MEDXCHANGE LIVE™ SPECIAL EDITION 2

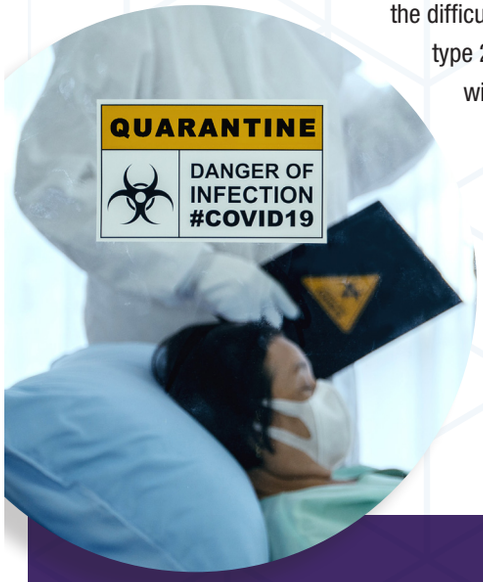
Management of Patients with **TYPE 2 DIABETES** and **DIABETIC KIDNEY DISEASE** During the **CORONAVIRUS PANDEMIC**

Patients with Type 2 Diabetes and Diabetic Kidney Disease: Likelihood of Serious Complications from COVID-19

Compared with the general population, patients with type 2 diabetes do not appear to be at an increased risk of contracting coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1–2] Although diabetic patients are considered to be at higher risk of contracting infections due to immune dysfunctions, these remain primarily bacterial and fungal in nature.[3–4] Viral infections, such as seasonal flu, are as frequent in patients with diabetes as they are in the general population, although diabetes is a risk factor for developing more severe or potentially critical forms of viral infections.[5]

Data collected from the epidemics of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) have shown that diabetic patients are at increased risk for developing severe and fatal forms of viruses; these facts have also been demonstrated during the COVID-19 pandemic.[1,6–7] Therefore, the difficulty faced by patients with type 2 diabetes, and associated with COVID-19, is primarily the occurrence of a more serious disease course, with worsening outcomes, and significant complications, but not a greater chance of contracting the virus.[2]

> The risk of diabetics contracting COVID-19 is the same as the general population



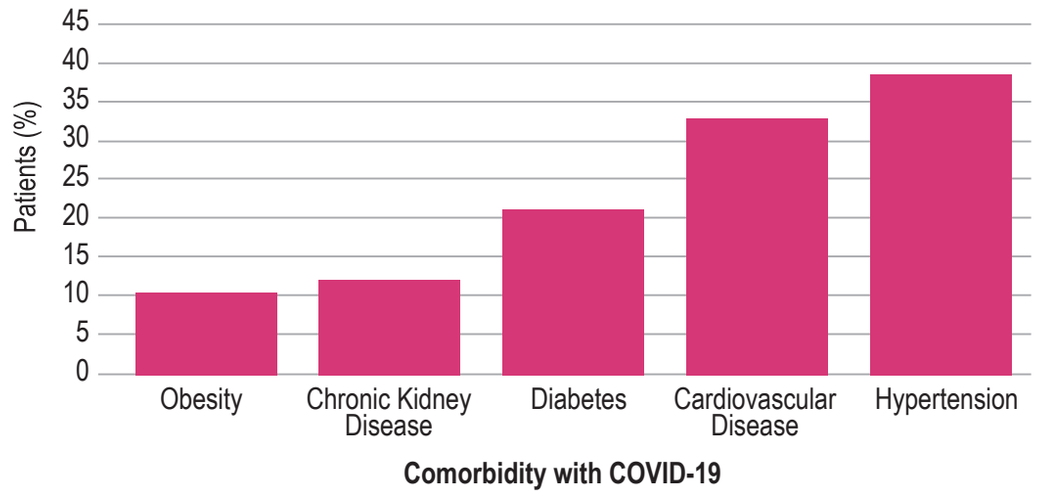
Diabetic patients clearly appear to be at increased risk of serious disease, with multiple datasets demonstrating that patients with diabetes have much higher rates of serious complications and death versus patients without diabetes.[2] A diabetes prevalence rate exceeding 50% has been reported in patients from the United States admitted to the ICU for a serious or critical form of COVID-19.[8] According to Chinese data of more than 70,000 cases, the overall mortality linked to COVID-19 was 2.3% compared with over three times that rate (7.3%) for patients with diabetes.[9] In the study from Guo and colleagues, diabetic patients died much more often than patients without diabetes (10.8% versus 3.6%, respectively),[10] and it has been reported that the risk of a fatal outcome from COVID-19 is upwards of 50% higher in patients with diabetes.[11]

Through data such as these, it has been established that diabetes is a risk factor for developing severe and critical forms of COVID-19 in patients that contract the virus who require hospitalization, necessitating the use of mechanical ventilation, and associated with high mortality rates. [1–2,6–7] Diabetic patients with diabetic kidney disease (DKD) often have a chronic systemic inflammation contributing to the immunosuppressed state that may lead to infectious complications, which accounts for the morbidity and mortality rates associated with patients with DKD and type 2 diabetes.[12] Therefore, patients with type 2 diabetes and DKD are even more likely to be affected nega-

tively by COVID-19.[12]

Chronic kidney disease affects 8% to 16% of the worldwide population, with diabetes mellitus being the most common cause. DKD leads to multiple complications including end-stage renal disease (ESRD), cardiovascular disease, infection, and death.[13-15] Outside of COVID-19, DKD is associated with most of the excess of all-cause and cardiovascular mortality in patients with diabetes.[12] Having heart disease or other complications, such as DKD, in addition to type 2 diabetes, could worsen the chance of becoming seriously ill from COVID-19, like other viral infections, because the body's ability to fight off an infection is compromised.[2] Therefore, the more comorbidities a patient with type 2 diabetes has, including DKD, the higher are his or her chances of suffering serious complications from COVID-19.[2]

Common Comorbidities in Patients with COVID-19



Adapted from Orioli, et al. 2020.[1]

Diabetes is among the most frequently reported comorbidities in patients infected with COVID-19.[1] In addition, obesity, the main risk factor for type 2 diabetes, is more common in patients with critical forms of COVID-19 requiring invasive mechanical ventilation.[1] Common comorbidities have been reported in hospitalized patients), with the mean prevalence of diabetes being approximately 25%, along with obesity (10%), Chronic Kidney Disease or DKD (12%), cardiovascular disease (33%), and hypertension (39%).[1,16] Therefore, the fatality rate for COVID-19 is reported to be elevated among those with such preexisting comorbid conditions (10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, and 6.0% for hypertension).[17]

