

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

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

INDICATIONS AND USAGE

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

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

Limitations of Use:

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

DOSAGE AND ADMINISTRATION

- Individualize the starting dose of SYNJARDY XR based on the patient's current regimen (2.1)
- The maximum recommended total daily dose is 25 mg empagliflozin and 2000 mg metformin hydrochloride (2.1)
- Take once daily with a meal in the morning, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.1)
- Swallow whole; do not split, crush, dissolve, or chew (2.1)
- Assess renal function before initiating. SYNJARDY XR is contraindicated in patients with an eGFR below 45 mL/min/1.73 m² (2.2, 4)
- SYNJARDY XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures (2.3)

DOSAGE FORMS AND STRENGTHS

SYNJARDY XR Tablets:

- 5 mg empagliflozin/1000 mg metformin hydrochloride extended-release
- 10 mg empagliflozin/1000 mg metformin hydrochloride extended-release
- 12.5 mg empagliflozin/1000 mg metformin hydrochloride extended-release
- 25 mg empagliflozin/1000 mg metformin hydrochloride extended-release (3)

CONTRAINDICATIONS

- Moderate to severe renal impairment (eGFR below 45 mL/min/1.73 m²), end stage renal disease, or dialysis (4, 5.1, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)

- History of serious hypersensitivity reaction to empagliflozin, metformin or any of the excipients in SYNJARDY XR (4)

WARNINGS AND PRECAUTIONS

- *Lactic acidosis:* See boxed warning (5.1)
- *Hypotension:* Before initiating SYNJARDY XR assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.2)
- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue SYNJARDY 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. (5.3)
- *Acute kidney injury and impairment in renal function:* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy (5.4)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.5)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating SYNJARDY XR (5.6)
- *Genital mycotic infections:* Monitor and treat as appropriate (5.7)
- *Hypersensitivity reactions:* Discontinue SYNJARDY XR, treat promptly, and monitor until signs and symptoms resolve (5.8)
- *Vitamin B₁₂ deficiency:* Metformin may lower vitamin B₁₂ levels. Monitor hematologic parameters annually. (5.9)
- *Increased LDL-C:* Monitor and treat as appropriate (5.10)
- *Macrovascular outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SYNJARDY XR. (5.11)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

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

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

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

If metformin-associated lactic acidosis is suspected, immediately discontinue SYNJARDY 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 indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and metformin hydrochloride is appropriate.

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

Limitations of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating SYNJARDY XR [see *Warnings and Precautions (5.2)*].
- Individualize the starting dose of SYNJARDY XR based on the patient's current regimen:
 - In patients on metformin hydrochloride, switch to SYNJARDY XR containing a similar total daily dose of metformin hydrochloride 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 hydrochloride extended-release 1000 mg;

- In patients already treated with empagliflozin and metformin hydrochloride, switch to SYNJARDY XR containing the same total daily doses of empagliflozin and a similar total daily dose of metformin hydrochloride.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin hydrochloride 2000 mg and empagliflozin 25 mg [*see Dosage and Administration (2.2)*].
- The dose of metformin hydrochloride should be gradually escalated to reduce the gastrointestinal side effects due to metformin hydrochloride [*see Dosage Forms and Strengths (3)*].
- Take SYNJARDY XR orally once daily with a meal in the morning
- Swallow SYNJARDY XR tablets whole. Do not split, crush, dissolve, or chew before swallowing. There have been reports of incompletely dissolved tablets being eliminated in the feces for other tablets containing metformin hydrochloride extended-release. If a patient reports seeing tablets in feces, the healthcare provider should assess adequacy of glycemic control.
- 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.

2.2 Recommended Dosage in Patients with Renal Impairment

- Assess renal function prior to initiation of SYNJARDY XR and periodically, thereafter.
- SYNJARDY XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m² [*see Contraindications (4) and Warnings and Precautions (5.1, 5.4)*].

2.3 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 between 45 and 60 mL/min/1.73 m²; 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 (empagliflozin and metformin hydrochloride extended-release) oval-shaped, film-coated tablets are available in the following strengths:

- 5 mg empagliflozin/1000 mg metformin hydrochloride olive green tablets 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 empagliflozin/1000 mg metformin hydrochloride orange tablets 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 empagliflozin/1000 mg metformin hydrochloride blue tablets 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 empagliflozin/1000 mg metformin hydrochloride light green tablets 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:

- Moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m²), end stage renal disease, or dialysis [*see Warnings and Precautions (5.1, 5.4) and Use in Specific Populations (8.6)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin [*see Warnings and Precautions (5.1)*].
- History of serious hypersensitivity reaction to empagliflozin, metformin or any of the excipients in SYNJARDY XR [*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* (2.2), *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 45 mL/min/1.73 m² [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* (7.2)]. Therefore, consider more frequent monitoring of patients.

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

Radiological Studies with Contrast: Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop SYNJARDY XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 45 and 60 mL/min/1.73 m²; 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 Hypotension

Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin [see *Adverse Reactions (6.1)*] particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating SYNJARDY XR, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected [see *Use in Specific Populations (8.5)*].

5.3 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin. 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 due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating 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. In patients treated with SYNJARDY XR consider monitoring for ketoacidosis and temporarily discontinuing SYNJARDY XR in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.4 Acute Kidney Injury and Impairment in Renal Function

Empagliflozin causes intravascular volume contraction [*see Warnings and Precautions (5.2)*] and can cause renal impairment [*see Adverse Reactions (6.1)*]. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Before initiating SYNJARDY XR, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing SYNJARDY XR in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue SYNJARDY XR promptly and institute treatment.

