMHA.

Next Meeting Date

The next meeting is scheduled for July 9, 2021.

Adjourn

There being no further business, the meeting was adjourned at 2:52 p.m.

Approved: *David Moron*

David Moron, MD, Chairman

Minutes Prepared by:

Jean Baemayr, PharmD

Appendix

- Appendix A – Canagliflozin (Invokana®) monograph
- Appendix B – Empagliflozin (Jardiance®) monograph

Appendix A

Canagliflozin (Invokana®)

Classification:
Antidiabetic Agents

Pharmacology
Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE).

Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure.

Indication -FDA & literature supported non-FDA
- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- To reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- To reduce the risk of end-stage-kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day

Limitations of Use

- Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. Likely to be ineffective in this setting based upon mechanism of action.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Mean absolute oral bioavailability = approx. 65%. Co-administration with high-fat meal had no effect on PK, may be taken with or without food. Based on potential to delay intestinal glucose absorption and reduce postprandial plasma glucose excursions, recommended to take before first meal of the day.
Distribution	Following a single IV infusion, mean steady state volume of distribution = 83.5 L, which suggests extensive tissue distribution. Extensively bound to proteins in plasma (99%), mainly to albumin.

Pharmacokinetic Parameter	Details
Metabolism	O-glucuronidation is the major metabolic elimination pathway. Mainly glucuronidated by UGT1A9 and UGT2B4 to inactive O-glucuronide metabolites. CYP3A4-mediated (oxidative) metabolism is minimal (approx. 7%)
Excretion	Feces (41.5%) as unchanged drug, 7% as hydroxylated metabolite, 3.2% as O-glucuronide metabolite); urine approx. 33% (30.5% as O-glucuronide metabolites, < 1% as unchanged drug)

Dosage/Administration

Assess renal function before initiating canagliflozin and as clinically indicated. Correct volume depletion before starting canagliflozin.

- Starting dose is 100 mg once daily, taken before the first meal of the day.
- Dose can be increased to 300 mg once daily in patients tolerating canagliflozin 100 mg once daily who have an **eGFR of 60 mL/min/1.73 m^2 or greater** and require additional glycemic control.
- **eGFR 30 to less than 60**: 100 mg once daily
- **eGFR less than 30**: Initiation not recommended. Patients with albuminuria > 300 mg/day may continue 100 mg once daily to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure.
- **On dialysis**: Contraindicated

Use in Special Population

Pregnancy

Risk Summary: Based on animal data showing adverse renal effects, canagliflozin is not recommended during the second and third trimesters of pregnancy.

Limited data with canagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a $HbA1_c$ > 7 and has been reported to be as high as 20-25% in women with a $HbA1_c$ > 10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Lactation

Risk Summary: There is no information regarding the presence of canagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production.

Canagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first two years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of canagliflozin is not recommended while breastfeeding.

Pediatric Use

Safety and effectiveness of canagliflozin in pediatric patients under 18 years of age have not been established.

Geriatric Use

In 13 clinical trials of canagliflozin, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to canagliflozin.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with canagliflozin (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older.

Renal Impairment

The efficacy and safety of canagliflozin for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2.) These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of study. Patients with renal impairment using canagliflozin for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury.

Efficacy and safety studies with canagliflozin did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. Canagliflozin is contraindicated in patients with ESKD on dialysis.

Hepatic Impairment

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of canagliflozin has not been studied in patients with severe hepatic impairment and is therefore not recommended.

Contraindication

- Serious hypersensitivity reaction to canagliflozin, such as anaphylaxis or angioedema
- Patients on dialysis

Warnings and Precautions

Lower Limb Amputation

An increased risk of lower limb amputations associated with canagliflozin use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and

CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving canagliflozin in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving canagliflozin in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before staring canagliflozin, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving canagliflozin for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue canagliflozin if these complications occur.

Volume Depletion

Canagliflozin can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of AKI which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including canagliflozin. Patients with impaired renal function (eGFR less than 60 ml/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating canagliflozin in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after starting therapy.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and post-marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including canagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have

been reported in patients taking canagliflozin. Canagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with canagliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with canagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, canagliflozin should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the post-marketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating canagliflozin, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing canagliflozin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing canagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting canagliflozin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue canagliflozin and seek medical attention immediately if signs and symptoms occur.

Urosepsis and Pyelonephritis

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including canagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. Canagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with canagliflozin.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including canagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with canagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue canagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

Canagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.

Hypersensitivity Reactions

Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with canagliflozin. These reactions generally occurred within hours to days after initiating canagliflozin. If hypersensitivity reactions occur, discontinue use of canagliflozin; treat and monitor until signs and symptoms resolve.

Bone Fracture

An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using canagliflozin in the CANVAS trial. Consider factors that contribute to fracture risk prior to initiating canagliflozin.

