SYNJARDY- empagliflozin and metformin hydrochloride tablet
Boehringer Ingelheim Pharmaceuticals, Inc.

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

SYNJARDY® (empagliflozin and metformin hydrochloride tablets), for oral use
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, hepatic impairment, and mitochondrial diseases. 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 or SYNJARDY XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)**

RECENT MAJOR CHANGES

Boxed Warning	8/2026
Warnings and Precautions, Lactic Acidosis (5.1)	8/2026
Warnings and Precautions, Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections (5.4)	10/2025

INDICATIONS AND USAGE

SYNJARDY
SYNJARDY is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin hydrochloride (HCl) immediate-release, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

SYNJARDY XR
SYNJARDY XR is a combination of empagliflozin, a SGLT2 inhibitor and metformin HCl extended-release, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Empagliflozin
Empagliflozin, when used as a component of SYNJARDY or SYNJARDY XR, is indicated in adults with type 2 diabetes mellitus to reduce the risk of:

- Cardiovascular (CV) death in adults with established CV disease. (1)
- CV death and hospitalization for heart failure in adults with heart failure. (1)
- Sustained decline in eGFR, end-stage kidney disease, CV death, and hospitalization in adults with chronic kidney disease at risk of progression. (1)

Limitations of Use:

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. (1)
- Because of the metformin HCl component, the use of SYNJARDY or SYNJARDY XR is limited to patients with type 2 diabetes mellitus for all indications. (1)
- Empagliflozin, when used as a component of SYNJARDY or SYNJARDY XR, is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of intravenous immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for kidney disease. Empagliflozin is not expected to be effective in these populations. (1)

DOSAGE AND ADMINISTRATION

- Assess renal function before initiating and as clinically indicated. Assess volume status and correct volume depletion before initiating. (2.1)
- Individualize the starting dosage based on the patient's current regimen and renal function. (2.2, 2.3, 2.4)
- The maximum recommended dosage is 25 mg/day of empagliflozin and 2,000 mg/day of metformin HCl. (2.2, 2.3)
- Initiation of SYNJARDY or SYNJARDY XR is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin HCl component. (2.4)
- SYNJARDY: take orally twice daily with meals, with gradual dosage escalation to reduce the gastrointestinal adverse reactions due to metformin HCl. (2.2, 2.3)
- SYNJARDY XR: take orally once daily with a meal in the morning, with gradual dosage escalation to reduce the gastrointestinal adverse reactions due to metformin HCl. Swallow whole; do not split, crush, dissolve, or chew. (2.2)
- SYNJARDY or SYNJARDY XR may need to be discontinued at time of, or prior to, iodinated contrast

imaging procedures. (2.5)
- Withhold SYNJARDY or SYNJARDY XR at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. (2.6)

DOSAGE FORMS AND STRENGTHS

SYNJARDY Tablets:
- 5 mg empagliflozin/500 mg metformin HCl (3)
- 5 mg empagliflozin/1,000 mg metformin HCl (3)
- 12.5 mg empagliflozin/500 mg metformin HCl (3)
- 12.5 mg empagliflozin/1,000 mg metformin HCl (3)

SYNJARDY XR Tablets:
- 5 mg empagliflozin/1,000 mg metformin HCl extended-release (3)
- 10 mg empagliflozin/1,000 mg metformin HCl extended-release (3)
- 12.5 mg empagliflozin/1,000 mg metformin HCl extended-release (3)
- 25 mg empagliflozin/1,000 mg metformin HCl extended-release (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:* Consider ketone monitoring in patients at risk of ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue SYNJARDY or SYNJARDY XR if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.2)
- *Volume Depletion:* Before initiating SYNJARDY or SYNJARDY XR, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy. (5.3)
- *Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections:* Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated. Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis and if suspected, discontinue SYNJARDY or SYNJARDY XR, and promptly institute appropriate medical and/or surgical intervention. (5.4)
- *Hypoglycemia:* Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher regardless of insulin use. Consider lowering the dosage of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating SYNJARDY or SYNJARDY XR. (5.5)
- *Lower Limb Amputation:* Monitor patients for infections or ulcers of lower limbs, and institute appropriate treatment. (5.6)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., angioedema) have occurred with empagliflozin. If hypersensitivity reactions occur, discontinue SYNJARDY or SYNJARDY XR, treat promptly, and monitor until signs and symptoms resolve. (5.7)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematologic parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.8)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2026

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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, hepatic impairment, and mitochondrial diseases *[see Warnings and Precautions (5.1)]*.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information *[see Dosage and Administration (2.1), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)].*

If metformin-associated lactic acidosis is suspected, immediately discontinue SYNJARDY or 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

SYNJARDY is a combination of empagliflozin and metformin hydrochloride (HCl) immediate-release indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

SYNJARDY XR

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

Empagliflozin

Empagliflozin, when used as a component of SYNJARDY or SYNJARDY XR, is indicated in adults with type 2 diabetes mellitus to reduce the risk of:

- Cardiovascular (CV) death in adults with established CV disease.
- CV death and hospitalization for heart failure in adults with heart failure.
- Sustained decline in eGFR, end-stage kidney disease, CV death, and hospitalization in adults with chronic kidney disease at risk of progression.

Limitations of Use

- SYNJARDY and SYNJARDY XR are not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.2)]*.
- Because of the metformin HCl component, the use of SYNJARDY or SYNJARDY XR is limited to patients with type 2 diabetes mellitus for all indications.
- Empagliflozin, when used as a component of SYNJARDY or SYNJARDY XR, is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of intravenous immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for kidney disease *[see Clinical Studies (14.5)]*. Empagliflozin is not expected to be effective in these populations.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of SYNJARDY or SYNJARDY XR

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

2.2 Recommended Dosage and Administration of SYNJARDY or SYNJARDY XR in Adults

- When switching to SYNJARDY or SYNJARDY XR from:
  - Metformin HCl: initiate SYNJARDY or SYNJARDY XR at a similar total daily dosage of metformin HCl and a total daily empagliflozin dosage of 10 mg.
  - Empagliflozin: initiate SYNJARDY or SYNJARDY XR at the same total daily dosage of empagliflozin and a total daily metformin HCl dosage of 1,000 mg.
  - Empagliflozin and metformin HCl: initiate SYNJARDY or SYNJARDY XR at the same total daily dosages of each component.
- Recommended dosage of SYNJARDY or SYNJARDY XR:
  - The recommended total daily dosage of empagliflozin is 10 mg.
  - For additional glycemic control, empagliflozin may be increased to a maximum total daily dosage of 25 mg in patients tolerating 10 mg daily and metformin HCl may be increased to a maximum total daily dosage of 2,000 mg, with gradual escalation to reduce gastrointestinal adverse reactions with metformin HCl *[see Adverse Reactions (6.1)]*.
- Take SYNJARDY orally twice daily with meals.
- Take SYNJARDY XR orally once daily with a meal in the morning. Swallow each tablet whole. Do not split, crush, dissolve, or chew.

2.3 Recommended Dosage and Administration of SYNJARDY in Pediatric Patients Aged 10 Years and Older

- Individualize the dosage of SYNJARDY based on the patient's current regimen.
- Monitor effectiveness and tolerability, and adjust dosage as appropriate, not to exceed the maximum total daily dosage of empagliflozin 25 mg and metformin HCl 2,000 mg.
- Take SYNJARDY orally twice daily with meals; with gradual dose escalation to reduce gastrointestinal adverse reactions with metformin HCl *[see Adverse Reactions (6.1)]*.

2.4 Dosage Recommendations in Patients with Renal Impairment

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

2.5 Discontinuation for Iodinated Contrast Imaging Procedures

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

2.6 Temporary Interruption for Surgery

Withhold SYNJARDY or SYNJARDY XR for at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. Resume SYNJARDY or SYNJARDY XR when the patient is clinically stable and has resumed oral intake *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.2)]*.

2.7 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Advise patients not to double up the next dose.

3 DOSAGE FORMS AND STRENGTHS

SYNJARDY Tablets:

	Metformin		

Empagliflozin Strength	Metformin HCl Strength	Color/Shape	Tablet Markings
5 mg	500 mg	orange yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "500".
5 mg	1,000 mg	brownish yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "1000".
12.5 mg	500 mg	pale brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "500".
12.5 mg	1,000 mg	dark brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "1000".

SYNJARDY XR Tablets:

Empagliflozin Strength	Metformin HCl Extended - Release Strength	Color/Shape	Tablet Markings
5 mg	1,000 mg	olive green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol and "S5" on the top line and "1000 M" on the bottom line.
10 mg	1,000 mg	orange, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol and "S10" on the top line and "1000 M" on the bottom line.
12.5 mg	1,000 mg	blue, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol and "S12" on the top line and "1000 M" on the bottom line.
25 mg	1,000 mg	light green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol and "S25" on the top line and "1000 M" on the bottom line.

4 CONTRAINDICATIONS

SYNJARDY and SYNJARDY XR are contraindicated in patients with:

- severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].*

- acute or chronic metabolic acidosis, including diabetic ketoacidosis *[see Warnings and Precautions (5.1)]*.
- hypersensitivity to empagliflozin, metformin HCl or any of the excipients in SYNJARDY or SYNJARDY XR, reactions such as angioedema have occurred *[see Warnings and Precautions (5.7)]*.

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 or SYNJARDY XR. In SYNJARDY or 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 or 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 (2.4) and Clinical Pharmacology (12.3)]*:
- Before initiating SYNJARDY or SYNJARDY XR, obtain an estimated glomerular filtration rate (eGFR).
- SYNJARDY and SYNJARDY XR are contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2 *[see Contraindications (4)].*
- Obtain an eGFR at least annually in all patients taking SYNJARDY or 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 or SYNJARDY XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation *[see Drug Interactions (7)]*. Therefore, consider more frequent monitoring of patients.

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

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

Mitochondrial Diseases: Metformin may increase the risk of lactic acidosis in patients with mitochondrial diseases such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD). SYNJARDY and SYNJARDY XR are not recommended in patients with mitochondrial diseases such as MELAS syndrome and MIDD.

If a patient taking SYNJARDY or SYNJARDY XR develops elevated lactic acid levels (with or without accompanying neurologic signs and symptoms), discontinue SYNJARDY or SYNJARDY XR. Depending on the clinical context, consider evaluating the patient for MELAS, MIDD, or other mitochondrial disease.

5.2 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, empagliflozin, a component of SYNJARDY or SYNJARDY XR, significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium glucose co-transporter 2 (SGLT2) inhibitors compared to patients who received placebo and fatal ketoacidosis has occurred with empagliflozin. SYNJARDY and SYNJARDY XR are not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including SYNJARDY or SYNJARDY XR.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing SYNJARDY or SYNJARDY XR *[see Clinical Pharmacology (12.2)]*; however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue SYNJARDY or SYNJARDY XR, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting SYNJARDY or SYNJARDY XR.

Withhold SYNJARDY or SYNJARDY XR, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume SYNJARDY or SYNJARDY XR when the patient is clinically stable and has resumed oral intake *[see Dosage and Administration (2.6)]*.

Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to

discontinue SYNJARDY or SYNJARDY XR and seek medical attention immediately if signs and symptoms occur.