Empagliflozin increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating SYNJARDY XR [*see Adverse Reactions (6.1)*]. Renal function should be evaluated prior to initiation of SYNJARDY XR and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m². Use of SYNJARDY XR is contraindicated in patients with an eGFR less than 45 mL/min/1.73 m² [*see Dosage and Administration (2.2), Contraindications (4) and Use in Specific Populations (8.6)*].

5.5 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including 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)*].

5.6 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Empagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when empagliflozin 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.

Metformin

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as SUs and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β -adrenergic blocking drugs. Monitor for a need to lower the dose of SYNJARDY XR to minimize the risk of hypoglycemia in these patients.

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.

5.8 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with empagliflozin, one of the components of SYNJARDY XR. 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 a previous serious hypersensitivity reaction to empagliflozin or any of the excipients in SYNJARDY XR [see *Contraindications (4)*].

5.9 Vitamin B₁₂ Levels

In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of metformin-treated patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B₁₂ levels appears to be rapidly reversible with discontinuation of metformin or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on SYNJARDY XR and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurement at 2- to 3-year intervals may be useful.

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

Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

5.11 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SYNJARDY XR.

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)*]
- Hypotension [see *Warnings and Precautions (5.2)*]
- Ketoacidosis [see *Warnings and Precautions (5.3)*]
- Acute Kidney Injury and Impairment in Renal Function [see *Warnings and Precautions (5.4)*]
- Urosepsis and Pyelonephritis [see *Warnings and Precautions (5.5)*]
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [see *Warnings and Precautions (5.6)*]
- Genital Mycotic Infections [see *Warnings and Precautions (5.7)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.8)*]
- Vitamin B₁₂ Deficiency [see *Warnings and Precautions (5.9)*]
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) [see *Warnings and Precautions (5.10)*]

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 $\geq 5\%$ of patients and more commonly than in patients given placebo.

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 $\geq 5\%$ 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 $\geq 5\%$ of Patients Treated with Empagliflozin added on to Metformin plus Sulfonylurea and Greater than with Placebo in a 24-week Placebo Controlled Clinical Study

| | Number (%) of Patients | | |
|-------------------------|------------------------|------------------------------|------------------------------|
| | Placebo n=225 | Empagliflozin 10 mg n=224 | Empagliflozin 25 mg n=217 |
| Hypoglycemia | 22 (9.8) | 35 (15.6) | 28 (12.9) |
| Urinary tract infection | 15 (6.7) | 21 (9.4) | 15 (6.9) |
| Nasopharyngitis | 11 (4.9) | 18 (8.0) | 13 (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 m²).

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 $\geq 2\%$ of Patients Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of Empagliflozin Monotherapy or Combination Therapy

| | Number (%) of Patients | | |
|--|------------------------|------------------------------|------------------------------|
| | 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% |

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

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

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

^dMale genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), 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 *Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6)*].

Increased Urination

In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 3). 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.

Acute Impairment in Renal Function

Treatment with empagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 3). Patients with moderate renal impairment at baseline had larger mean changes [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.5, 8.6)*].

In a long-term cardiovascular outcome trial, the acute impairment in renal function was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes play a role in the renal function changes observed with empagliflozin.

Table 3 Changes from Baseline in Serum Creatinine and eGFR^a in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study

| | | Pool of 24-Week Placebo-Controlled Studies | | |
|------------------------------------|------------------------------------|--|---------------------|---------------------|
| | | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
| Baseline Mean | N | 825 | 830 | 822 |
| | Creatinine (mg/dL) | 0.84 | 0.85 | 0.85 |
| | eGFR (mL/min/1.73 m ²) | 87.3 | 87.1 | 87.8 |
| Week 12 Change | N | 771 | 797 | 783 |
| | Creatinine (mg/dL) | 0.00 | 0.02 | 0.01 |
| | eGFR (mL/min/1.73 m ²) | -0.3 | -1.3 | -1.4 |
| Week 24 Change | N | 708 | 769 | 754 |
| | Creatinine (mg/dL) | 0.00 | 0.01 | 0.01 |
| | eGFR (mL/min/1.73 m ²) | -0.3 | -0.6 | -1.4 |
| | | Moderate Renal Impairment ^b | | |
| | | Placebo | | Empagliflozin 25 mg |
| Baseline Mean | N | 187 | -- | 187 |
| | Creatinine (mg/dL) | 1.49 | -- | 1.46 |
| | eGFR (mL/min/1.73 m ²) | 44.3 | -- | 45.4 |
| Week 12 Change | N | 176 | -- | 179 |
| | Creatinine (mg/dL) | 0.01 | -- | 0.12 |
| | eGFR (mL/min/1.73 m ²) | 0.1 | -- | -3.8 |
| Week 24 Change | N | 170 | -- | 171 |
| | Creatinine (mg/dL) | 0.01 | -- | 0.10 |
| | eGFR (mL/min/1.73 m ²) | 0.2 | -- | -3.2 |
| Week 52 Change | N | 164 | -- | 162 |
| | Creatinine (mg/dL) | 0.02 | -- | 0.11 |
| | eGFR (mL/min/1.73 m ²) | -0.3 | -- | -2.8 |
| Post-treatment Change ^c | N | 98 | -- | 103 |
| | Creatinine (mg/dL) | 0.03 | -- | 0.02 |
| | eGFR (mL/min/1.73 m ²) | 0.16 | -- | 1.48 |

^aObserved cases on treatment.

