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

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

WARNING: RISK OF LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue SYNJARDY and hospitalize the patient immediately (5.1)**

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

SYNJARDY is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and metformin, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. (1)

Limitation of Use:

- Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.1)

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

- Individualize the starting dose of SYNJARDY based on the patient's current regimen (2.1)
- The maximum recommended dose is 12.5 mg empagliflozin/1000 mg metformin twice daily (2.1)
- Take twice daily with meals, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin (2.1)
- Assess renal function before initiating SYNJARDY. Do not initiate or continue SYNJARDY if creatinine levels are greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or if eGFR is below 45 mL/min/1.73 m^2 (2.2)

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

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

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

- Renal Impairment, ESRD, or on dialysis (4, 5.1, 5.3)
- Metabolic acidosis, including diabetic ketoacidosis (1, 4, 5.1)
- History of serious hypersensitivity reaction to empagliflozin or metformin (4)

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

- *Lactic acidosis:* Warn against excessive alcohol use. SYNJARDY is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (5.1, 5.3, 5.4, 5.9, 5.10)
- *Hypotension:* Before initiating SYNJARDY assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.2)
- *Impairment in renal function:* Monitor renal function during therapy. (5.3)
- *Radiological studies and surgical procedures:* Temporarily discontinue SYNJARDY in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food and fluids. (5.3)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating SYNJARDY (5.5)
- *Genital mycotic infections:* Monitor and treat as appropriate (5.6)
- *Urinary tract infections:* Monitor and treat as appropriate (5.7)
- *Vitamin B_{12} deficiency:* Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually. (5.8)
- *Increased LDL-C:* Monitor and treat as appropriate (5.11)
- *Macrovascular outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SYNJARDY. (5.12)

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

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

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

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

- *Cationic drugs eliminated by renal tubular secretion:* May reduce metformin elimination. Use with caution. (7.2)

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

- *Pregnancy:* No adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- *Nursing mothers:* Discontinue SYNJARDY or discontinue nursing (8.3)
- *Geriatric patients:* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.2, 5.3, 8.5)
- *Patients with renal impairment:* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2015

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure.

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, SYNJARDY should be discontinued and the patient hospitalized immediately *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

SYNJARDY is a combination of empagliflozin and metformin HCl indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin *[see Clinical Studies (14)]*.

1.1 Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Individualize the starting dose of SYNJARDY based on the patient's current regimen:
  - In patients on metformin, switch to SYNJARDY containing empagliflozin 5 mg with a similar total daily dose of metformin;
  - In patients on empagliflozin, switch to SYNJARDY containing metformin 500 mg with a similar total daily dose of empagliflozin;
  - In patients already treated with empagliflozin and metformin, switch to SYNJARDY containing the same total daily doses of each component.
- Take SYNJARDY twice daily with meals; with gradual dose escalation to reduce the gastrointestinal side effects due to metformin *[see Dosage Forms and Strengths (3)]*.
- In patients with volume depletion not previously treated with empagliflozin, correct this condition before initiating SYNJARDY *[see Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.
- Adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of metformin 2000 mg and empagliflozin 25 mg *[see Dosage and Administration (2.2)]*.

2.2 Recommended Dosage in Patients with Renal Impairment

- Assess renal function prior to initiation of SYNJARDY and periodically, thereafter.
- Do not initiate or continue SYNJARDY in patients with serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females. In patients eligible for SYNJARDY based on creatinine cutoff criteria do not initiate or continue SYNJARDY if eGFR is persistently less than 45 mL/min/1.73 m^2. In patients eligible for SYNJARDY based on creatinine cutoff criteria, no dose adjustment is needed if eGFR is greater than or equal to 45 mL/min/1.73 m^2 *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

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3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

SYNJARDY is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR is less than 45 mL/min/1.73 m^2), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia; end stage renal disease (ESRD) or patients on dialysis *[see Warnings and Precautions (5.1, 5.3) and Use in Specific Populations (8.6)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin *[see Warnings and Precautions (5.1)]*.
- History of serious hypersensitivity reaction to empagliflozin or metformin hydrochloride.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with SYNJARDY and is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels of >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin is approximately 0.03 cases/1000 patient-years, (with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, particularly when accompanied by hypoperfusion and hypoxemia due to unstable or acute failure, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal impairment and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic

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function may significantly limit the ability to clear lactate, metformin should be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking metformin, since alcohol potentiates the effects of metformin on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may cause dose-dependent metabolic acidosis and may exacerbate the risk of metformin-induced lactic acidosis *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

The onset of lactic acidosis is often subtle, and accompanied by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. More severe acidosis may be associated with signs such as hypothermia, hypotension, and resistant bradyarrhythmias. Patients should be educated to recognize and promptly report these symptoms. If present, SYNJARDY should be discontinued until lactic acidosis is ruled out. Gastrointestinal symptoms, which are commonly reported during initiation of metformin therapy are less frequently observed in subjects on a chronic, stable, dose of metformin. Gastrointestinal symptoms in subjects on chronic, stable, dose of metformin could be caused by lactic acidosis or other serious disease.

To rule out lactic acidosis, serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be due to other mechanisms, such as poorly-controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and supportive measures promptly instituted. Metformin is dialyzable (clearance of up to 170 mL/min under good hemodynamic conditions) and prompt hemodialysis is recommended to remove the accumulated metformin and correct the metabolic acidosis. Such management often results in prompt reversal of symptoms and recovery *[see Boxed Warning and Contraindications (4)]*.

5.2 Hypotension

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

5.3 Impairment in Renal Function

Empagliflozin increases serum creatinine and decreases eGFR *[see Adverse Reactions (6.1)]*. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment.

Metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, SYNJARDY is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2) *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.6)]*.

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Before initiation of therapy with SYNJARDY and at least annually thereafter, renal function should be assessed and verified to be normal. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and SYNJARDY discontinued if evidence of renal impairment is present (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2).

Use of concomitant medications that may affect renal function or metformin disposition:
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or interfere with the disposition of metformin should be used with caution *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3)]*.

Radiological studies and surgical procedures:
Radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, SYNJARDY should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been confirmed to be normal.

SYNJARDY should be temporarily discontinued for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

5.4 Impaired Hepatic Function
Because impaired hepatic function has been associated with some cases of lactic acidosis with metformin therapy, SYNJARDY should generally be avoided in patients with clinical or laboratory evidence of hepatic disease *[see Warnings and Precautions (5.1)]*.

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

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

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

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5.7 Urinary Tract Infections
Empagliflozin increases the risk for urinary tract infections *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

5.8 Vitamin B_{12} Levels
In controlled, 29-week clinical trials of metformin, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, 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, is, however, very rarely associated with anemia or neurologic manifestations due to the short duration (<1 year) of the clinical trials. This risk may be more relevant to patients receiving long-term treatment with metformin, and adverse hematologic and neurologic reactions have been reported postmarketing. The decrease in vitamin B_{12} levels appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on SYNJARDY and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurement at 2- to 3-year intervals may be useful.

5.9 Alcohol Intake
Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake while receiving SYNJARDY *[see Warnings and Precautions (5.1)]*.

5.10 Hypoxic States
Cardiovascular collapse (shock) from whatever cause (e.g., acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia) have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on SYNJARDY therapy, the drug should be promptly discontinued *[see Warnings and Precautions (5.1)]*.

5.11 Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with empagliflozin. Monitor and treat as appropriate.

5.12 Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with SYNJARDY, or any other antidiabetic drug.

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, 5.3, 5.4, 5.9, 5.10)]*
- Hypotension *[see Warnings and Precautions (5.2)]*
- Impairment in Renal Function *[see Warnings and Precautions (5.3)]*
- Impaired Hepatic Function *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*
- Urinary Tract Infections *[see Warnings and Precautions (5.7)]*
- Vitamin B_{12} Deficiency *[see Warnings and Precautions (5.8)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[see Warnings and Precautions (5.11)]*

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

Empagliflozin Add-On Combination Therapy with Metformin

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

Empagliflozin Add-On Combination Therapy with Metformin and Sulfonylurea

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

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

	Number (%) of Patients		
	Placebo n=225	**Empagliflozin 10 mg n=224**	**Empagliflozin 25 mg n=217**
Hypoglycemia	22 (9.8)	35 (15.6)	28 (12.9)
Urinary tract infection	15 (6.7)	21 (9.4)	15 (6.9)
Nasopharyngitis	11 (4.9)	18 (8.0)	13 (6.0)

Empagliflozin

The data in Table 2 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with basal insulin. Empagliflozin was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (14)]*.