5.3 Volume Depletion

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

5.4 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Empagliflozin increases urinary glucose excretion *[see Clinical Pharmacology (12.2)]* and increases the risk of genitourinary infections including urinary tract infections and genital mycotic infections in both male and female patients *[see Adverse Reactions (6.1)]*.

Serious genitourinary infections, including urosepsis, pyelonephritis, and necrotizing fasciitis of the perineum (Fournier's gangrene, a rare life-threatening infection requiring urgent surgical intervention), have occurred in patients receiving SGLT2 inhibitors, including empagliflozin *[see Adverse Reactions (6.2)]*. Cases have required hospitalization. In patients with Fournier's gangrene, serious outcomes have included multiple surgeries and death. SYNJARDY and SYNJARDY XR are only indicated for use in patients with type 2 diabetes mellitus.

Patients with a history of genitourinary infections are more likely to develop genitourinary infections when using SYNJARDY or SYNJARDY XR. Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated.

Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis. If suspected, discontinue SYNJARDY or SYNJARDY XR and promptly institute appropriate medical and/or surgical intervention.

5.5 Hypoglycemia

Insulin and insulin secretagogues are known to cause hypoglycemia. In adult patients, the risk of hypoglycemia may be increased when SYNJARDY or SYNJARDY XR is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin. In pediatric patients aged 10 years and older, the risk of hypoglycemia was higher with empagliflozin regardless of insulin use *[see Adverse Reactions (6.1)]*.

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.6 Lower Limb Amputation

In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Across four empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95% CI: 0.81, 1.36).

In a long-term cardio-renal outcome trial with empagliflozin, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and empagliflozin 10 mg treatment arms, respectively. Amputation of the toe and mid-foot were most frequent (21 out of 28 empagliflozin 10 mg treated patients with lower limb amputations), and some involving above and below the knee. Some patients had multiple amputations.

Peripheral artery disease, and diabetic foot infection (including osteomyelitis), were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of diabetic foot,

peripheral artery disease (including previous amputation) or diabetes.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving SYNJARDY or SYNJARDY XR for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

5.7 Hypersensitivity Reactions

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

5.8 Vitamin B_{12} Deficiency

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

6 ADVERSE REACTIONS

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

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Volume Depletion *[see Warnings and Precautions (5.3)]*
- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections *[see Warnings and Precautions (5.4)]*
- Hypoglycemia *[see Warnings and Precautions (5.5)]*
- Lower Limb Amputation *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (5.8)]*

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 dosage 10 mg or 25 mg) and metformin HCl (mean daily dosage of approximately 1,800 mg) has been evaluated in 3,456 adult patients with type 2 diabetes mellitus treated for 16 to 24 weeks, of which 926 patients received placebo, 1,271 patients received a daily dosage of empagliflozin 10 mg, and 1,259 patients received a daily dosage 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.

Adverse Reactions in a Clinical Trial with Empagliflozin (Add-On Combination Therapy with Metformin HCl and Sulfonylurea) for Glycemic Control in Adults with Type 2 Diabetes Mellitus

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

Table 1 Adverse Reactions Reported in ≥5% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin added on to Metformin HCl plus Sulfonylurea and Greater than with

Placebo in a 24-week Placebo Controlled Clinical Trial

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

Empagliflozin

Clinical Trials in Adults with Type 2 Diabetes Mellitus

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 in adult patients with type 2 diabetes mellitus. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (14.1)]*.

These data reflect exposure of 1,976 adult 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 mellitus more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes mellitus at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2).

Table 2 shows adverse reactions (excluding hypoglycemia) that were not present at baseline, occurred more commonly in empagliflozin-treated patients than placebo-treated patients, and occurred in greater than or equal to 2% of empagliflozin-treated patients.

Table 2 Adverse Reactions Reported in ≥2% of Adults with Type 2 Diabetes Mellitus Treated with Empagliflozin and Greater than Placebo in Pooled Placebo-Controlled Clinical Trials of Empagliflozin Monotherapy or Combination Therapy

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

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

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

[c]Predefined adverse event grouping, including, but not limited to,

polyuria, pollakiuria, and nocturia
[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), empagliflozin 10 mg (N=556), empagliflozin 25 mg (N=557).

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

Volume Depletion

Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials in adults, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction *[see Use in Specific Populations (8.5, 8.6)]*.

Increased Urination

In the pool of five placebo-controlled clinical trials in adults, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 2). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Hypoglycemia in Clinical Trials with Empagliflozin for Glycemic Control in Adults with Type 2 Diabetes Mellitus

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

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus[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 HCl (24 weeks)	**Placebo + Metformin HCl (n=206)**	**Empagliflozin 10 mg + Metformin HCl (n=217)**	**Empagliflozin 25 mg + Metformin HCl (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin HCl + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**Empagliflozin 10 mg + Metformin HCl + Sulfonylurea (n=224)**	**Empagliflozin 25 mg + Metformin HCl + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin HCl (24 weeks)	**Placebo (n=165)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin HCl (n=165)**	**Empagliflozin 25 mg + Pioglitazone +/- Metformin HCl (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin HCl (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 HCl (18 weeks[d])	**Placebo (n=188)**	**Empagliflozin 10 mg (n=186)**	**Empagliflozin 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL

[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose

[c]Treated set (patients who had received at least one dosage of trial drug)

[d]Insulin dosage could not be adjusted during the initial 18-week treatment period

Other Adverse Reactions in Clinical Trials with Empagliflozin in Adults

- *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 trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either empagliflozin 10 mg or 25 mg.
  Genital mycotic infections occurred more frequently in female than male patients (see Table 2).
  Phimosis occurred more frequently in male patients treated with empagliflozin 10 mg (less than 0.1%) and empagliflozin 25 mg (0.1%) than placebo (0%).
- *Urinary Tract Infections*: In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with empagliflozin compared to placebo (see Table 2). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Use in Specific Populations (8.5)]*.
- *Lower Limb Amputations*: Across four empagliflozin outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the empagliflozin 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95% CI) (0.81, 1.36). In a long-term cardio-renal outcome trial with empagliflozin, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and empagliflozin 10 mg treatment arms, respectively.

Clinical Trial of Empagliflozin in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus

Empagliflozin was administered to 52 patients in a trial of 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus with a mean exposure to empagliflozin of 23.8 weeks *[see Clinical Studies (14.2)]*. Background therapies as adjunct to diet and exercise included metformin HCl (51%), a combination of metformin HCl and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2.1 years. The mean age was 14.5 years (range: 10-17 years) and 51.6% were aged 15 years and older. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The mean BMI was 36.0 kg/m^2 and mean BMI Z-score was 3.0. Approximately 25% of the trial population had microalbuminuria or macroalbuminuria.

The risk of hypoglycemia was higher in pediatric patients treated with empagliflozin regardless of concomitant insulin use. Hypoglycemia, defined as a blood glucose <54 mg/dL, occurred in 10 (19.2%) patients and in 4 (7.5%) patients treated with empagliflozin and placebo, respectively. No severe hypoglycemic events occurred (severe hypoglycemia was defined as an event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions).

Adverse Reactions with Clinical Trials of Metformin HCl

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

In a 24-week clinical trial in which extended-release metformin HCl 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%).

Pediatric Patients

In clinical trials with metformin HCl immediate-release tablets in pediatric patients with type 2 diabetes mellitus, the profile of adverse reactions was similar to that observed in adults.

Laboratory Test Abnormalities in Clinical Trials of Empagliflozin or Metformin HCl

Empagliflozin

- *Increases in Serum Creatinine and Decreases in eGFR:* Initiation of empagliflozin causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a trial of adults with moderate renal impairment, larger mean changes were observed. In a long-term CV outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with empagliflozin.
- *Increase in Low-Density Lipoprotein Cholesterol (LDL-C):* Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in adults treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.
- *Increase in Hematocrit:* In a pool of four placebo-controlled trials in adults, 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 HCl

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

6.2 Postmarketing Experience

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

Empagliflozin

Gastrointestinal Disorders: Constipation
Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis
Metabolism and Nutrition Disorders: Ketoacidosis
Renal and Urinary Disorders: Acute kidney injury
Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

Metformin HCl

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

7 DRUG INTERACTIONS

See Table 4 for clinically relevant interactions with SYNJARDY or SYNJARDY XR.

Table 4 Clinically Relevant Interactions with SYNJARDY or SYNJARDY XR

Carbonic Anhydrase Inhibitors

Clinical Impact	Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with SYNJARDY or SYNJARDY XR may increase the risk of lactic acidosis.
Intervention	Consider more frequent monitoring of these patients.
Drugs that Reduce Metformin Clearance	
Clinical Impact	Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*.
Intervention	Consider the benefits and risks of concomitant use.
Alcohol	
Clinical Impact	Alcohol is known to potentiate the effect of metformin on lactate metabolism.
Intervention	Warn patients against excessive alcohol intake while receiving SYNJARDY or SYNJARDY XR.
Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating SYNJARDY or SYNJARDY XR, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating SYNJARDY or SYNJARDY XR. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when SYNJARDY or SYNJARDY XR is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of SYNJARDY or SYNJARDY XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Drugs Affecting Glycemic Control	
Clinical Impact	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid.
Intervention	When such drugs are administered to a patient receiving SYNJARDY or SYNJARDY XR, the patient should be closely observed to maintain adequate glycemic control. When such drugs are withdrawn from a patient receiving SYNJARDY or SYNJARDY XR, the patient should be observed closely for hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during SYNJARDY or SYNJARDY XR initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

The limited available data with SYNJARDY, 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 HCl use during pregnancy have not reported a clear association with metformin HCl and major birth defect or miscarriage risk *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

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

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Human Data

Published data from postmarketing studies have not reported a clear association with metformin HCl and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin HCl 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 HCl: Metformin HCl did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits at doses up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of approximately 2- and 6-times a clinical dose of 2,000 mg, based on body surface area (mg/m^2) for rats and rabbits, respectively.

Empagliflozin and Metformin HCl: No adverse developmental effects were observed when empagliflozin and metformin HCl 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 HCl associated with the 2,000 mg dose.

8.2 Lactation

Risk Summary

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

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of SYNJARDY or 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 HCl 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 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.3 Females and Males of Reproductive Potential

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

8.4 Pediatric Use

SYNJARDY

The safety and effectiveness of SYNJARDY as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older. Use of SYNJARDY for this indication is supported by evidence from a 26-week double-blind, placebo-controlled clinical trial of empagliflozin, with a double-blind active treatment safety extension period of up to 52 weeks in 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus and a pediatric pharmacokinetic study *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2)]*.

The safety profile of pediatric patients treated with empagliflozin was similar to that observed in adults with type 2 diabetes mellitus, with the exception of hypoglycemia risk which was higher in pediatric patients treated with empagliflozin regardless of concomitant insulin use *[see Warnings and Precautions (5.5) and Adverse Reactions (6.1)]*.

Use of SYNJARDY for this indication is also supported by evidence from adequate and well-controlled studies of metformin HCl immediate-release tablets in adults with additional data from a controlled clinical study using metformin HCl immediate-release tablets in pediatric patients 10 to 16 years old with type 2 diabetes mellitus *[see Clinical Studies (14)]*. In this study, adverse reactions were similar to those described in adults.

The safety and effectiveness of SYNJARDY have not been established in pediatric patients less than 10 years of age.