In general, there is no reason to conclude that COVID-19 will pose a difference in risk between diabetes types; the risk is associated with age, comorbidities, and level of diabetes management.[2] Patients who have diabetes-related health problems are likely to have worse outcomes if they contract COVID-19 compared with patients with diabetes who are otherwise healthy.[2] Therefore, the COVID-19 pandemic represents a real threat for patients with diabetes with comorbidities such as hypertension, and cardiovascular, renal, or hepatic impairment.[18–19]

Diabetic patients are at an increased risk of serious complications from COVID-19

For millions of patients struggling with lipid management,[1] you can help

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NEXLETOL:
Oral, once-daily, nonstatin

In clinical trials, NEXLETOL delivered:

- **18% mean reduction in LDL-C** (compared to placebo) when added to maximally tolerated statin dose ($P<0.001$)[2]*
- Incidence of **skeletal muscle adverse events comparable to placebo**[2]

For more information about NEXLETOL, visit NEXLETOLHCP.com

INDICATION

NEXLETOL is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.
Limitations of Use: The effect of NEXLETOL on cardiovascular morbidity and mortality has not been determined.

IMPORTANT SAFETY INFORMATION

Dosage Form and Quantity: NEXLETOL is available as an oral tablet containing 180 mg of bempedoic acid, taken once a day with or without food.

Contraindications: None.

Warnings and Precautions: *Hyperuricemia:* NEXLETOL may increase blood uric acid levels. Hyperuricemia may occur early in treatment and persist throughout treatment, and may lead to the development of gout, especially in patients with a history of gout.
Tendon Rupture: NEXLETOL is associated with an increased risk of tendon rupture, most commonly involving the biceps tendon, rotator cuff, or Achilles tendon. Tendon rupture occurred within weeks to months of starting NEXLETOL. Tendon rupture may occur more frequently in patients over 60 years of age, patients taking corticosteroid or fluoroquinolone drugs, patients with renal failure and patients with previous tendon disorders.

Adverse Events: In clinical trials, the most commonly reported adverse events were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Events reported less frequently, but still more often than in placebo, included benign prostatic hyperplasia and atrial fibrillation.

Laboratory Tests: NEXLETOL was associated with persistent changes in laboratory tests within the first four weeks of treatment, including increases in creatinine and blood urea nitrogen, decreases in hemoglobin and

IMPORTANT SAFETY INFORMATION (cont.)

leukocytes, increases in platelet counts, increases in liver enzymes (AST and/or ALT), and increases in creatine kinase. Laboratory abnormalities generally did not require medical intervention. Laboratory test values generally returned to baseline following discontinuation of treatment.

Drug Interactions:
Simvastatin and Pravastatin: Concomitant use results in increased concentrations and increased risk of simvastatin or pravastatin-related myopathy. Use with greater than 20 mg of simvastatin or 40 mg of pravastatin should be avoided.

Special Populations: It is not recommended that NEXLETOL be taken during breastfeeding. A pregnant patient should consult with their healthcare provider about whether to continue treatment with NEXLETOL during the pregnancy. The safety and efficacy of NEXLETOL have not been established in patients under the age of 18. Patients over 65 accounted for nearly 60% of patients in clinical trials. No adjustments in dosing are required for age, or for patients with mild or moderate renal or hepatic impairment.

NEXLETOL is available only by prescription.

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or ESPERION at 833-377-7633 (833 ESPRMED).

Please see adjacent Brief Summary.

*LDL-C changes from baseline (LS mean) in CLEAR Harmony: NEXLETOL: -17% (n=1,488); placebo: +2% (n=742).[2]

CLEAR Harmony (Study 1) was a 52-week, randomized, double-blind, Phase 3 trial in 2,230 patients randomized 2:1 to receive NEXLETOL (n=1,488) or placebo (n=742). CLEAR Harmony included patients aged ≥18 years with fasting LDL-C ≥70 mg/dL, and high-risk patients with ASCVD and/or HeFH. NEXLETOL was added to whatever patient's maximally tolerated statin dose was, either alone or with other lipid-lowering therapies. Primary endpoint was general safety, which included adverse events, clinical safety laboratories, physical examinations, vital signs, and electrocardiogram. Secondary endpoint was % change from baseline to Week 12 in LDL-C.[3,4]

LDL-C=low-density lipoprotein cholesterol; LS=least squares; ASCVD=atherosclerotic cardiovascular disease; HeFH=heterozygous familial hypercholesterolemia.

References: 1. Wong ND, Young D, Zhao Y, et al. Prevalence of the American College of Cardiology/American Heart Association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US adults using the National Health and Nutrition Examination Survey 2011-2012. *J Clin Lipidol*. 2016;10(5):1109-1118. **2.** NEXLETOL. Prescribing information. ESPERION Therapeutics, Inc.; 2020. **3.** Data on file. CSR 1002-040. October 2018. **4.** Ray KK, Bays HE, Catapano AL, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. *N Engl J Med*. 2019;380(11):1022-1032.

ESPERION®

NEXLETOL™ (bempedoic acid) tablets

NEXLETOL™ (bempedoic acid) tablets
Prescription Only
Professional Brief Summary. Please consult package insert for full Prescribing Information.

INDICATIONS AND USAGE

NEXLETOL is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.
Limitations of Use: The effect of NEXLETOL on cardiovascular morbidity and mortality has not been determined.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Hyperuricemia: NEXLETOL inhibits renal tubular OAT2 and may increase blood uric acid levels. In clinical trials, 26% of NEXLETOL-treated patients with normal baseline uric acid values (versus 9.5% placebo) experienced hyperuricemia one or more times, and 3.5% of patients experienced clinically significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). Increases in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment. After 12 weeks of treatment, the mean placebo-adjusted increase in uric acid compared to baseline was 0.8 mg/dL for patients treated with NEXLETOL. Elevated blood uric acid may lead to the development of gout. Gout was reported in 1.5% of patients treated with NEXLETOL and 0.4% of patients treated with placebo. The risk for gout events was higher in patients with a prior history of gout (11.2% NEXLETOL versus 1.7% placebo), although gout also occurred more frequently than placebo in patients treated with NEXLETOL who had no prior gout history (1.0% NEXLETOL versus 0.3% placebo).
Advise patients to contact their healthcare provider if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.
Tendon Rupture: NEXLETOL is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.5% of patients treated with NEXLETOL versus 0% of placebo-treated patients and involved the rotator cuff (the shoulder), biceps tendon, or Achilles tendon. Tendon rupture occurred within weeks to months of starting NEXLETOL. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders.
Discontinue NEXLETOL immediately if the patient experiences rupture of a tendon. Consider discontinuing NEXLETOL if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their healthcare provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.

