



NEWS RELEASE

Media Inquiries:

Christina Holden
908-927-3581 office
201-650-2355 cell
cholden7@its.jnj.com

Bill Foster
908-704-4404 office
908-392-6057 cell
wfoster@its.jnj.com

Investor Relations:

Stan Panasewicz
732-524-2524 office

Louise Mehrotra
732-524-6491 office

U.S. FDA Approves INVOKAMET™ (canagliflozin/metformin HCl) for the Treatment of Adults with Type 2 Diabetes

In Phase 3 studies, INVOKANA® plus metformin lowered blood sugar and reduced secondary endpoints of body weight and systolic blood pressure to a greater degree than metformin alone

RARITAN, N.J., August 8, 2014 – Janssen Pharmaceuticals, Inc. announced today the U.S. Food and Drug Administration (FDA) has approved INVOKAMET™, a fixed-dose therapy combining canagliflozin and metformin hydrochloride in a single tablet, for the treatment of adults with type 2 diabetes. INVOKAMET™ provides the clinical attributes of INVOKANA® (canagliflozin), the first sodium glucose co-transporter 2 (SGLT2) inhibitor available in the United States, together with metformin, which is commonly prescribed early in the treatment of type 2 diabetes. INVOKAMET™ is the first fixed-dose combination of an SGLT2 inhibitor with metformin approved in the United States.

“INVOKAMET™ combines, in one tablet, two complementary therapeutic approaches proven effective for managing type 2 diabetes,” said Richard Aguilar, M.D.*, Medical Director of Diabetes Nation.

“Canagliflozin works with the kidney to promote the loss of glucose in the urine, whereas metformin decreases the production of glucose in the liver and improves the body’s response to insulin.”

INVOKAMET™ is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled by treatment that includes either canagliflozin



or metformin, or who are already being treated with both canagliflozin and metformin as separate medications. INVOKAMET™ should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Study results demonstrated that administration of INVOKAMET™ was equivalent to co-administration of corresponding doses of canagliflozin and metformin as individual tablets.

INVOKAMET™ will be available 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.

“As with INVOKANA®, INVOKAMET™ provides adults with type 2 diabetes an oral therapy that lowers blood sugar and is also associated with reductions in body weight and systolic blood pressure,” said Jimmy Ren, Ph.D., Therapeutic Area Lead, Metabolics, Medical Affairs, Janssen Pharmaceuticals, Inc. “The available doses of INVOKAMET™ allow physicians to tailor therapy for individual patient needs and offer an alternative for patients who may be able to reduce the number of tablets they take each day.”

In March 2013, the FDA [approved](#) canagliflozin -- INVOKANA® -- as a single agent, and it is the number-one branded non-insulin type 2 diabetes medication newly prescribed by U.S. endocrinologists.¹ It is also the second most common branded therapy prescribed by primary care physicians when adding or switching therapies in patients.² Since its launch, more than one million prescriptions have been written for INVOKANA®.³

The co-administration of INVOKANA® and metformin has been studied in six Phase 3 clinical studies that enrolled 4,732 patients with type 2 diabetes. The Phase 3 studies evaluated INVOKANA® in combination with metformin compared to metformin alone or to metformin plus another diabetes therapy. The studies were part of the comprehensive global Phase 3 program for INVOKANA® that enrolled 10,285 patients, one of the largest clinical programs in type 2 diabetes submitted to health authorities to date. The Phase 3 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. A1C is the percent of red blood cell hemoglobin with glucose attached to it and an indicator of average blood glucose over the previous



two to three months. In the two studies, the overall incidence of adverse events was similar with INVOKANA[®] and the comparators.

Results from the Phase 3 studies showed that the most common adverse events with INVOKANA[®] are female genital mycotic (fungal) infections, urinary tract infections and increased urination. These specific adverse events were generally mild to moderate in intensity and infrequently led to discontinuation in Phase 3 studies. 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[™].