^bSubset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m².

^cApproximately 3 weeks after end of treatment.

Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 4. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea [see *Warnings and Precautions (5.6)*].

Table 4 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% |

^aOverall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL

^bSevere hypoglycemic events: requiring assistance regardless of blood glucose

^cTreated set (patients who had received at least one dose of study drug)

^dInsulin 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 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

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 Warnings and Precautions (5.5) and 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%).

Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anemia) [*see Warnings and Precautions (5.9)*].

Laboratory Tests

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 [*see Warnings and Precautions (5.10)*]. 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

In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum Vitamin B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation [*see Warnings and Precautions (5.9)*].

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

- Ketoacidosis [*see Warnings and Precautions (5.3)*]
- Urosepsis and pyelonephritis [*see Warnings and Precautions (5.5)*]
- Angioedema [*see Warnings and Precautions (5.8)*]

- Skin reactions (e.g., rash, urticaria)

Metformin hydrochloride

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

7 DRUG INTERACTIONS

7.1 Drug Interactions with Empagliflozin

Diuretics

Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion [see *Warnings and Precautions (5.2)*].

Insulin or Insulin Secretagogues

Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia [see *Warnings and Precautions (5.6)*].

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

7.2 Drug Interactions with Metformin Hydrochloride

Drugs that Reduce Metformin Clearance

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)*]. Consider the benefits and risks of concomitant use.

Carbonic Anhydrase Inhibitors

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. Consider more frequent monitoring of these patients [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

Drugs Affecting Glycemic Control

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. When such drugs are administered to a patient receiving SYNJARDY XR, the patient should be closely observed to maintain adequate glycemic control [see *Clinical Pharmacology (12.3)*]. When such drugs are withdrawn from a patient receiving SYNJARDY XR, the patient should be observed closely for hypoglycemia.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving SYNJARDY XR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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, adverse renal changes were observed in rats when empagliflozin was 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. Empagliflozin was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg when administered during organogenesis. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during the period of organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area (*see Data*).

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% 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 2-4% and 15-20%, 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, stillbirth, 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 post-marketing 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.

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 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/m²) 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 no information regarding the presence of SYNJARDY XR or empagliflozin 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*). However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. 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 women 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.

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 -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 in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

Because renal function abnormalities can occur after initiating empagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients [*see Dosage and Administration (2.2) and Warnings and Precautions (5.1, 5.4)*].

Empagliflozin

No empagliflozin dosage change is recommended based on age [*see Dosage and Administration (2)*]. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished glycemic efficacy in elderly patients with renal impairment [*see Use in Specific Populations (8.6)*]. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively [*see Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].

Metformin hydrochloride

Controlled clinical studies of metformin hydrochloride did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [*see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

SYNJARDY XR is contraindicated in patients with moderate to severe renal impairment (eGFR less than 45 mL/min/1.73 m²).

Empagliflozin

The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations [*see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.2, 5.4)*].

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment [*see Warnings and Precautions (5.4)*], volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Empagliflozin may be used in patients with an eGFR greater than or equal to 45 mL/min/1.73 m² [*see Clinical Pharmacology (12.3)*]. Empagliflozin is not recommended in patients with an eGFR less than 45 mL/min/1.73 m².

Metformin hydrochloride

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. SYNJARDY XR is contraindicated in moderate to severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m² [see *Contraindications (4) and Warnings and Precautions (5.1)*].

8.7 Hepatic Impairment

SYNJARDY XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease [see *Warnings and Precautions (5.1)*].

Empagliflozin

Empagliflozin may be used in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

Metformin hydrochloride

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. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied. However, metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful partly for removal of accumulated metformin from patients in whom SYNJARDY XR overdose is suspected.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Boxed Warning and Warnings and Precautions (5.1)*].

11 DESCRIPTION

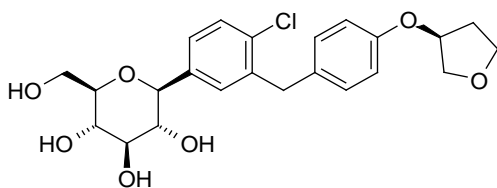
SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use, contain two antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and metformin hydrochloride.

Empagliflozin

Empagliflozin is an orally-active 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).

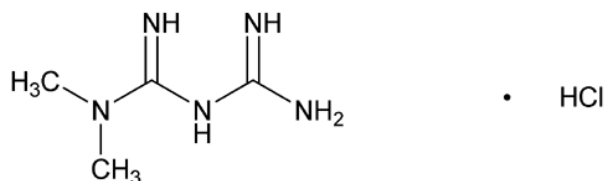
Its molecular formula is C₂₃H₂₇ClO₇ and the molecular weight is 450.91. The structural formula is:



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 not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ 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:



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, ferrosferic 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 combines 2 antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin, a member of the biguanide class.

Empagliflozin

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

Metformin hydrochloride

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 (5.6)*] 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)*].

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.

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%.

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.

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. Following administration of an oral [¹⁴C]-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 hydrochloride

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) 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, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin hydrochloride, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Elimination

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

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 [*see Contraindications (4) and Warnings and Precautions (5.4)*].

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m²), moderate (eGFR: 30 to less than 60 mL/min/1.73 m²), and severe (eGFR: less than 30 mL/min/1.73 m²) renal impairment and subjects with kidney failure/end stage renal disease (ESRD) patients, 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 subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects 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 hydrochloride: 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 subjects 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.