ADVERSE REACTIONS

The data described below reflect exposure to NEXLETOL in two placebo-controlled trials that included 2009 patients treated with NEXLETOL for 52 weeks (median treatment duration of 52 weeks). The mean age for NEXLETOL-treated patients was 65.4 years, 29% were women, 3% were Hispanic, 95% White, 3% Black, 1% Asian, and 1% other races. All patients received NEXLETOL 180 mg orally once daily plus maximally tolerated statin therapy alone or in combination with other lipid-lowering therapies. At baseline, 97% of patients had clinical atherosclerotic cardiovascular disease (ASCVD) and about 4% had a diagnosis of heterozygous familial hypercholesterolemia (HeFH). Patients on simvastatin 40 mg/day or higher were excluded from the trials.
Adverse reactions led to discontinuation of treatment in 11% of NEXLETOL-treated patients and 8% of placebo-treated patients. The most common reasons for NEXLETOL treatment discontinuation were muscle spasms (0.5% versus 0.3% placebo), diarrhea (0.4% versus 0.1% placebo), and pain in extremity (0.3% versus 0.0% placebo). Adverse reactions reported in at least 2% of NEXLETOL-treated patients and more frequently than in placebo-treated patients are shown in Table 1.

Table 1. Adverse Reactions (≥ 2% and Greater than placebo) in NEXLETOL-Treated Patients with ASCVD and HeFH (Studies 1 and 2)

Adverse Reaction	NEXLETOL + Statin and ± Other Lipid Lowering Therapies (N = 2009) %	Placebo (N = 999) %
Upper respiratory tract infection	4.5	4.0
Muscle spasms	3.6	2.3
Hyperuricemia[a]	3.5	1.1
Back pain	3.3	2.2
Abdominal pain or discomfort[b]	3.1	2.2
Bronchitis	3.0	2.5
Pain in extremity	3.0	1.7
Anemia	2.8	1.9
Elevated liver enzymes[c]	2.1	0.8

[a] Hyperuricemia includes hyperuricemia and blood uric acid increased.
[b] Abdominal pain or discomfort includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.
[c] Elevated liver enzymes includes AST increased, ALT increased, hepatic enzyme increased, and liver function test increased.

Tendon Rupture: NEXLETOL was associated with an increased risk of tendon rupture, occurring in 0.5% of NEXLETOL-treated patients versus 0% of placebo-treated patients.
Gout: NEXLETOL was associated with an increased risk of gout, occurring in 1.5% of NEXLETOL-treated patients versus 0.4% of placebo-treated patients.
Benign Prostatic Hyperplasia: NEXLETOL was associated with an increased risk of benign prostatic hyperplasia (BPH) or prostatomegaly in men with no reported history of BPH, occurring in 1.3% of NEXLETOL-treated patients versus 0.1% of placebo-treated patients. The clinical significance is unknown.
Atrial Fibrillation: NEXLETOL was associated with an imbalance in atrial fibrillation, occurring in 1.7% of NEXLETOL-treated patients versus 1.1% of placebo-treated patients.
Laboratory Tests: NEXLETOL was associated with persistent changes in multiple laboratory tests within the first 4 weeks of treatment. Laboratory test values returned to baseline following discontinuation of treatment.
Increase in Creatinine and Blood Urea Nitrogen: Overall, there was a mean increase in serum creatinine of 0.05 mg/dL compared to baseline with NEXLETOL at Week 12. Approximately 3.8% of patients treated with NEXLETOL had blood urea nitrogen values that doubled (versus 1.5% placebo), and about 2.2% of patients had creatinine values that increased by 0.5 mg/dL (versus 1.1% placebo).
Decrease in Hemoglobin and Leukocytes: Approximately 5.1% of patients (versus 2.3% placebo) had decreases in hemoglobin levels of 2 or more g/dL and below the lower limit of normal on one or more occasion. Anemia was reported in 2.8% of patients treated with NEXLETOL and 1.9% of patients treated with placebo. Hemoglobin decrease was generally asymptomatic and did not require medical intervention. Decreased leukocyte count was also observed. Approximately 9.0% of NEXLETOL-treated patients with normal baseline leukocyte count had a decrease to less than the lower limit of normal on one or more occasion (versus 6.7% placebo). Leukocyte decrease was generally asymptomatic and did not require medical intervention. In clinical trials, there was a small imbalance in skin or soft tissue infections, including cellulitis (0.8% versus 0.4%), but there was no imbalance in other infections.
Increase in Platelet Count: Approximately 10.1% of patients (versus 4.7% placebo) had increases in platelet counts of 100×10^9/L or more on one or more occasion. Platelet count increase was asymptomatic, did not result in increased risk for thromboembolic events, and did not require medical intervention.
Increase in Liver Enzymes: Increases in hepatic transaminases (AST and/or ALT) were observed with NEXLETOL. In most cases, the elevations were transient and resolved or improved with continued therapy or after discontinuation of therapy. Increases to more than 3× the upper limit of normal (ULN) in AST occurred in 1.4% of patients treated with NEXLETOL versus 0.4% of placebo patients, and increases to more than 5× ULN occurred in 0.4% of NEXLETOL-treated versus 0.2% of placebo-treated patients. Increases in ALT occurred with similar incidence between NEXLETOL- and placebo-treated patients. Elevations in transaminases were generally asymptomatic and not associated with elevations ≥2× ULN in bilirubin or with cholestasis.
Increase in Creatine Kinase: Approximately 1.0% of patients (versus 0.6% placebo) had elevations of CK levels of 5 or more times the normal value on one or more occasions, and 0.4% of patients (versus 0.2% placebo) had elevations of CK levels of 10 or more times.

DRUG INTERACTIONS

Simvastatin: Concomitant use of NEXLETOL with simvastatin causes an increase in simvastatin concentration and may increase the risk of simvastatin-related myopathy. Avoid concomitant use of NEXLETOL with simvastatin greater than 20 mg.
Pravastatin: Concomitant use of NEXLETOL with pravastatin causes an increase in pravastatin concentration and may increase the risk of pravastatin-related myopathy. Avoid concomitant use of NEXLETOL with pravastatin greater than 40 mg.