These data reflect exposure of 1976 patients to empagliflozin with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), empagliflozin 10 mg (N=999), or empagliflozin 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2).

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

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

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

[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, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Empagliflozin may increase the risk of hypotension in patients at risk for volume contraction *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6)]*.

Increased Urination

In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on empagliflozin than on placebo (see Table 3). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Impairment in Renal Function

Use of empagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 3). Patients with moderate renal impairment at baseline had larger mean changes *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6)]*.

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

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

[a]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2.
[b]Approximately 3 weeks after end of treatment.

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Hypoglycemia

The incidence of hypoglycemia by study is shown in Table 4. The incidence of hypoglycemia increased when empagliflozin was administered with insulin or sulfonylurea *[see Warnings and Precautions (5.5)]*.

Table 4 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies

Monotherapy (24 weeks)	**Placebo (n=229)**	**Empagliflozin 10 mg (n=224)**	**Empagliflozin 25 mg (n=223)**
Overall (%)	0.4%	0.4%	0.4%
Severe (%)	0%	0%	0%
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**Empagliflozin 10 mg + Metformin (n=217)**	**Empagliflozin 25 mg + Metformin (n=214)**
Overall (%)	0.5%	1.8%	1.4%
Severe (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**Empagliflozin 10 mg + Metformin + Sulfonylurea (n=224)**	**Empagliflozin 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4%	16.1%	11.5%
Severe (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**Empagliflozin 10 mg + Pioglitazone +/- Metformin (n=165)**	**Empagliflozin 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8%	1.2%	2.4%
Severe (%)	0%	0%	0%
In Combination with Basal Insulin (18 weeks[c])	**Placebo (n=170)**	**Empagliflozin 10 mg (n=169)**	**Empagliflozin 25 mg (n=155)**
Overall (%)	20.6%	19.5%	28.4%
Severe (%)	0%	0%	1.3%
In Combination with MDI Insulin +/- Metformin (18 weeks[c])	**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]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections

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

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to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.5)]*.

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

Long-term treatment with metformin has been associated with a decrease in vitamin B_{12} absorption which may very rarely result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anemia) *[see Warnings and Precautions (5.8)]*.

Laboratory Tests
Empagliflozin
Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively *[see Warnings and Precautions (5.11)]*. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

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

Metformin hydrochloride
In controlled clinical trials of metformin of 29 weeks' duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation *[see Warnings and Precautions (5.8)]*.

7 DRUG INTERACTIONS

7.1 Drug Interactions with Empagliflozin

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

Insulin or Insulin Secretagogues
Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions (5.5)]*.

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

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

7.2 Drug Interactions with Metformin Hydrochloride

Cationic Drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of SYNJARDY and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Carbonic Anhydrase Inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with SYNJARDY, as the risk of lactic acidosis may increase *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Drugs Affecting Glycemic Control
Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving SYNJARDY, the patient should be closely observed to maintain adequate glycemic control *[see Clinical Pharmacology (12.3)]*. When such drugs are withdrawn from a patient receiving SYNJARDY, the patient should be observed closely for hypoglycemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
SYNJARDY
There are no adequate and well-controlled studies in pregnant women with SYNJARDY or its individual components. SYNJARDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
An embryo-fetal development study in pregnant rats did not indicate a teratogenic effect attributed to the coadministration of empagliflozin and metformin at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 mg and 25 mg doses, respectively; and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose.

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Empagliflozin
Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters.

Empagliflozin was not teratogenic in embryo-fetal development studies in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg. At higher doses, causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154 times the 25 mg maximum clinical dose in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139 times the 25 mg maximum clinical dose.

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

Metformin hydrochloride
Metformin has been studied for embryo-fetal effects in 2 rat strains and in rabbits. Metformin was not teratogenic in Sprague Dawley rats up to 600 mg/kg or in Wistar Han rats up to 200 mg/kg (2-3 times the clinical dose based on body surface area or exposure, respectively). At higher maternally toxic doses (9 and 23 times the clinical dose based on exposure), an increased incidence of rib and scapula skeletal malformations was observed in the Wistar Han strain. Metformin was not teratogenic in rabbits at doses up to 140 mg/kg (similar to clinical dose based on body surface area).