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 hydrochloride 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, 5.4) 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.

Pediatric

Studies characterizing the pharmacokinetics of empagliflozin or metformin after administration of SYNJARDY XR in pediatric patients have not been performed.

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 hydrochloride.

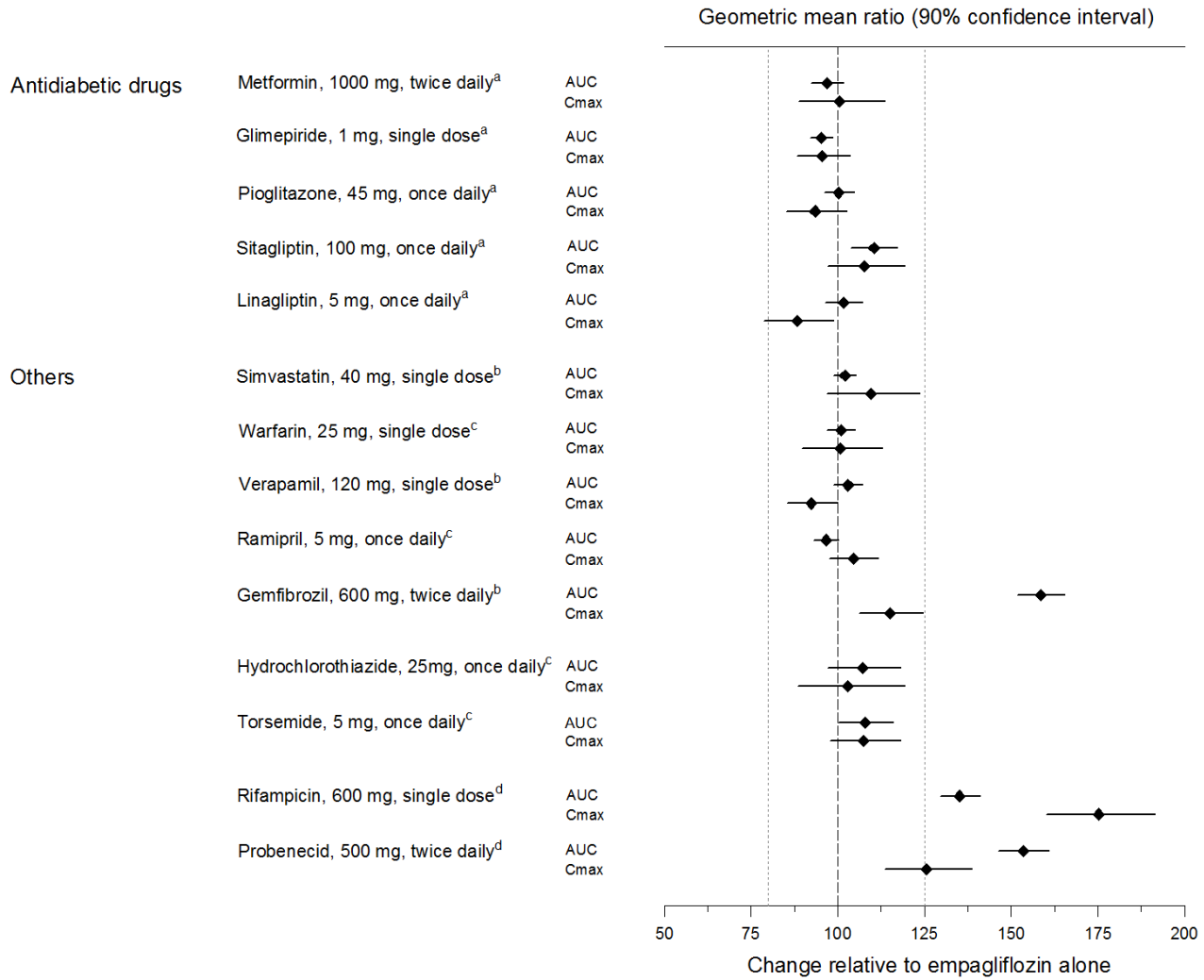
Empagliflozin

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.

In vivo Assessment of Drug Interactions: No dose adjustment of empagliflozin is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. 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). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. 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.

