NEWS RELEASE

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U.S. FDA Expands Indication of INVOKAMET® (canagliflozin/metformin HCl) to Include First-Line Treatment of Adults with Type 2 Diabetes

In a Phase 3 study of patients not previously treated with any diabetes medication, combination therapy with canagliflozin and metformin lowered blood sugar more than either medicine alone

RARITAN, N.J., May 24, 2016 – Janssen Pharmaceuticals, Inc. (Janssen), today announced the U.S. Food and Drug Administration (FDA) has approved INVOKAMET®, a fixed-dose combination therapy of INVOKANA® (canagliflozin) and metformin hydrochloride, for first-line treatment of adults with type 2 diabetes. With this new approval, INVOKAMET® may now be prescribed in adults with type 2 diabetes who are not already being treated with canagliflozin or metformin and may benefit from dual therapy.[1]

INVOKAMET®, the first combination of a sodium glucose co–transporter 2 (SGLT2) inhibitor and metformin available in the United States, was previously approved by the FDA in August 2014 as an adjunct to diet and exercise to improve blood glucose control in adults with type 2 diabetes not adequately controlled by either canagliflozin or metformin, or who are already being treated with both medications separately.

“Physicians increasingly try to achieve greater initial blood sugar control by using dual therapy at the outset, versus single-agent therapy alone, especially for patients with higher A1C levels,” said John Anderson, M.D.*, Frist Clinic, Nashville, Tenn. “INVOKAMET® combines two effective, complementary medicines—canagliflozin and metformin—into one convenient pill, to lower A1C significantly more than metformin alone.”

A1C is a measure of average blood glucose over the past two to three months; the American Diabetes Association recommends most adults with type 2 diabetes maintain A1C levels of 7 percent or less.[2]

The new INVOKAMET® indication aligns with recent type 2 diabetes treatment guidelines, which recommend dual therapy for patients with higher A1C levels. Specifically, guidelines recommend dual therapy for patients who have an initial A1C level of 7.5 percent or higher;[3] and for those who have an

initial level below 7.5 percent and do not achieve an A1C treatment goal after about three months on single therapy, often metformin.[3,4] In addition, dual or triple therapy is recommended as first-line therapy in asymptomatic patients with an initial A1C level above 9 percent.[3]

Studies have demonstrated that administration of INVOKAMET® results in the same levels and effects of canagliflozin and metformin in the body as co-administration of corresponding doses of both drugs as individual tablets. Canagliflozin works with the kidneys to help adults with type 2 diabetes lose some sugar through the process of urination, and metformin decreases the production of glucose in the liver and improves the body's response to insulin. INVOKAMET® should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.[1]

INVOKAMET® is available in four dose strengths, in tablets containing canagliflozin 50 milligrams (mg) or 150 mg, and metformin 500 mg or 1000 mg. The recommended dosing is twice daily. The prescribing information for INVOKAMET® also contains a boxed warning for lactic acidosis, a rare, but serious complication that can occur due to metformin accumulation.[1]

“The available doses of INVOKAMET® allow physicians to tailor therapy for individual patient needs and offer an alternative for people living with type 2 diabetes who may be able to reduce the number of pills they take each day,” said Paul Burton, M.D., Ph.D., Vice President, Medical Affairs, Janssen. “This expansion marks an important milestone as we continue to study INVOKAMET® and INVOKANA®—the number-one prescribed SGLT2 inhibitor with more than 8 million prescriptions to date—for the treatment of type 2 diabetes.”

Phase 3 Study Supports Expanded Indication

The expanded indication for INVOKAMET® was based largely on a 26-week, double-blind, active-controlled, multicenter Phase 3 study in 1,186 adults with type 2 diabetes inadequately controlled with diet and exercise, and who had not been treated previously with any glucose-lowering medications. The participants were assigned randomly to one of five treatment groups: metformin hydrochloride extended release (MET), canagliflozin 100 mg (CANA100), canagliflozin 300 mg (CANA300), canagliflozin 100 mg + MET (CANA100/MET), or canagliflozin 300 mg + MET (CANA300/MET). The mean baseline A1C across all groups was 8.8 percent. The primary endpoint was the change in A1C. A report on the study findings was published in *Diabetes Care* in March 2016.[5]