Metformin administered to female Sprague Dawley rats from gestation day 6 to lactation day 21 up to 600 mg/kg/day (2 times the maximum clinical dose based on body surface area) had no effect on prenatal or postnatal development of offspring.

Metformin crosses the placenta into the fetus in rats and humans.

8.3 Nursing Mothers
No studies in lactating animals have been conducted with the combined components of SYNJARDY. In studies performed with the individual components, both empagliflozin and metformin were secreted in the milk of lactating rats.

It is not known whether empagliflozin is excreted in human milk. Metformin is excreted in human milk in low concentrations. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in nursing infants may exist from SYNJARDY, a decision should be made whether to discontinue nursing or to discontinue SYNJARDY, taking into account the importance of the drug to the mother.

Empagliflozin
Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. 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.

Metformin hydrochloride
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers.

8.4 Pediatric Use
Safety and effectiveness of SYNJARDY in pediatric patients under 18 years of age have not been established.

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8.5 Geriatric Use

Because renal function abnormalities can occur after initiating empagliflozin, metformin is substantially excreted by the kidney, and aging can be associated with reduced renal function, monitor renal function more frequently after initiating SYNJARDY in the elderly and then adjust dose based on renal function *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3)]*.

Empagliflozin

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

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function *[see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

SYNJARDY is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2).

Empagliflozin

The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations *[see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.2, 5.3)]*.

The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment *[see Warnings and Precautions (5.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

Empagliflozin may be used in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2 or greater *[see Clinical Pharmacology (12.3)]*. Empagliflozin is not recommended in patients with a persistent eGFR less than 45 mL/min/1.73 m^2.

Metformin hydrochloride

Metformin is known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. Therefore, metformin is contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females) *[see Contraindications (4) and Warnings and Precautions (5.1, 5.3)]*.

8.7 Hepatic Impairment

SYNJARDY should generally be avoided in patients with clinical or laboratory evidence of hepatic disease *[see Warnings and Precautions (5.4)]*.

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

Metformin hydrochloride
Because impaired hepatic function has been associated with some cases of lactic acidosis with metformin therapy, SYNJARDY should generally be avoided in patients with clinical or laboratory evidence of hepatic disease *[see Warnings and Precautions (5.1)]*.

10 OVERDOSAGE

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

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

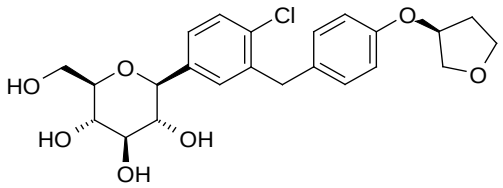
11 DESCRIPTION

SYNJARDY tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and metformin hydrochloride.

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

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

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



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

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

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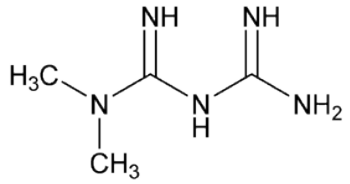

• HCl

SYNJARDY
SYNJARDY tablets for oral administration are available in four dosage strengths containing 5 mg empagliflozin and 500 mg metformin hydrochloride, 5 mg empagliflozin and 1000 mg metformin hydrochloride, 12.5 mg empagliflozin and 500 mg metformin hydrochloride, or 12.5 mg empagliflozin and 1000 mg metformin hydrochloride.

Each film-coated tablet of SYNJARDY contains the following inactive ingredients: copovidone, corn starch, colloidal silicon dioxide, magnesium stearate. Film-coating: hypromellose, titanium dioxide, talc, polyethylene glycol 400, and yellow ferric oxide (5 mg/500 mg, 5 mg/1000 mg) or red ferric oxide and black ferrosoferric oxide (12.5 mg/500 mg, 12.5 mg/1000 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.2 Pharmacodynamics

Empagliflozin
Urinary Glucose Excretion
In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily *[see Clinical Studies (14)]*.

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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

The results of a bioequivalence study in healthy subjects demonstrated that SYNJARDY (empagliflozin/metformin hydrochloride) 5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, and 12.5 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5 mg empagliflozin/1000 mg metformin 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.

Empagliflozin

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

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%.

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.

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Elimination
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life. Following administration of an oral [^{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 hydrochloride
Absorption
The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50% to 60%. Studies using single oral doses of metformin tablets 500 mg to 1500 mg, and 850 mg to 2550 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.