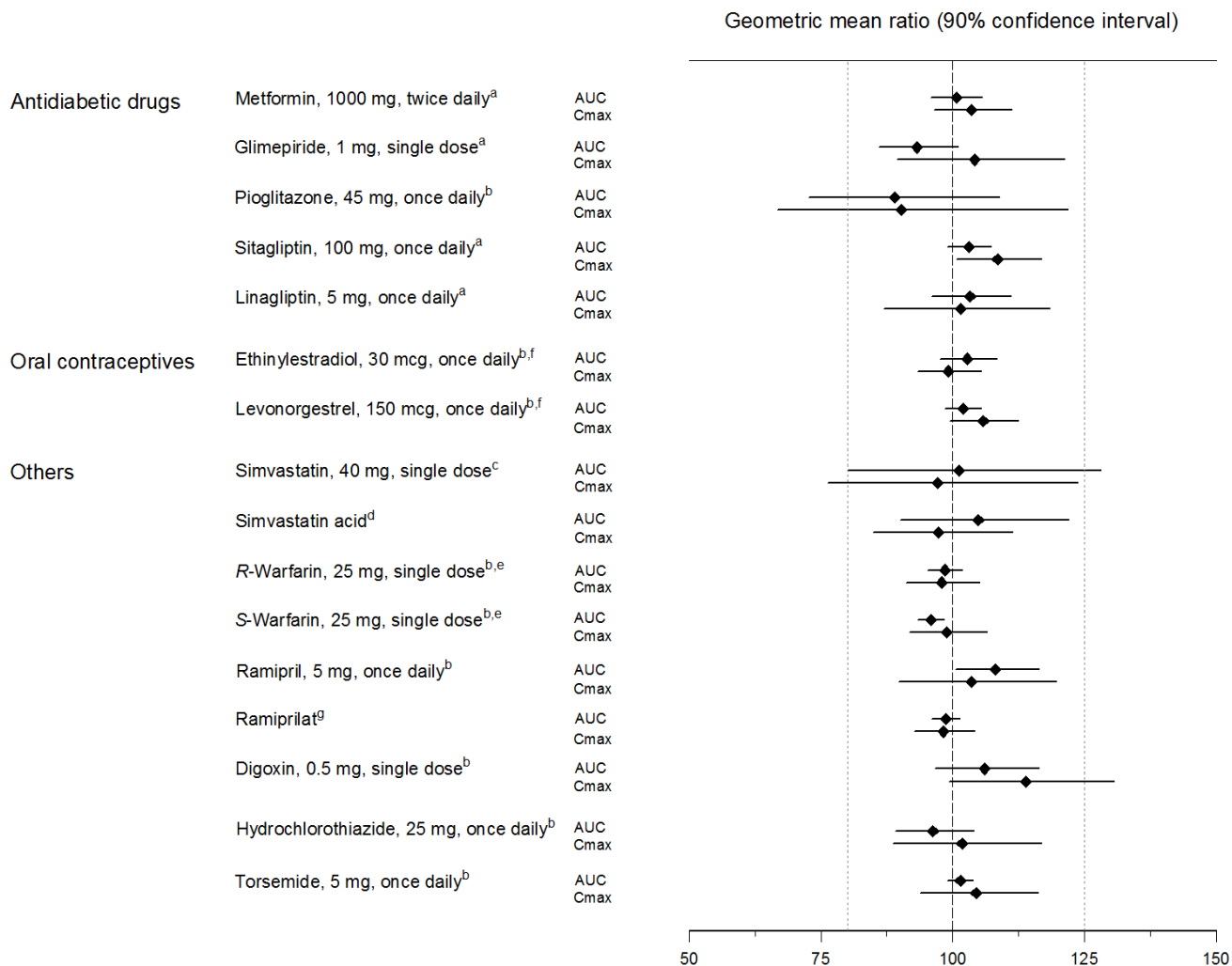
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, single dose; ^cempagliflozin, 25 mg, once daily; ^dempagliflozin, 10 mg, single dose

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%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, once daily; ^cempagliflozin, 25 mg, single dose; ^dadministered as simvastatin; ^eadministered as warfarin racemic mixture; ^fadministered as Microgynon[®]; ^gadministered as ramipril

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

| Coadministered Drug | Dosing of Coadministered Drug* | Dose of Metformin hydrochloride* | Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0 | | |
|--|--------------------------------|----------------------------------|---|-------------------|-------------------|
| | | | | AUC [†] | C _{max} |
| No dosing adjustments required for the following coadministered drugs: | | | | | |
| 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 [‡] |
| Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin [see Warnings and Precautions (5.1) and Drug Interactions (7.1)]. | | | | | |
| Cimetidine | 400 mg | 850 mg | metformin | 1.40 | 1.61 |
| Carbonic anhydrase inhibitors may cause metabolic acidosis [see Warnings and Precautions (5.1) and Drug Interactions (7.1)]. | | | | | |
| 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 = AUC0-12h

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

| Coadministered Drug | Dosing of Coadministered Drug* | Dose of Metformin hydrochloride* | Geometric Mean Ratio (ratio with/without metformin) No effect=1.0 | | |
|---|--------------------------------|----------------------------------|---|-------------------|-------------------|
| | | | | AUC [†] | C _{max} |
| No dosing adjustments required for the following coadministered drugs: | | | | | |
| 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 hr) 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 animal studies have been conducted with the combination of empagliflozin and metformin hydrochloride to evaluate carcinogenesis, mutagenesis, or impairment of fertility. 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

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

Mutagenesis

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.

Impairment of Fertility

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

Carcinogenesis

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times 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 mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

Mutagenesis

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*Salmonella typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Impairment of Fertility

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 2 times the MRHD based on body surface area comparisons.

14 CLINICAL STUDIES

14.1 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).

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) | -- |

^aModified 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.

^bANCOVA 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.)

^cFPG (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).

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%) |

^aMetformin hydrochloride total daily dose, administered in two equally divided doses per day.

^bp-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).

^cp-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).

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) | -- |

^aModified 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.

^bANCOVA 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.)

^cFPG (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.