USE IN SPECIFIC POPULATIONS

Pregnancy: Discontinue NEXLETOL when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.
There are no available data on NEXLETOL use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, bempedoic acid was not teratogenic in rats and rabbits when administered at doses resulting in exposures up to 11 and 12 times, respectively, the human exposures at the maximum clinical dose, based on AUC. NEXLETOL decreases cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol; therefore, NEXLETOL may cause fetal harm when administered to pregnant women based on the mechanism of action. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.
The estimated background risk of major birth defects and 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.
Data
Animal Data
Bempedoic acid was not teratogenic when given orally at doses of 60 and 80 mg/kg/day, resulting in 11 and 12 times the systemic exposure in humans at the maximum recommended human dose (MRHD) of 180 mg to pregnant rats and rabbits, respectively. In an embryofetal development study in rats, bempedoic acid was given orally to pregnant rats at 10, 30, and 60 mg/kg/day during the period of organogenesis from gestation day 6 to 17. There were increases in the incidence of non-adverse fetal skeletal variations (bent long bones and bent scapula and incomplete ossification) at doses ≥ 10 mg/kg/day (less than the clinical exposure) in the absence of maternal toxicity. At maternally toxic doses, bempedoic acid caused decreases in the numbers of viable fetuses, increases in post-implantation loss, and increased total resorptions at 60 mg/kg/day (11 times MRHD) and reduced fetal body weight at ≥ 30 mg/kg/day (4 times the MRHD). No adverse development effects were observed when bempedoic acid was given to pregnant rabbits during the period of organogenesis (gestation day 6 to 18) at doses up to 80 mg/kg/day (12 times MRHD).
In a pre- and post-natal development study in pregnant rats given oral doses of bempedoic acid at 5, 10, 20, 30 and 60 mg/kg/day throughout pregnancy and lactation (gestation day 6 to lactation day 20), there were adverse effects on delivery in the presence of maternal toxicity, including: increases in stillborn pups, reductions in numbers of live pups, pup survival, pup growth and slight delays in learning and memory at ≥ 10 mg/kg/day (at exposures equivalent to the MRHD).
Lactation: There is no information regarding the presence of NEXLETOL in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. NEXLETOL decreases cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant. Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with NEXLETOL.
Pediatric Use: The safety and effectiveness of NEXLETOL have not been established in pediatric patients.
Geriatric Use: Of the 3009 patients in clinical trials of NEXLETOL, 1753 (58%) were 65 years and older, while 478 (16%) were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

03/20 US-NXTL-2000177

Renal Damage in COVID-19 Patients with Type 2 Diabetes

The prevalence of diabetes in patients with severe COVID-19 is higher than the 6% prevalence observed in the general adult population.[1] Diminished immune defenses and other renal-related factors make diabetic patients more prone to certain infections.[12] Therefore, the COVID-19 pandemic will surely more heavily affect patients with renal-related illnesses, such as DKD.[12]

Acute kidney injury (AKI) is a relatively common finding among patients hospitalized with and dying from COVID-19 disease.[20] AKI has been strongly linked to the occurrence of respiratory failure in patients with COVID-19, and it was rarely a severe disease among patients not requiring mechanical ventilation.[20] The development of AKI in patients hospitalized for COVID-19 disease conferred a poor prognosis.[20]

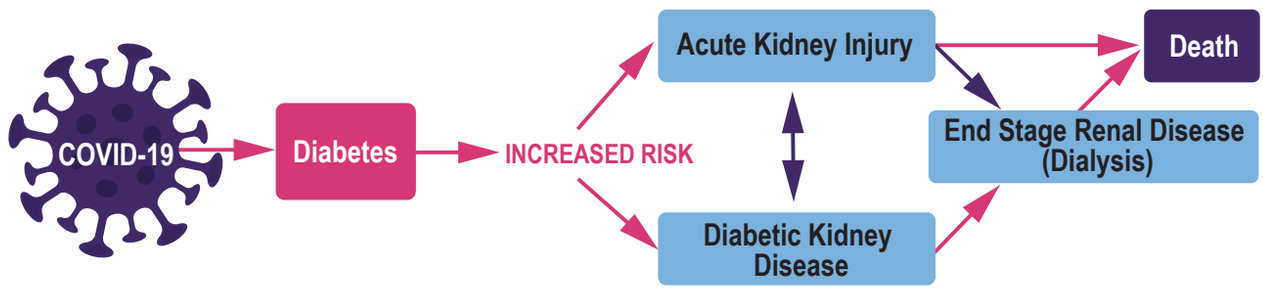
There is a strong association between AKI and the development of chronic kidney disease (CKD) and ESRD.[21] DKD is one of the main microvascular complications associated with diabetes.[21] It has been shown that diabetes is an independent risk factor for AKI.[22] The incidence of AKI is higher in patients with diabetes, even without precipitating events such as COVID-19.[21] Risk factors for DKD include higher uric acid levels, increased age and BMI, smoking history, lower total cholesterol level, history of diabetic retinopathy, high blood pressure, higher level of glycated hemoglobin A1c, and increased HDL cholesterol, triglycerides, and eGFR.[23–24]

It is known that COVID-19 targets respiratory cells; however, other organs seem to be affected by the virus, with the kidneys being an organ system with high a vulnerability to damage, according to the relationship with angiotensin-converting enzyme 2 (ACE2) expression.[5,20] To date, the direct mechanism of kidney involvement in COVID-19 is unclear, but mechanisms that include a cytokine storm syndrome through sepsis pathways, or direct viral renal tubular cells injury, have been suggested.[12,25] At present, the main expression of renal damage in COVID-19 patients appears to be acute; however, some cases of macroalbuminuria/proteinuria and or haematuria may be associated with observed endothelial dysfunction seen in the kidneys.[12]

Diabetes predisposes COVID-19 patients to a more severe renal sequelae

Despite the mechanisms being unclear, it is understood that during the COVID-19 pandemic, a worsening of DKD may be observed, leading patients to progress to a more severe stage of DKD, AKI, or even to ESRD (renal replacement therapies/dialysis), or death.[12] Beyond immune system impairment, if a patient with type 2 diabetes and DKD is infected with COVID-19, increased attention must be paid to uremic state, oxidative stress status, and accumulation of oxidative products.[12]

COVID-19 and Diabetes: Increased Risk of DKD, AKI, ESRD, and Death



Adapted from Orioli, et al. 2020.