SYNJARDY XR

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

8.5 Geriatric Use

Assess renal function more frequently in SYNJARDY or SYNJARDY XR-treated geriatric patients because there is a greater risk of empagliflozin-associated intravascular volume contraction and symptomatic hypotension in geriatric patients and there is a greater risk of metformin-associated lactic acidosis in geriatric patients *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1, 5.3)].*

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

Empagliflozin

In empagliflozin type 2 diabetes mellitus trials, 2,721 empagliflozin-treated patients were 65 years of age and older and 491 patients were 75 years of age and older. In these trials, volume depletion-related adverse reactions occurred in 2.1%, 2.3%, and 4.4% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively; and urinary tract infections occurred in 10.5%, 15.7%, and 15.1% of patients 75 years of age and older in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg once daily groups, respectively.

In the EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY trials, no overall differences in safety and effectiveness have been observed between patients 65 years of age and older and younger adult patients. EMPEROR-Reduced included 1,188 (64%) patients treated with empagliflozin 65 years of age and older, and 503 (27%) patients 75 years of age and older. EMPEROR-Preserved included 2,403 (80%) patients treated with empagliflozin 65 years of age and older, and 1,281 (43%) patients 75 years of age and older. EMPA-KIDNEY included 1,803 (55%) patients treated with empagliflozin 65 years of age and older, and 758 (23%) patients 75 years of age and older.

Metformin HCl

Clinical studies of metformin HCl did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

8.6 Renal Impairment

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

Empagliflozin

The glucose lowering benefit of empagliflozin 25 mg decreased in adult patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function *[see Warnings and Precautions (5.3)]*. In the trial of pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, patients with an eGFR less than 60 mL/min/1.73 m^2 were not enrolled.

Metformin HCl

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

In the event of an overdose with SYNJARDY or SYNJARDY XR, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

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

Removal of empagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

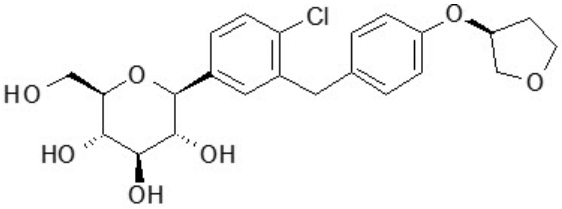
SYNJARDY and SYNJARDY XR tablets for oral use contain: empagliflozin and metformin HCl.

Empagliflozin

Empagliflozin is an inhibitor of the SGLT2.

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

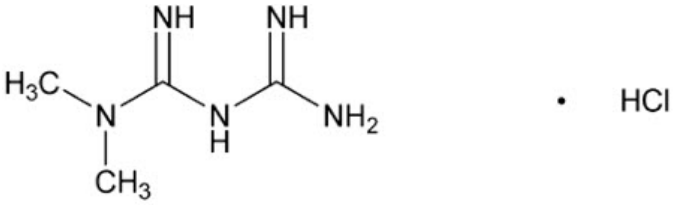
Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



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

Metformin HCl

Metformin HCl (*N,N*-dimethylimidodicarbonimidic diamide HCl) is a biguanide. Metformin HCl is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin HCl 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 HCl is 6.68. The structural formula is:



SYNJARDY

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

- 5 mg empagliflozin and 500 mg metformin HCl (equivalent to 389.93 mg of metformin)
- 5 mg empagliflozin and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 12.5 mg empagliflozin and 500 mg metformin HCl (equivalent to 389.93 mg of metformin)
- 12.5 mg empagliflozin and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)

Each film-coated tablet of SYNJARDY contains the following inactive ingredients: colloidal

silicon dioxide, copovidone, corn starch, and magnesium stearate. Film-coating: black ferrosoferric oxide and ferric oxide red (12.5 mg/500 mg, 12.5 mg/1,000 mg) or ferric oxide yellow (5 mg/500 mg, 5 mg/1,000 mg), hypromellose, polyethylene glycol 400, talc and titanium dioxide.

SYNJARDY XR

Each film-coated tablet of SYNJARDY XR consists of an extended-release metformin HCl 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 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 10 mg empagliflozin and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 12.5 mg empagliflozin and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)
- 25 mg empagliflozin and 1,000 mg metformin HCl (equivalent to 779.86 mg of metformin)

Each film-coated tablet of SYNJARDY XR contains the following inactive ingredients: Tablet Core: hypromellose, magnesium stearate, and polyethylene oxide. Film-coatings and Printing Ink: carnauba wax, FD&C blue#2/indigo carmine aluminum lake (12.5 mg/1,000 mg, 25 mg/1,000 mg), ferric oxide red (10 mg/1,000 mg), ferric oxide yellow (5 mg/1,000 mg, 10 mg/1,000 mg, 25 mg/1,000 mg), ferrosoferric oxide, hypromellose, isopropyl alcohol, polydextrose, polyethylene glycol, propylene glycol, purified water, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SYNJARDY or SYNJARDY XR

SYNJARDY and SYNJARDY XR contain: empagliflozin, a SGLT2 inhibitor, and metformin HCl, a biguanide.

Empagliflozin

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

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart and downregulating sympathetic activity.

Metformin HCl

Metformin HCl 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 HCl decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin HCl does not produce hypoglycemia in either patients with type 2 diabetes mellitus or normal subjects (except in special circumstances) *[see Warnings and Precautions (5.5)]* and does not cause hyperinsulinemia. With metformin HCl therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

12.2 Pharmacodynamics

Empagliflozin

Urinary Glucose Excretion

In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78

grams per day with 25 mg empagliflozin once daily *[see Clinical Studies (14)]*. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

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

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

Administration of 12.5 mg empagliflozin/1,000 mg metformin HCl under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C_{max} for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C_{max} decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant.

SYNJARDY XR

Administration of SYNJARDY XR with food resulted in no change in overall exposure of empagliflozin. For metformin HCl 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

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes mellitus and no clinically relevant differences were noted between the two populations. The steady-state mean plasma AUC and C_{max} were 1,870 nmol•h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4,740 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. Empagliflozin does not appear to have time-dependent pharmacokinetic characteristics. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state.

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

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

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.

Metabolism

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

Excretion

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

Metformin HCl

Absorption

The absolute bioavailability of a metformin HCl 500 mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin HCl tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower C_{max}, a 25% lower AUC, and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Metformin HCl extended-release

Following a single oral dose of 1,000 mg (2 × 500 mg tablets) metformin HCl 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 1,000 mg (2 × 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 HCl extended-release from 500 mg to 2,500 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 HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time.

Elimination

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

Metabolism

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

Excretion

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

Specific Populations

Geriatric Patients

SYNJARDY or SYNJARDY XR: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY or SYNJARDY XR in geriatric patients have not been performed *[see Warnings and Precautions (5.1, 5.3) 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 HCl: Limited data from controlled pharmacokinetic studies of metformin HCl 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 Patients

Empagliflozin: The pharmacokinetics and pharmacodynamics of empagliflozin were investigated in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus. Oral administration of empagliflozin at 10 mg and 25 mg resulted in exposure within the range observed in adult patients.

Metformin: After administration of a single oral metformin HCl 500 mg immediate-release tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

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

Empagliflozin: Age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

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

Patients with Renal Impairment

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

Empagliflozin: In adult patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patients on dialysis due to kidney failure, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients 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 HCl: 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)]*.

Patients with Hepatic Impairment

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

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

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

Drug Interaction Studies

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

Empagliflozin

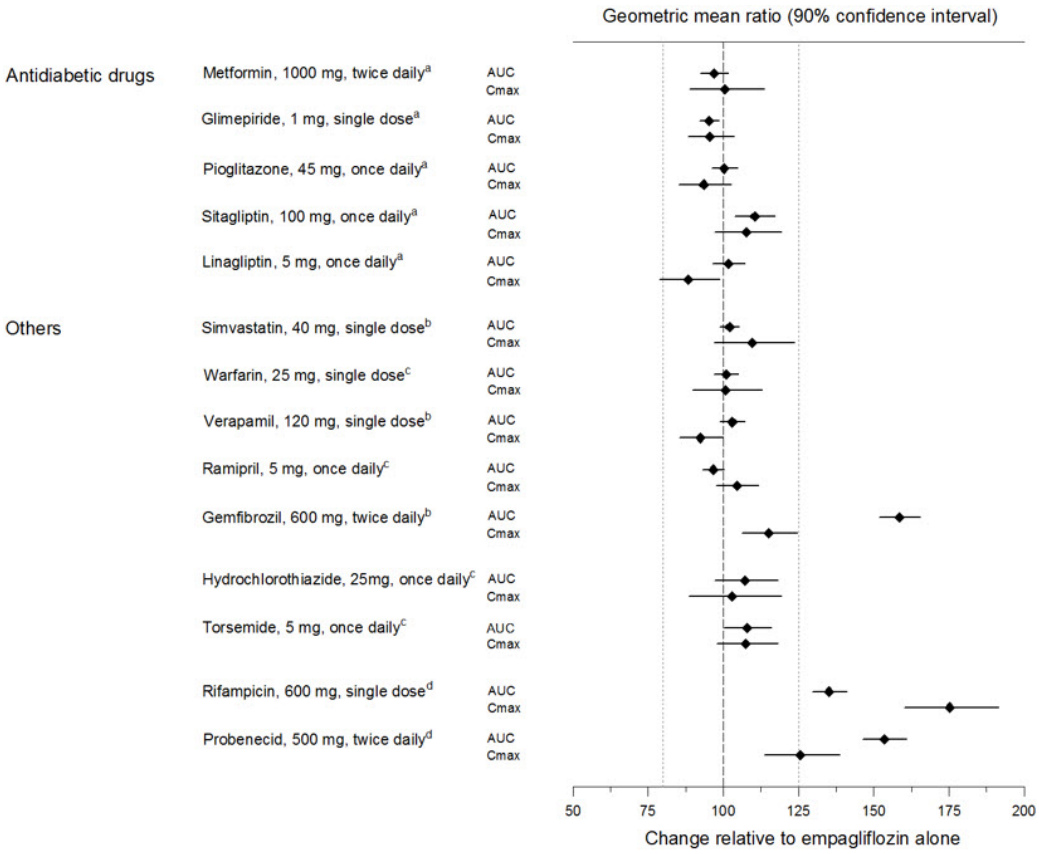
In vitro Assessment of Drug Interactions: Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-

glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

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

In vivo Assessment of Drug Interactions: Empagliflozin pharmacokinetics were similar with and without coadministration of metformin HCl, 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 mellitus (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