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) | -- |

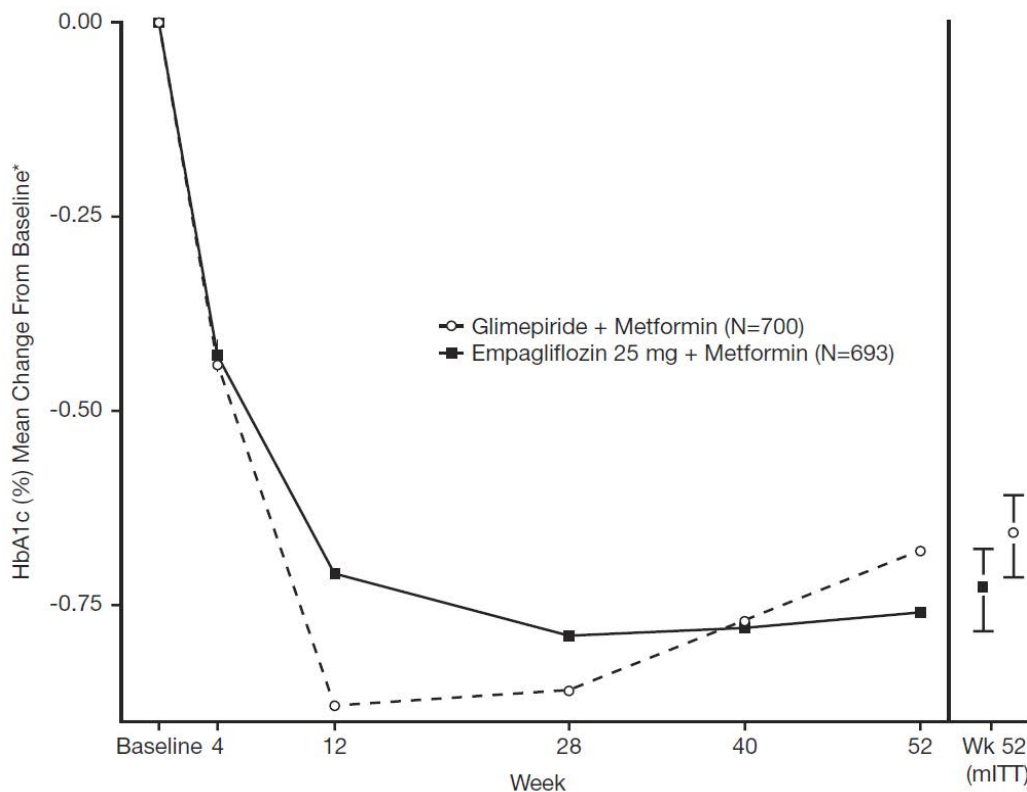
^aModified intent to treat population. Last observation on study (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to empagliflozin 25 mg and glimepiride, respectively.

^bNon-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)

^cANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^dFPG (mg/dL); for empagliflozin 25 mg, n=764, for placebo, 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.

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).

14.2 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. However, the effectiveness of SYNJARDY XR on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease has not been established. 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, multi-national, 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 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 m². 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 nonfatal myocardial infarction (MI) or a nonfatal stroke. The statistical analysis plan had pre-specified that 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 Figure 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

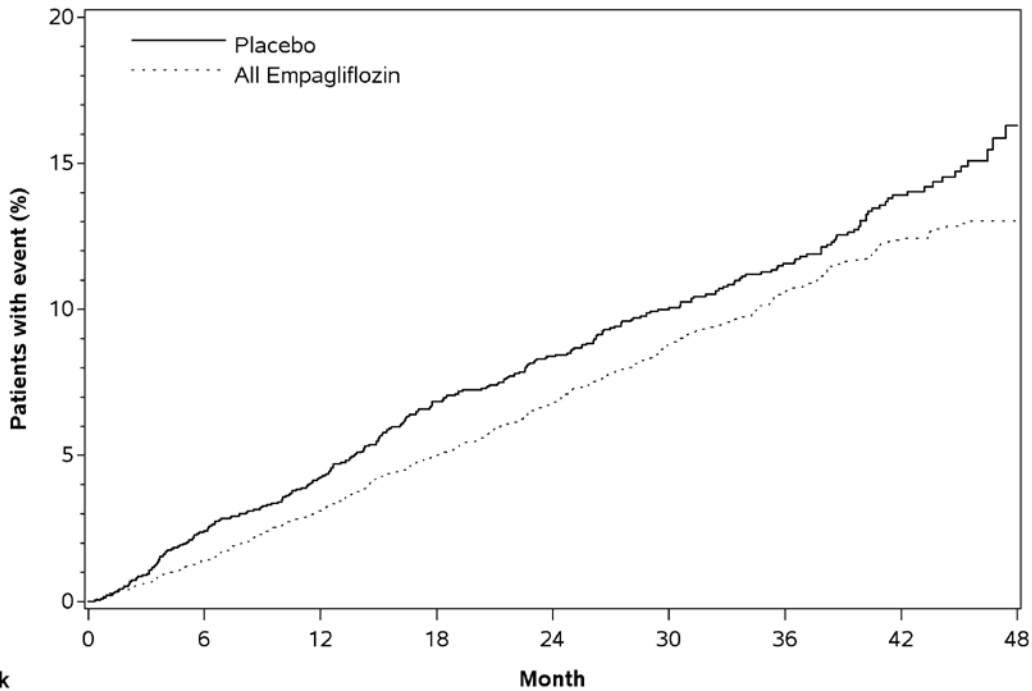
| | Placebo N=2333 | Empagliflozin N=4687 | Hazard ratio vs placebo (95% CI) |
|--|---------------------------|---------------------------------|---|
| Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence) ^b | 282 (12.1%) | 490 (10.5%) | 0.86 (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) |

^aTreated set (patients who had received at least one dose of study drug)