Adverse Effects

Pool of Placebo-Controlled Trials for Glycemic Control

The data in the table below are derived from four 26-week placebo-controlled trials in which canagliflozin was used as monotherapy in one trial and as add-on therapy in three trials (metformin, metformin and sulfonylurea, metformin and pioglitazone). These data reflect exposure of 1,667 patients to canagliflozin and a mean duration of exposure to canagliflozin of 24 weeks. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was

male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline, the population had diabetes for an average of 7.3 years, a mean HbA1c of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

These adverse reactions were not present at baseline, occurred more commonly on canagliflozin than on placebo, and occurred in at least 2% of patients treated with either canagliflozin 100 mg or canagliflozin 300 mg.

Adverse Reactions from Pool of Four 26-Week Placebo-Controlled Studies Reported in $\geq$ 2% of canagliflozin-Treated Patients

Adverse Reaction	**Placebo N = 646**	**Canagliflozin 100 mg N = 833**	**Canagliflozin 300 mg N = 834**
Urinary tract infections	3.8%	5.9%	4.4%
Increased urination	0.7%	5.1%	4.6%
Thirst	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
Female genital mycotic infections	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
Male genital mycotic infections	0.7%	4.2%	3.8%

Diabetic Ketoacidosis (DKA)

CREDENCE. Patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day. 2,201 patients exposed to canagliflozin with an average duration of exposure of 137 weeks.

Canagliflozin 100 mg, 11/2200, 2.2 events per 1000 patient-years

Placebo, 1/2197, 0.2 events per 1000 patient-years

HR (95% CI), 10.80 (1.39-83.65)

Lower Limb Amputation

CREDENCE. Patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day. 2,201 patients exposed to canagliflozin with an average duration of exposure of 137 weeks.

Canagliflozin 100 mg, 70/2200, 12.3 events per 1000 patient years

Placebo, 63/2197, 11.2 events per 1000 patient years

HR (95% CI), 1.11 (0.79-1.56)

CANVAS (mean duration = 5.7 years), CANVAS-R (mean duration = 2.1 years). Two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who

had either established cardiovascular disease or were at risk for cardiovascular disease.

CANVAS Amputations

Data	Placebo N = 1441	Canagliflozin 100 mg N = 1445	Canagliflozin 300 mg N = 1441	Canagliflozin (Pooled) N = 2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	n/a	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Incidence is based on the number of patients with at least one amputation event. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had > 1 amputation.

CANVAS-R Amputations

Data	Placebo N = 2903	Canagliflozin 100 mg (w/ up-titration to 300 mg) N = 2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	n/a	1.80 (1.10, 2.93)

Incidence is based on the number of patients with at least one amputation event. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had > 1 amputation.

Renal Cell Carcinoma

In the CANVAS trial (mean duration 5.7 y), the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and canagliflozin, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to canagliflozin could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions

Canagliflozin results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with canagliflozin was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was

observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume-depletion-related adverse reactions in these trials were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older.

Proportion of Patients with at least one Volume-Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

Baseline Characteristic	Comparator Group* %	Canagliflozin 100 mg %	Canagliflozin 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older**	2.6%	4.9%	8.7%
eGFR < 60 mL/min/1.73m2**	2.5%	4.7%	8.1%
Use of loop diuretic**	4.7%	3.2%	8.8%

*Includes placebo and active-comparator groups

** Patients could have more than 1 of the listed risk factors

Falls

In a pool of nine clinical trials with mean duration of exposure to canagliflozin of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The higher risk of falls for patients treated with canagliflozin was observed within the first few weeks of treatment.

Genital Mycotic Infections

In the pool of four placebo-controlled trials for glycemic control, female genital mycotic infections (vulvovaginal mycotic infection, vulvovaginal candidiasis, vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on canagliflozin. Female patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and canagliflozin, respectively.

In the pool of four placebo-controlled trials for glycemic control, male genital mycotic infections (candida balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on canagliflozin were more likely to experience recurrent infections and require treatment with oral or topical antifungal agents and antimicrobial agents than patients on comparators.

Discontinuation due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and canagliflozin, respectively.

Hypoglycemia

In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (blood glucose $\leq$ 70 mg/dL). *Severe* hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether there was biochemical documentation of low blood glucose). In individual clinical trials of glycemic control, episodes of hypoglycemia occurred at a higher rate when canagliflozin was co-administered with insulin or sulfonylureas.

Monotherapy (26 weeks)	Placebo (N=192)	Canagliflozin 100 mg (N=195)	Canagliflozin 300 mg (N=197)
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)

In Combination with Metformin (26 weeks)	Placebo + Metformin (N=183)	Canagliflozin 100 mg + Metformin (N=368)	Canagliflozin 300 mg + Metformin (N=367)
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]	0 (0)	1 (0.3)	1 (0.3)

In Combination with Metformin (52 weeks)	Glimepiride + Metformin (N=482)	Canagliflozin 100 mg + Metformin (N=483)	Canagliflozin 300 mg + Metformin (N=485)
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]	15 (3.1)	2 (0.4)	3 (0.6)

In Combination with Sulfonylurea (18 weeks)	Placebo + Sulfonylurea (N=69)	Canagliflozin 100 mg + Sulfonylurea (N=74)	Canagliflozin 300 mg + Sulfonylurea (N=72)
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)

