This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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

SYNJARDY® XR (empagliflozin and metformin hydrochloride extended-release 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 XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

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

Warnings and Precautions (5.4, 5.6) 10/2022

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

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

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. (1)

Limitation of Use:
Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. (1)

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

- Assess renal function before initiating and as clinically indicated (2.1).
- Individualize the starting dose based on the patient's current regimen and renal function (2.2, 2.3)
- Initiation is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component (2.3)
- The maximum recommended total daily dose is 25 mg empagliflozin and 2000 mg metformin HCl (2.2)
- Take once daily with a meal in the morning, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.2)
- Swallow whole; do not split, crush, dissolve, or chew (2.2)
- SYNJARDY XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.4)

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

Tablets:
- 5 mg empagliflozin/1000 mg metformin HCl extended-release (3)
- 10 mg empagliflozin/1000 mg metformin HCl extended-release (3)
- 12.5 mg empagliflozin/1000 mg metformin HCl extended-release (3)
- 25 mg empagliflozin/1000 mg metformin HCl extended-release (3)

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

- Severe renal impairment (eGFR below 30 mL/min/1.73 m^2), end stage renal disease, or on dialysis (4, 5.1)
- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)
- Hypersensitivity to empagliflozin, metformin or any of the excipients in SYNJARDY XR (4)

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

- *Lactic Acidosis:* See boxed warning (5.1)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue SYNJARDY XR, evaluate and treat promptly. Before initiating SYNJARDY XR, consider risk factors for ketoacidosis. Patients on SYNJARDY XR may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- *Volume Depletion:* Before initiating SYNJARDY XR, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy. (5.3, 6.1)
- *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 SYNJARDY XR (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.6)
- *Genital Mycotic Infections:* Monitor and treat as appropriate (5.7)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., angioedema) have occurred with empagliflozin. If hypersensitivity reactions occur, discontinue SYNJARDY XR, treat promptly, and monitor until signs and symptoms resolve (5.8)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematologic parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.9)

----------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 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)
- *Drugs that Reduce Metformin Clearance:* May increase risk of lactic acidosis. Consider benefits and risks of concomitant use. (7)
- See full prescribing information for additional drug interactions and information on interference of SYNJARDY XR with laboratory tests. (7)

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

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* 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. (5.1, 5.3, 8.5, 8.6)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (2.1, 5.1, 5.3, 8.6)
- *Hepatic Impairment:* Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2022

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LACTIC ACIDOSIS
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Prior to Initiation of SYNJARDY XR
2.2 Recommended Dosage and Administration
2.3 Dosage Recommendations in Patients with Renal Impairment
2.4 Discontinuation for Iodinated Contrast Imaging Procedures
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Lactic Acidosis
5.2 Ketoacidosis
5.3 Volume Depletion
5.4 Urosepsis and Pyelonephritis
5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues
5.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
5.7 Genital Mycotic Infections
5.8 Hypersensitivity Reactions
5.9 Vitamin B_{12} Deficiency
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

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 (2.1), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.

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

1 INDICATIONS AND USAGE

SYNJARDY XR is a combination of empagliflozin and metformin hydrochloride (HCl) indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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)]*.

Limitation of Use

SYNJARDY XR is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of SYNJARDY XR

- Assess renal function before initiating SYNJARDY XR and as clinically indicated *[see Warnings and Precautions (5.1, 5.3)]*.
- In patients with volume depletion, correct this condition before initiating SYNJARDY XR *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage and Administration

- Individualize the starting dose of SYNJARDY XR based on the patient's current regimen:
    - In patients on metformin HCl, switch to SYNJARDY XR containing a similar total daily dose of metformin HCl and a total daily dose of empagliflozin 10 mg;
    - In patients on empagliflozin, switch to SYNJARDY XR containing the same total daily dose of empagliflozin and a total daily dose of metformin HCl extended-release 1000 mg;

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

- In patients already treated with empagliflozin and metformin HCl, switch to SYNJARDY XR containing the same total daily doses of empagliflozin and a similar total daily dose of metformin HCl.

- Monitor effectiveness and tolerability, and adjust dosing as appropriate, not to exceed the maximum recommended daily dose of empagliflozin 25 mg and metformin HCl 2000 mg.
- The dose of metformin HCl should be gradually escalated to reduce the gastrointestinal side effects due to metformin.
- Take SYNJARDY XR orally once daily with a meal in the morning
- Swallow SYNJARDY XR tablets whole. Do not split, crush, dissolve, or chew.
- SYNJARDY XR 10 mg/1000 mg and 25 mg/1000 mg tablets should be taken as a single tablet once daily. SYNJARDY XR 5 mg/1000 mg and 12.5 mg/1000 mg tablets should be taken as two tablets together once daily.

2.3 Dosage Recommendations in Patients with Renal Impairment

- Initiation of SYNJARDY XR is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component.
- SYNJARDY XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 or in patients on dialysis *[see Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

2.4 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue SYNJARDY XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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 XR if renal function is stable *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

SYNJARDY XR Tablets:

Empagliflozin Strength	Metformin HCl Strength	Color/Shape	Tablet Markings
5 mg	1000 mg	olive green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S5" on the top line and "1000 M" on the bottom line.
10 mg	1000 mg	orange, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S10" on the top line and "1000 M" on the bottom line.
12.5 mg	1000 mg	blue, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S12" on the top line and "1000 M" on the bottom line.
25 mg	1000 mg	light green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S25" on the top line and "1000 M" on the bottom line.

4 CONTRAINDICATIONS

SYNJARDY XR is contraindicated in patients with:

- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease, or dialysis *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis *[see Warnings and Precautions (5.1)]*.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

- Hypersensitivity to empagliflozin, metformin or any of the excipients in SYNJARDY XR, reactions such as angioedema have occurred *[see Warnings and Precautions (5.8)]*.

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 XR. In SYNJARDY XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin 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 XR 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 (2.3) and Clinical Pharmacology (12.3)]*.

- Before initiating SYNJARDY XR, obtain an estimated glomerular filtration rate (eGFR).
- SYNJARDY XR is contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 *[see Contraindications (4)]*.
- Obtain an eGFR at least annually in all patients taking SYNJARDY XR. 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 XR 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)]*. 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

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

SYNJARDY XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR less than 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 XR 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 XR should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States: Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue SYNJARDY XR.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving SYNJARDY XR.

Hepatic Impairment: Patients with hepatic impairment have developed cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of SYNJARDY XR in patients with clinical or laboratory evidence of hepatic disease.

5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. SYNJARDY XR is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

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

Before initiating SYNJARDY XR, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

For patients who undergo scheduled surgery, consider temporarily discontinuing SYNJARDY XR for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing SYNJARDY XR in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting SYNJARDY XR.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue SYNJARDY XR and seek medical attention immediately if signs and symptoms occur.

5.3 Volume Depletion

Empagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions (6.1)]*. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating SYNJARDY XR in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating SYNJARDY XR. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.