^bp-value for superiority (2-sided) 0.04

^cTotal number of events

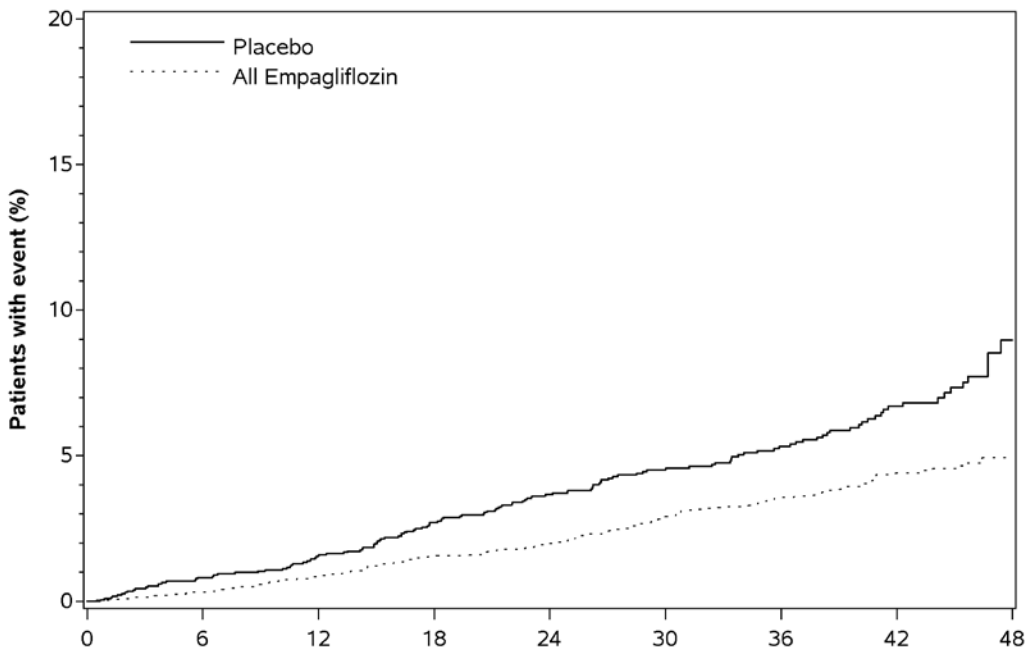
Figure 4 Estimated Cumulative Incidence of First MACE



Subjects at risk

| | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|-------------------|------|------|------|------|------|------|------|------|-----|
| 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

| | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 |
|-------------------|------|------|------|------|------|------|------|------|-----|
| Placebo | 2333 | 2303 | 2280 | 2243 | 2012 | 1503 | 1281 | 825 | 177 |
| All Empagliflozin | 4687 | 4651 | 4608 | 4556 | 4128 | 3079 | 2617 | 1722 | 414 |

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 (empagliflozin and metformin hydrochloride extended-release) tablets are available in the following strengths and packages:

| Tablet Strength | Film-Coated Tablet, Color/Shape | Tablet Markings | Package Size | NDC Number |
|-----------------|---------------------------------|--|---------------------------------|------------------------------|
| 5 mg/1000 mg | olive green, oval, biconvex | 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/1000 mg | orange, oval, biconvex | 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/1000 mg | blue, oval, biconvex | 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/1000 mg | light green, oval, biconvex | 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 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Store in a safe place out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

Medication Guide

Instruct patients to read the Medication Guide before starting SYNJARDY XR therapy and to reread it each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients of the potential risks and benefits of SYNJARDY XR and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic

blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Lactic Acidosis

Inform patients of the risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development [see *Warnings and Precautions (5.1)*]. Advise patients to discontinue SYNJARDY XR immediately and to notify their doctor promptly if unexplained hyperventilation, malaise, myalgia, unusual somnolence, slow or irregular heart beat, sensation of feeling cold (especially in the extremities), or other nonspecific symptoms occur. GI symptoms are common during initiation of metformin treatment and may occur during initiation of SYNJARDY XR therapy; however, advise patients to consult their doctor if they develop unexplained symptoms. Although GI symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to metformin-induced lactic acidosis or other serious disease.

Hypotension

Inform patients that hypotension may occur with SYNJARDY XR and advise them to contact their healthcare provider if they experience such symptoms [see *Warnings and Precautions (5.2)*]. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of empagliflozin. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood 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 advice immediately [see *Warnings and Precautions (5.3)*].

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of empagliflozin. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue SYNJARDY XR use in those settings [see *Warnings and Precautions (5.4)*].

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 (5.5)*].

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)*].

Monitoring of Renal Function

Inform patients about the importance of regular testing of renal function when receiving treatment with SYNJARDY XR.

Instruct patients to inform their doctor that they are taking SYNJARDY XR prior to any surgical or radiological procedure, as temporary discontinuation of SYNJARDY XR may be required until renal function has been confirmed to be normal [*see Warnings and Precautions (5.1)*].

Hypoglycemia

Inform patients that the risk of hypoglycemia is increased when SYNJARDY XR is used in combination with an insulin secretagogue (e.g., sulfonylurea), and that a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia [*see Warnings and Precautions (5.6)*].

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 physician [*see Warnings and Precautions (5.8)*].

Laboratory Tests

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

Pregnancy

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

Lactation

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

Females and Males of Reproductive Potential

Inform females that treatment with metformin may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy [*see Use in Specific Populations (8.3)*].

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.

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. Patients should be told that, if they see tablets in feces, they should report this finding to their healthcare provider. The healthcare provider should assess adequacy of glycemic control if a patient reports observing tablets in feces [*see Dosage and Administration (2.1)*].