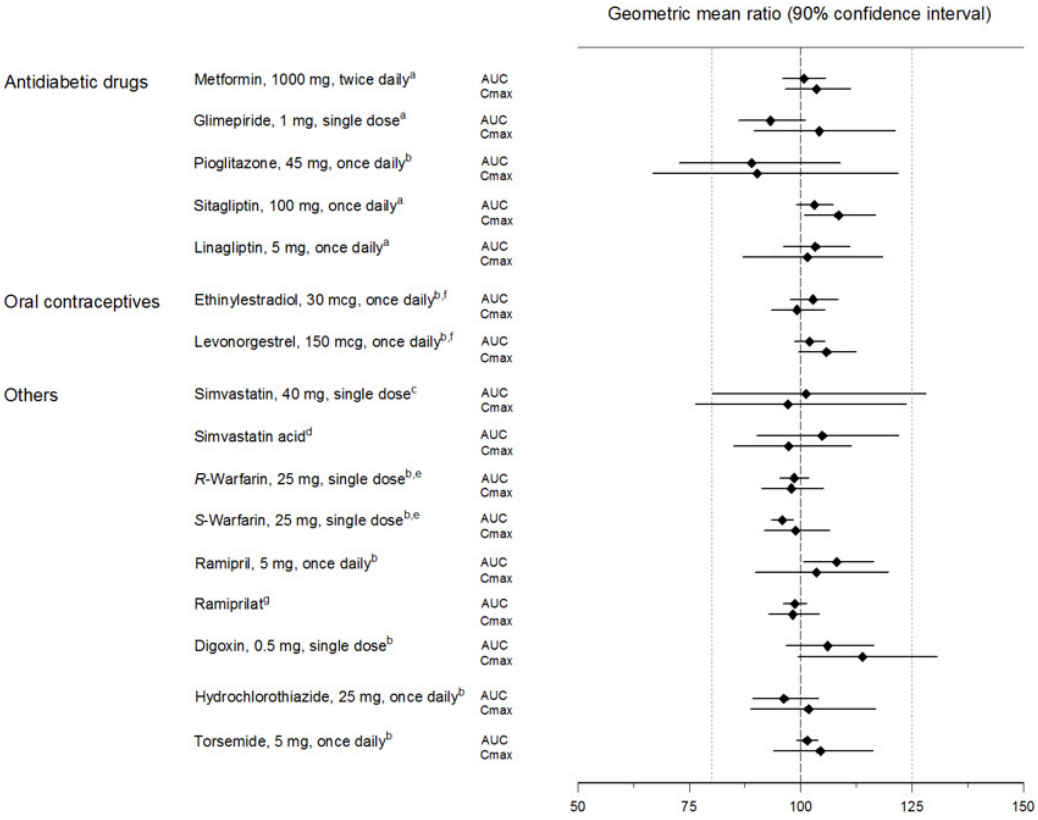
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



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

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 in healthy volunteers (see Figure 2).

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



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

Metformin HCl

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

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

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

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

			Geometric Mean

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SYNJARDY or SYNJARDY XR

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

Empagliflozin

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1,000 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 1,000 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.

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

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

Metformin HCl

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 1,500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2,000 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.

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.

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 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

In adult patients with type 2 diabetes mellitus, treatment with empagliflozin and metformin HCl produced clinically and statistically significant improvements in HbA1c compared to placebo and metformin HCl. Reductions in HbA1c were observed across subgroups including age, sex, race, and baseline BMI.

Empagliflozin Add-On Combination Therapy with Metformin HCl in Adult Patients with Type 2 Diabetes Mellitus

A total of 637 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of empagliflozin in combination with metformin HCl.

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 mg of metformin HCl 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 Trial for Empagliflozin used in Combination with Metformin HCl

	Empagliflozin 10 mg N=217	**Empagliflozin 25 mg N=213**	**Placebo 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 HCl (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 HCl (adjusted mean)	-26	-29	--
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0[b] (-2.6, -1.4)	-2.5[b] (-3.1, -1.9)	--

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

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

Empagliflozin Initial Combination Therapy with Metformin HCl

A total of 1,364 patients with type 2 diabetes mellitus participated in a double-blind,

randomized, active-controlled trial to evaluate the efficacy of empagliflozin in combination with metformin HCl as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes mellitus 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 HCl 1,000 mg, or 2,000 mg; empagliflozin 10 mg in combination with 1,000 mg or 2,000 mg metformin HCl; or empagliflozin 25 mg in combination with 1,000 mg or 2,000 mg metformin HCl.

At Week 24, initial therapy of empagliflozin in combination with metformin HCl 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 Trial Comparing Empagliflozin and Metformin HCl to the Individual Components as Initial Therapy

	Empagliflozin 10 mg + Metformin HCl 1,000 mg[a] N=161	**Empagliflozin 10 mg + Metformin HCl 2,000 mg[a] N=167**	**Empagliflozin 25 mg + Metformin HCl 1,000 mg[a] N=165**	**Empagliflozin 25 mg + Metformin HCl 2,000 mg[a] N=169**	**Empagliflozin 10 mg N=169**	**Empagliflozin 25 mg N=163**	**Metformin HCl 1,000 mg[a] N=167**	**Metformin HCl 2,000 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 HCl (adjusted mean) (95% CI)	-0.8[b] (-1.0, -0.6)	-0.3[b] (-0.6, -0.1)	-0.8[c] (-1.0, -0.5)	-0.3[c] (-0.6, -0.1)	--	--	--	--
Patients [n (%)] achieving HbA1c <7%	96 (63%)	112 (70%)	91 (57%)	111 (68%)	69 (43%)	51 (32%)	63 (38%)	92 (58%)

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

Empagliflozin Add-On Combination Therapy with Metformin HCl and Sulfonylurea

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

Patients with inadequately controlled type 2 diabetes mellitus on at least 1,500 mg per day of metformin HCl 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 Trial for Empagliflozin in Combination with Metformin HCl and Sulfonylurea

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

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

Active-Controlled Trial vs Glimepiride in Combination with Metformin HCl

The efficacy of empagliflozin was evaluated in a double-blind, glimepiride-controlled, trial in 1,545 patients with type 2 diabetes mellitus with insufficient glycemic control despite metformin HCl 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 dosage of glimepiride was 2.7 mg and the maximal approved dosage in the United States is 8 mg per day.

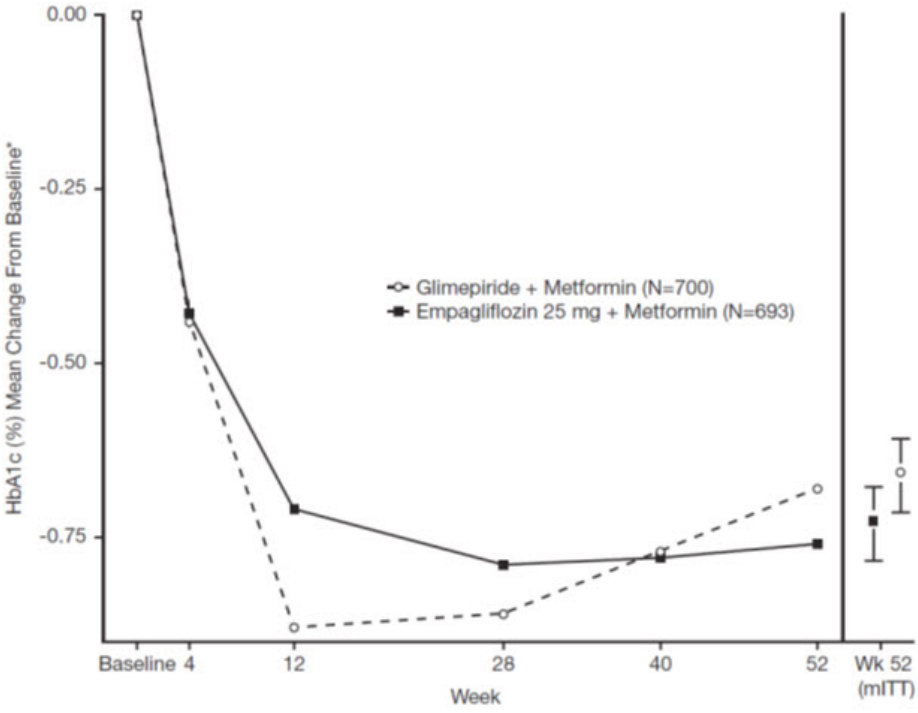
Table 10 Results at Week 52 from an Active-Controlled Trial Comparing Empagliflozin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin HCl

	Empagliflozin 25 mg N=765	Glimepiride N=780
HbA1c (%)[a]		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07[b] (-0.15, 0.01)	--

FPG (mg/dL)[d]		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9[c] (-6.3, -5.5)	--

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

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



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

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 dosage of glimepiride was 2.7 mg and the maximal approved dosage 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 Glycemic Control Trials in Pediatric Patients with Type 2 Diabetes Mellitus

Glycemic Control Trial of Empagliflozin in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus

DINAMO (NCT03429543) was a 26-week, double-blind, randomized, placebo-controlled, parallel group trial, with a double-blind active treatment safety extension period up to 52 weeks to assess the efficacy of empagliflozin. The trial enrolled pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (HbA1c 6.5 to 10.5%). Patients treated with metformin HCl (at least 1,000 mg daily or maximally tolerated dose), with or without insulin therapy, and those with a history of intolerance to metformin HCl therapy were enrolled. Patients were randomized to 3 treatment arms (empagliflozin 10 mg, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or placebo) over 26 weeks. Patients in the empagliflozin 10 mg group who failed to achieve HbA1c <7.0% at Week 12 underwent a second randomization at Week 14 to remain on the 10 mg dose or increase to 25 mg. Patients on placebo were re-randomized at Week 26 to one of the empagliflozin doses (10 mg or 25 mg) or a DPP-4 inhibitor.

A total of 157 patients were treated with either empagliflozin (10 mg or 25 mg; N=52), a DPP-4 inhibitor (N=52), or placebo (N=53). Background therapies as adjunct to diet and exercise included metformin HCl (51%), a combination of metformin HCl and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2.1 years. The mean age was 14.5 years (range: 10-17 years) and 51.6% were aged 15 years and older. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The mean BMI was 36.0 kg/m^2 and mean BMI Z-score was 3.0. Patients with an eGFR less than 60 mL/min/1.73 m^2 were not enrolled in the trial. Approximately 25% of the trial population had microalbuminuria or macroalbuminuria.

At Week 26, treatment with empagliflozin was superior in reducing HbA1c from baseline versus placebo (see Table 11).

Table 11 Results at Week 26 for a Placebo-Controlled Trial for Empagliflozin in Combination with Metformin HCl and/or Insulin or as Monotherapy in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus[a]

	Empagliflozin 10 mg and 25 mg	**Placebo**
HbA1c (%)[b]		
Number of patients	n=52	n=53
Baseline (mean)	8.0	8.1
Change from baseline[c]	-0.2	0.7
Difference from placebo[c] (95% CI)	-0.8[e] (-1.5, -0.2)	--
FPG (mg/dL)[b,d]		
Number of patients	n=48	n=52
Baseline (mean)	154	159
Change from baseline[c]	-19	17
Difference from placebo[c] (95% CI)	-36 (-60.7, -10.7)	--

[a]Modified intent-to-treat set (All randomized and treated patients with baseline measurement).
[b]Multiple imputations using placebo wash-out approach with 500 iterations for missing data. Imputed for HbA1c (empagliflozin N=5 (9.6%), placebo N=3 (5.7%)), for FPG (empagliflozin N=4 (8.3%), placebo N=2 (3.8%)).
[c]Least-Square Mean from Analysis of Covariance (ANCOVA) adjusted for baseline value and baseline age stratum (< 15 years vs 15 to < 18 years).
[d]Not evaluated for statistical significance, not part of sequential testing procedure.
[e]p-value=0.0116 (two-sided)

Glycemic Control Trial of Metformin HCl Immediate-Release in Pediatric Patients Aged 10 to 16 Years with Type 2 Diabetes Mellitus:

A double-blind, placebo-controlled trial was conducted in pediatric patients aged 10 to 16

years with type 2 diabetes mellitus (mean FPG 182.2 mg/dL), where patients were treated with metformin HCl immediate-release tablets (up to 2,000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks). The results are displayed in Table 12.