In Combination with Metformin + Sulfonylurea (26 weeks)	Placebo + Metformin + Sulfonylurea (N=156)	Canagliflozin 100 mg + Metformin + Sulfonylurea (N=157)	Canagliflozin 300 mg + Metformin + Sulfonylurea (N=156)
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]	1 (0.6)	1 (0.6)	0

In Combination with Metformin + Sulfonylurea (52 weeks)	Sitagliptin + Metformin + Sulfonylurea (N=378)	N/A	Canagliflozin 300 mg + Metformin + Sulfonylurea (N=377)
Overall [N (%)]	154 (40.7)	N/A	163 (43.2)
Severe [N (%)]	13 (3.4)	N/A	15 (4.0)

In Combination with Metformin + Pioglitazone (26 weeks)	Placebo + Metformin + Pioglitazone (N=115)	Canagliflozin 100 mg + Metformin + Pioglitazone (N=113)	Canagliflozin 300 mg + Metformin + Pioglitazone (N=114)
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)

In Combination with Insulin (18 weeks)	Placebo (N=565)	Canagliflozin 100 mg (N=566)	Canagliflozin 300 mg (N=587)
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]	14 (2.5)	10 (1.8)	16 (2.7)

Bone Fracture

In CANVAS, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up for placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained throughout the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities.

Laboratory and Imaging Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of canagliflozin causes an increase in serum creatinine and decrease in estimated GFR. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes.

Increases in Serum Potassium

In a pooled population of patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with canagliflozin 100 mg, and 1.3% of patients treated with canagliflozin 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers.

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with canagliflozin 100 mg relative to placebo.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C)

In the pool of four glycemic control placebo-controlled trials, dose-related increases in LDL-C with canagliflozin were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with canagliflozin 100 mg and canagliflozin 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

Dose-related increases in non-HDL-C with canagliflozin were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with canagliflozin 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin

In the pool of four placebo-controlled trials of glycemic control, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with canagliflozin 100 mg, and 0.51 g/dL (3.8%) with canagliflozin 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, canagliflozin 100 mg, and canagliflozin 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years). At 2 years, patients randomized to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both canagliflozin doses and 0.4% at the distal forearm for patients randomized to canagliflozin 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to canagliflozin 100 mg was 0%.

Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of canagliflozin. Because these reactions are reported voluntarily from a population of

uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ketoacidosis, Acute Kidney Injury, Anaphylaxis, Angioedema, Urosepsis and Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's gangrene).

Monitoring

- Blood glucose, HbA1c (at least twice yearly in patients who are meeting treatment goals, quarterly in patients not meeting treatment goals or with therapy change)
- Renal function (baseline and periodically during treatment)
- Volume status (eg, blood pressure, hematocrit, electrolytes)
- Serum potassium (periodically after initiation in renal impairment and those predisposed to hyperkalemia)
- Serum magnesium and phosphate
- LDL-C
- Genital mycotic infections and UTI
- Blood pressure
- Lower limb and feet (sores, ulcers, infection)
- If signs/symptoms of ketoacidosis (eg, n/v, abdominal pain, malaise, SOB), confirm diagnosis by direct measurement of blood ketones and arterial pH

Interactions

Concomitant Use with UDP-Glucuronosyl Transferase (UGT) Enzyme Inducers:

Co-administration with rifampin, a nonselective inducer of several UGT enzymes, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure may decrease efficacy.

Patients with eGFR 60 ml/min/1.73 m^2 or greater

If an inducer of UGTs (e.g. rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with canagliflozin, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating the 100 mg dose. Dose may be increased to 300 mg once daily in patients currently tolerating 200 mg who require additional glycemic control.

Patients with eGFR less than 60 mL/min/1.73 m^2

If an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with canagliflozin, increase the dose to 200 mg once daily in patients currently tolerating the 100 mg dose. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.

Digoxin

Increase in AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with canagliflozin 300 mg. Patients should be monitored appropriately.

Efficacy

CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation)

In a double-blind, multi-center, placebo-controlled randomized trial, the Credence investigators assessed the effect of canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric chronic (CKD). Inclusion criteria included age $\geq$ 30 yo, Type 2 DM (HgA1c = 6.5-12.0%), and a diagnosis of CKD. Chronic kidney disease was defined as an estimated GFR of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (urinary albumin-to-creatinine ratio > 300 to 5000 mg/g). Patients were also required to have been on a stable dose of ACE-I or ARB for at least four weeks before randomization.

Local guidelines determined patients' background therapy for glycemic management and control of cardiovascular risk factors. Investigators randomized 4401 patients in a 1:1 ratio to canagliflozin 100 mg qd or placebo. Study groups were stratified according to GFR (30 to < 45, 45 to < 60, 60 to 90 ml per minute per 1.73 m^2 of body-surface-area). Treatment was to be continued until trial completion, initiation of dialysis, kidney transplantation, occurrence of diabetic ketoacidosis, pregnancy, or receipt of a disallowed therapy. Trials visits (telephone calls, in-clinic) occurred at weeks 3, 13, 26 and then at 13-week intervals.