Distribution
The apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins, in contrast to SUs, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin tablets, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

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

Elimination
Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations
Renal Impairment
SYNJARDY: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY in renally impaired patients have not been performed. Since metformin is contraindicated in patients with renal impairment, use of SYNJARDY is also contraindicated in patients with renal impairment (serum creatinine levels greater than or equal to 1.5 mg/dL for males or 1.4 mg/dL for females, or eGFR less than 45 mL/min/1.73 m^2) *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Empagliflozin: In patients with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and subjects with

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kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Metformin hydrochloride: In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Hepatic Impairment

SYNJARDY: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY in hepatically impaired patients have not been performed. However, use of metformin alone in patients with hepatic impairment has been associated with some cases of lactic acidosis. Therefore, use of SYNJARDY is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.4)]*.

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

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

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

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

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

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

Geriatric

SYNJARDY: Studies characterizing the pharmacokinetics of empagliflozin and metformin after administration of SYNJARDY in geriatric patients have not been performed *[see Warnings and Precautions (5.2, 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 hydrochloride: Limited data from controlled pharmacokinetic studies of metformin 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.

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

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

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

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

In vivo Assessment of Drug Interactions: No dose adjustment of empagliflozin is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, hydrochlorothiazide, and torsemide in healthy volunteers (see Figure 1). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

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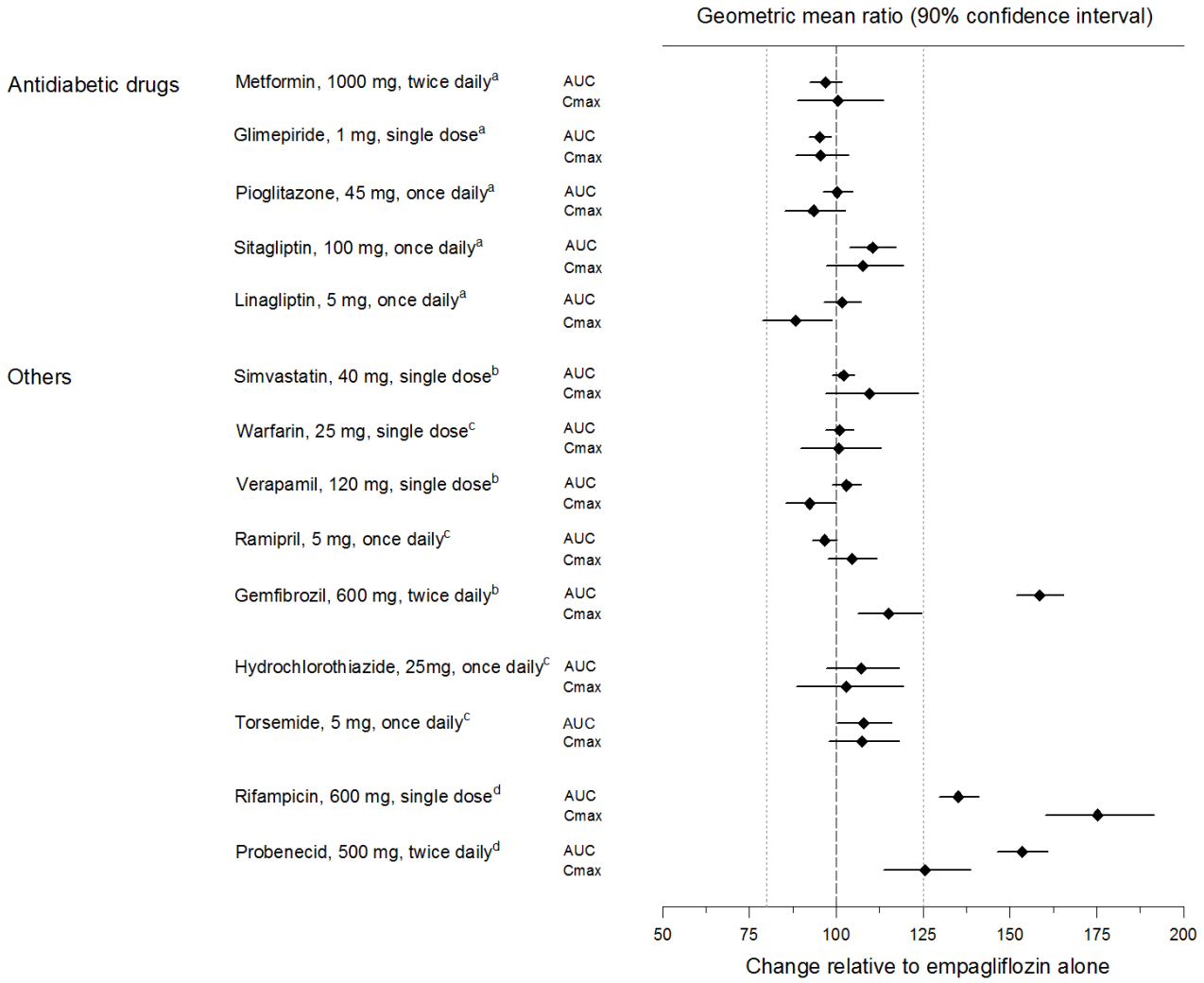
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