Table 12 Mean Change in Fasting Plasma Glucose at Week 16 Comparing Metformin HCl vs. Placebo in Pediatric Patients[a] with Type 2 Diabetes Mellitus

	Metformin HCl	**Placebo**	**p-value**
FPG (mg/dL)	**(n=37)**	**(n=36)**	
Baseline	162.4	192.3	
Change at FINAL VISIT	-42.9	21.4	<0.001

[a] Pediatric patients mean age 13.8 years (range 10-16 years)

Mean baseline body weight was 205 lbs and 189 lbs in the metformin HCl immediate-release and placebo arms, respectively. Mean change in body weight from baseline to week 16 was -3.3 lbs and -2.0 lbs in the metformin HCl and placebo arms, respectively.

14.3 Empagliflozin CV Outcome Trial in Adult Patients with Type 2 Diabetes Mellitus and Atherosclerotic CV Disease

EMPA-REG OUTCOME was a multicenter, multinational, randomized, double-blind parallel group trial that compared the risk of experiencing a major adverse CV event (MACE) between empagliflozin and placebo when these were added to and used concomitantly with standard of care treatments for diabetes mellitus and atherosclerotic CV disease. Concomitant antidiabetic medications were 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 7,020 patients were treated (empagliflozin 10 mg = 2,345; empagliflozin 25 mg = 2,342; placebo = 2,333) and followed for a median of 3.1 years. Approximately 72% of the trial population was White, 22% was Asian, and 5% was Black or African American. The mean age was 63 years and approximately 72% were male.

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

All patients had established atherosclerotic CV 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 CV death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg dosages 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 CV 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 CV 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 13 and Figures 4 and 5). Results for the 10 mg and 25 mg empagliflozin dosages were consistent with results for the combined dosage groups.

Table 13 Treatment Effect for the Primary Composite Endpoint and its Components[a]

	Placebo N=2,333	Empagliflozin N=4,687	Hazard ratio vs placebo (95% CI)
Composite of CV 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)
CV death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

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

Figure 4 Estimated Cumulative Incidence of First MACE

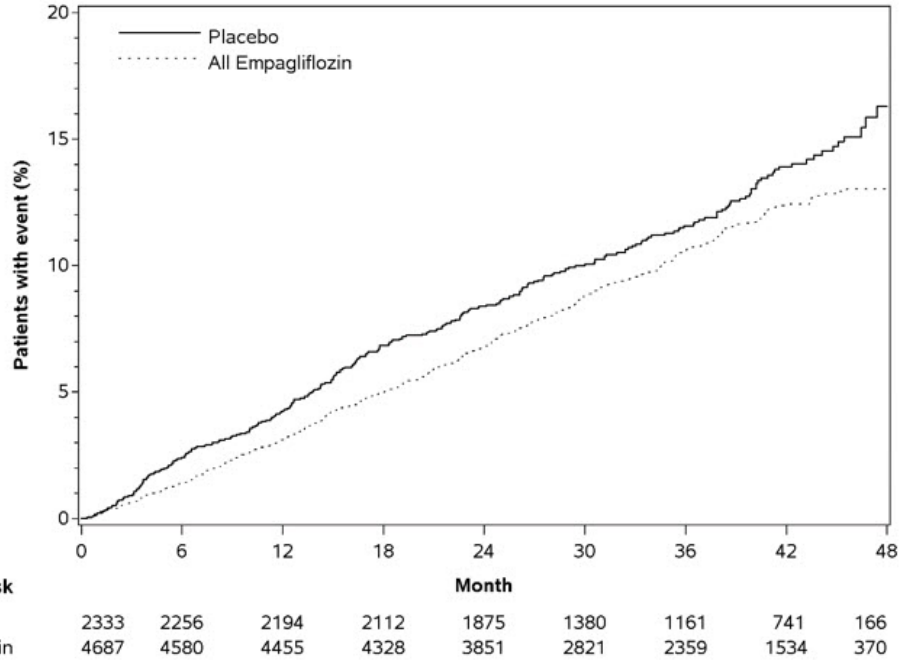
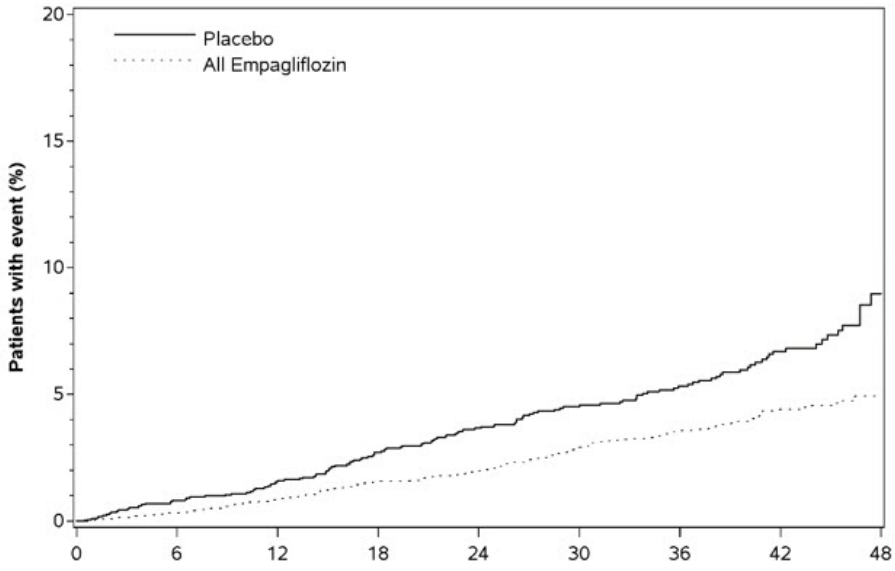


Figure 5 Estimated Cumulative Incidence of CV Death



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

The efficacy of empagliflozin on CV 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 CV deaths. The non-CV 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).

14.4 Empagliflozin Heart Failure Trials, Including Adult Patients with Type 2 Diabetes Mellitus

EMPEROR-Reduced Trial (Chronic Heart Failure with Left Ventricular Ejection Fraction ≤ 40%)

EMPEROR-Reduced (NCT03057977) was a double-blind trial conducted in adults with chronic heart failure [New York Heart Association (NYHA) functional class II-IV] with left ventricular ejection fraction (LVEF) ≤40% to evaluate the efficacy of empagliflozin as adjunct to standard of care heart failure therapy. Of 3,730 patients, 1,863 were randomized to empagliflozin 10 mg once daily and 1,867 to placebo once daily and were followed for a median of 16 months.

Baseline Disease Characteristics and Demographics

EMPEROR-Reduced included patients with type 2 diabetes mellitus (n=1,856) and patients without type 2 diabetes mellitus (n=1,874). The mean age of the trial population was 67 years (range: 25 to 94 years) and 76% were males, 24% were women, and 27% were 75 years of age or older. Approximately 71% of the trial population were White, 18% Asian and 7% Black or African American. At randomization, 75% of patients were NYHA class II, 24% were class III and 0.5% were class IV. The mean LVEF was 28%. At baseline, the mean eGFR was 62 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. Approximately half of the patients (52%) had eGFR equal to or above 60 mL/min/1.73 m^2, 24% had eGFR 45 to less than 60 mL/min/1.73 m^2, and 19% had eGFR 30 to less than 45 mL/min/1.73 m^2. At baseline, 88% of patients were treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI), 95% with beta-blockers, 71% with mineralocorticoid receptor antagonists (MRA), and 95% with diuretics.

In EMPEROR-Reduced, history of type 2 diabetes mellitus was present in 50% of the patients, and 46% of these patients were treated with metformin HCl (444 patients in the empagliflozin group and 418 in the placebo group) and 25% were treated with insulin. In the type 2 diabetes mellitus subpopulation, the mean age was 67 years; 77% were males; 69% White, 19% Asian and 7% Black or African American; 32% were Hispanic/Latino. In the type 2 diabetes mellitus subpopulation, at baseline, 71% of patients were classified as NYHA class II, 28% class III and 0.7% class IV; the mean LVEF was 27%; the mean baseline eGFR was 61 mL/min/1.73 m^2. In this subpopulation, at

baseline, 88% of patients were treated with ACE inhibitors, ARB, or ARNI, 95% with beta-blockers, 70% with MRA, and 96% with diuretics.

Results

In EMPEROR-Reduced, empagliflozin 10 mg, compared with placebo, reduced the risk of the primary composite endpoint of CV death or hospitalization for heart failure (HHF) mostly through a reduction in HHF (HR 0.75 [95% CI 0.65, 0.86]). Empagliflozin reduced the risk of first and recurrent HHF, a key secondary endpoint. Because of the metformin HCl component, SYNJARDY and SYNJARDY XR are not indicated for use in patients with heart failure without type 2 diabetes mellitus *[see Indications and Usage (1)]*.

The effect of empagliflozin in reducing the risk of the primary composite endpoint was consistent in patients with type 2 diabetes mellitus (HR 0.73 [95% CI 0.60, 0.87]), and in patients with type 2 diabetes mellitus and metformin HCl as background therapy (HR 0.65 [95% CI 0.49, 0.86]).

EMPEROR-Preserved Trial (Chronic Heart Failure with Left Ventricular Ejection Fraction > 40%)

EMPEROR-Preserved (NCT03057951) was a double-blind trial conducted in patients with chronic heart failure NYHA Class II-IV with LVEF >40% to evaluate the efficacy of empagliflozin as adjunct to standard of care therapy. Of 5,988 patients, 2,997 patients were randomized to empagliflozin 10 mg once daily and 2,991 patients to placebo once daily and were followed for a median of 26 months.

Baseline Disease Characteristics and Demographics

EMPEROR-Preserved included patients with type 2 diabetes mellitus (n=2,928) and patients without type 2 diabetes mellitus (n=3,060). The mean age of the trial population was 72 years (range: 22 to 100 years) and 55% were males, 45% were women, and 43% were 75 years of age or older. Approximately 76% of the trial population were White, 14% Asian and 4% Black or African American. At randomization, 82% of patients were NYHA class II, 18% were class III and 0.3% were class IV. This trial included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 61 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. Approximately half of the patients (50%) had eGFR equal to or above 60 mL/min/1.73 m^2, 26% had eGFR 45 to less than 60 mL/min/1.73 m^2, and 19% had eGFR 30 to less than 45 mL/min/1.73 m^2. At baseline, 81% of patients were treated with ACE inhibitors, ARBs, or ARNI, 86% with beta-blockers, 38% with MRAs, and 86% with diuretics.

In EMPEROR-Preserved, history of type 2 diabetes mellitus was present in 49% of the patients, and 54% of these patients were treated with metformin HCl (773 patients in the empagliflozin group and 803 in the placebo group) and 29% were treated with insulin. In the type 2 diabetes mellitus subpopulation, the mean age was 71 years, 57% were males, 75% White, 13% Asian and 5% Black or African American. In the type 2 diabetes mellitus subpopulation, at baseline, 79% of patients were classified as NYHA class II, 20% class III and 0.2% class IV; the trial also included type 2 diabetics with LVEF <50% (35%), with a LVEF 50 to <60% (34%) and a LVEF ≥60% (31%). For this subpopulation, the mean baseline eGFR was 60 mL/min/1.73 m^2; and at baseline, 83% of patients were treated with ACE inhibitors, ARB, or ARNI, 88% with beta-blockers, 39% with MRA, and 89% with diuretics.