Blood Glucose and A1C Monitoring

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels toward the normal range. Hemoglobin A1c monitoring is especially useful for evaluating long-term glycemic control.

Inform patients that the most common adverse reactions associated with the use of SYNJARDY XR are hypoglycemia, urinary tract infection, and nasopharyngitis.

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MEDICATION GUIDE
SYNJARDY® XR (sin-JAR-dee XR)
(empagliflozin and metformin hydrochloride extended-release)
Tablets

What is the most important information I should know about SYNJARDY XR?

Serious side effects can happen in people taking SYNJARDY XR, including:

Lactic Acidosis. Metformin, 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.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with SYNJARDY XR if you:

- have moderate to severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye.
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in the 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 surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your SYNJARDY XR for a while if you have any of these things.

SYNJARDY XR can have other serious side effects. See **“What are the possible side effects of SYNJARDY XR?”**

What is SYNJARDY XR?

- SYNJARDY XR is a prescription medicine that contains 2 prescription diabetes medicines, empagliflozin and metformin. 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 both empagliflozin and metformin is appropriate and empagliflozin is needed to reduce the risk of cardiovascular death.
- SYNJARDY XR is not for people with type 1 diabetes.
- SYNJARDY XR is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- It is not known if SYNJARDY XR is safe and effective in children under 18 years of age.

Who should not take SYNJARDY XR?

Do not take SYNJARDY XR if you:

- have moderate to severe kidney problems or are on dialysis
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine)
- are allergic to empagliflozin, metformin, or any of the ingredients in SYNJARDY XR. See the end of this Medication Guide for a list of ingredients in SYNJARDY XR.

What should I tell my doctor before using SYNJARDY XR?

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

- have moderate to severe kidney problems
- have liver problems
- have a history of urinary tract infection or problems with urination
- have heart problems, including congestive heart failure
- are going to have surgery
- are eating less due to illness, surgery, or 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 doctor 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 any other medical conditions
- are pregnant or plan to become pregnant. SYNJARDY XR may harm your unborn baby. If you become pregnant while taking SYNJARDY XR, tell your doctor as soon as possible. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are a premenopausal woman (before the “change of life”), who does not have periods regularly or at all. Talk to your doctor about birth control choices while taking SYNJARDY XR if you are not planning to become pregnant since SYNJARDY XR may increase your chance of becoming pregnant. Tell your doctor right away if you become pregnant while taking SYNJARDY XR.
- are breastfeeding or plan to breastfeed. SYNJARDY XR may pass into your breast milk and may harm your baby. Talk with your doctor about the best way to feed your baby if you are taking SYNJARDY XR. Do not breastfeed while taking SYNJARDY XR.

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

How should I take SYNJARDY XR?

- Take SYNJARDY XR exactly as your doctor 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.
- Take SYNJARDY XR tablets whole. Do not break, cut, crush, dissolve, or chew SYNJARDY XR tablets before swallowing. If you cannot swallow SYNJARDY XR tablets whole, tell your doctor.
- You may see something that looks like the SYNJARDY XR tablet in your stool (bowel movement). If you see tablets in your stool talk to your doctor. Do not stop taking SYNJARDY XR without talking to your doctor.
- Your doctor will tell you how much SYNJARDY XR to take and when to take it.
- Your doctor 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 doctor if you have questions about a missed dose.
- Your doctor 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 doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor’s instructions.
- Check your blood sugar as your doctor tells you to.
- When taking SYNJARDY XR, you may have sugar in your urine, which will show up on a urine test.
- Stay on your prescribed diet and exercise program while taking SYNJARDY XR.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with SYNJARDY XR.
- Your doctor may do certain blood tests before you start SYNJARDY XR and during treatment.

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?”**
- **Dehydration.** SYNJARDY XR can cause some people to have dehydration (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). You may be at higher risk of dehydration if you:
 - have low blood pressure
 - 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)
- **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 is a serious condition, which may need 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 doctor right away 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.

- **Kidney problems.** Sudden kidney injury has happened to people taking SYNJARDY XR. Talk to your doctor 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

- **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 doctor 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 sulfonyleurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonyleurea medicine or insulin may need to be lowered while you take SYNJARDY XR. Signs and symptoms of low blood sugar may include:

- headache
- drowsiness
- weakness
- irritability
- hunger
- fast heartbeat
- confusion
- shaking or feeling jittery
- dizziness
- sweating

- **Vaginal yeast infection.** Women who take SYNJARDY XR may get vaginal yeast infections. 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).** Men who take SYNJARDY XR may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis 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 doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor 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)

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

- **Low vitamin B₁₂ (vitamin B₁₂ deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B₁₂ in your blood, especially if you have had low vitamin B₁₂ blood levels before. Your doctor may do blood tests to check your vitamin B₁₂ levels.

- **Increased fats in your blood (cholesterol)**

Other common side effects of SYNJARDY XR include diarrhea, nausea, vomiting, gas, stomach pain, indigestion, weakness, and headache.

These are not all the possible side effects of SYNJARDY XR. For more information, ask your doctor 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).

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.

This Medication Guide summarizes the most important information about SYNJARDY XR. If you would like more information, talk with your doctor. 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, ferrosferric 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 (12.5mg/1000mg, 25mg/1000mg).

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For more information, go to www.synjardyxr.com, or scan the adjacent code, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.



This Medication Guide has been approved by the U.S. Food and Drug Administration

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