

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JARDIANCE safely and effectively. See full prescribing information for JARDIANCE.

JARDIANCE® (empagliflozin) tablets, for oral use
Initial U.S. Approval: 2014

| | |
|--------------------------------|---------|
| -----RECENT MAJOR CHANGES----- | |
| Indications and Usage (1) | 12/2016 |
| Warnings and Precautions (5) | 12/2016 |

-----INDICATIONS AND USAGE-----

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)

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

-----DOSAGE AND ADMINISTRATION-----

- The recommended dose of JARDIANCE is 10 mg once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg once daily (2.1)
- Assess renal function before initiating JARDIANCE. Do not initiate JARDIANCE if eGFR is below 45 mL/min/1.73 m² (2.2)
- Discontinue JARDIANCE if eGFR falls below 45 mL/min/1.73 m² (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 10 mg, 25 mg (3)

-----CONTRAINDICATIONS-----

- History of serious hypersensitivity reaction to JARDIANCE (4)
- Severe renal impairment, end-stage renal disease, or dialysis (4)

-----WARNINGS AND PRECAUTIONS-----

- **Hypotension:** Before initiating JARDIANCE assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.1)

- **Ketoacidosis:** Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue JARDIANCE, evaluate and treat promptly. Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients on JARDIANCE may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- **Acute kidney injury and impairment in renal function:** Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy. (5.3)
- **Urosepsis and Pyelonephritis:** Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.4)
- **Hypoglycemia:** Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating JARDIANCE (5.5)
- **Genital mycotic infections:** Monitor and treat as appropriate (5.6)
- **Increased LDL-C:** Monitor and treat as appropriate (5.7)

-----ADVERSE REACTIONS-----

- The most common adverse reactions associated with JARDIANCE (5% or greater incidence) were urinary tract infections and female genital mycotic infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or 1-800-459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

- **Pregnancy:** Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- **Lactation:** JARDIANCE is not recommended when breastfeeding (8.2)
- **Geriatric patients:** Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.1, 5.3, 8.5)
- **Patients with renal impairment:** Higher incidence of adverse reactions related to reduced renal function (2.2, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JARDIANCE 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 cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food. In patients tolerating JARDIANCE, the dose may be increased to 25 mg [*see Clinical Studies (14)*].

In patients with volume depletion, correcting this condition prior to initiation of JARDIANCE is recommended [*see Warnings and Precautions (5.1), Use in Specific Populations (8.5), and Patient Counseling Information (17)*].

2.2 Patients with Renal Impairment

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

JARDIANCE should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m².

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m².

JARDIANCE should be discontinued if eGFR is less than 45 mL/min/1.73 m² [*see Warnings and Precautions (5.1, 5.3), and Use in Specific Populations (8.6)*].

3 DOSAGE FORMS AND STRENGTHS

JARDIANCE tablets available as:

- 10 mg pale yellow, round, biconvex and bevel-edged, film-coated tablets debossed with “S 10” on one side and the Boehringer Ingelheim company symbol on the other side.
- 25 mg pale yellow, oval, biconvex, film-coated tablets debossed with “S 25” on one side and the Boehringer Ingelheim company symbol on the other side.

4 CONTRAINDICATIONS

- History of serious hypersensitivity reaction to JARDIANCE.
- Severe renal impairment, end-stage renal disease, or dialysis [*see Use in Specific Populations (8.6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE [*see Adverse Reactions (6.1)*] particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension

after initiating therapy and increase monitoring in clinical situations where volume contraction is expected [*see Use in Specific Populations (8.5)*].

5.2 Ketoacidosis

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

Patients treated with JARDIANCE 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 JARDIANCE may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE 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 due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating JARDIANCE, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.3 Acute Kidney Injury and Impairment in Renal Function

JARDIANCE causes intravascular volume contraction [*see Warnings and Precautions (5.1)*] and can cause renal impairment [*see Adverse Reactions (6.1)*]. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including JARDIANCE; some reports involved patients younger than 65 years of age.

Before initiating JARDIANCE, 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 JARDIANCE in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment.

JARDIANCE increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDIANCE [*see Adverse Reactions (6.1)*]. Renal function should be evaluated prior to initiation of JARDIANCE and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m². Use of JARDIANCE is not recommended when eGFR is persistently less than 45

mL/min/1.73 m² and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m² [see Dosage and Administration (2.2), Contraindications (4), Use in Specific Populations (8.6)].

5.4 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 JARDIANCE. 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 (6)].

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin [see Adverse Reactions (6.1)]. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE.

5.6 Genital Mycotic Infections

JARDIANCE increases the risk for genital mycotic infections [see Adverse Reactions (6.1)]. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate.

5.7 Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with JARDIANCE [see Adverse Reactions (6.1)]. Monitor and treat as appropriate.

6 ADVERSE REACTIONS

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

- Hypotension [see Warnings and Precautions (5.1)]
- Ketoacidosis [see Warnings and Precautions (5.2)]
- Acute Kidney Injury and Impairment in Renal Function [see Warnings and Precautions (5.3)]
- Urosepsis and Pyelonephritis [see Warnings and Precautions (5.4)]
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [see Warnings and Precautions (5.5)]
- Genital Mycotic Infections [see Warnings and Precautions (5.6)]
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) [see Warnings and Precautions (5.7)]

6.1 Clinical Trials 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 rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg

The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials [see Clinical Studies (14)].

These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than

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half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m²).

Table 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline, occurred more commonly on JARDIANCE than on placebo and occurred in greater than or equal to 2% of patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy

| | Number (%) of Patients | | |
|--|------------------------|--------------------------|--------------------------|
| | Placebo N=995 | JARDIANCE 10 mg N=999 | JARDIANCE 25 mg N=977 |
| Urinary tract infection ^a | 7.6% | 9.3% | 7.6% |
| Female genital mycotic infections ^b | 1.5% | 5.4% | 6.4% |
| Upper respiratory tract infection | 3.8% | 3.1% | 4.0% |
| Increased urination ^c | 1.0% | 3.4% | 3.2% |
| Dyslipidemia | 3.4% | 3.9% | 2.9% |
| Arthralgia | 2.2% | 2.4% | 2.3% |
| Male genital mycotic infections ^d | 0.4% | 3.1% | 1.6% |
| Nausea | 1.4% | 2.3% | 1.1% |

^aPredefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

^bFemale genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).

^cPredefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

^dMale genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

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

Volume Depletion

JARDIANCE causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg respectively.

JARDIANCE may increase the risk of hypotension in patients at risk for volume contraction [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.5, 8.6)*].

Increased Urination

In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on JARDIANCE than on placebo (see Table 1).

Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

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