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

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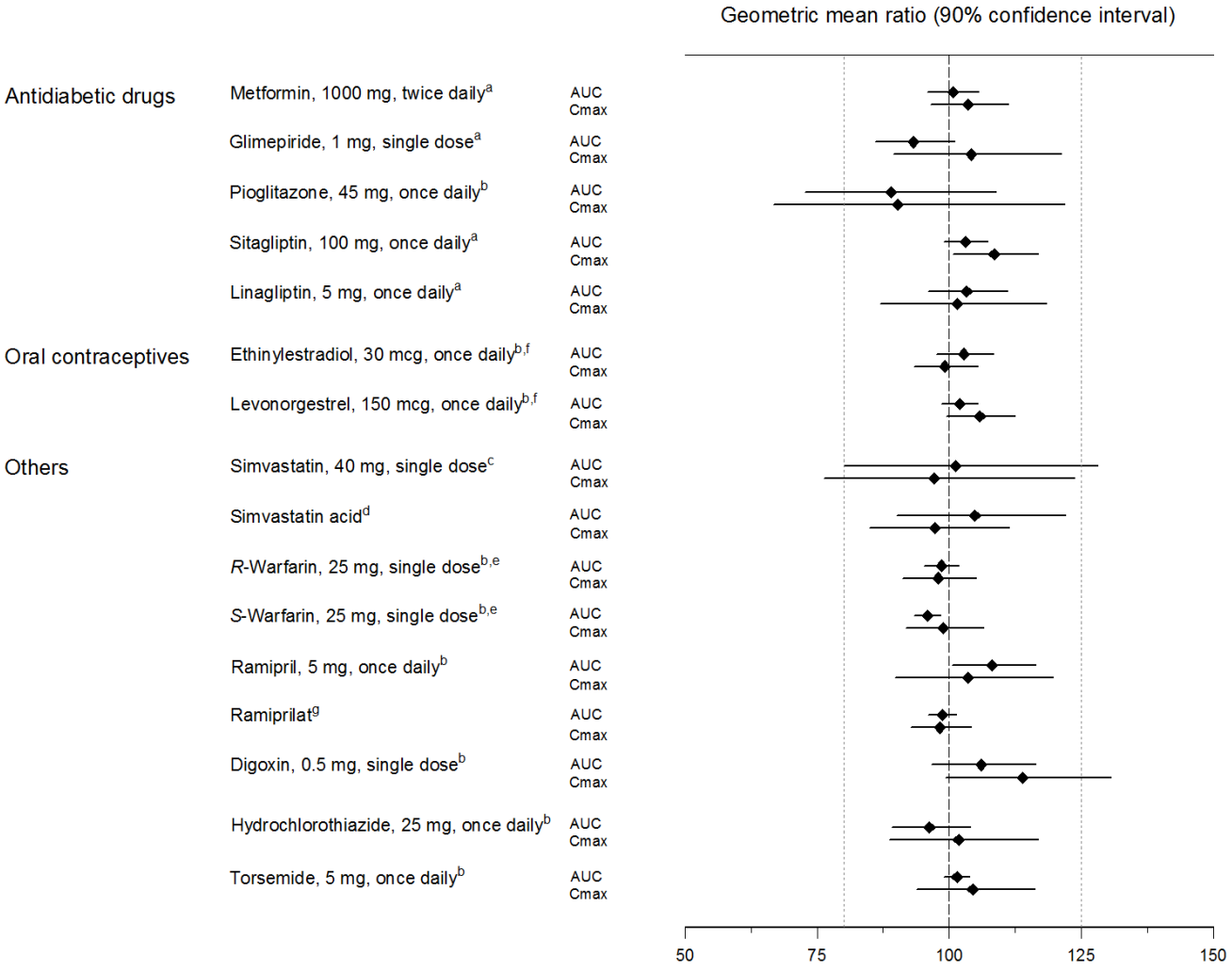
Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