Effective Management of Type 2 Diabetes and Diabetic Kidney Disease During the Coronavirus Pandemic Lowers Risk of Severe Disease

Patients with unmanaged type 2 diabetes and fluctuating, or above-target blood sugars, remain at risk for a number of diabetes-related complications. Viral infections, such as COVID-19, can cause glucose levels to rise along with the symptoms of the virus, leading to increased inflammation of the respiratory tract and increased diabetic complications.[2,26] According to the American Diabetes Foundation, if patients with type 2 diabetes have unmanaged diabetes with fluctuating blood sugars, they are generally at an increased risk of becoming seriously ill from COVID-19 because the body's ability to fight off an infection is compromised if diabetes is uncontrolled.[2] With effective management of type 2 diabetes, the risk of getting severely sick from COVID-19 is about the same as that which appears in the general patient population.[2]

Effective blood-glucose management is tantamount for avoiding a worsening of renal function in diabetic patients with CKD during the COVID-19 pandemic

The first step in treating type 2 diabetic and DKD patients with COVID-19 is to treat and control diabetes through blood glucose control and, if needed, to control hypertension, in an effort to delay or prevent kidney dysfunction and other complications associated with DKD.[27] Due to the damaging effects of hyperglycemia on immunity, strict monitoring and control of blood glucose must be part of the management of diabetic patients with COVID-19.[1] A study showed that well-controlled blood glucose (maintaining levels between 0.70 g/L to 1.8 g/L) in type 2 diabetic patients with COVID-19 was associated with reduced mortality and reduction in the development of Acute Respiratory Distress Syndrome and AKI.[28] In these patients, optimal management of DKD is important and should include treatment of albuminuria, discontinuation of potential nephrotoxins (for example, nonsteroidal anti-inflammatory drugs), and dosage adjustments for the concomitant use of certain drugs (for example, many antibiotics and oral hypoglycemic agents).[13,29] Patients with DKD will also require monitoring for possible additional complications, such as hyperkalemia, metabolic acidosis, hyperphosphatemia, vitamin D deficiency, secondary hyperparathyroidism, and anemia.[13] Ideally, hemoglobin A1C should be controlled as strictly as possible, and eGFR and urine albumin-to-creatinine ratio should be monitored routinely for progression, adding medication management with available treatments if necessary.[30] Other factors, such as blood pressure control, smoking cessation, weight loss, a low protein diet, and cholesterol control, are also important key steps in the management of patients with DKD with type 2 diabetes,[29-34] especially in those patients with COVID-19. Effective management of diabetes and cardiovascular risk factors are essential to reduce the risk of morbidity and mortality in patients with DKD.[35]

Patients with type 2 diabetes and DKD who have not yet been infected with the COVID-19 virus should intensify their metabolic control as needed as a means of primary prevention of severe complications of COVID-19 disease.[36] This includes continuation of strict control of blood pressure and lipids.[36] Patients with type 2 diabetes and DKD often have other components of metabolic syndrome, including hypertension and dyslipidaemia, and in those patients, continuation with an appropriate antihypertensive and lipid-lowering regimen is very important.[36] Antihypertensive medications that interact with the renin-angiotensin-aldosterone system do not need to be discontinued in those patients taking them.[1] Intensified multifactorial interventions, including blood pressure and glycemic control, along with renin-angiotensin aldosterone system (RAAS) blockade and smoking cessation, remain the standard of care to delay the development of DKD and progression to ESRD.[37,38] Due to the increased

cardiovascular risk associated with DKD and type 2 diabetes, sodium glucose co-transporter 2 inhibitors (SGLT-2) inhibitors may be considered as preferred add-on therapy for most patients.[39,40] The blood pressure-lowering effect of SGLT-2 inhibitors is maintained in people with DKD and could potentially reduce renal burden and offer complementary effects with antihypertensives in patients who do not have COVID-19.[41]

For patients with type 2 diabetes and DKD, regimented and strict blood glucose management is key to improving the odds of having an uncomplicated recovery from COVID-19.[42] Managing blood glucose levels as optimally as possible, staying hydrated, and getting rest helps support immune function and is important for patients with type 2 diabetes and DKD to improve outcomes.[42]

Telemedicine and Support Groups in the Management of Type 2 Diabetes and Diabetic Kidney Disease During the Pandemic

The coronavirus pandemic has placed an additional psychological and safety burden on patients with underlying health conditions that are associated with poor outcomes, such DKD, type 2 diabetes, and high blood pressure.[43] Identification and treatment of type 2 diabetes and DKD complications helps improve quality-of-life and improves patient outcomes, especially during the COVID-19 pandemic.[31] COVID-19 has changed the paradigm of routine doctor office visits to telemedicine and has made going out of the home for picking up medications, getting blood drawn, or dialysis treatment, to be thought of as not life sustaining, but as a risk for exposure to the virus.[43]

> Patient-readiness plays a significant role in the effectiveness of telemedicine appointments

Wherever and whenever possible, remote patient consultations and visits should be used to reduce exposure for these patients who are vulnerable to serious complications associated with COVID-19.[36] Telemedicine should be used to continue regular reviews and virtual self-management education programs and especially to ensure patients are adherent to therapy.[36] This is especially true for patients with type 2 diabetes, because it is known that sticking to a regimented and strict blood glucose management program as optimally as possible is key to improving outcomes during the pandemic for these patients.[36,42]

Patients with type 2 diabetes and DKD should be informed during Telemedicine visits to pay very close attention to their own health for potential COVID-19 symptoms, including fever, dry cough, shortness of breath, chills, muscle pain, headache, sore throat, and new loss of taste or smell, and to contact a physician immediately if such symptoms associated with COVID-19 develop.[2]

Things to tell patients they should have available for telehealth appointments:[2]

- Have Glucose Reading Available
- Have Ketone Reading Available
- Keep Track Of Your Fluid Consumption To Report
- Clear List Of Any Symptoms (For Example: Nausea, Fever, Muscle Aches)
- List Of Questions On How To Best Manage Diabetes

Importance of Educating Patients with Type 2 Diabetes and Diabetic Kidney Disease about the Risk of Coronavirus

The COVID-19 pandemic challenges both patients and physicians to ensure continuity of care and to prevent the risks related to various pre-existing chronic conditions.[1] Patients with type 2 diabetes need to understand that in general, patients with diabetes are more likely to experience severe symptoms and complications when infected with a virus, but that the risk of suffering from more serious complications from COVID-19 is likely to be lower if their type 2 diabetes is well-managed.[2]

Patients with type 2 diabetes should be encouraged to strictly follow general advice from the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and state and local governments about hand washing and physical distancing.[36] Some specific reminders to share with patients with type 2 diabetes to avoid COVID-19 include compulsive hand washing, getting a flu shot, being careful to avoid others with signs of respiratory illness, and keeping a social distance and wearing a face mask when out of the home.[26] They could also be told to use a humidifier if possible, because a humid environment is beneficial to keep nasal passages from drying out.[26] All of the standard precautions to avoid infection that have been widely reported have become even more important to patients with underlying conditions when dealing with a pandemic, such as COVID-19.[2]

> Diabetic patients with CKD must be extra vigilant to CDC and WHO recommendations for prevention during the COVID-19 pandemic

Regarding glucose control, which becomes more of a challenge for patients with type 2 diabetes when they become ill, these patients need to be told that this is very important during the pandemic because when glucose levels are elevated, the human body provides the virus with additional fuel to grow off of and high blood glucose levels make symptoms much worse.[6] Therefore, sick day management should be reviewed with patients with type 2 diabetes—preparing for a sick day before exposure to the virus occurs can make it easier for patients.[2]

SICK DAY PLAN

TAKE YOUR MEDICATIONS AND INSULIN

Do not skip your diabetes pills even if you feel too sick to eat. If you vomit up the pills or are not eating, call your healthcare provider. Do not take your pills again.