Results

In EMPEROR-Preserved, empagliflozin 10 mg, compared with placebo, reduced the risk of the primary composite endpoint (time to first event of either CV death or HHF) mostly through a reduction in hospitalization for heart failure (HR 0.79 [95% CI 0.69, 0.90]). Empagliflozin reduced the risk of first and recurrent HHF, a key secondary endpoint. Because of the metformin HCl component, SYNJARDY and SYNJARDY XR are not indicated for use in patients with heart failure without type 2 diabetes mellitus *[see Indications and Usage (1)]*.

The effect of empagliflozin in reducing the risk of the primary composite endpoint was consistent in patients with type 2 diabetes mellitus (HR 0.80 [95% CI 0.67, 0.95]), and in patients with type 2 diabetes mellitus and metformin HCl as background therapy (HR 0.79 [95% CI 0.61, 1.02]).

14.5 Empagliflozin Chronic Kidney Disease Trial, Including Adult Patients with Type 2 Diabetes Mellitus

The effectiveness of empagliflozin, a component of SYNJARDY and SYNJARDY XR, to reduce the risk of sustained decline in eGFR, end-stage kidney disease, CV death, and

hospitalization has been established in adults with chronic kidney disease at risk of progression based on an adequate and well-controlled study of empagliflozin [EMPA-KIDNEY (NCT03594110)]. This trial was designed to determine the treatment effect of empagliflozin compared to placebo in adults with CKD (with and without type 2 diabetes). The trial, which studied empagliflozin rather than SYNJARDY or SYNJARDY XR, included adults taking metformin HCl as a concomitant medication. The efficacy results of EMPA-KIDNEY are reported below.

EMPA-KIDNEY was a randomized, double-blind, placebo-controlled trial conducted in adults with chronic kidney disease [eGFR ≥20 to <45 mL/min/1.73 m^2; or eGFR ≥45 to <90 mL/min/1.73 m^2 with urine albumin to creatinine ratio (UACR) ≥200 mg/g]. The trial excluded patients with polycystic kidney disease or patients requiring intravenous immunosuppressive therapy in the preceding three months or >45 mg of prednisone (or equivalent) at the time of screening. The primary objective of the trial was to assess the effects of empagliflozin as an adjunct to standard of care therapy, including RAS-inhibitor therapy when appropriate, on time to kidney disease progression or CV death. A total of 6,609 patients, were equally randomized to empagliflozin 10 mg orally once-daily or placebo and were followed for a median of 24 months.

Baseline Disease Characteristics and Demographics

EMPA-KIDNEY included patients with type 2 diabetes mellitus (n=2,936) and patients without type 2 diabetes mellitus (n=3,673). The mean age of the study population was 63 years (range: 18 to 94 years) and 67% were male. Approximately 58% of the study population were White, 36% Asian, and 4% Black or African American. At baseline, the mean eGFR was 37 mL/min/1.73 m^2, 21% of patients had an eGFR equal to or above 45 mL/min/1.73 m^2, and 44% had an eGFR 30 to less than 45 mL/min/1.73 m^2. The median UACR was 329 mg/g, 20% of patients had a UACR <30 mg/g, 28% had a UACR 30 to ≤300 mg/g, and 52% had a UACR >300 mg/g. The most common etiologies of CKD were diabetic nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%). At baseline, 85% of patients were treated with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), 64% with statins, and 34% with antiplatelet agents.

In EMPA-KIDNEY, history of type 2 diabetes mellitus was present in 44% of the patients, and 23% of these patients were treated with metformin HCl (329 patients in the empagliflozin group and 334 in the placebo group). In the type 2 diabetes mellitus subpopulation, the mean age was 68 years, 67% were males, 59% White, 33% Asian and 6% Black or African American. In the type 2 diabetes mellitus subpopulation, at baseline, the mean eGFR was 36 mL/min/1.73 m^2, 17% of patients had an eGFR equal to or above 45 mL/min/1.73 m^2, and 45% had an eGFR 30 to less than 45 mL/min/1.73 m^2; the median UACR was 256 mg/g, 22% of patients had a UACR <30 mg/g, 31% had a UACR 30 to ≤300 mg/g, and 47% had a UACR >300 mg/g. The most common etiologies of CKD at baseline in this subpopulation were diabetic nephropathy/diabetic kidney disease (67%), glomerular disease (6%), hypertensive/renovascular disease (14%) and other/unknown (13%). In this subpopulation, at baseline, 85% of patients were treated with ACE inhibitor or ARB, 79% with statins, and 48% with antiplatelet agents.

Results

In EMPA-KIDNEY, empagliflozin 10 mg, compared with placebo, reduced the risk of the primary composite endpoint of sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73 m^2, progression to end-stage kidney disease, or CV or renal death. The treatment effect reflected a reduction in a sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73 m^2, progression to end-stage kidney disease, and CV death. There were few renal deaths during the trial. Empagliflozin also reduced the risk of first and recurrent hospitalization; information collected on the reason for hospitalization was insufficient to further characterize the benefit. Because of the metformin HCl component, SYNJARDY and SYNJARDY XR are not indicated for use in patients with CKD without type 2 diabetes mellitus *[see Indications and Usage (1)]*.

The effect of empagliflozin in reducing the risk of the primary composite endpoint was consistent in patients with type 2 diabetes mellitus [HR 0.65 (95% CI 0.54, 0.78)], and in patients with type 2 diabetes mellitus and metformin HCl as background therapy [HR 0.72 (95% CI 0.48, 1.09)].

16 HOW SUPPLIED/STORAGE AND HANDLING

SYNJARDY tablets are available as follows:

Tablet	Color/Shape	Tablet	Package	NDC

Strength	Color/Shape	Markings	Size	Number
5 mg Empagliflozin 500 mg Metformin HCl	orange yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "500".	Bottles of 60 Bottles of 180	0597-0159-60 0597-0159-18
5 mg Empagliflozin 1,000 mg Metformin HCl	brownish yellow, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "1000".	Bottles of 60 Bottles of 180	0597-0175-60 0597-0175-18
12.5 mg Empagliflozin 500 mg Metformin HCl	pale brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "500".	Bottles of 60 Bottles of 180	0597-0180-60 0597-0180-18
12.5 mg Empagliflozin 1,000 mg Metformin HCl	dark brownish purple, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "1000".	Bottles of 60 Bottles of 180	0597-0168-60 0597-0168-18

SYNJARDY XR extended-release tablets are available as follows:

Tablet Strength	Color/Shape	Tablet Markings	Package Size	NDC Number
5 mg Empagliflozin 1,000 mg Metformin HCl	olive green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol and "S5" on the top line and "1000 M" on the bottom line.	Bottles of 60 Bottles of 180	0597-0290-74 0597-0290-59
10 mg Empagliflozin 1,000 mg Metformin HCl	orange, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol 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
		Printed on one side in black ink with the		

12.5 mg Empagliflozin 1,000 mg Metformin HCl	blue, oval, biconvex, film-coated tablet	Boehringer Ingelheim company symbol and "S12" on the top line and "1000 M" on the bottom line.	Bottles of 60 Bottles of 180	0597-0300-45 0597-0300-93
25 mg Empagliflozin 1,000 mg Metformin HCl	light green, oval, biconvex, film-coated tablet	Printed on one side in black ink with the Boehringer Ingelheim company symbol and "S25" on the top line and "1000 M" on the bottom line.	Bottles of 30 Bottles of 90	0597-0295-88 0597-0295-78

Storage

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

17 PATIENT COUNSELING INFORMATION

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

Lactic Acidosis

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

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

Inform patients that SYNJARDY or SYNJARDY XR can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed insulin doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue SYNJARDY or SYNJARDY XR and seek medical attention immediately *[see Warnings and Precautions (5.2)]*.

Volume Depletion

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

Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Counsel patients that genitourinary infections may occur when taking empagliflozin, a component of SYNJARDY and SYNJARDY XR, and may become serious. Educate patients on the symptoms and advise them to seek medical advice if symptoms occur. Specifically, advise patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the

rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.4)]*.

Hypoglycemia

Inform patients that hypoglycemia has been reported when SYNJARDY or SYNJARDY XR is used with insulin secretagogues or insulin. Hypoglycemia may occur in pediatric patients regardless of concomitant antidiabetic treatment. Educate patients or caregivers on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.5)]*.

Lower Limb Amputation

Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[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 and SYNJARDY XR. Advise patients to report immediately any skin reaction or angioedema, and to discontinue the drug until they have consulted prescribing healthcare provider *[see Warnings and Precautions (5.7)]*.

Vitamin B_{12} Deficiency

Inform patients about the importance of regular hematological parameters while receiving SYNJARDY or SYNJARDY XR *[see Warnings and Precautions (5.8)]*.

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking SYNJARDY or SYNJARDY XR *[see Drug Interactions (7)]*.

Pregnancy

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

Lactation

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

Patients of Reproductive Potential

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

Administration Instructions

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

Missed Dose

Instruct patients to take SYNJARDY or 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 *[see Dosage and Administration (2.7)]*.

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

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

SYNJARDY or SYNJARDY XR can cause serious side effects, including:

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

  You have a higher chance of getting lactic acidosis with SYNJARDY or SYNJARDY XR if you:
  - have moderate to severe kidney problems.
  - have liver problems.
  - drink a lot of alcohol (very often or short-term "binge" drinking).
  - get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
  - have certain x-ray tests with injectable dyes or contrast agents.
  - have surgery or other procedure for which you need to restrict the amount of food and liquid you eat and drink.
  - have congestive heart failure.
  - have a heart attack, severe infection, or stroke.
  - are 65 years of age or older.
  - have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as mitochondrial encephalomyopathy with lactic acidosis, and stroke-like episodes (MELAS) syndrome and maternally inherited diabetes and deafness (MIDD).

