



Media contacts:

Sarah Freeman
Mobile: (215) 510-4758
sfreem21@its.jnj.com

Christina Chan
Mobile: (908) 635-2406
cchan20@its.jnj.com

Investor contacts:

Johnson & Johnson
Lesley Fishman
Office: (732) 524-3922

Christopher DeOrefice
Office: (732) 524-2955

U.S. FDA Approves INVOKANA[®] (canagliflozin) to Reduce the Risk of Heart Attack, Stroke or Cardiovascular Death in Adults with Type 2 Diabetes and Established Cardiovascular Disease

INVOKANA[®] is now the only oral diabetes treatment approved to reduce the risk of these cardiovascular events

Approval aligns with ADA and AACE treatment guidance and supports use of INVOKANA[®] across a broad range of patients

TITUSVILLE, NJ, October 30, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the U.S. Food and Drug Administration (FDA) has approved INVOKANA[®] (canagliflozin) to reduce the risk of major adverse cardiovascular (CV) events, including heart attack, stroke or death due to a cardiovascular cause in adults with type 2 diabetes (T2D) who have established CV disease. INVOKANA[®] is the first and only oral diabetes treatment approved with this indication.

“This FDA approval makes INVOKANA® the only oral type 2 diabetes treatment indicated to reduce the risk of heart attack, stroke or CV death. It is an important step forward for patients and the physicians who treat them,” said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. “Not only does INVOKANA® enable patients to control their diabetes symptoms by lowering their A1C levels, but it now also helps protect them from potentially devastating cardiovascular events.”

[Click to Tweet](#): Janssen’s oral diabetes treatment is now the first and only oral diabetes treatment to have an indication to reduce the risk of heart attack, stroke or cardiovascular death.

The [CANVAS](#) (CANagliflozin cardioVascular Assessment Study) Program evaluated the effect of INVOKANA® on CV risk in a broad population of more than 10,000 adults with T2D who had established CV disease (65 percent) or were at risk for cardiovascular disease with two or more risk factors (35 percent). Overall, treatment with INVOKANA® as compared with placebo in addition to standard of care reduced the combined risk of heart attack, stroke and CV death by 14 percent (events occurred in 26.9 vs. 31.5 participants, respectively, per 1000 patient-years; HR: 0.86; 95 percent CI: 0.75 to 0.97; $p < 0.0001$ for non-inferiority and $p = 0.0158$ for superiority). In patients with established CV disease, treatment with INVOKANA® reduced the combined risk of heart attack, stroke and CV death by 18 percent compared to placebo (events occurred in 34.1 vs. 41.3 participants, respectively, per 1000 patient-years; HR: 0.82; 95 percent CI: 0.72 to 0.95).

[Click to Tweet](#): Janssen’s oral #diabetes treatment now approved to reduce the risk of major cardiovascular (CV) events in adults with #T2D who have established CV disease.

This FDA approval builds on recent consensus reports from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) that support the use of INVOKANA® across a broad range of patients. For patients

with T2D and clinical CV disease, the ADA recommends medication management with SGLT2 (sodium-glucose cotransporter-2) inhibitors that specifically have a proven cardiovascular benefit.¹ AACE also notes that for appropriate patients, INVOKANA[®] has been shown to reduce major adverse CV events.²

“Americans living with type 2 diabetes are two to three times more likely to die from heart disease than adults without diabetes,” said Ralph DeFronzo, M.D., professor of medicine and chief of the Division of Diabetes at University of Texas, Health Diabetes Center, San Antonio.⁴ “With this approval, INVOKANA[®] now plays an even more important role in the overall treatment mix with its demonstrated ability to reduce the risk of potentially devastating cardiovascular events.”

This new indication also applies to the fixed-dose combinations of INVOKAMET[®] (canagliflozin/metformin HCl) tablets and INVOKAMET[®] XR (canagliflozin/metformin HCl extended-release) tablets.

ABOUT CANVAS

CANVAS is part of the longest, largest and broadest completed CV outcomes program of any SGLT2 inhibitor. The program evaluated the CV safety and efficacy of INVOKANA[®] relative to placebo in more than 10,000 adults with T2D who had either established CV disease or were at risk for CV disease (defined as having two or more CV risk factors). The primary endpoint was defined as major adverse CV events (MACE), composed of nonfatal heart attack, nonfatal stroke and CV death, and the secondary endpoint was defined as progression of albuminuria, beta-cell function, estimated glomerular filtration rate changes and urine albumin-to-creatinine ratio.

Each CV disease component evenly contributed to the MACE risk reduction, including nonfatal heart attack by 15 percent (HR: 0.85; 95% CI: 0.69 to 1.05), and nonfatal stroke by 10 percent (HR: 0.90; 95 percent CI: 0.71 to 1.15) and CV death by 13 percent (HR: 0.87; 95 percent CI: 0.72 to 1.06). These outcomes were broadly consistent across various patient subgroups. Overall adverse events seen in

the CANVAS Program were generally consistent with previous findings. A low, but increased risk of below-knee lower extremity amputation was seen in the CANVAS Program and is reflected in the INVOKANA[®] U.S. full Prescribing Information (PI).³ The PI also includes information on renal cell carcinoma from the CANVAS Program in the Adverse Reactions section.

INVOKANA[®] was first approved by the FDA on March 29, 2013 as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Janssen Pharmaceuticals, Inc. and its affiliates have rights to canagliflozin through a license agreement with Mitsubishi Tanabe Pharma Corporation, including in the United States.

WHAT IS INVOKANA[®]?

INVOKANA[®] is a prescription medicine used:

- along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes
- to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes who have known cardiovascular disease. INVOKANA[®] is not for people with type 1 diabetes or with diabetic ketoacidosis (increased ketones in blood or urine). It is not known if INVOKANA[®] is safe and effective in children under 18 years of age.