If you are on insulin, you may have to take extra insulin to bring down the higher blood glucose levels. Adjust your insulin according to your sick day plan. Do not skip your insulin even if you are not eating. Talk with your doctor about your insulin doses and your sick day plan.

Do not take over-the-counter medications, such as those for colds or the flu, without first checking with your healthcare provider. They can cause your blood sugar to go up.

EATING AND DRINKING WHEN YOU ARE SICK

You may not feel like eating but your body needs fuel to help you get better. Try to eat or drink 45 grams of carbohydrates (CHO) every hour to keep your blood sugar stable.

EACH OF THESE IS 15 GRAMS OF CHO

- 1/2 cup of fruit juice
- 1 cup of soup
- 1 cup melon
- 1/4 cup gelatin
- 1 slice toast
- 1 cup milk
- 1 double ice pop
- 1 cup sports drink
- 1/2 cup oatmeal

CALL YOUR DOCTOR FOR

- Blood sugar levels less than 70 mg/dL
- Blood sugar levels more thann 250 mg/dL for more than 2 checks
- Fever at or over 101.5 for an illness that lasts more than 24 hours
- Vomiting or diarrhea for more than 6 hours
- Moderate to large amounts of ketones in your urine for more than 6 hours
- You feel too sick to eat or drink
- Symptoms at high or low blood sugar or itaridosis

In adults who have T2D and diabetic nephropathy (ie, DKD) with albuminuria >300 mg/day,

INVOKANA® is the only SGLT2i proven to slow the progression of DKD

and reduce the risk of hospitalization for heart failure[1-4]

INVOKANA® is the only T2D therapy approved by the FDA to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults who have T2D and diabetic nephropathy with albuminuria >300 mg/day[1]

In patients with DKD* and T2D

The landmark CREDENCE trial primary composite outcome[5]:

30% RRR

- **End-stage kidney disease†**
  (dialysis, transplant, or eGFR <15)
- **Doubling of serum creatinine**
- **Renal death‡**
- **CV death**

HR=0.70 (95% CI: 0.59, 0.82); *P*=0.00001

‡There were not enough events to evaluate the risk of renal death (placebo, n=5; INVOKANA®, n=2). **INVOKANA® is not indicated to reduce the risk of renal death.**
§Prespecified secondary endpoint.

- **Reduced risk of hospitalization for heart failure[6§]**
  39% RRR‖ in hospitalization for heart failure
- **Proven safety profile in patients with an eGFR of 30 to <90[1,5]**
  Similar overall AEs with INVOKANA® vs placebo (35.1 vs 37.9 per 100 patient-years), except for DKA and male GMI. No imbalance in fracture or amputation. Hypotension incidence was 2.8% vs 1.5%, respectively

Learn more at INVOKANAhcp.com.

INDICATIONS

INVOKANA® is indicated:

- 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 >300 mg/day

INVOKANA® is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

WARNING: LOWER-LIMB AMPUTATION

- **An increased risk of lower-limb amputations associated with INVOKANA® 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 large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
- **Monitor patients receiving INVOKANA® for infection, new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.**

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®
- Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) who are being treated for glycemic control
- Patients on dialysis

Please read additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING for INVOKANA®, on the following pages.

Invokana™ (canagliflozin) tablets

AE=adverse event; CREDENCE=Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DKA=diabetic ketoacidosis; DKD=diabetic kidney disease; GMI=genital mycotic infection; HR=hazard ratio; RRR=relative risk reduction; SGLT2i=sodium-glucose co-transporter 2 inhibitor; T2D=type 2 diabetes.
eGFR is measured in mL/min/1.73 m^2.
*With albuminuria >300 mg/day.
†End-stage kidney disease was defined as dialysis for ≥30 days, kidney transplantation, or an eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days.
‖RRR was calculated using the following formula: 100 x (1–HR).

References: 1. INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Jardiance® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Farxiga® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **4.** Steglatro™ [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. **5.** Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. Supplementary appendix available at: doi:10.1056/NEJMoa1811744. **6.** Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation*. 2019;140(9):739-750.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

- **Lower-Limb Amputation:** An increased risk of lower-limb amputations associated with INVOKANA® 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 INVOKANA® 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 INVOKANA® 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 initiating, 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 for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.
- **Hypotension:** INVOKANA® causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA®, particularly in the elderly, and in patients with impaired renal function, low systolic blood pressure, or on diuretics or medications that interfere with the renin-angiotensin-aldosterone system. Before initiating INVOKANA®, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating.
- **Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA® for at least 3 days prior to surgery. Monitor for ketoacidosis and temporarily discontinue in other clinical situations known to predispose to ketoacidosis. Ensure risk factors for ketoacidosis are resolved prior to restarting therapy. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA® and seek medical attention immediately if signs and symptoms occur.
- **Acute Kidney Injury:** INVOKANA® causes intravascular volume contraction and can cause acute kidney injury. Acute kidney injury, requiring hospitalization and dialysis, has been reported. Initiation of INVOKANA® may increase serum creatinine and decrease eGFR. Before initiation, consider factors that may predispose patients to acute kidney injury. Consider temporarily discontinuing INVOKANA® in any setting of reduced oral intake or fluid losses; monitor patients for signs and symptoms of acute kidney injury. If it occurs, promptly discontinue and treat. Evaluate renal function prior to initiation and monitor periodically thereafter.
- **Urosepsis and Pyelonephritis:** Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** INVOKANA® can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be required.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Necrotizing fasciitis of the perineum, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, has been identified in postmarketing surveillance in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections, especially in uncircumcised males or patients with prior infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Prior to initiation, consider factors that contribute to fracture risk.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Co-administration with rifampin lowered INVOKANA® exposure, which may reduce the efficacy of INVOKANA®. For patients with eGFR ≥60 mL/min/1.73 m^2, if an inducer of UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA® 200 mg and who require additional glycemic control. For patients with eGFR <60 mL/min/1.73 m^2, if an inducer of UGTs is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** INVOKANA® is not recommended in pregnant women, especially during the second and third trimesters.
- **Lactation:** INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume, particularly with the 300-mg dose; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years.
- **Renal Impairment:** The efficacy and safety of INVOKANA® for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to <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 the study. Patients with renal impairment using INVOKANA® for glycemic control may be more likely to experience hypotension and may be at a higher risk for acute kidney injury. INVOKANA® is contraindicated in patients with ESKD on dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

cp-68813v4

Please read Brief Summary of full Prescribing Information, including Boxed WARNING for INVOKANA®, on the following pages.