5.4 Urosepsis and Pyelonephritis

There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including empagliflozin. 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 SYNJARDY XR 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 SYNJARDY XR.

5.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with SYNJARDY XR presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue SYNJARDY XR, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.7 Genital Mycotic Infections

Empagliflozin 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 genital mycotic infections. Monitor and treat as appropriate.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

5.8 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin. If a hypersensitivity reaction occurs, discontinue SYNJARDY XR; treat promptly per standard of care, and monitor until signs and symptoms resolve. SYNJARDY XR is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in SYNJARDY XR *[see Contraindications (4)]*.

5.9 Vitamin B_{12} Deficiency

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2 to 3 year intervals in patients on SYNJARDY XR and manage any abnormalities *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

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

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Volume Depletion *[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)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (5.9)]*

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.

The safety of concomitantly administered empagliflozin (daily dose 10 mg and 25 mg) and metformin hydrochloride (mean daily dose of approximately 1800 mg) has been evaluated in 3456 patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1271 patients received a daily dose of empagliflozin 10 mg, and 1259 patients received a daily dose of empagliflozin 25 mg. Discontinuation of therapy due to adverse events across treatment groups was 3.0%, 2.8%, and 2.9% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Empagliflozin Add-On Combination Therapy with Metformin

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

In a 24-week placebo-controlled trial of empagliflozin 10 mg and 25 mg administered once daily added to metformin and sulfonylurea, adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo are presented in Table 1 (see also Table 4).

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with Empagliflozin added on to Metformin plus Sulfonylurea and Greater than with Placebo in a 24-week Placebo Controlled Clinical Study

Adverse Reactions	Placebo (%) n=225	Empagliflozin 10 mg (%) n=224	Empagliflozin 25 mg (%) n=217
Hypoglycemia	9.8	15.6	12.9
Urinary tract infection	6.7	9.4	6.9
Nasopharyngitis	4.9	8.0	6.0

Empagliflozin

The data in Table 2 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin. Empagliflozin 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 empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), empagliflozin 10 mg (N=999), or empagliflozin 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 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 m^2).

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

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

Adverse Reactions	Placebo (%) N=995	Empagliflozin 10 mg (%) N=999	Empagliflozin 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

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

[b]Female 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), empagliflozin 10 mg (N=443), empagliflozin 25 mg (N=420).

[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

[d]Male 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), empagliflozin 10 mg (N=556), empagliflozin 25 mg (N=557).

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

Volume Depletion

Empagliflozin 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, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction *[see 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 empagliflozin than on placebo (see Table 2). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea.

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**Empagliflozin 10 mg (n=224)**	**Empagliflozin 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**Empagliflozin 10 mg + Metformin (n=217)**	**Empagliflozin 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)**	**Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)**	**Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/-Metformin (18 weeks[d])	**Placebo (n=170)**	**Empagliflozin 10 mg (n=169)**	**Empagliflozin 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/-Metformin (18 weeks[d])	**Placebo (n=188)**	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Treated set (patients who had received at least one dose of study drug)
[d]Insulin dose could not be adjusted during the initial 18-week treatment period

Genital Mycotic Infections

In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with empagliflozin compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 mg or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see Table 2).

Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 25 mg (0.1%) than placebo (0%).

Urinary Tract Infections

In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

to placebo (see Table 2). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Use in Specific Populations (8.5)]*.

Metformin
The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common (>5% and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs 4.9%), diarrhea (12.5% vs 5.6%), and nausea (6.7% vs 4.2%).

Laboratory Tests
Empagliflozin
Increases in Serum Creatinine and Decreases in eGFR: Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg-treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Metformin
Decrease in Vitamin B_{12}: In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients.

6.2 Postmarketing Experience
Additional adverse reactions have been identified during postapproval use. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Empagliflozin
Gastrointestinal Disorders: Constipation
Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis
Metabolism and Nutrition Disorders: Ketoacidosis

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Renal and Urinary Disorders: Acute kidney injury
Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

Metformin hydrochloride
Hepatobiliary Disorders: Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

Table 4 Clinically Relevant Interactions with SYNJARDY XR

Carbonic Anhydrase Inhibitors	
Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with SYNJARDY XR may increase the risk of lactic acidosis.
Intervention	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving SYNJARDY XR.
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating SYNJARDY XR, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating SYNJARDY XR. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when SYNJARDY XR is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of SYNJARDY XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving SYNJARDY XR, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving SYNJARDY XR, the patient should be observed closely for hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Intervention	Monitor serum lithium concentration more frequently during SYNJARDY XR initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects from empagliflozin, SYNJARDY XR is not recommended during the second and third trimesters of pregnancy.

The limited available data with SYNJARDY XR or empagliflozin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, empagliflozin, a component of SYNJARDY XR, resulted in adverse renal changes in rats when administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. No adverse developmental effects were observed when metformin was administered to pregnant rats or rabbits *(see Data)*.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Human Data

Published data from postmarketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was used during pregnancy. However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Animal Data

Empagliflozin: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30, and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week, drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16-times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4-times the 25 mg maximum clinical dose).

Metformin hydrochloride: Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at doses up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2000 mg, based on body surface area (mg/m^2) for rats and rabbits, respectively.

Empagliflozin and Metformin hydrochloride: No adverse developmental effects were observed when empagliflozin and metformin hydrochloride were coadministered to pregnant rats during the period of organogenesis at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

8.2 Lactation

Risk Summary

There is limited information regarding the presence of SYNJARDY XR or its components (empagliflozin or metformin) in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk *(see Data)*. Empagliflozin is present in the milk of lactating rats *(see Data)*. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of SYNJARDY XR is not recommended while breastfeeding.

Data

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

8.4 Pediatric Use

Safety and effectiveness of SYNJARDY XR have not been established in pediatric patients.

8.5 Geriatric Use

Assess renal function more frequently in SYNJARDY XR-treated geriatric patients because there is a greater risk of empagliflozin-associated intravascular volume contraction and symptomatic hypotension in geriatric patients and there is a greater risk of metformin-associated lactic acidosis in geriatric patients *[see Warnings and Precautions (5.1, 5.3)]*.

The recommended dosage for the metformin component of SYNJARDY XR in geriatric patients should usually start at the lower end of the dosage range.

Empagliflozin

In empagliflozin type 2 diabetes studies, 2721 empagliflozin-treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these studies, volume depletion-related adverse reactions occurred in 2.1%, 2.3%, and 4.4% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively; and urinary tract infections occurred in 10.5%, 15.7%, and 15.1% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively.

Metformin

Clinical studies of metformin did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger adult patients.

8.6 Renal Impairment

SYNJARDY XR should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2 due to the metformin component and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.

Empagliflozin

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.2)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Metformin

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment *[see Warnings and Precautions (5.1)]*.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

8.7 Hepatic Impairment

Use of metformin hydrochloride in patients with hepatic impairment has been associated with some cases of lactic acidosis. SYNJARDY XR is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

In the event of an overdose with SYNJARDY XR, contact the Poison Control Center.

