HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SYNJARDY safely and effectively. See full prescribing information for SYNJARDY.

SYNJARDY® (empagliflozin and metformin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. (5.1)**
- **Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)**
- **If lactic acidosis is suspected, discontinue SYNJARDY and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

----------RECENT MAJOR CHANGES----------

Contraindications (4)	12/2017
Warnings and Precautions (5)	12/2017

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

SYNJARDY is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin hydrochloride, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride is appropriate.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. However, the effectiveness of SYNJARDY on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established. (1)

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

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

- Individualize the starting dose of SYNJARDY based on the patient's current regimen (2.1)
- The maximum recommended dose is 12.5 mg empagliflozin/1000 mg metformin hydrochloride twice daily (2.1)
- Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.1)
- Assess renal function before initiating. SYNJARDY is contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2 (2.2, 4)
- SYNJARDY may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

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

Tablets:
5 mg empagliflozin/500 mg metformin hydrochloride
5 mg empagliflozin/1000 mg metformin hydrochloride
12.5 mg empagliflozin/500 mg metformin hydrochloride
12.5 mg empagliflozin/1000 mg metformin hydrochloride (3)

----------CONTRAINDICATIONS----------

- Moderate to severe renal impairment (eGFR below 45 mL/min/1.73 m^2), end stage renal disease, or dialysis (4, 5.1, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)
- History of serious hypersensitivity reaction to empagliflozin, metformin or any of the excipients in SYNJARDY (4)

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

- *Lactic acidosis:* See boxed warning (5.1)
- *Hypotension:* Before initiating SYNJARDY 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. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue SYNJARDY, evaluate and treat promptly. Before initiating SYNJARDY, consider risk factors for ketoacidosis. Patients on SYNJARDY may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.3)
- *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 (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.5)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating SYNJARDY (5.6)
- *Genital mycotic infections:* Monitor and treat as appropriate (5.7)
- *Hypersensitivity reactions:* Discontinue SYNJARDY, treat promptly, and monitor until signs and symptoms resolve (5.8)
- *Vitamin B_{12} deficiency:* Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.9)
- *Increased LDL-C:* Monitor and treat as appropriate (5.10)
- *Macrovascular outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SYNJARDY. (5.11)

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

- Most common adverse reactions associated with empagliflozin (5% or greater incidence) were urinary tract infection and female genital mycotic infections. (6.1)
- Most common adverse reactions associated with metformin (>5%) are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. (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.

----------DRUG INTERACTIONS----------

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.2)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.2)

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

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* SYNJARDY is not recommended when breastfeeding. (8.2)
- *Females and Males of Reproductive Potential:* Advise premenopausal females of the potential for an unintended pregnancy (8.3).
- *Geriatric patients:* Higher incidence of adverse reactions related to volume depletion and reduced renal function. Assess renal function more frequently (5.2, 5.4, 8.5)
- *Patients with renal impairment:* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.4, 8.6)
- *Hepatic Impairment:* Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (5.1)]*.

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7.2), and Use in Specific Populations (8.6, 8.7)]*.

If metformin-associated lactic acidosis is suspected, immediately discontinue SYNJARDY and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

SYNJARDY is a combination of empagliflozin and metformin hydrochloride indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride is appropriate.

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease *[see Clinical Studies (14.2)]*. However, the effectiveness of SYNJARDY on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established.

Limitations of Use

SYNJARDY is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis *[see Warnings and Precautions (5.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating SYNJARDY *[see Warnings and Precautions (5.2)]*.
- Individualize the starting dose of SYNJARDY based on the patient's current regimen:
  - In patients on metformin hydrochloride, switch to SYNJARDY containing empagliflozin 5 mg with a similar total daily dose of metformin hydrochloride;
  - In patients on empagliflozin, switch to SYNJARDY containing metformin hydrochloride 500 mg with a similar total daily dose of empagliflozin;
  - In patients already treated with empagliflozin and metformin hydrochloride, switch to SYNJARDY containing the same total daily doses of each component.

- Take SYNJARDY twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin *[see Dosage Forms and Strengths (3)]*.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg *[see Dosage and Administration (2.2)]*.

2.2 Recommended Dosage in Patients with Renal Impairment

- Assess renal function prior to initiation of SYNJARDY and periodically, thereafter.
- SYNJARDY is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.1, 5.4)]*.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue SYNJARDY at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart SYNJARDY if renal function is stable *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

SYNJARDY is a combination of empagliflozin and metformin hydrochloride. SYNJARDY is available in the following dosage forms and strengths:

- 5 mg empagliflozin/500 mg metformin hydrochloride tablets are orange yellow, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S5"; the other side is debossed with "500".
- 5 mg empagliflozin/1000 mg metformin hydrochloride tablets are brownish yellow, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S5"; the other side is debossed with "1000".
- 12.5 mg empagliflozin/500 mg metformin hydrochloride tablets are pale brownish purple, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S12"; the other side is debossed with "500".
- 12.5 mg empagliflozin/1000 mg metformin hydrochloride tablets are dark brownish purple, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S12"; the other side is debossed with "1000".

4 CONTRAINDICATIONS

SYNJARDY is contraindicated in patients with:

- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m^2), end stage renal disease, or dialysis *[see Warnings and Precautions (5.1, 5.4) and Use in Specific Populations (8.6)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin *[see Warnings and Precautions (5.1)]*.
- History of serious hypersensitivity reaction to empagliflozin, metformin or any of the excipients in SYNJARDY.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or

ketonemia), and an increased lactate:pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of SYNJARDY. In SYNJARDY-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/minute under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue SYNJARDY and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

- Before initiating SYNJARDY, obtain an estimated glomerular filtration rate (eGFR).
- SYNJARDY is contraindicated in patients with an eGFR below 45 mL/min/1.73 m^2 *[see Contraindications (4)]*.
- Obtain an eGFR at least annually in all patients taking SYNJARDY. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions: The concomitant use of SYNJARDY with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation *[see Drug Interactions (7.2)]*. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater: The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (8.5)]*.

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop SYNJARDY at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart SYNJARDY if renal function is stable.

Surgery and Other Procedures: Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. SYNJARDY should be temporarily discontinued while patients have restricted food and fluid intake.

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