Invokana™ (canagliflozin) tablets

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Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

 February 2020 cp-122493v2

INVOKANA®

(canagliflozin) tablets, for oral use
Brief Summary of Prescribing Information.

WARNING: LOWER LIMB AMPUTATION

- **An increased risk of lower limb amputations associated with INVOKANA 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 large, randomized, placebo-controlled trials in patients with type 2 diabetes who had established cardiovascular disease (CVD) or were at risk for CVD *[see Warnings and Precautions]*.**
- **Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs *[see Warnings and Precautions]*.**
- **Before initiating, consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers *[see Warnings and Precautions]*.**
- **Monitor patients receiving INVOKANA for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue if these complications occur *[see Warnings and Precautions]*.**

INDICATIONS AND USAGE

INVOKANA® (canagliflozin) is indicated:

- 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 > 300 mg/day.

Limitations of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions and Adverse Reactions]*.
- Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) who are being treated for glycemic control *[see Use in Specific Populations]*.
- Patients on dialysis *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA 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. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Adverse Reactions]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA 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 INVOKANA 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 initiating INVOKANA, 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 INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*.

Patients treated with INVOKANA 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 INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA 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 INVOKANA, 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 INVOKANA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA 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 INVOKANA.

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

Acute Kidney Injury: INVOKANA causes intravascular volume contraction *[see Warnings and Precautions]* and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including INVOKANA.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of INVOKANA *[see Adverse Reactions and Clinical Pharmacology (12.1) in Full Prescribing Information]*. Before initiating INVOKANA, 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 INVOKANA in the 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 INVOKANA promptly and institute treatment.

Renal function should be evaluated prior to initiation of INVOKANA and monitored periodically thereafter.

Urosepsis and Pyelonephritis: There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. 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 *[see Adverse Reactions]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

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 postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA.

Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with INVOKANA 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 INVOKANA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections: INVOKANA 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 *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Bone Fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lower Limb Amputation *[see Boxed Warning and Warnings and Precautions]*
- Hypotension *[see Warnings and Precautions]*
- Ketoacidosis *[see Warnings and Precautions]*
- Acute Kidney Injury *[see Warnings and Precautions]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Bone Fracture *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials for Glycemic Control: The data in Table 1 is derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. 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, had a mean HbA_{1C} 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).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions from Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 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%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

INVOKANA® (canagliflozin) tablets

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Placebo-Controlled Trial in Diabetic Nephropathy: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in CREDENCE, a study in patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.3) in Full Prescribing Information]*. These data reflect exposure of 2,201 patients to INVOKANA and a mean duration of exposure to INVOKANA of 137 weeks.

The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively, in CREDENCE, an outcomes study of patients with type 2 diabetes and diabetic nephropathy, with 2.6 years mean duration of follow-up *[see Clinical Studies (14.3) in Full Prescribing Information]*.

In CREDENCE, incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with INVOKANA 100 mg and placebo, respectively *[see Warnings and Precautions]*. The incidence of acute kidney injury was similar between INVOKANA 100 mg and placebo in CREDENCE *[see Warnings and Precautions]*.

In CREDENCE, the incidence of hypotension was 2.8% and 1.5% on INVOKANA 100 mg and placebo, respectively *[see Warnings and Precautions]*.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 patients to INVOKANA) were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA 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. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.2) in Full Prescribing Information]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively *[see Warnings and Precautions]*.

Table 2: CANVAS Amputations

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (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)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

	Placebo N=2903	INVOKANA 100 mg (with 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)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma: In the CANVAS trial (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and INVOKANA, 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 INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with INVOKANA 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 (Table 4) *[see Dosage and Administration (2.2) in Full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 4: 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* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	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 INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA 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 INVOKANA, respectively *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 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 INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 randomized trials evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 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 biochemical documentation of a low glucose value was obtained). In individual clinical trials of glycemic control *[see Clinical Studies (14.1) in Full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 5) *[see Warnings and Precautions]*.

Table 5: Incidence of Hypoglycemia* in Randomized Clinical Studies of Glycemic Control

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 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)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 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)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 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)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 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)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 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)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 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)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 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)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population
† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture: In the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through 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 *[see Warnings and Precautions]*.

Laboratory and Imaging Tests*: Increases in Serum Creatinine and Decreases in eGFR*: Initiation of INVOKANA 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 *[see Warnings and Precautions and Mechanism of Action (12.1) in Full Prescribing Information]*. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

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, INVOKANA 100 mg, and INVOKANA 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 INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 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 *[see Warnings and Precautions and Use in Specific Populations]*.

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 INVOKANA 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 INVOKANA 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 INVOKANA 100 mg and INVOKANA 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 INVOKANA 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 INVOKANA 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 INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 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, INVOKANA 100 mg, and INVOKANA 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) *[see Clinical Studies (14.1) in Full Prescribing Information]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 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 INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

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Postmarketing Experience: Additional adverse reactions have been identified during post-approval use of INVOKANA. 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)

DRUG INTERACTIONS

UGT Enzyme Inducers: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy.

For 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 INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA 200 mg and who require additional glycemic control.

For 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 INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

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.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

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

Limited data with INVOKANA 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 *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >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*: Disease-associated maternal and/or embryo/fetal risk*: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data: Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal

development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Lactation: Risk Summary: There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. 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, advise women that use of INVOKANA is not recommended while breastfeeding.

Data: *Animal Data*: Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (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 *[see Dosage and Administration (2.1) in Full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA 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) *[see Clinical Studies (14.1) in Full Prescribing Information]*. 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 INVOKANA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury *[see Warnings and Precautions]*.

Efficacy and safety studies with INVOKANA did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is contraindicated in patients with ESKD on dialysis *[see Contraindications and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Lower Limb Amputation: Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Boxed Warning and Warnings and Precautions]*.

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Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of INVOKANA, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical attention immediately *[see Warnings and Precautions]*.