After 26 weeks, participants in the CANA100/MET and CANA300/MET groups had significantly greater decreases in A1C compared to those in the CANA100, CANA300 and MET groups: 1.77 percent and 1.78 percent vs. 1.37 percent, 1.42 percent and 1.3 percent, respectively (p-values for all differences between the combination therapies vs. individual therapies less than 0.001). Additionally, significantly more participants in the CANA100/MET and CANA300/MET groups compared to the MET group achieved the goal of reducing A1C to less than 7 percent: 47 percent and 51 percent vs. 38 percent, respectively (p less than 0.05 for both combination groups vs. MET).[1]

Other Phase 3 Studies of Canagliflozin-Metformin Therapy

The co-administration of canagliflozin—INVOKANA®—and metformin has been evaluated in six other Phase 3 clinical studies that enrolled 4,732 patients with type 2 diabetes and who were already taking glucose-lowering medications. The studies showed that the combination of INVOKANA® and metformin lowered blood sugar and, in pre-specified secondary endpoints, was associated with significant reductions in body weight and systolic blood pressure.

In two studies comparing INVOKANA® plus metformin to current standard treatments plus metformin—one studying sitagliptin and the other studying glimepiride—INVOKANA® dosed at 300 mg provided greater reductions in A1C levels and body weight than either comparator. The overall incidence of adverse events was similar with INVOKANA® and the comparators.

Results from the Phase 3 studies showed that INVOKANA® was generally well tolerated, and the most common adverse events include genital yeast infections, urinary tract infections, and changes in urination. The most common adverse reactions due to initiation of metformin, as noted in the prescribing information for that medication, are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use. INVOKANA® can increase the risk of hypoglycemia when combined with insulin or a medication that increases insulin levels (e.g., a sulfonylurea). Therefore, a lower dose of insulin or insulin-raising medication may be required to minimize the risk of hypoglycemia when used in combination with INVOKAMET®.

About Type 2 Diabetes
Of the approximately 29 million people who have diabetes in the United States, 90 to 95 percent of them have type 2 diabetes, which is chronic and affects the body's ability to metabolize sugar (glucose), and is characterized by the inability of pancreatic beta cell function to keep up with the body's demand for insulin.

WHAT IS INVOKAMET®?

INVOKAMET® contains two prescription medicines called canagliflozin (INVOKANA®) and metformin hydrochloride (GLUCOPHAGE®). It is used along with diet and exercise to improve blood sugar (glucose) control in adults with type 2 diabetes when treatment with either canagliflozin or metformin has not controlled your blood sugar. INVOKAMET® is not for people with type 1 diabetes or with diabetic ketoacidosis (increased ketones in blood or urine). It is not known if INVOKAMET® is safe and effective in children under 18 years of age.

IMPORTANT SAFETY INFORMATION

INVOKAMET® can cause serious side effects, including:

- **Lactic Acidosis.** Metformin, one of the medicines in INVOKAMET®, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital. **Stop taking INVOKAMET® and call your doctor right away if you have any of the following symptoms which could be signs of lactic acidosis:** feel very weak or tired; have unusual (not normal) muscle pain; have trouble breathing; have unusual sleepiness or sleep longer than usual; have stomach pains, nausea, or vomiting; feel dizzy or lightheaded; or have a slow/irregular heartbeat

You have a higher chance of getting lactic acidosis with INVOKAMET® if you have conditions such as: kidney problems, or your kidneys are affected by certain X-ray tests that use injectable dye; liver problems; congestive heart failure; drink alcohol very often, (or drink a lot of alcohol in short-term); get dehydrated; have surgery; have a heart attack, severe infection, or stroke; or are 80 years of age or older and have not had your kidneys tested.

Do not take INVOKAMET® if you:

- Have severe kidney problems or are on dialysis, have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine). Are allergic to canagliflozin, metformin, or any of the ingredients in INVOKAMET®. See the end of the Medication Guide for a list of ingredients in INVOKAMET®. Symptoms of allergic reaction may include: rash; raised red patches on your skin (hives); swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

Before you take INVOKAMET®, tell your doctor if you: have kidney problems; liver problems; pancreas problems; are on a low sodium (salt) diet; are going to have surgery; are eating less due to illness, surgery, or a very low calorie diet; have ever had an allergic reaction to INVOKAMET®; are going to get an injection of dye or contrast agents for an X-ray procedure (INVOKAMET® will need to be stopped for a short time); have heart problems (including congestive heart failure); drink alcohol very often (or drink a lot of alcohol in short-term); or have any other medical conditions.