Overdose of metformin HCl has occurred, including ingestion of amounts greater than 50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases *[see Warnings and Precautions (5.1)]*. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Removal of empagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

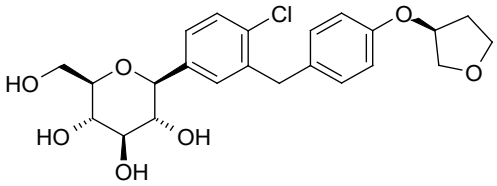
SYNJARDY XR tablets for oral use contain: empagliflozin and metformin hydrochloride.

Empagliflozin

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

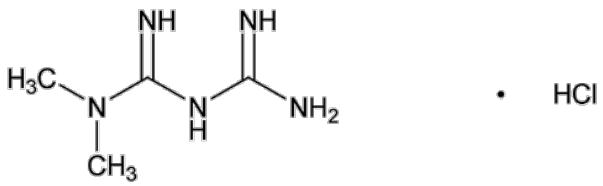
Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Each film-coated tablet of SYNJARDY XR consists of an extended-release metformin hydrochloride core tablet that is coated with the immediate-release drug substance empagliflozin.

SYNJARDY XR tablets for oral administration are available in four dosage strengths containing:

- 5 mg empagliflozin and 1000 mg metformin hydrochloride extended-release
- 10 mg empagliflozin and 1000 mg metformin hydrochloride extended-release
- 12.5 mg empagliflozin and 1000 mg metformin hydrochloride extended-release
- 25 mg empagliflozin and 1000 mg metformin hydrochloride extended-release

Each film-coated tablet of SYNJARDY XR contains the following inactive ingredients: Tablet Core: polyethylene oxide, hypromellose, and magnesium stearate. Film Coatings and Printing Ink: hypromellose, titanium dioxide, polydextrose, polyethylene glycol, talc, carnauba wax, purified water, ferrosoferric oxide, propylene glycol, isopropyl alcohol, ferric oxide yellow (5 mg/1000 mg, 10 mg/1000 mg, 25 mg/1000 mg), ferric oxide red (10 mg/1000 mg), FD&C blue#2/indigo carmine aluminum lake (12.5 mg/1000 mg, 25 mg/1000 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYNJARDY XR

SYNJARDY XR contains: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a biguanide.

Empagliflozin

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2), the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Metformin HCl

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike SUs, metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) *[see Warnings and Precautions (5.5)]* and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

12.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily *[see Clinical Studies (14)]*. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

12.3 Pharmacokinetics

SYNJARDY XR

Administration of SYNJARDY XR with food resulted in no change in overall exposure of empagliflozin. For metformin hydrochloride extended-release high-fat meals increased systemic exposure to metformin (as measured by area-under-the-curve [AUC]) by approximately 70% relative to fasting, while C_{max} is not affected. Meals prolonged T_{max} by approximately 3 hours.

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady-state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life.

Metabolism: No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion: Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Metformin

Absorption

Following a single oral dose of 1000 mg (2 x 500 mg tablets) metformin hydrochloride extended-release after a meal, the time to reach maximum plasma metformin concentration (T_{max}) is achieved at approximately 7 to 8 hours. In both single- and multiple-dose studies in healthy subjects, once daily 1000 mg (2 x 500 mg tablets)

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

dosing provides equivalent systemic exposure, as measured by AUC, and up to 35% higher C_{max} of metformin relative to the immediate-release given as 500 mg twice daily.

Single oral doses of metformin hydrochloride extended-release from 500 mg to 2500 mg resulted in less than proportional increase in both AUC and C_{max}. Low-fat and high-fat meals increased the systemic exposure (as measured by AUC) from metformin extended-release tablets by about 38% and 73%, respectively, relative to fasting. Both meals prolonged metformin T_{max} by approximately 3 hours but C_{max} was not affected.

Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

Metformin has a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Metabolism: Intravenous single-dose studies in normal subjects demonstrate that metformin does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Excretion: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

Specific Populations

Renal Impairment

SYNJARDY XR: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY XR in renally impaired patients have not been performed.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patients on dialysis due to kidney failure, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Metformin: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Hepatic Impairment

SYNJARDY XR: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY XR in hepatically impaired patients have not been performed *[see Warnings and Precautions (5.1)]*.

Empagliflozin: In patients with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Metformin hydrochloride: No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Effects of Age, Body Mass Index, Gender, and Race

Empagliflozin: Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Use in Specific Populations (8.5)]*.

Metformin hydrochloride: Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin HCl in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Caucasians (n=249), Blacks (n=51), and Hispanics (n=24).

Geriatric

SYNJARDY XR: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY XR in geriatric patients have not been performed *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5)]*.

Empagliflozin: Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis *[see Use in Specific Populations (8.5)]*.

Metformin hydrochloride: Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared with healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Drug Interactions

Pharmacokinetic drug interaction studies with SYNJARDY XR have not been performed; however, such studies have been conducted with the individual components empagliflozin and metformin HCl.