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

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Metformin hydrochloride

Table 5 Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No effect=1.0		
				AUC†	C_{max}
No dosing adjustments required for the following coadministered drugs:					
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: use with caution *[see Warnings and Precautions (5.3) and Drug Interactions (7.1)]*.					
Cimetidine	400 mg	850 mg	metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.					
Topiramate**	100 mg	500 mg	metformin	1.25	1.17

* All metformin and coadministered drugs were given as single doses
† AUC = AUC(INF)
‡ Ratio of arithmetic means
**At steady state with topiramate 100 mg every 12 hours and metformin 500 mg every 12 hours; AUC = AUC0-12h

Table 6 Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug	Dosing of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No effect=1.0		
				AUC†	C_{max}
No dosing adjustments required for the following coadministered drugs:					
Glyburide	5 mg	500 mg§	glyburide	0.78‡	0.63‡
Furosemide	40 mg	850 mg	furosemide	0.87‡	0.69‡
Nifedipine	10 mg	850 mg	nifedipine	1.10§	1.08
Propranolol	40 mg	850 mg	propranolol	1.01§	0.94
Ibuprofen	400 mg	850 mg	ibuprofen	0.97¶	1.01¶

* 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 hr) reported
¶ Ratio of arithmetic means

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

SYNJARDY

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

Empagliflozin

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the

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

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

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

Metformin hydrochloride
Carcinogenesis
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg/kg/day based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

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

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

14 CLINICAL STUDIES

The coadministration of empagliflozin and metformin has been studied in combination with sulfonylurea.

There have been no clinical efficacy studies conducted with SYNJARDY; however, bioequivalence of SYNJARDY to empagliflozin and metformin coadministered as individual tablets was demonstrated in healthy subjects.

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

14.1 Combination Therapy

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

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

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

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

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

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

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

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

Patients with inadequately controlled type 2 diabetes on at least 1500 mg per day of metformin 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 8).

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Table 8 Results at Week 24 from a Placebo-Controlled Study for Empagliflozin in Combination with Metformin and Sulfonylurea

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

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

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

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

At Week 52, empagliflozin 25 mg and glimepiride lowered HbA1c and FPG (see Table 9, Figure 3). The difference in observed effect size between empagliflozin 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose in the United States is 8 mg per day.

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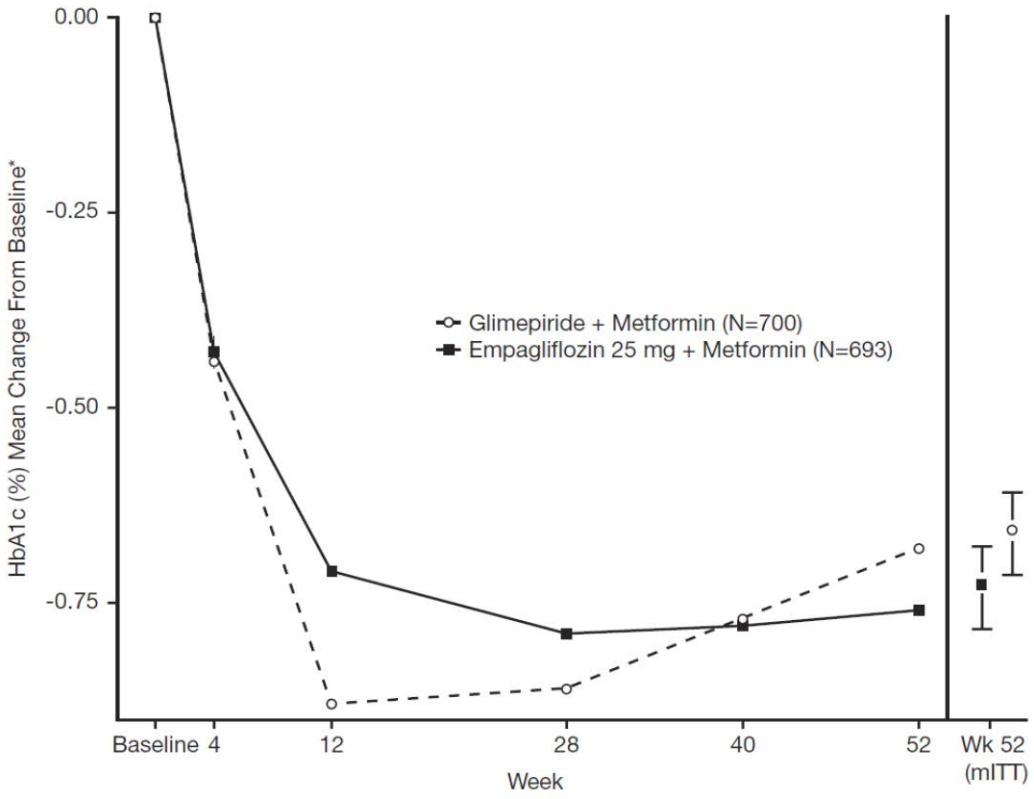
Table 9 Results at Week 52 from an Active-Controlled Study Comparing Empagliflozin to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