Tell your doctor if you are or plan to become pregnant, are breastfeeding or plan to breastfeed. It is not known if INVOKAMET® will harm your unborn baby. It is also not known if INVOKAMET® passes into your breast milk.

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 INVOKAMET®

INVOKAMET® may cause serious side effects, including:

- **Dehydration:** INVOKAMET® can cause some people to have dehydration (the loss of body water and salt)
- **Ketoacidosis** (increased ketones in your blood or urine) can happen with INVOKAMET®, even if your blood sugar is less than 250 mg/dL. **Stop taking INVOKAMET® 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, a high amount of potassium in your blood (hyperkalemia), liver problems, or low blood sugar (hypoglycemia)**. If you take INVOKAMET® 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 INVOKAMET®
- **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

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

Vaginal yeast infection: Women taking INVOKAMET® may get vaginal yeast infections. Symptoms include: vaginal odor, white or yellowish discharge, or vaginal itching.

Yeast infection of the penis (balanitis or balanoposthitis): Men taking INVOKAMET® may get a yeast infection of the skin around the penis. Symptoms include: redness, itching, or swelling of the penis; rash; foul smelling discharge; or pain in the skin around penis.

Serious allergic reaction: If you have any symptoms of a serious allergic reaction, stop taking INVOKAMET® 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.

Low vitamin B12 (vitamin B12 deficiency): Using metformin for long periods of time may cause a decrease in the amount of vitamin B12 in your blood. Your doctor may do blood tests to check your levels.

The most common side effects of INVOKAMET® include: urinary tract infection; changes in urination, including urgent need to urinate more often, in larger amounts, or at night; diarrhea, nausea and vomiting, gas, weakness, indigestion, upset stomach, or headache.

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 see the full Product Information, including Boxed Warning, and Medication Guide.

WHAT IS INVOKANA®?

INVOKANA® is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. 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:

- **Dehydration** (the loss of body water and salt), 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 kidney problems; liver problems; pancreas problems; are on a low sodium (salt) diet; are going to have surgery; are eating less due to illness, surgery, or a very low calorie diet; ever had an allergic reaction to INVOKANA®; drink alcohol very often (or drink a lot of alcohol in short-term); or have other medical conditions.

Tell your doctor if you are or plan to become pregnant, are breastfeeding, or plan to breastfeed. It is not known if INVOKANA® will harm your unborn baby. It is also not known if INVOKANA® passes into your breast milk.

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) 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, a high amount of potassium in your blood (hyperkalemia), or 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®
- **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

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The most common side effects of INVOKANA® include: vaginal yeast infections and yeast infections of the penis; urinary tract infection; or 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 see full Product Information and Medication Guide.

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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 at @JanssenUS.

**Dr. Anderson was not compensated for any media work. He has been a paid consultant to Janssen Pharmaceuticals, Inc.*

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1 INVOKAMET® (canagliflozin and metformin hydrochloride) tablets, for oral use. Prescribing information, updated 05/2016. Janssen Pharmaceuticals, Inc., Titusville, NJ, 08560.

2 American Diabetes Association. Glycemic targets. Sec. 5. In Standards of Medical Care in Diabetes – 2016. Diabetes Care 2016;39(Suppl. 1):S39–S46.

3 Garber AJ, Abrahamson MJ, Barzilay JI, et al. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2016 EXECUTIVE SUMMARY. Endocr Pract. 2016 Jan;22(1):84-113.

4 American Diabetes Association. Approaches to glycemic treatment. Sec. 7. In Standards of Medical Care in Diabetesd2016. Diabetes Care 2016;39(Suppl. 1):S52–S59

5 Rosenstock J, Chuck L, González-Ortiz M, Merton K, Craig J, Capuano G, Qiu R. Initial Combination Therapy With Canagliflozin Plus Metformin Versus Each Component as Monotherapy for Drug-Naïve Type 2 Diabetes. Diabetes Care. 2016 Mar;39(3):353-62.