Demographic and clinical characteristics of the patients at baseline

Characteristic	Canagliflozin (n = 2202)	Placebo (n = 2199)	All Patients (n = 4401)
Age—yr	62.9 ± 9.2	63.2 ± 9.2	63.0 ± 9.2
Female sex—no (%)	762 (34.6)	732 (33.3)	1494 (33.9)
Race or ethnic group- White no. (%)	1487 (67.5)	1444 (65.7)	2931 (66.6)
Race or ethnic group- Black no. (%)	112 (5.1)	112 (5.1)	224 (5.1)
Race or ethnic group- Asian no. (%)	425 (19.3)	452 (20.6)	877 (19.9)
Race or ethnic group- Other no. (%)	178 (8.1)	191 (8.7)	369 (8.4)
Current smoker—no. (%)	341 (15.5)	298 (13.6)	639 (14.5)
Hypertension—no. (%)	2131 (96.8)	2129 (96.8)	4260 (96.8)
Heart failure—no. (%)	329 (14.9)	323 (14.7)	652 (14.8)
Duration of diabetes—yr	15.5 ± 8.7	16.0 ± 8.6	15.8 ± 8.6
Cardiovascular disease—no. (%)	1113 (50.5)	1107 (50.3)	2220 (50.4)
Amputation—no. (%)	119 (5.4)	115 (5.2)	234 (5.3)
BMI	31.4 ± 6.2	31.3 ± 6.2	31.3 ± 6.2
Systolic Blood pressure—mm Hg	139.8 ± 15.6	140.2 ± 15.6	140.0 ± 15.6

Characteristic	Canagliflozin (n = 2202)	Placebo (n = 2199)	All Patients (n = 4401)
Diastolic Blood pressure—mm Hg	78.2 ± 9.4	78.4 ± 9.4	78.3 ± 9.4
Glycated hemoglobin--%	8.3 ± 1.3	8.3 ± 1.3	8.3 ± 1.3
Estimated GFR—ml/min/1.73 m^2	56.3 ± 18.2	56.0 ± 18.3	56.2 ± 18.2
Median urinary albumin-to-creatinine ratio (IQR)	923 (459-1794)	931 (473-1868)	927 (463-1833)

The primary outcome was a composite of (1) ESKD, (2) doubling of serum creatinine from baseline, and (3) death from renal or cardiovascular disease. The primary outcome occurred less frequently in the canagliflozin group than in the placebo group (43.2 and 61.2 per 1000 patient-years, respectively; HR = 0.70, 95% CI = 0.59-0.82, p = 0.00001). This represented a 30% lower relative risk in the canagliflozin group.

The canagliflozin group also had a lower risk of the following secondary outcomes: (1) Renal specific composite (ESKD, doubling of serum creatinine, death from renal causes), HR = 0.66 (95% CI = 0.53-0.81, p < 0.001, 34% lower relative risk); (2) Composite of cardiovascular death, mi, or stroke, HR = 0.80, 95% CI = 0.67-0.95, p = 0.01; (3) hospitalization for heart failure, HR = 0.61, 95% CI = 0.47-0.80, p < 0.001.

A requisite number of primary outcome events occurred earlier than expected and an interim analysis was performed. Investigators stopped the trial after the interim analysis; median patient follow-up was 2.62 years (range 0.02 to 4.53)

The following intermediate outcomes were lower in the canagliflozin group compared to the placebo group. At 13 weeks, HgA1c was 0.31 percentage points lower (95% CI, 0.26-0.37). Overall, HgA1c was 0.25 percentage points lower (95% CI, 0.20-0.31). Systolic blood pressure was an average of 3.30 mm Hg lower (95% CI, 2.73-3.87). Body weight was an average of 0.80 kg lower (95% CI, 0.69-0.92). Urinary albumin-to-creatinine ratio was 31% lower (95% CI, 26-35).

During the first three weeks of the trial, there was a greater reduction in the estimated GFR in the canagliflozin group than in the placebo group (-3.72 vs -0.55, between group difference = -3.17 ml/min). After Week 3, the decline in estimated GFR was slower in the canagliflozin group than in the placebo group (-1.85 vs -4.59 ml per min per 1.73 m^2 per year, between group difference = 2.74 ml per min per 1.73 m^2 per year).

See Adverse Effects section for a discussion of this trial's safety outcomes.

The authors concluded that in patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years.

Dosage Forms/Cost

Invokana 100 mg tablets/$551 for #30, www.drugs.com
Invokana 300 mg tablets/$551 for #30, www.drugs.com

Special Considerations

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Summary/Conclusion

Canagliflozin (Invokana) and other sodium-glucose cotransporter 2 (SGLT-2) inhibitors lower blood glucose and provide significant cardiorenal protection. The current ADA guidelines recommend them early in therapy (along with metformin) for patients with diabetes and either high risk or established ASCVD, CKD, or heart failure. Along with substantial clinical benefits, SGLT-2 inhibitor use is associated with serious adverse events and requires careful monitoring.

Recommendation

Canagliflozin (Invokana) should be added to the formulary.