IMPORTANT SAFETY INFORMATION

INVOKANA[®] can cause important side effects, including:

- **Amputations.** INVOKANA[®] may increase your risk of lower-limb amputations. Amputations mainly involve removal of the toe or part of the foot; however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body. You may be at a higher risk of lower-limb amputation if you: have a history of amputation, have heart disease or are at risk for heart disease, have had blocked or narrowed blood vessels (usually in leg), have damage to the nerves (neuropathy) in the leg, or have had diabetic foot ulcers or sores. **Call your doctor right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot.** Your doctor may decide to stop your INVOKANA[®] for a while if you have any of these signs or symptoms. Talk to your doctor about proper foot care

- **Dehydration.** INVOKANA[®] can cause some people to become dehydrated (the loss of too much body water), which may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). You may be at higher risk of dehydration if you have low blood pressure, take medicines to lower your blood pressure (including diuretics [water pills]), are on a low sodium (salt) diet, have kidney problems, or are 65 years of age or older
- **Vaginal yeast infection.** Women who take INVOKANA[®] may get vaginal yeast infections. Symptoms include: vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), or vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKANA[®] may get a yeast infection of the skin around the penis. Symptoms include: redness, itching, or swelling of the penis; rash of the penis; foul-smelling discharge from the penis; or pain in the skin around penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis.

Do not take INVOKANA[®] if you:

- are allergic to canagliflozin or any of the ingredients in INVOKANA[®]. Symptoms of allergic reaction may include: rash; raised red patches on your skin (hives); or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
- have severe kidney problems or are on dialysis

Before you take INVOKANA[®], tell your doctor if you have a history of amputation; heart disease or are at risk for heart disease; blocked or narrowed blood vessels (usually in leg); damage to the nerves (neuropathy) of your leg; diabetic foot ulcers or sores; kidney problems; liver problems; history of urinary tract infections or problems with urination; are on a low sodium (salt) diet; are going to have surgery; are eating less due to illness, surgery, or change in diet; pancreas problems; drink alcohol very often (or drink a lot of alcohol in short-term); ever had an allergic reaction to INVOKANA[®]; or have other medical conditions.

Tell your doctor if you are or plan to become pregnant, are breastfeeding, or plan to breastfeed. INVOKANA[®] may harm your unborn baby. If you become pregnant while taking INVOKANA[®], tell your doctor right away. INVOKANA[®] may pass into your breast milk and may harm your baby. Do not breastfeed while taking INVOKANA[®].

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take diuretics (water pills), rifampin (used to treat or prevent tuberculosis), phenytoin or phenobarbital (used to control seizures),

ritonavir (Norvir[®], Kaletra[®] – used to treat HIV infection), or digoxin (Lanoxin[®] – used to treat heart problems).

Possible Side Effects of INVOKANA[®]

INVOKANA[®] may cause serious side effects, including:

- **Ketoacidosis** (increased ketones in your blood or urine). **Ketoacidosis has happened in people who have type 1 or type 2 diabetes**, during treatment with INVOKANA[®]. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with INVOKANA[®] even if your blood sugar is less than 250 mg/dL. Stop taking INVOKANA[®] and call your doctor right away if you get any of the following symptoms: nausea, vomiting, stomach-area pain, tiredness, or trouble breathing**
- **Kidney problems.** Sudden kidney injury has happened to people taking INVOKANA[®]. Talk to your doctor right away if you: 1) reduce the amount of food or liquid you drink, if you are sick, or cannot eat or 2) you start to lose liquids from your body from vomiting, diarrhea, or being in the sun too long
- **A high amount of potassium in your blood (hyperkalemia)**
- **Serious Urinary Tract Infections:** may lead to hospitalization and have happened in people taking INVOKANA[®]. Tell your doctor if you have signs or symptoms of a urinary tract infection such as: burning feeling while urinating, need to urinate often or right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Some people may also have high fever, back pain, nausea, or vomiting
- **Low blood sugar (hypoglycemia).** If you take INVOKANA[®] with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take INVOKANA[®]

Signs and symptoms of low blood sugar may include: headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, shaking, or feeling jittery.

- **A rare but serious bacterial infection that destroys the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take INVOKANA[®]. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around your anus and genitals:** pain or tenderness, swelling, or redness of the skin (erythema).

Serious allergic reaction. If you have any symptoms of a serious allergic reaction, stop taking INVOKANA[®] and call your doctor right away or go to the nearest hospital emergency room.

Broken Bones (fractures): Bone fractures have been seen in patients taking INVOKANA[®]. Talk to your doctor about factors that may increase your risk of bone fracture.

The most common side effects of INVOKANA[®] include: vaginal yeast infections and yeast infections of the penis; changes in urination, including urgent need to urinate more often, in larger amounts, or at night.

Tell your doctor if you have any side effect that bothers you or that does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Janssen Scientific Affairs, LLC at 1-800-526-7736.

Please click here for full [Product Information](#), including **Boxed Warning**, and [Medication Guide](#) for INVOKANA[®].

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About the Janssen Pharmaceutical Companies

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science.

We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us on Twitter at [@JanssenUS](https://twitter.com/JanssenUS). Janssen Pharmaceuticals, Inc. and Janssen Research & Development, LLC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private

Securities Litigation Reform Act of 1995 regarding the potential benefits and further development of canagliflozin. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Reports on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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¹ Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018 Sep; dci180033.

² Consensus Statement By The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm. *Endocrine Practice*. Vol 24 No. 1 January 2018.

³ INVOKANA® (canagliflozin) U.S. Prescribing Information.

⁴ Dr. Ralph DeFronzo was not involved with the CANVAS Program, nor was he compensated for his contributions to this announcement.