Empagliflozin

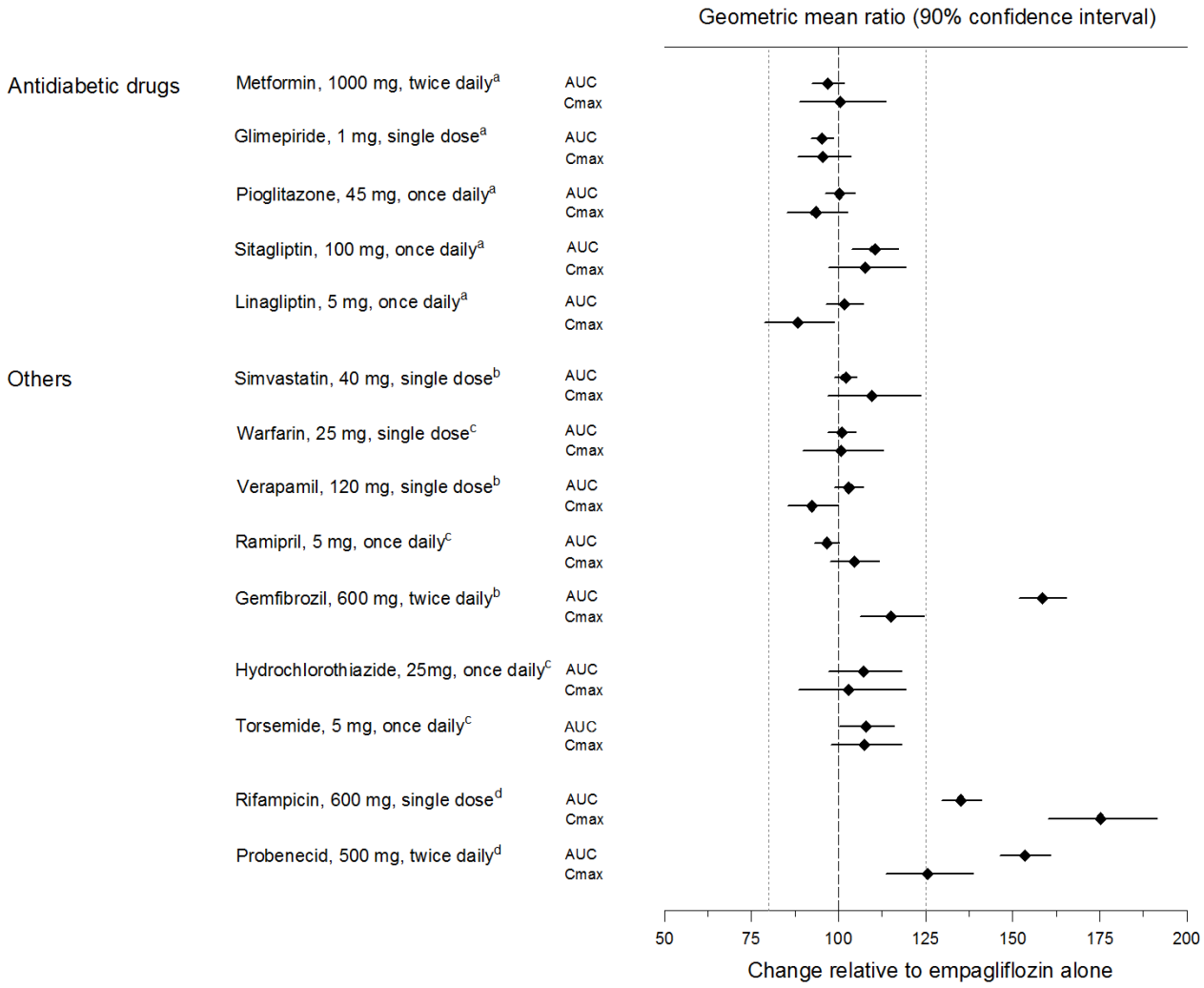
In vitro Assessment of Drug Interactions: Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

In vivo Assessment of Drug Interactions: Empagliflozin pharmacokinetics were similar with and without coadministration of metformin hydrochloride, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]

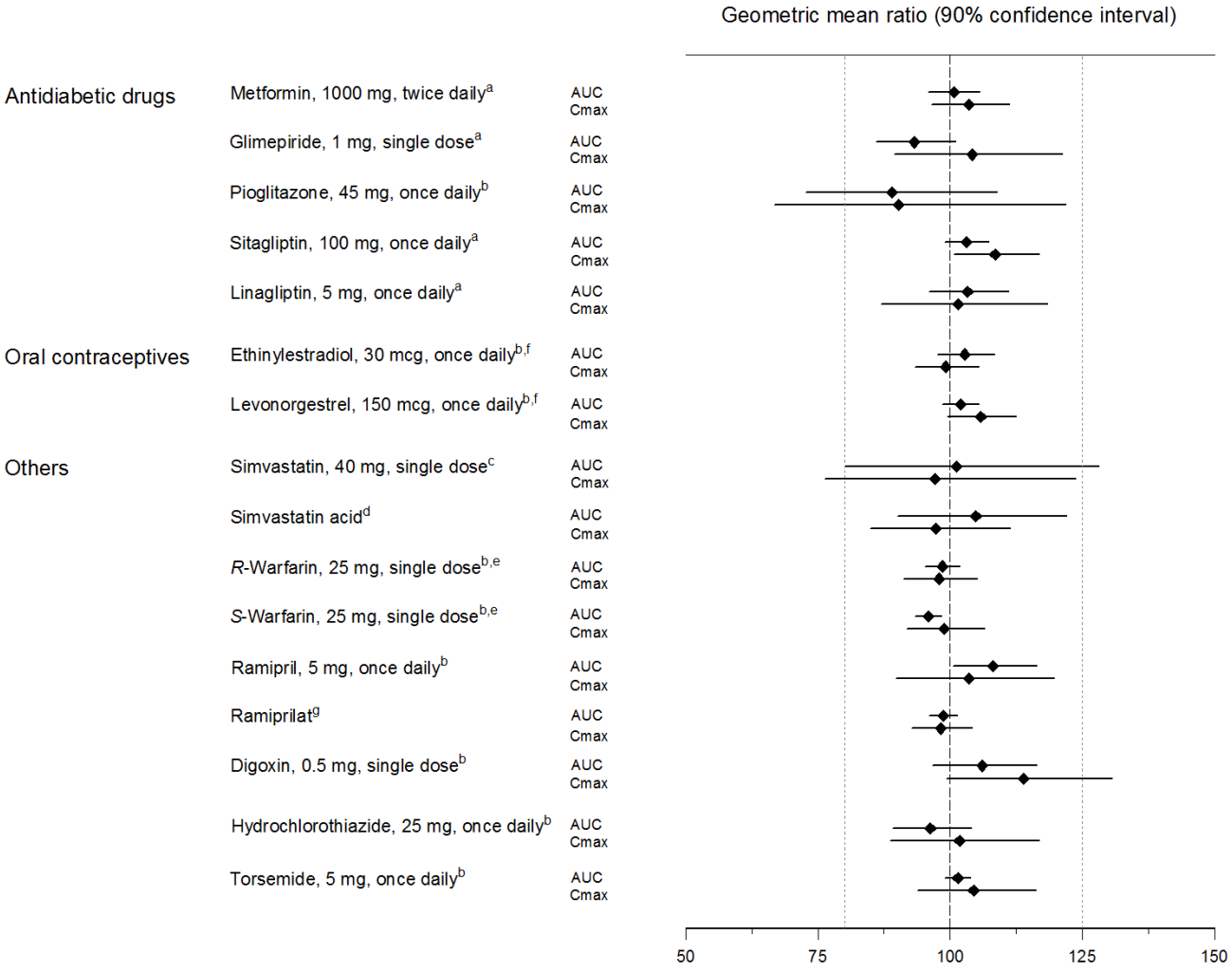


[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered with empagliflozin (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC†	C_{max}
Glyburide	5 mg	500 mg≠	metformin	0.98‡	0.99‡
Furosemide	40 mg	850 mg	metformin	1.09‡	1.22‡
Nifedipine	10 mg	850 mg	metformin	1.16	1.21
Propranolol	40 mg	850 mg	metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	metformin	1.05‡	1.07‡
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination *[see Drug Interactions (7)]*.					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis *[see Drug Interactions (7)]*.					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
≠ Metformin hydrochloride extended-release tablets 500 mg
‡ Ratio of arithmetic means
**At steady-state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC(0-12hours)

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin hydrochloride*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC†	C_{max}
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶
Cimetidine	400 mg	850 mg	cimetidine	0.95§	1.01

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF) unless otherwise noted
§ AUC(0-24 hours) reported
‡ Ratio of arithmetic means, p-value of difference <0.05
¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SYNJARDY XR

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with the combination of empagliflozin and metformin HCl. General toxicity studies in rats up to 13 weeks were performed with the combined components. These studies indicated that no additive toxicity is caused by the combination of empagliflozin and metformin.