  Tell your healthcare provider if you have any of the problems in the list above. Tell your healthcare provider that you are taking SYNJARDY or SYNJARDY XR before you have surgery or x-ray tests. Your healthcare provider may need to stop your SYNJARDY or SYNJARDY XR for a while if you have surgery or certain x-ray tests. SYNJARDY or SYNJARDY XR can have other serious side effects. See **"What are the possible side effects of SYNJARDY or SYNJARDY XR?"**
- **Diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 and other ketoacidosis.** SYNJARDY or SYNJARDY XR can cause ketoacidosis that can be life-threatening and may lead to death. Ketoacidosis is a serious condition which needs to be treated in a hospital. People with type 1 diabetes have a high risk of getting ketoacidosis. People with type 2 diabetes or pancreas problems also have an increased risk of getting ketoacidosis. Ketoacidosis can also happen in people who: are sick, cannot eat or drink as usual, skip meals, are on a diet high in fat and low in carbohydrates (ketogenic diet), take less than the usual

amount of insulin or miss insulin doses, drink too much alcohol, have a loss of too much fluid from the body (volume depletion), or who have surgery. Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Your healthcare provider may ask you to periodically check ketones in your urine or blood.
Stop taking SYNJARDY or SYNJARDY XR and call your healthcare provider or get medical help right away if you get any of the following. If possible, check for ketones in your urine or blood, even if your blood sugar is less than 250 mg/dL:

- nausea
- vomiting
- stomach-area (abdominal) pain
- tiredness
- trouble breathing
- ketones in your urine or blood

- **Dehydration. SYNJARDY or SYNJARDY XR can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking SYNJARDY or SYNJARDY XR.** You may be at higher risk of dehydration if you:
  - take medicines to lower your blood pressure, including diuretics (water pills)
  - are on a low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older

  Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Call your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you are sick or you cannot eat, or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.
- **Genital and urinary tract infections.** Empagliflozin, one of the medicines in SYNJARDY and SYNJARDY XR, can cause serious infections in your genital area or urinary tract that could require hospitalization. **A rare but serious bacterial infection called necrotizing fasciitis can cause damage to the tissue under the skin in the area between and around the anus and genitals (perineum).** This infection may require hospitalization, multiple surgeries, and could lead to death. **Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:**

  - pain or tenderness
  - swelling
  - redness of skin (erythema)

  Also tell your healthcare provider if you have any of these signs or symptoms of urinary tract infections or yeast infections:
  - **Urinary tract infection:**
    - burning feeling when you urinate
    - need to urinate often or right away
    - pain in the lower part of your stomach (pelvis)
    - blood in your urine

    You may also have a fever, back pain, nausea, or vomiting.
  - **Vaginal yeast infection:**
    - vaginal odor
    - white or yellowish vaginal discharge (may be lumpy or look like cottage cheese)
    - vaginal itching
  - **Yeast infection of the skin around the penis (balanitis or balanoposthitis):** If you are uncircumcised, swelling may make it difficult to pull back the skin around the tip of your penis. Other symptoms include:
    - redness, itching, or swelling of the penis
    - bad smelling discharge from the penis
    - rash on the penis
    - pain in the skin around the penis

    Talk to your healthcare provider about what to do if you get symptoms of a yeast infection. They may suggest you use an over-the-counter antifungal medicine. Contact your healthcare provider right away if your symptoms do not improve after using an over-the-counter antifungal medicine.

What is SYNJARDY or SYNJARDY XR?

- SYNJARDY is a prescription medicine that contains 2 diabetes medicines, empagliflozin (JARDIANCE) and metformin HCl immediate-release.
- SYNJARDY XR is a prescription medicine that contains 2 diabetes medicines, empagliflozin (JARDIANCE) and metformin HCl extended-release.
- SYNJARDY can be used along with diet and exercise to improve blood sugar (glucose) in adults and children who are 10 years of age and older with type 2 diabetes.
- SYNJARDY XR can be used along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes.
- One of the medicines in SYNJARDY and SYNJARDY XR, empagliflozin (JARDIANCE), can also be used in adults with type 2 diabetes:
  - who have known cardiovascular disease to reduce the risk of cardiovascular death.
  - who have heart failure (when the heart cannot pump enough blood to the rest of your body) to reduce the risk of cardiovascular death and hospitalization for heart failure.
  - to reduce the risk of further worsening of kidney disease, end-stage kidney disease (ESKD), death due to cardiovascular disease, and hospitalization in adults with chronic kidney disease.
- SYNJARDY or SYNJARDY XR is not for use to lower blood sugar (glucose) in people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine).
- SYNJARDY or SYNJARDY XR is only for use in people with type 2 diabetes, because it contains the prescription medicine metformin HCl.
- One of the medicines in SYNJARDY or SYNJARDY XR, empagliflozin (JARDIANCE), is not for people with polycystic kidney disease, or who are taking or have recently received certain types of immunosuppressive therapy to treat kidney disease. Empagliflozin (JARDIANCE) is not expected to work if you have these conditions.
- It is not known if SYNJARDY is safe and effective in children under 10 years of age.
- It is not known if SYNJARDY XR is safe and effective in children.

Who should not take SYNJARDY or SYNJARDY XR?
Do not take SYNJARDY or SYNJARDY XR if you:

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

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

What should I tell my healthcare provider before taking SYNJARDY or SYNJARDY XR?
Before taking SYNJARDY or SYNJARDY XR, tell your healthcare provider about all of your medical conditions, including if you:

- have type 1 diabetes or have had diabetic ketoacidosis.
- have a decrease in your insulin dose.
- have a serious infection.
- have a history of infection of the vagina or penis.
- have a history of amputation.
- have kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- are 65 years of age or older.
- have a history of urinary tract infections or problems with urination.
- are on a low sodium (salt) diet. Your healthcare provider may change your diet or your dose.
- are going to have surgery. Your healthcare provider may stop your SYNJARDY or SYNJARDY XR before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking SYNJARDY or SYNJARDY XR and when to start it again.

- are eating less, or there is a change in your diet.
- are dehydrated.
- 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).
- have ever had an allergic reaction to SYNJARDY or SYNJARDY XR.
- are going to get an injection of dye or contrast agents for an x-ray procedure. SYNJARDY or SYNJARDY XR may need to be stopped for a short time. Talk to your healthcare provider about when you should stop SYNJARDY or SYNJARDY XR and when you should start SYNJARDY or SYNJARDY XR again. See **"What is the most important information I should know about SYNJARDY or SYNJARDY XR?"**
- have low levels of vitamin B_{12} in your blood.
- are pregnant or plan to become pregnant. SYNJARDY or SYNJARDY XR may harm your unborn baby. If you become pregnant while taking SYNJARDY or SYNJARDY XR, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. SYNJARDY or SYNJARDY XR may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking SYNJARDY or SYNJARDY XR. Do not breastfeed while taking SYNJARDY or SYNJARDY XR.
- are a person who has not gone through menopause (premenopausal) who does not have periods regularly or at all. SYNJARDY or SYNJARDY XR can cause the release of an egg from an ovary in a person (ovulation). This can increase your chance of getting pregnant. Tell your healthcare provider right away if you become pregnant while taking SYNJARDY or SYNJARDY XR.
- have a genetically inherited disease affecting mitochondria (the energy-producing parts within cells) such as MELAS syndrome and MIDD.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SYNJARDY or SYNJARDY XR may affect the way other medicines work, and other medicines may affect how SYNJARDY or SYNJARDY XR works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take SYNJARDY or SYNJARDY XR?

- Take SYNJARDY or SYNJARDY XR exactly as your healthcare provider tells you to take it.
- **If you are prescribed SYNJARDY:**
  - take SYNJARDY by mouth 2 times each day with meals. Taking SYNJARDY with meals may lower your chance of having an upset stomach.
- **If you are prescribed SYNJARDY XR:**
  - take SYNJARDY XR by mouth 1 time each day with a meal in the morning. Taking SYNJARDY XR with a meal may lower your chance of having an upset stomach.
  - swallow SYNJARDY XR tablets whole. Do not break, cut, crush, dissolve, or chew SYNJARDY XR tablets. If you cannot swallow SYNJARDY XR tablets whole, tell your healthcare provider.
  - you may see something that looks like the SYNJARDY XR tablet in your stool (bowel movement). This is not harmful and should not affect the way SYNJARDY XR works to control your diabetes.
- Your healthcare provider will tell you how much SYNJARDY or SYNJARDY XR to take and when to take it. Your healthcare provider may change your dose if needed.
- Your healthcare provider may tell you to take SYNJARDY or SYNJARDY XR along with other diabetes medicines. Low blood sugar can happen more often when SYNJARDY or SYNJARDY XR is taken with certain other diabetes medicines. See **"What are the possible side effects of SYNJARDY or SYNJARDY XR?"**
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take two doses of SYNJARDY or SYNJARDY XR at the same time. Talk with your healthcare provider if you have questions about a missed dose.
- If you take too much SYNJARDY or SYNJARDY XR, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.
- When taking SYNJARDY or SYNJARDY XR, you may have sugar in your urine, which will show up on a urine test.
- 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 you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.

- Your healthcare provider may do certain blood tests before you start SYNJARDY or SYNJARDY XR and during your treatment as needed.

What should I avoid while taking SYNJARDY or 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 or SYNJARDY XR?
SYNJARDY or SYNJARDY XR may cause serious side effects, including:

- See **"What is the most important information I should know about SYNJARDY or SYNJARDY XR?"**

- **Low blood sugar (hypoglycemia).** In adults, if you take SYNJARDY or SYNJARDY XR with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. In children 10 years of age and older, the risk for low blood sugar is higher with SYNJARDY even if you do not use another medicine that can also lower blood sugar. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take SYNJARDY or 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

- **Amputations. SGLT2 inhibitors may increase your risk of lower limb amputations.**
  You may be at a higher risk of lower limb amputation if you:
  - have a history of amputation
  - have had blocked or narrowed blood vessels, usually in your leg
  - have had diabetic foot infection, ulcers or sores

  Call your healthcare provider right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Talk to your healthcare provider about proper foot care.
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking SYNJARDY or SYNJARDY XR and call your healthcare provider right away or go to the nearest hospital emergency room. See "**Who should not take SYNJARDY or SYNJARDY XR?**".
- **Low vitamin B_{12} (vitamin B_{12} deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B_{12} in your blood, especially if you have had low vitamin B_{12} blood levels before. Your healthcare provider may do blood tests to check your vitamin B_{12} levels.

The most common side effects of SYNJARDY or SYNJARDY XR include:

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

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

How should I store SYNJARDY or SYNJARDY XR?

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

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

What are the ingredients in SYNJARDY?
Active Ingredients: empagliflozin and metformin HCl
Inactive Ingredients: colloidal silicon dioxide, copovidone, corn starch, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, polyethylene glycol 400, talc, and titanium dioxide. 5 mg/500 mg and 5 mg/1,000 mg tablets also contain ferric oxide yellow. 12.5 mg/500 mg and 12.5 mg/1,000 mg tablets also contain black ferrosoferric oxide and ferric oxide red.
What are the ingredients in SYNJARDY XR?
Active Ingredients: empagliflozin and metformin HCl
Inactive Ingredients: Tablet core contains: hypromellose, magnesium stearate, and polyethylene oxide. The film coatings and printing ink contain: carnauba wax, FD&C blue#2/indigo carmine aluminum lake (12.5 mg/1,000 mg, 25 mg/1,000 mg), ferric oxide red (10 mg/1,000 mg), ferric oxide yellow (5 mg/1,000 mg, 10 mg/1,000 mg, 25 mg/1,000 mg), ferrosoferric oxide, hypromellose, isopropyl alcohol, polydextrose, polyethylene glycol, propylene glycol, purified water, talc, and titanium dioxide.
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SYNJARDY is a registered trademark of and used under license from Boehringer Ingelheim International GmbH.
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For more information about SYNJARDY or SYNJARDY XR, including current prescribing information and Medication Guide, go to **www.synjardy.com** or **www.synjardyxr.com**, scan the code, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.