Janssen Pharmaceuticals, Inc. and its affiliates have rights to canagliflozin through a license agreement with Mitsubishi Tanabe Pharma Corporation. Janssen Pharmaceuticals, Inc. and its affiliates have marketing rights in North America, South America, Europe, the Middle East, Africa, Australia, New Zealand and parts of Asia.

On April 25, 2014, Janssen-Cilag International NV announced that the European Commission (EC) [approved VOKANAMET[®]](#) (a fixed-dose therapy combining canagliflozin and immediate release metformin hydrochloride in a single tablet) in the European Union, for the treatment of adults with type 2 diabetes mellitus to improve glycemic control. INVOKANA[®] is approved as a single agent in Aruba, Australia, Brazil, Canada, Chile, Costa Rica, El Salvador, the European Union (31 countries), Guatemala, Kuwait, Mexico, Peru, Singapore, South Korea, Switzerland, United Arab Emirates, and the United States.

About Type 2 Diabetes

An estimated 371 million people worldwide are living with diabetes⁴ and approximately 29 million people have diabetes in the United States.⁵ Type 2 diabetes comprises 90 to 95 percent of people with diabetes,⁵ 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.

Nearly half of adults with type 2 diabetes do not achieve recommended levels of glucose control, and if left uncontrolled, type 2 diabetes can lead to serious complications.^{6,7,8} Improved glycemic control has been demonstrated to reduce the onset and progression of these complications.⁹



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, or both medications, 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, have liver problems, are on a low sodium (salt) diet, have ever had an allergic reaction to INVOKAMET™, or 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®, Lopinavir®-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), **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™.

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.

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, are on a low sodium (salt) diet, 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. 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 nonprescription 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[®], Lopinavir[®] - 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: **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[®].

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

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.



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 the full [Prescribing Information](#) and [Medication Guide](#).

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

Trademarks are those of their respective owners.

About Janssen Pharmaceuticals, Inc.

As a member of the Janssen Pharmaceutical Companies of Johnson & Johnson, Janssen Pharmaceuticals, Inc. is dedicated to addressing and resolving the major unmet medical needs of our time. Driven by our commitment to patients, healthcare professionals, and caregivers, we strive to develop sustainable and integrated healthcare solutions by working in partnership with all stakeholders on the basis of trust and transparency. Our daily work is guided by meeting goals of excellence in quality, innovation, safety, and efficacy in order to advance patient care.

For more information on Janssen Pharmaceuticals, Inc., visit us at www.janssenpharmaceuticalsinc.com or follow us on Twitter at www.twitter.com/JanssenUS and on YouTube at www.Youtube.com/JanssenUS.

**Dr. Aguilar was not associated with the INVOKANA[®] clinical trials and was not compensated for any media work. He has been a paid consultant to Janssen Pharmaceuticals, Inc.*

###

¹ Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data, showing INVOKANA[®] has been the leading branded non-insulin type 2 diabetes medication newly prescribed by U.S. endocrinologists for eight weeks, through July 25, 2014, the most recent data available at time of approval of INVOKAMET[™].

² Data on file. Based on NBRx data sourced from IMS NPA Market Dynamics Database, weekly data through July 25, 2014.

³ Data on file. Based on total prescription data sourced from IMS NPA National Database, weekly data through July 25, 2014.

⁴ International Diabetes Federation, Diabetes Atlas 5th Edition 2012 Update, New estimates for 2012 of diabetes prevalence, mortality, and healthcare expenditures. Available at: http://www.idf.org/sites/default/files/5E_IDFAtlasPoster_2012_EN.pdf

⁵ Centers for Disease Control and Prevention, National Diabetes Statistics Report, 2014. Available at: <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>

⁶ Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. Trends Pharmacol Sci. 2011;32(2):63-71.

⁷ Casagrande SS, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care. 2013 Feb 15. Epub ahead of print.

⁸ World Health Organization, Media Centre, Diabetes, Fact sheet Number 312. Available at: <http://www.who.int/mediacentre/factsheets/fs312/en/>. Accessed April 1, 2013.

⁹ Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.