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1000 mg/kg/day, which is approximately 45 times the exposure of the maximum

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

Metformin hydrochloride
Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses of up to 2000 mg/kg/day applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

14 CLINICAL STUDIES

SYNJARDY XR Glycemic Control Studies
In patients with type 2 diabetes, treatment with empagliflozin and metformin produced clinically and statistically significant improvements in HbA1c compared to placebo. Reductions in HbA1c were observed across subgroups including age, gender, race, and baseline body mass index (BMI).

Empagliflozin Add-On Combination Therapy with Metformin
A total of 637 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin.

Patients with type 2 diabetes inadequately controlled on at least 1500 mg of metformin hydrochloride per day entered an open-label 2-week placebo run-in. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

At Week 24, treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 7).

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Table 7 Results at Week 24 From a Placebo-Controlled Study for Empagliflozin used in Combination with Metformin

	Empagliflozin 10 mg + Metformin N=217	Empagliflozin 25 mg + Metformin N=213	Placebo + Metformin N=207
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	-0.1
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6[b] (-0.7, -0.4)	-0.6[b] (-0.8, -0.5)	--
Patients [n (%)] achieving HbA1c <7%	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL)[c]			
Baseline (mean)	155	149	156
Change from baseline (adjusted mean)	-20	-22	6
Difference from placebo + metformin (adjusted mean)	-26	-29	--
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0[b] (-2.6, -1.4)	-2.5[b] (-3.1, -1.9)	--

[a]Modified intent-to-treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for empagliflozin 10 mg, n=216, for empagliflozin 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for empagliflozin 25 mg.

Empagliflozin Initial Combination Therapy with Metformin
A total of 1364 patients with type 2 diabetes participated in a double-blind, randomized, active-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized to one of 8 active-treatment arms: empagliflozin 10 mg or 25 mg; metformin hydrochloride 1000 mg, or 2000 mg; empagliflozin 10 mg in combination with 1000 mg or 2000 mg metformin; or empagliflozin 25 mg in combination with 1000 mg or 2000 mg metformin hydrochloride.

At Week 24, initial therapy of empagliflozin in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 8).

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Table 8 Glycemic Parameters at 24 Weeks in a Study Comparing Empagliflozin and Metformin to the Individual Components as Initial Therapy

	Empagliflozin 10 mg + Metformin 1000 mg[a] N=161	Empagliflozin 10 mg + Metformin 2000 mg[a] N=167	Empagliflozin 25 mg + Metformin 1000 mg[a] N=165	Empagliflozin 25 mg + Metformin 2000 mg[a] N=169	Empagliflozin 10 mg N=169	Empagliflozin 25 mg N=163	Metformin 1000 mg[a] N=167	Metformin 2000 mg[a] N=162
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs empagliflozin (adjusted mean) (95% CI)	-0.6[b] (-0.9, -0.4)	-0.7[b] (-1.0, -0.5)	-0.6[c] (-0.8, -0.3)	-0.7[c] (-1.0, -0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8[b] (-1.0, -0.6)	-0.3[b] (-0.6, -0.1)	-0.8[c] (-1.0, -0.5)	-0.3[c] (-0.6, -0.1)	--	--	--	--
Patients [n (%)] achieving HbA1c <7%	96 (63%)	112 (70%)	91 (57%)	111 (68%)	69 (43%)	51 (32%)	63 (38%)	92 (58%)

[a]Metformin hydrochloride total daily dose, administered in two equally divided doses per day.
[b]p-value ≤0.0062 (modified intent-to-treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).
[c]p-value ≤0.0056 (modified intent-to-treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

A total of 666 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of empagliflozin in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes on at least 1500 mg per day of metformin hydrochloride and on a sulfonylurea, entered a 2-week open-label placebo run-in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, empagliflozin 10 mg, or empagliflozin 25 mg.

Treatment with empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 9).

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Table 9 Results at Week 24 from a Placebo-Controlled Study for Empagliflozin in Combination with Metformin and Sulfonylurea

	Empagliflozin 10 mg + Metformin + SU N=225	Empagliflozin 25 mg + Metformin + SU N=216	Placebo + Metformin + SU N=225
HbA1c (%)[a]			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.8	-0.8	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.6[b] (-0.8, -0.5)	-0.6[b] (-0.7, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL)[c]			
Baseline (mean)	151	156	152
Change from baseline (adjusted mean)	-23	-23	6
Difference from placebo (adjusted mean)	-29	-29	--
Body Weight			
Baseline mean in kg	77	78	76
% change from baseline (adjusted mean)	-2.9	-3.2	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.4[b] (-3.0, -1.8)	-2.7[b] (-3.3, -2.1)	--

[a]Modified intent-to-treat population. Last observation on study (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for empagliflozin 10 mg, n=225, for empagliflozin 25 mg, n=215, for placebo, n=224

Active-Controlled Study vs Glimepiride in Combination with Metformin

The efficacy of empagliflozin was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2-week run-in period were randomized to glimepiride or empagliflozin 25 mg.

At Week 52, empagliflozin 25 mg and glimepiride lowered HbA1c and FPG (see Table 10, Figure 3). The difference in observed effect size between empagliflozin 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day.

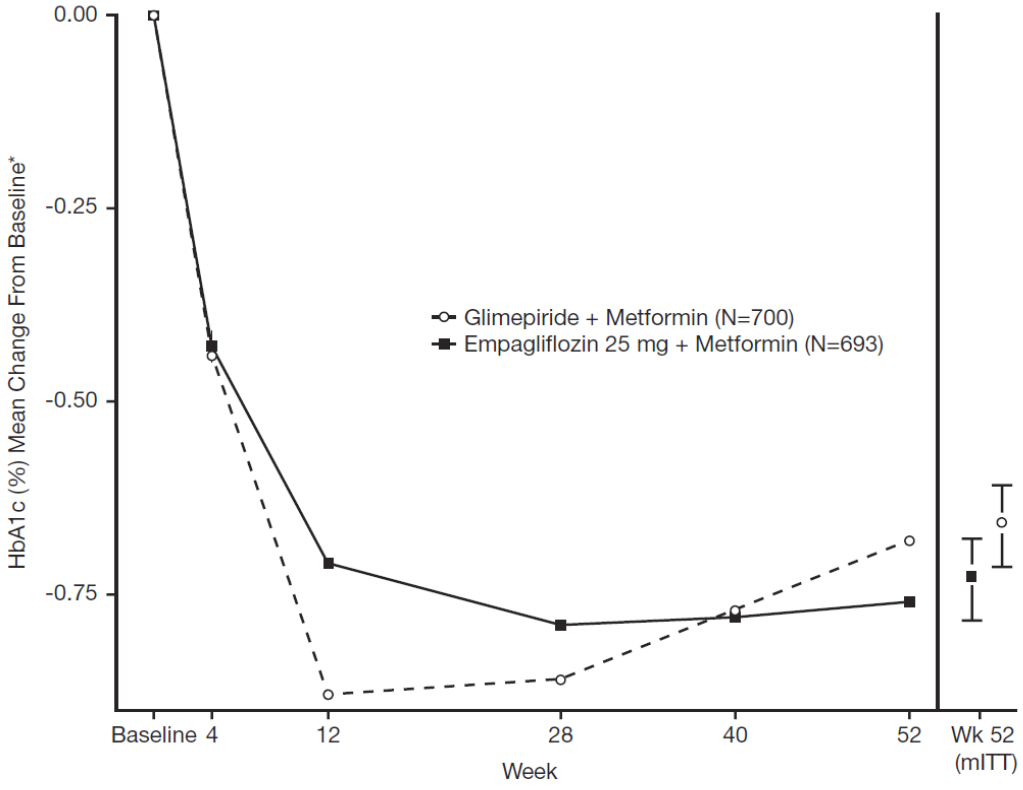
This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Table 10 Results at Week 52 from an Active-Controlled Study Comparing Empagliflozin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	Empagliflozin 25 mg + Metformin N=765	Glimepiride + Metformin N=780
HbA1c (%)[a]		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07[b] (-0.15, 0.01)	--
FPG (mg/dL)[d]		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9[c] (-6.3, -5.5)	--