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

Revised: August 2026

PRINCIPAL DISPLAY PANEL - 5 mg/500 mg Tablet Bottle Label

NDC 0597-0159-60

DISPENSE WITH ACCOMPANYING
MEDICATION GUIDE

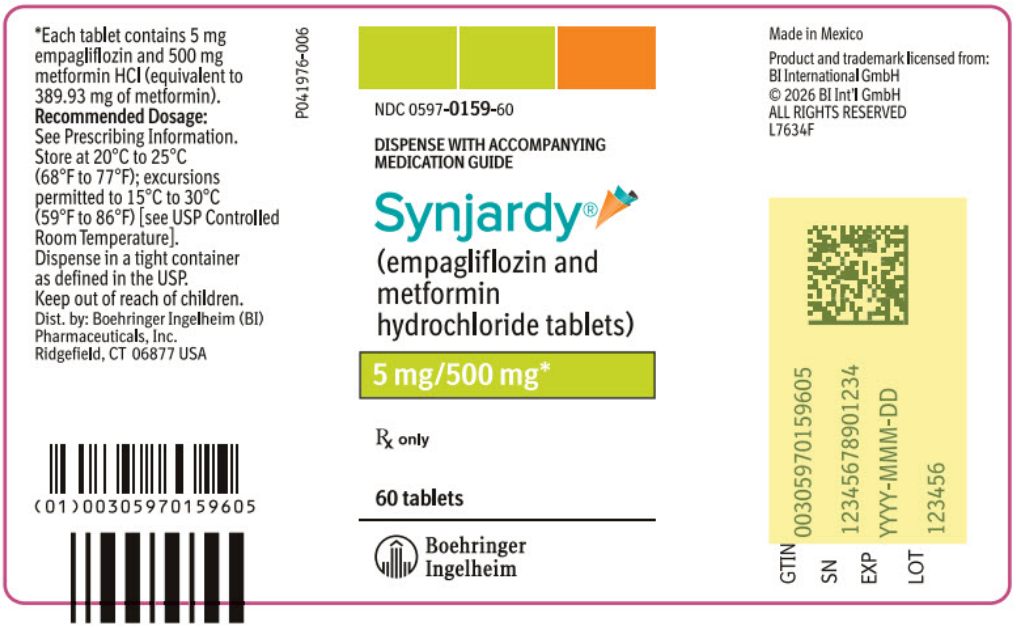
Synjardy®
(empagliflozin and
metformin
hydrochloride tablets)

5 mg/500 mg*

Rx only

60 tablets

Boehringer
Ingelheim



PRINCIPAL DISPLAY PANEL - 5 mg/1,000 mg Tablet Bottle Label

NDC 0597-0175-60

DISPENSE WITH ACCOMPANYING
MEDICATION GUIDE

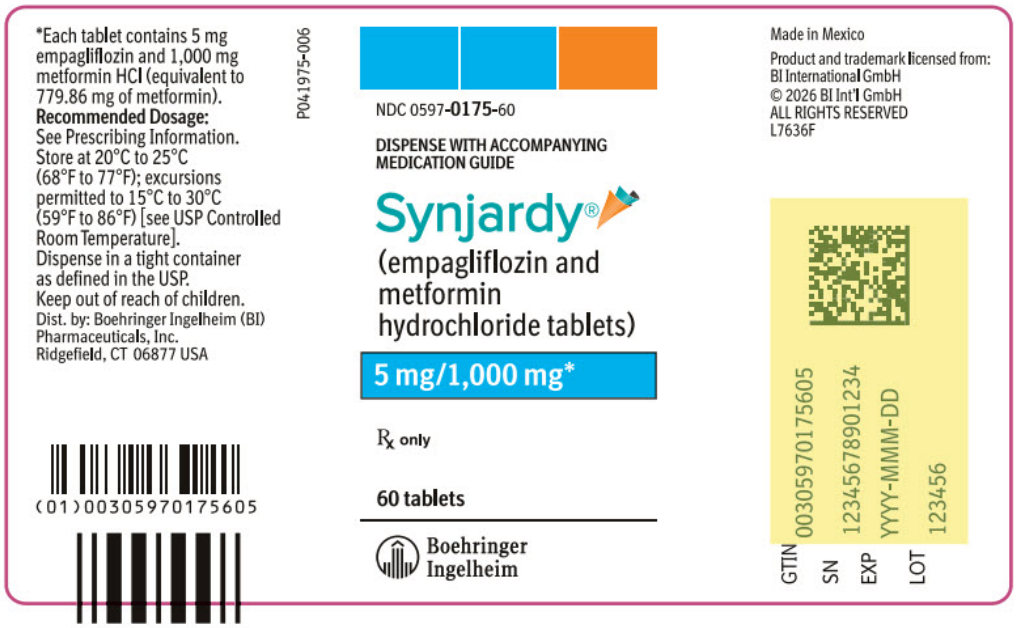
Synjardy®
(empagliflozin and
metformin
hydrochloride tablets)

5 mg/1,000 mg*

Rx only

60 tablets

Boehringer
Ingelheim



PRINCIPAL DISPLAY PANEL - 12.5 mg/500 mg Tablet Bottle Label

NDC 0597-0180-60

DISPENSE WITH ACCOMPANYING
MEDICATION GUIDE

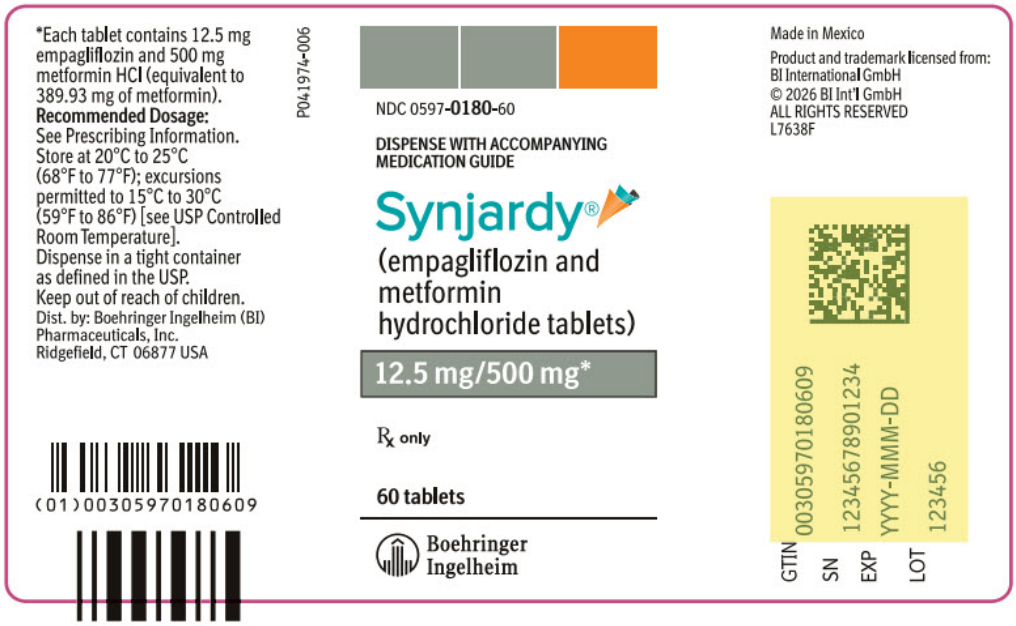
Synjardy®
(empagliflozin and
metformin
hydrochloride tablets)

12.5 mg/500 mg*

Rx only

60 tablets

Boehringer
Ingelheim



PRINCIPAL DISPLAY PANEL - 12.5 mg/1,000 mg Tablet Bottle Label

NDC 0597-0168-60

DISPENSE WITH ACCOMPANYING
MEDICATION GUIDE

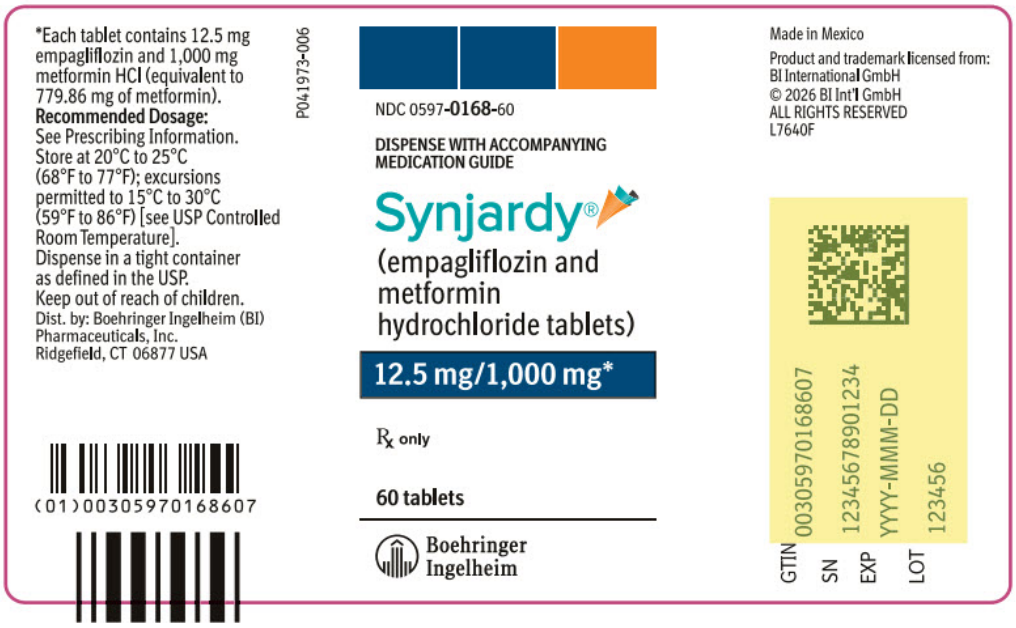
Synjardy®
(empagliflozin and
metformin
hydrochloride tablets)

12.5 mg/1,000 mg*

Rx only

60 tablets

Boehringer
Ingelheim



SYNJARDY

empagliflozin and metformin hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0159
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Product Characteristics			
Color	ORANGE (orange yellow)	**Score**	no score
Shape	OVAL	**Size**	16mm
Flavor		**Imprint Code**	S5;500
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0597-0159-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
2	NDC:0597-0159-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
3	NDC:0597-0159-66	1 in 1 CARTON	09/12/2015	09/30/2023
3		14 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206111	08/26/2015	

SYNJARDY

empagliflozin and metformin hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0175
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	1000 mg

Product Characteristics			
Color	BROWN (brownish yellow)	**Score**	no score
Shape	OVAL	**Size**	21mm
Flavor		**Imprint Code**	S5;1000
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0175-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
2	NDC:0597-0175-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
3	NDC:0597-0175-66	1 in 1 CARTON	09/12/2015	03/31/2024
3		14 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206111	08/26/2015	

SYNJARDY

empagliflozin and metformin hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0180
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	12.5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	500 mg

Product Characteristics			
Color	PURPLE (pale brownish purple)	**Score**	no score
Shape	OVAL	**Size**	16mm
Flavor		**Imprint Code**	S12;500
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0180-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	

2	NDC:0597-0180-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
3	NDC:0597-0180-66	1 in 1 CARTON	09/12/2015	11/30/2023
3		14 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206111	08/26/2015	

SYNJARDY

empagliflozin and metformin hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0597-0168
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	12.5 mg
METFORMIN HYDROCHLORIDE (UNII: 786Z46389E) (METFORMIN - UNII:9100L32L2N)	METFORMIN HYDROCHLORIDE	1000 mg

Product Characteristics

Color	PURPLE (dark brownish purple)	**Score**	no score
Shape	OVAL	**Size**	21mm
Flavor		**Imprint Code**	S12;1000
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0597-0168-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
2	NDC:0597-0168-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	09/12/2015	
3	NDC:0597-0168-66	1 in 1 CARTON	09/12/2015	12/31/2026
3		14 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206111	08/26/2015	

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