References

1. Invokana (canagliflozin) Prescribing Information. Revised: 8/2020
2. Pamulapati LG, Rochester-Eyeguokan CD, Pincus KJ. Best practices for safe use of SGLT-2 inhibitors developed from an expert panel Delphi consensus process. Am J Health-Syst Pharm. 2020;77:1727-1738.
3. Perkovic V, Jardine MJ, Neal B. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med 2019;380:2295-306.
4. Zelniker T and Braunwald E. Clinical Benefit of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors. Journal of the American College of Cardiology 2020;75:435-47.

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Appendix B

Empagliflozin (Jardiance®)

Classification:

Antidiabetic Agents

Pharmacology

Sodium-glucose co-transporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases urinary glucose excretion (UGE).

Empagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption. This is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure.

Indication -FDA & literature supported non-FDA

- As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes
- To reduce the risk of cardiovascular death in patients with type 2 diabetes mellitus and established cardiovascular disease

Limitations of Use: Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	Peak plasma concentration 1.5 hours post-dose – linear pharmacokinetics. Administration after a high-fat and high-calorie meal results in slightly lower exposure (AUC decreased by 16% and Cmax by 37% (not clinically relevant)
Distribution	Red blood cell partitioning = 36.8% and plasma protein binding = 86.2%
Metabolism	Glucuronidation by uridine 5'-diphospho glucuronosyltransferases (UGTs) UGT2B7, UGT1A3, UGT1A8, and UGT1A9 to minor metabolites
Excretion	Elimination half-life = 12.4 hours (oral clearance = 10.6 L/h), 41.2% of drug eliminated in feces and 54.4% eliminated in urine.

Dosage/Administration

Recommended Dosage

The recommended dose of Jardiance is 10 mg once daily in the morning, taken with or without food. In patients tolerating Jardiance, the dose may be increased to 25 mg.

In patients with volume depletion, correcting this condition prior to initiation of empagliflozin is recommended.

Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of empagliflozin and periodically thereafter.

Empagliflozin should not be initiated in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m^2.

Empagliflozin should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

Use in Special Population

Pregnancy

Risk Summary: Based on animal data showing adverse renal effects, empagliflozin is not recommended during the second and third trimesters of pregnancy.

Limited data available with empagliflozin in pregnant women are not sufficient to determine a drug associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Lactation

Risk Summary: There is no information regarding the presence of empagliflozin in human milk, the effects of empagliflozin on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise women that use of empagliflozin is not recommended while breastfeeding.

Pediatric Use

The safety and effectiveness of empagliflozin in pediatric patients under 18 years of age have not been established.

Geriatric Use

No empagliflozin dosage change is recommended based on age. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished glycemic efficacy in elderly patients with renal impairment. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo,

empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Renal Impairment

The efficacy and safety of empagliflozin were evaluated in a study of patients with mild and moderate renal impairment. In this study, 195 patients exposed to empagliflozin had an eGFR between 60 and 90 mL/min/1.73 m^2 , 91 patients exposed to empagliflozin had an eGFR between 45 and 60 mL/min/1.73 m^2 and 97 patients exposed to empagliflozin had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

In a large cardiovascular outcomes study, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings.

The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations.

Hepatic Impairment

Empagliflozin may be used in patients with hepatic impairment.

Contraindication

- History of serious hypersensitivity reaction to empagliflozin or any of the excipients in Jardiance.
- Severe renal impairment (gfr < 30 ml/min, end-stage renal disease, or dialysis).

Warnings and Precautions

Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin, particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating empagliflozin, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in post-marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2

(SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. Empagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with empagliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with empagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, empagliflozin should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating empagliflozin, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing empagliflozin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing empagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or postsurgery). Ensure risk factors for ketoacidosis are resolved prior to restarting empagliflozin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue empagliflozin and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction and can cause renal impairment. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Before initiating empagliflozin, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart

failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing empagliflozin in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue empagliflozin promptly and institute treatment.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating empagliflozin. Renal function should be evaluated prior to initiation of empagliflozin and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. The use of empagliflozin is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with empagliflozin.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with empagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue empagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

Empagliflozin increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue empagliflozin; treat promptly per standard of care, and monitor until signs and symptoms resolve. Empagliflozin is contraindicated in patients with a previous serious hypersensitivity reaction to empagliflozin or any of the excipients in empagliflozin.

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

Adverse Effects

Most common adverse effect (5% or greater incidence) were urinary tract infections and female genital mycotic infections.

The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials. The adverse reactions were not present at baseline, occurred more commonly on empagliflozin than on placebo and occurred in greater than or equal to 2% of patients treated with empagliflozin 10 mg or empagliflozin 25 mg.

Adverse Reaction	Placebo (n = 995)	empagliflozin 10 mg (n = 999)	empagliflozin 25 mg (n = 977)
Urinary tract infection	7.6%	9.3%	7.6%
Female genital mycotic infection	1.5%	5.4%	6.4%
Increased urination	1.0%	3.4%	3.2%
Male genital mycotic infections	0.4%	3.1%	1.6%
Nausea	1.4%	2.3%	1.1%

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Volume Depletion

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased,

dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. empagliflozin may increase the risk of hypotension in patients at risk for volume contraction.

Urinary Tract Infections

In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively.