[a]Modified intent-to-treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to empagliflozin 25 mg and glimepiride, respectively.
[b]Non-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)
[c]ANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[d]FPG (mg/dL); for empagliflozin 25 mg, n=764, for glimepiride, n=779

Figure 3 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for empagliflozin 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for empagliflozin 25 mg and 12.9% for glimepiride.

At Week 104, empagliflozin 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for empagliflozin 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

Empagliflozin Cardiovascular Outcome Study in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease is presented below.

The EMPA-REG OUTCOME study, a multicenter, multinational, randomized, double-blind parallel group trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between empagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Coadministered antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7020 patients were treated (empagliflozin 10 mg = 2345; empagliflozin 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators, respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), and sulfonylurea (43%).

All patients had established atherosclerotic cardiovascular disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

Empagliflozin significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI: 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects randomized to empagliflozin (HR: 0.62; 95% CI: 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 11 and Figures 4 and 5). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

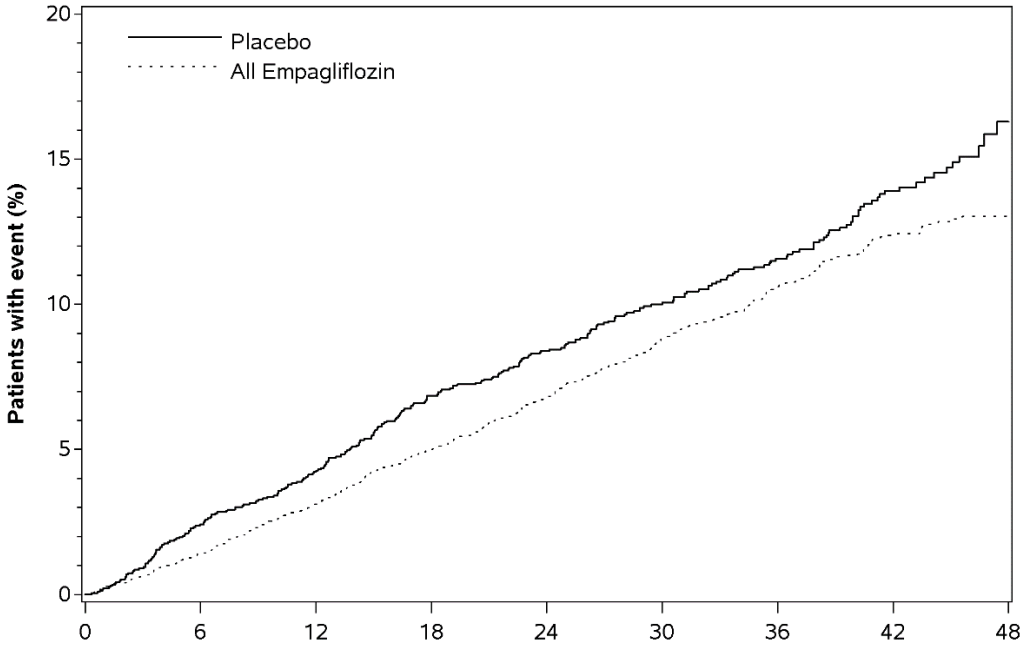
Table 11 Treatment Effect for the Primary Composite Endpoint and its Components[a]

	Placebo N=2333	**Empagliflozin N=4687**	**Hazard ratio vs placebo (95% CI)**
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

[a]Treated set (patients who had received at least one dose of study drug)
[b]p-value for superiority (2-sided) 0.04
[c]Total number of events

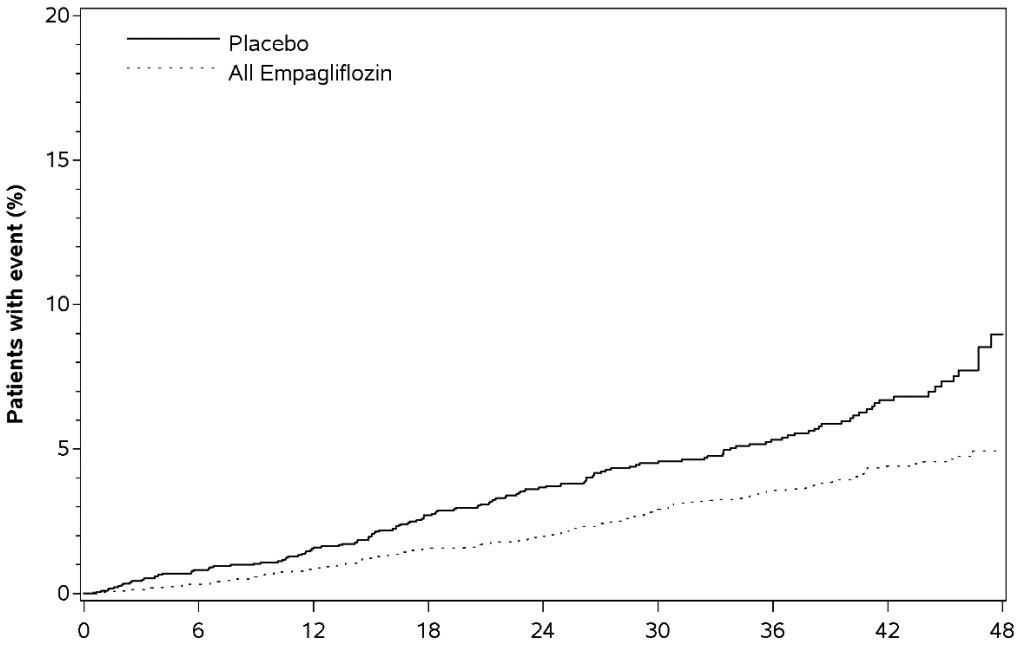
This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Figure 4 Estimated Cumulative Incidence of First MACE



Subjects at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Figure 5 Estimated Cumulative Incidence of Cardiovascular Death



Subjects at risk									
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

The efficacy of empagliflozin on cardiovascular death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths and were balanced between the treatment groups (2.1% in patients treated with empagliflozin, and 2.4% of patients treated with placebo).