Acute Kidney Injury: Inform patients that acute kidney injury has been reported during use of INVOKANA. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOKANA use in those settings *[see Warnings and Precautions]*.

Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKANA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions]*.

Bone Fracture: Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions]*.

Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations]*.

Laboratory Tests: Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions]*.

Missed Dose: If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Active ingredient made in Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

cp-109200v2

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COVID-19 Diabetes Plan for Medication Use

Leading health organizations, such as the WHO and the CDC, have not recommended that patients with type-2 diabetes and DKD stop any particular drug in order to decrease the chance of getting COVID-19 or making it less severe.[46] Yet, some considerations should be taken in regards to potential metabolically interfering effects of certain pharmaceutical treatments in COVID-19 positive patients with type 2 diabetes and DKD.[36]

Regular insulin therapy should not be discontinued and should be regularly carefully adjusted if necessary to reach therapeutic goals according to comorbidities, and health status.[36] It is not recommended that angiotensin converting enzyme inhibitors (ACEs) and angiotensin receptor blockers (ARBs) be stopped, unless recommended by a healthcare professional.[46] This is because discontinuing ACEs and ARBs may lead to a heart attack, stroke, or decreased kidney function.[36,46] Treatment with ACE inhibitors and angiotensin 2 receptor blockers could increase the expression of ACE2, which could accelerate the entry of the virus into the cells.[36] However, as COVID-19 might impair the protective ACE2/Mas receptor pathway and increase deleterious angiotensin-2 activity, the use of ACE inhibitors and angiotensin 2 receptor blockers could protect against severe lung injury following infection.[36] In addition, dipeptidyl peptidase-4 inhibitors should not be stopped.[36]

Control of lipid concentrations is recommended in all patients with type 2 diabetes and DKD with COVID-19.[36] Elevated hemoglobin A1c in patients with diabetes compromises immune function and makes these patients more susceptible to serious disease.[36] Therefore, these

Consideration of Potential Metabolically Interfering Effects of Drugs in COVID-19 Positive Patients with Type 2 Diabetes and DKD

Metformin	• Dehydration and lactic acidosis will probably occur if patients are dehydrated, so patients should stop taking the drug and follow sick day rules • During illness, renal function should be carefully monitored because of the high risk of DKD or AKI
Sodium-glucose-co-transporter 2 inhibitors *(canagliflozin, dapagliflozin, and empagliflozin)*	• Risk of dehydration and diabetic ketoacidosis during illness, so patients should stop taking the drugs and follow sick day rules • Patients should avoid initiating therapy during respiratory illness • Renal function should be carefully monitored for acute kidney injury
Glucagon-like peptide-1 receptor agonists *(albiglutide, dulaglutide, exenatide-extended release, liraglutide, lixisenatide, and semaglutide)*	• Dehydration is likely to lead to a serious illness so patients should be closely monitored • Adequate fluid intake and regular meals should be encouraged
Dipeptidyl peptidase-4 inhibitors *(alogliptin, linagliptin, saxagliptin, and sitagliptin)*	• These drugs are generally well tolerated and can be continued
Insulin	• Insulin therapy should not be stopped • Regular self-monitoring of blood-glucose every 2–4 hours should be encouraged, or continuous glucose monitoring • Carefully adjust regular therapy if appropriate to reach therapeutic goals according to comorbidities and health status

Adapted from Bornstein 2020.[36]

patients need intense monitoring and supportive therapy to reduce the risk of metabolic decompensation including DKA, in particular for those taking SGLT-2.[36] Screening for hyperinflammation using laboratory tests (for example, increasing ferritin, decreasing platelet counts, high-sensitivity C-reactive protein, or erythrocyte sedimentation rate) is important and may assist in identifying those patients that could use immunosuppression, with steroids, immunoglobulins, or selective cytokine blockade, to improve outcomes.[36]

In patients with type 2 diabetes and severe forms of COVID-19, metformin and SGLT-2 inhibitors should be discontinued given the associated risk of lactic acidosis and ketoacidosis, respectively.[1,36] The current recommendation is to continue renin–angiotensin–aldosterone system (RAAS) inhibitors in both diabetic and non-diabetic patients during acute COVID-19 infection.[47] Patients taking glucagon-like peptide-1 receptor agonists should be closely monitored.[36]

Differences in COVID-19 Symptoms in Patients With and Without Diabetes

A study comparing the clinical presentation between patients with diabetes (with or without comorbidities) and patients without diabetes, and COVID-19, found that the COVID-19 symptoms seem to be milder at first in patients with diabetes.[10] In addition to milder symptoms, fever was less frequent in patients with diabetes, which could unfortunately delay initial diagnosis.[10] Analysis of chest CT-scans of these patients revealed more severe pneumonia in patients with diabetes.[10] Also, patients with diabetes had more pronounced biological abnormalities, including elevated inflammatory biomarkers [eg. C-reactive protein (CRP) and interleukin 6 (IL6)], elevated tissue enzymes [eg. lactate dehydrogenase (LDH)], and clotting abnormalities (eg. elevated D-dimer).[10] Such biological abnormalities are related to severe multi-organ damage and thromboembolic events, as well as to the cytokine storm that has been described as an aggravating factor in COVID-19.[10]

Lymphopenia was also more frequent and more severe in diabetic patients.[10]

COVID-19 infection can also present with digestive symptoms such as vomiting and diarrhea, leading to dehydration.[1] Hyperglycemia may precede the symptoms of COVID-19 and predispose patients to acute metabolic complications, such as ketoacidosis and hyperosmolar coma.[1] In a study of patients with type 2 diabetes with COVID-19 (n=29), hyperglycemia was frequent over the course of the infection.[44] Another study showed that COVID-19 infection was associated with ketoacidosis in 12% of diabetic patients.[45]

COVID-19 symptomatology is different in diabetes than that which occurs in the general population

Clinical Presentaton of COVID-19 in Patients with Diabetes Compared with Non-diabetic Patients

SYMPTOM SEVERITY	Covid-19 symptoms milder at first in patients with diabetes
FEVER	Fever less frequent at first in patients with diabetes
PNEUMONIA	CT-scans revealed more sever pneumonia in patients with diabetes
BIALOGICAL ABNORMALITIES	Diabetic patients had more pronounced biological abnormalities, including elevated C-reactive protien, IL6, LDH, and D-dimer
LYMPHOPENIA	Lymphopenia was more frequent and more severe in diabetic patients

Adapted from Guo et al. 2020.[10]

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Management of Patients with **TYPE 2 DIABETES** and **DIABETIC KIDNEY DISEASE** During the **CORONAVIRUS PANDEMIC**

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