Laboratory Tests

Increase in Low-Density Lipoprotein Cholesterol (LDL-C)

Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit

In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Monitoring

Blood glucose, HbA1c (at least twice yearly in patients who have stable glycemic control and are meeting treatment goals; quarterly in patients in whom treatment goals have not been met or with therapy change (ADA 2020); renal function (baseline and periodically during treatment); volume status (e.g., BP, hematocrit, electrolytes); monitor for genital mycotic infections and UTI; assess patients presenting with fever or malaise along with genital or perianal pain, tenderness, erythema, or swelling for necrotizing fasciitis; BP; if signs/symptoms of ketoacidosis (e.g., nausea/vomiting, abdominal pain, malaise, shortness of breath), confirm

diagnosis by direct measurement of blood ketones and arterial pH (measurement of serum bicarbonate or urinary ketones may not be adequate) (AACE [Handelsman 2016]).

Interactions

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

Insulin or Insulin Secretagogues

Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.

Efficacy

EMPA-REG OUTCOME

In a randomized, double-blind, placebo-controlled, multi-center study, Zinman and colleagues evaluated the effect on cardiovascular morbidity and mortality of adding empagliflozin (empagliflozin) to standard care in patients with type 2 diabetes at high cardiovascular risk.

Investigators randomized 7020 patients to one of three treatment groups: empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Patients were receiving standard care (local guidelines) for diabetes, hypertension, and lipids and had established cardiovascular disease (history of MI, multi or single vessel CAD, history of stroke, occlusive peripheral artery disease.) Randomization was stratified according to HgBA1c (< 8.5% or ≥ 8.5%), BMI (< 30 or ≥ 30), renal function (eGFR, 30 to 59 ml, 60 to 89 ml, or ≥ 90 ml per minute per 1.73 m^2), and geographic region (North America [plus Australia and New Zealand], Latin America, Europe, Africa, or Asia) Study patients met the following inclusion criteria: > 18 years old, type 2 dm (HgBA1c 7%-10%), BMI < 45, eGFR > 30 ml/min.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.

Baseline characteristics are shown in the table below Characteristic	**Placebo (n = 2333)**	**Empagliflozin 10 mg (n = 2345)**	**Empagliflozin 25 mg (n = 2342)**
Age-years	63.2 (± 8.8)	63.0 (± 8.6)	63.2 (± 8.6)
Male-no. (%)	1680 (72.0)	1653 (70.5)	1683 (71.9)
Race-no. (%)			
White	1678 (71.9)	1707 (72.8)	1696 (72.4)
Asian	511 (21.9)	505 (21.5)	501 (21.4)
Black/African-American	120 (5.1)	119 (5.1)	118 (5.0)

Baseline characteristics are shown in the table below Characteristic	Placebo (n = 2333)	Empagliflozin 10 mg (n = 2345)	Empagliflozin 25 mg (n = 2342)
Other/Missing	24 (1.0)	14 (0.6)	27 (1.2)
BMI	30.7 ± 5.2	30.6 ± 5.2	30.6 ± 5.3
HgA1c-%	8.08 ± 0.84	8.07 ± 0.86	8.06 ± 0.84
Systolic blood pressure—mmHg	135.8 ± 17.2	134.9 ± 16.8	135.6 ± 17.0
LDL	84.9 ± 35.3	86.3 ± 36.7	85.5 ± 35.2

Estimated gfr-no. (%)	Placebo (n = 2333)	Empagliflozin 10 mg (n = 2345)	Empagliflozin 25 mg (n = 2342)
≥ 90 mL/min	488 (20.9)	519 (22.1)	531 (22.7)
60 to < 90 mL/min	1238 (53.1)	1221 (52.1)	1202 (51.3)
< 60 mL/min	607 (26.0)	605 (25.8)	607 (25.9)

The median duration of treatment was 2.6 years and the median observation time was 3.1 years. Ninety-seven (97) percent of patients completed the study; 25.4% of patients prematurely stopped study medication.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. Death from cardiovascular causes included the following: sudden cardiac death, worsening of heart failure, acute mi, stroke, cardiogenic shock, other cardiovascular death (dysrhythmia, pulmonary embolism, CV intervention).

A significantly lower percentage of patients in the empagliflozin (pooled) group (490 of 4687 [10.5%]) experienced the primary outcome compared to the placebo group (282 of 2333 [12.1%]. Hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval 0.74 to 0.99; $p < 0.001$ for noninferiority and $p = 0.04$ for superiority. The difference between the empagliflozin and placebo groups was driven by a significant reduction in death from cardiovascular causes; there were no significant between group differences in the risk of mi or stroke.

The hazard ratios for the evaluations of 10 mg versus placebo (HR = 0.85, 95% CI 0.72-1.01, $p = 0.07$) and 25 mg versus placebo (HR = 0.86, 95% CI = 0.73-1.02, $p = 0.09$) were nearly identical to those from the pooled analysis but, because there were fewer outcome events in the individual dose groups, the effects were not statistically significant. This led the authors to conclude that in clinical practice, metabolic targets and adverse events would guide the dose.

The secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina. The secondary outcome occurred in 599 of 4687 patients

(12.8%) in the empagliflozin group and 333 of 2333 patients (14.3%) in the placebo group. Hazard ratio, 0.89; 95% CI, 0.78 to 1.01; p < 0.001 for noninferiority, p = 0.08 for superiority. Compared to patients treated with placebo.

The cardiovascular outcomes listed in the table below occurred in a lower percentage of patients treated with empagliflozin.

forms	Hazard Ratio	95% CI
Death from CV Causes	0.62	0.49-0.77, p < 0.001
Death from Any Cause	0.68	0.57-0.82, p < 0.001
Hospitalization for Heart Failure	0.65	0.50-0.85, p = 0.002

After 12 weeks, the adjusted mean differences in HgA1c between patients receiving empagliflozin and those receiving placebo were -0.54 percentage points (95% CI, -0.58 to -0.49) in the 10-mg group and -0.60 percentage points (95% CI, -0.64 to -0.55) in the 25-mg group. At week 206, the differences were -0.24 percentage points (95% CI, -0.40 to -0.08) in the 10-mg group and -0.36 percentage points (95% CI, -0.51 to -0.20) in the 25-mg group. Mean HgA1c was 7.81% in the pooled empagliflozin group versus 8.16% in the placebo group. Over the course of the study, the use of empagliflozin was also associated with small reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood pressure.

The authors concluded that patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

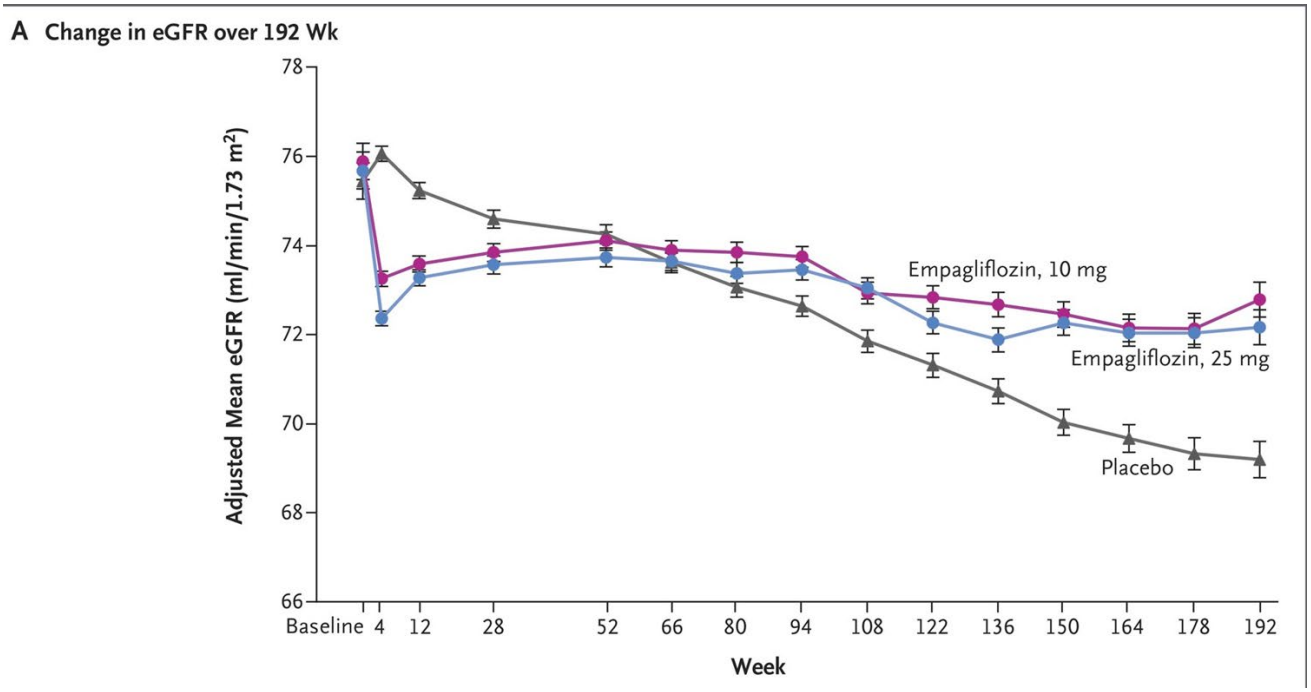
Wanner and colleagues reported on the renal microvascular outcomes of patients who completed the Empa-Reg Outcome trial, the primary goal of which was to assess cardiovascular outcomes.

Investigators randomly assigned patients with type 2 dm, established cardiovascular disease and an estimated gfr of at least 30 ml/min to receive either empagliflozin (10 mg or 25 mg) or placebo. Prespecified renal outcomes included (1) incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine, initiation of renal-replacement therapy, or death from renal disease) and (2) incident albuminuria. The median duration of treatment was 2.6 years, median observation time was 3.1 years.

Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group versus 388 of 2061 patients (18.8%) in the placebo group (HR in empagliflozin group = 0.61; 95% CI = 0.53-0.70, p < 0.001). Progression to macroalbuminuria occurred in 459 of 4091 patients (11.2%) in the empagliflozin group versus 330 of 2033 (16.2%) in the placebo group (HR = 0.62, 95% CI = 0.54-0.72, p < 0.001). A doubling of the serum creatinine occurred in 70 of 4645 patients (1.5%) in the empagliflozin group versus 60 of 2323 (2.6%) in the placebo group (HR = 0.56, 95% CI = 0.39-0.79, p < 0.001). The initiation of renal-replacement

therapy occurred in 13 of 4687 (0.3%) patients in the empagliflozin group versus 14 of 2333 (0.6%) in the placebo group, HR = 0.45 (0.21-0.97, p = 0.04). Three patients in the empagliflozin group died from renal disease (0.1%) versus none in the placebo group. Incident albuminuria occurred in 1430 of 2779 patients (51.5%) of patients treated with empagliflozin versus 703 of 1374 (51.2%) of patients treated with placebo; there was no significant between-group difference.

The figure below shows a graphic depiction of renal function over time in the three groups.



Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR-Reduced)

In a double-blind, placebo-controlled, multicenter trial, Packer and colleagues randomly assigned 3730 patients with class II-IV heart failure and an ejection fraction of < 40% to receive either empagliflozin 10 mg daily (1863) or placebo (1867). All patients were receiving appropriate treatments for heart failure (diuretics, inhibitors of the renin-angiotensin system and neprilysin, beta-blockers, mineralocorticoid receptor antagonists, and, when indicated, cardiac devices). The primary outcome was a composite of adjudicated cardiovascular death or hospitalization for heart failure. A secondary outcome was the rate of decline in estimated GFR.

The investigators' intent was to enroll patients with heart failure who were likely to experience a serious heart failure event. For patients with an ejection fraction (EF) > 30%, inclusion criteria required a heart failure hospitalization within the previous 12 months or a high level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Patients whose EF were < 30% were required to have a level of 600 pg per ml. Patients with an EF of 31-35% required a level of at least 1000 pg per ml.

Patients with an EF of 36-40% required a EF of at least 2500 pg per ml. Randomization was stratified according to geographical region (North America, Latin America, Europe, Asia), diabetes status, and GFR (< 60 or > 60 ml per minute per 1.73 m^2 of body surface area).

The empagliflozin and placebo groups had similar baseline characteristics. Half the patients had a history of diabetes, 73% had an EF < 30%, 79% had a NT-proBNP of at least 1000 pg per ml, 48% had GFR < 60 ml per minute, and close to 20% were receiving an angiotensin receptor-neprilysin inhibitor (ARNI).

The median duration of follow-up was 16 months. The primary outcome of death from cardiovascular causes or hospitalization for heart failure was 25% lower among patients who received empagliflozin [361 patients in empagliflozin group (19.4%) versus 462 patients in placebo group (24.7%) (hazard ratio, 0.75; 95% CI 0.65 to 0.86; p < 0.001)]. The difference was mainly related to a lower risk of hospitalization for heart failure. The effect was seen regardless of the presence or absence of diabetes and was consistent across other prespecified subgroups. In patients who were receiving sacubitril-valsartan at baseline, the hazard ratio was 0.64 (95% CI, 0.45 to 0.89) compared with 0.77 (95% CI, 0.66 to 0.90) among patients who were not receiving sacubitril-valsartan.

The GFR declined more slowly in patients treated with empagliflozin than in patients treated with placebo (-0.55 ml per minute per 1.73 m^2 per year versus -2.28 ml per minute per 1.73 m^2 per year. The between group difference was 1.73 ml per minute (95% CI, 1.10 to 2.37; p < 0.001). Patients treated with empagliflozin also had a lower risk of serious renal outcomes (chronic dialysis; renal transplantation; profound, sustained reduction in estimated GFR).

Uncomplicated genital tract infection was more common in patients treated with empagliflozin than in those treated with placebo. There was no difference between the two groups in the frequency of the following adverse effects: hypoglycemia, lower limb amputation, bone fracture, hypotension, volume depletion.

The authors concluded that in patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.

Dosage Forms/Cost

Jardiance 10 mg/$582 for #30, www.drugs.com
Jardiance 25 mg/$582 for #30, www.drugs.com

Special Considerations

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Summary/Conclusion

Sodium-glucose cotransporter 2 inhibitors lower blood glucose (0.5-1% reduction in A1c) and provide cardiovascular and renal benefits. In the state system, empagliflozin (Jardiance®) and canagliflozin (Invokana®) are the most widely used of the four available agents. Both Jardiance and Invokana are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Other indications include:

- Empagliflozin (Jardiance)
  - reduce the risk of cardiovascular death in adult patients with type 2 dm and established cardiovascular disease.

- Canagliflozin (Invokana)
  - reduce the risk of major adverse cardiovascular events in adults with type 2 dm and established cardiovascular disease
  - reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with type 2 dm and diabetic nephropathy with albuminuria greater than 300 mg/day.

The use of sodium-glucose cotransporter 2 inhibitors has also been associated with adverse events, the most common of which are genital mycotic infection, urinary tract infection, hypoglycemia (with concomitant insulin or insulin secretagogue), and volume depletion.

Recommendation

We recommend that empagliflozin (Jardiance®) be added to the formulary.

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