16 HOW SUPPLIED/STORAGE AND HANDLING

SYNJARDY XR tablets are available as follows:

Tablet Strength	Color/Shape	Tablet Markings	Package Size	NDC Number
5 mg Empagliflozin 1000 mg Metformin HCl	olive green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S5" on the top line and "1000 M" on the bottom line.	Bottles of 60 Bottles of 180	0597-0290-74 0597-0290-59
10 mg Empagliflozin 1000 mg Metformin HCl	orange, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S10" on the top line and "1000 M" on the bottom line.	Bottles of 30 Bottles of 90	0597-0280-73 0597-0280-90
12.5 mg Empagliflozin 1000 mg Metformin HCl	blue, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S12" on the top line and "1000 M" on the bottom line.	Bottles of 60 Bottles of 180	0597-0300-45 0597-0300-93
25 mg Empagliflozin 1000 mg Metformin HCl	light green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company logo and "S25" on the top line and "1000 M" on the bottom line.	Bottles of 30 Bottles of 90	0597-0295-88 0597-0295-78

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to metformin, its symptoms, and conditions that predispose to its development. Advise patients to discontinue SYNJARDY XR immediately and to notify their healthcare provider promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving SYNJARDY XR. Instruct patients to inform their healthcare provider that they are taking SYNJARDY XR prior to any surgical or radiological procedure, as temporary discontinuation may be required until renal function has been confirmed to be normal *[see Warnings and Precautions (5.1)]*.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of empagliflozin, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue SYNJARDY XR and seek medical attention immediately *[see Warnings and Precautions (5.2)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with SYNJARDY XR and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.3)]*. Inform patients that dehydration may increase the risk for hypotension, and to maintain adequate fluid intake.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the risk of hypoglycemia is increased when SYNJARDY XR is used in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin, and that a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.5)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with empagliflozin, a component of SYNJARDY XR. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria and angioedema, have been reported with empagliflozin, a component of SYNJARDY XR. Advise patients to report immediately any skin reaction or angioedema, and to discontinue the drug until they have consulted prescribing healthcare provider *[see Warnings and Precautions (5.8)]*.

Vitamin B_{12} Deficiency

Inform patients about importance of regular hematological parameters while receiving SYNJARDY XR *[see Warnings and Precautions (5.9)]*.

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking SYNJARDY XR.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Pregnancy
Advise pregnant patients, and patients of reproductive potential, of the potential risk to a fetus with treatment with SYNJARDY XR *[see Use in Specific Populations (8.1)]*. Instruct patients to report pregnancies to their healthcare provider as soon as possible.

Lactation
Advise patients that breastfeeding is not recommended during treatment with SYNJARDY XR *[see Use in Specific Populations (8.2)]*.

Patients of Reproductive Potential
Inform patients that treatment with metformin may result in ovulation in some premenopausal anovulatory patients, which may lead to unintended pregnancy *[see Use in Specific Populations (8.3)]*.

Administration Instructions
Inform patients that the tablets must be swallowed whole and never split, crushed, dissolved, or chewed and that incompletely dissolved SYNJARDY XR tablets may be eliminated in the feces.

Missed Dose
Instruct patients to take SYNJARDY XR only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Marketed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
and
Eli Lilly and Company
Indianapolis, IN 46285 USA

Licensed from:
Boehringer Ingelheim International GmbH, Ingelheim, Germany

SYNJARDY is a registered trademark of and used under license from Boehringer Ingelheim International GmbH.

Boehringer Ingelheim Pharmaceuticals, Inc. either owns or uses the Jardiance® and EMPA-REG OUTCOME® trademarks under license.

The other brands listed are trademarks of their respective owners and are not trademarks of Boehringer Ingelheim Pharmaceuticals, Inc.

Copyright © 2022 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

COL8977GI222022

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

MEDICATION GUIDE
SYNJARDY® XR (sin-JAR-dee XR)
(empagliflozin and metformin hydrochloride extended-release tablets)
for oral use

What is the most important information I should know about SYNJARDY XR?
SYNJARDY XR can cause serious side effects, including:

- **Lactic Acidosis. Metformin hydrochloride, one of the medicines in SYNJARDY XR 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 a hospital.**
  Stop taking SYNJARDY XR and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms of lactic acidosis:
  - feel very weak and tired
  - have unusual (not normal) muscle pain
  - have trouble breathing
  - have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
  - have unusual sleepiness or sleep longer than usual
  - feel cold, especially in your arms and legs
  - feel dizzy or lightheaded
  - have a slow or irregular heartbeat

  You have a higher chance of getting lactic acidosis with SYNJARDY XR if you:
  - have moderate to severe kidney problems.
  - have liver problems.
  - drink a lot of alcohol (very often or short-term “binge” drinking).
  - get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
  - have certain x-ray tests with injectable dyes or contrast agents.
  - have surgery or other procedure for which you need to restrict the amount of food and liquid you eat and drink.
  - have congestive heart failure.
  - have a heart attack, severe infection, or stroke.
  - are 65 years of age or older.

  Tell your healthcare provider if you have any of the problems in the list above. Tell your healthcare provider that you are taking SYNJARDY XR before you have surgery or x-ray tests. Your healthcare provider may need to stop your SYNJARDY XR for a while if you have surgery or certain x-ray tests. SYNJARDY XR can have other serious side effects. See **“What are the possible side effects of SYNJARDY XR?”**
- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes**, during treatment with empagliflozin, one of the medicines in SYNJARDY XR. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with SYNJARDY XR. Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death.
  Ketoacidosis can happen with SYNJARDY XR even if your blood sugar is less than 250 mg/dL. Stop taking SYNJARDY XR and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms:
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing

  If you get any of these symptoms during treatment with SYNJARDY XR, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- **Dehydration.** SYNJARDY XR can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking SYNJARDY XR.

  You may be at higher risk of dehydration if you:
  - have kidney problems
  - are 65 years of age or older
  - are on low sodium (salt) diet
  - take medicines to lower your blood pressure, including diuretics (water pills)

  Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

  Talk to your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you are sick or cannot eat or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

What is SYNJARDY XR?

SYNJARDY XR is a prescription medicine that contains 2 diabetes medicines, empagliflozin (JARDIANCE) and metformin hydrochloride. SYNJARDY XR can be used:

- along with diet and exercise to improve blood sugar in adults with type 2 diabetes,
- in adults with type 2 diabetes who have known cardiovascular disease when empagliflozin (JARDIANCE), one of the medicines in SYNJARDY XR, is needed to reduce the risk of cardiovascular death.

- SYNJARDY XR is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine).
- It is not known if SYNJARDY XR is safe and effective in children.

Who should not take SYNJARDY XR?

Do not take SYNJARDY XR if you:

- have severe kidney problems, end stage renal disease or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to empagliflozin (JARDIANCE), metformin, or any of the ingredients in SYNJARDY XR. See the end of this Medication Guide for a complete list of ingredients in SYNJARDY XR. Symptoms of a serious allergic reaction to SYNJARDY XR may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking SYNJARDY XR and call your healthcare provider right away or go to the nearest hospital emergency room.

What should I tell my healthcare provider before taking SYNJARDY XR?

Before taking SYNJARDY XR, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are 65 years of age or older.
- have a history of infection of the vagina or penis.
- have a history of urinary tract infection or problems with urination.
- are going to have surgery. Your healthcare provider may stop your SYNJARDY XR before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking SYNJARDY XR and when to start it again.
- are eating less, or there is a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short term (“binge” drinking).
- are going to get an injection of dye or contrast agents for an x-ray procedure. SYNJARDY XR may need to be stopped for a short time. Talk to your healthcare provider about when you should stop SYNJARDY XR and when you should start SYNJARDY XR again. See **“What is the most important information I should know about SYNJARDY XR?”**
- have type 1 diabetes. SYNJARDY XR should not be used to treat people with type 1 diabetes.
- have low levels of vitamin B_{12} in your blood.
- are pregnant or plan to become pregnant. SYNJARDY XR may harm your unborn baby. If you become pregnant while taking SYNJARDY XR, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. SYNJARDY XR may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking SYNJARDY XR. Do not breastfeed while taking SYNJARDY XR.
- are a person who has not gone through menopause (premenopausal) who does not have periods regularly or at all. SYNJARDY XR can cause the release of an egg from an ovary in a person (ovulation). This can increase your chance of getting pregnant. Tell your healthcare provider right away if you become pregnant while taking SYNJARDY XR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

SYNJARDY XR may affect the way other medicines work, and other medicines may affect how SYNJARDY XR works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

How should I take SYNJARDY XR?

- Take SYNJARDY XR exactly as your healthcare provider tells you to take it.
- Take SYNJARDY XR by mouth 1 time each day with a meal in the morning. Taking SYNJARDY XR with a meal may lower your chance of having an upset stomach.
- Swallow SYNJARDY XR tablets whole. Do not break, cut, crush, dissolve, or chew SYNJARDY XR tablets. If you cannot swallow SYNJARDY XR tablets whole, tell your healthcare provider.
- You may see something that looks like the SYNJARDY XR tablet in your stool (bowel movement). This is not harmful and should not affect the way SYNJARDY XR works to control your diabetes.
- Your healthcare provider may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of SYNJARDY XR at the same time. Talk with your healthcare provider if you have questions about a missed dose.
- Your healthcare provider may tell you to take SYNJARDY XR along with other diabetes medicines. Low blood sugar can happen more often when SYNJARDY XR is taken with certain other diabetes medicines. See **"What are the possible side effects of SYNJARDY XR?"**
- If you take too much SYNJARDY XR, call your healthcare provider or go to the nearest hospital emergency room right away.
- Your healthcare provider will do blood tests to check how well your kidneys are working before and during your treatment with SYNJARDY XR.
- When taking SYNJARDY XR, you may have sugar in your urine, which will show up on a urine test.

What should I avoid while taking SYNJARDY XR?

Avoid drinking alcohol very often, or drinking a lot of alcohol in a short period of time ("binge" drinking). It can increase your chances of getting serious side effects.

What are the possible side effects of SYNJARDY XR?

SYNJARDY XR may cause serious side effects, including:

- See **"What is the most important information I should know about SYNJARDY XR?"**
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking empagliflozin, one of the medicines in SYNJARDY XR. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** If you take SYNJARDY XR 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 SYNJARDY XR. Signs and symptoms of low blood sugar may include:
  - headache
  - irritability
  - confusion
  - dizziness
  - drowsiness
  - hunger
  - shaking or feeling jittery
  - sweating
  - weakness
  - fast heartbeat
- **A rare but serious bacterial infection that causes damage to 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 empagliflozin, one of the medicines in SYNJARDY XR. 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 a 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
  - redness of skin (erythema)
- **Vaginal yeast infection.** Symptoms of a vaginal yeast infection 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).** Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include redness, itching, or swelling of the penis, rash of the penis, foul smelling discharge from the penis, or pain in the skin around the penis.

  Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions have happened in people who are taking empagliflozin, one of the medicines in SYNJARDY XR. Symptoms may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

If you have any of these symptoms, stop taking SYNJARDY XR and call your healthcare provider right away or go to the nearest hospital emergency room.

- **Low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your healthcare provider may do blood tests to check your vitamin B_{12} levels.

The most common side effects of SYNJARDY XR include:

- low blood sugar
- urinary tract infection
- stuffy or runny nose and sore throat
- yeast infections in females
- diarrhea
- nausea or vomiting
- gas
- stomach discomfort
- indigestion
- weakness
- headache

These are not all the possible side effects of SYNJARDY XR. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SYNJARDY XR?

- Store SYNJARDY XR at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep SYNJARDY XR and all medicines out of the reach of children.**

General information about the safe and effective use of SYNJARDY XR.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYNJARDY XR for a condition for which it was not prescribed. Do not give SYNJARDY XR to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about SYNJARDY XR that is written for health professionals.

What are the ingredients in SYNJARDY XR?

Active Ingredients: empagliflozin and metformin hydrochloride
Inactive Ingredients: Tablet core contains: polyethylene oxide, hypromellose, and magnesium stearate. The Film Coatings and Printing Ink contain: hypromellose, titanium dioxide, polydextrose, polyethylene glycol, talc, carnauba wax, purified water, ferrosoferric oxide, propylene glycol, isopropyl alcohol, ferric oxide yellow (5 mg/1000 mg, 10 mg/1000 mg, 25 mg/1000 mg), ferric oxide red (10 mg/1000 mg), FD&C blue#2/indigo carmine aluminum lake (12.5 mg/1000 mg, 25 mg/1000 mg).

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT 06877 USA

Marketed by: Boehringer Ingelheim Pharmaceuticals, Inc.; Ridgefield, CT 06877 USA and Eli Lilly and Company, Indianapolis, IN 46285 USA

Licensed from: Boehringer Ingelheim International GmbH, Ingelheim, Germany

SYNJARDY is a registered trademark of and used under license from Boehringer Ingelheim International GmbH.

Boehringer Ingelheim Pharmaceuticals, Inc. either owns or uses the Jardiance® and EMPA-REG OUTCOME® trademarks under license.

The other brands listed are trademarks of their respective owners and are not trademarks of Boehringer Ingelheim Pharmaceuticals, Inc.

Copyright © 2022 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

COL8977GI222022

For more information about SYNJARDY XR including current prescribing information and Medication Guide, go to **www.synjardyxr.com**, or scan the code, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: October 2022