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

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

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



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

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

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

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

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16 HOW SUPPLIED/STORAGE AND HANDLING

SYNJARDY (empagliflozin and metformin hydrochloride) tablets are available in the following strengths and packages:

Tablet Strength	Film-Coated Tablet, Color/Shape	Tablet Markings	Package Size	NDC Number
5 mg/500 mg	orange yellow, oval, biconvex	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/1000 mg	brownish yellow, oval, biconvex	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/500 mg	pale brownish purple, oval, biconvex	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/1000 mg	dark brownish purple, oval, biconvex	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

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Store in a safe place out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

Instructions

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

Inform patients of the potential risks and benefits of SYNJARDY and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and

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hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

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

Instruct patients to take SYNJARDY 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.

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

Inform female patients of child bearing age that the use of SYNJARDY during pregnancy has not been studied in humans, and that SYNJARDY should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal data, empagliflozin may cause fetal harm in the second and third trimesters. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue SYNJARDY or nursing, taking into account the importance of the drug to the mother.

Hypotension

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

Urinary Tract Infections

Inform patients of the potential for urinary tract infections. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur.

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

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

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

Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Laboratory Tests

Inform patients that renal function should be assessed prior to initiation of SYNJARDY and monitored periodically thereafter.

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

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

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

What is the most important information I should know about SYNJARDY?
SYNJARDY can cause serious side effects, including:
Lactic Acidosis. Metformin, one of the medicines in SYNJARDY, 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 and call your doctor right away if you get any of the following symptoms of lactic acidosis:
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you have unusual sleepiness or sleep longer than usual
- you have stomach pains, nausea and vomiting or diarrhea
- you feel cold, especially in your arms and legs
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis with SYNJARDY if you:
- have kidney problems or your kidneys are affected by injectable dyes used for certain x-ray tests. People whose kidneys are not working properly should not take SYNJARDY.
- have liver problems
- have congestive heart failure that requires treatment with medicines
- drink alcohol very often, or drink a lot of alcohol in short-term ("binge" drinking)
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids.
- have surgery
- have a heart attack, severe infection, or stroke
- are 80 years of age or older and have not had your kidneys tested

SYNJARDY can have other serious side effects. See "What are the possible side effects of SYNJARDY?"

What is SYNJARDY?
- SYNJARDY is a prescription medicine that contains 2 diabetes medicines, empagliflozin and metformin. SYNJARDY can be used along with diet and exercise to improve blood sugar in adults with type 2 diabetes who have already been treated with either metformin or empagliflozin and their blood sugar is not controlled well enough, or patients who are currently taking both metformin and empagliflozin as separate medicines.
- SYNJARDY is not for people with type 1 diabetes.
- SYNJARDY is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- It is not known if SYNJARDY is safe and effective in children under 18 years of age.

Who should not take SYNJARDY?
Do not take SYNJARDY if you:
- have severe kidney problems or are on dialysis
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine)
- are allergic to empagliflozin, metformin, or any of the ingredients in SYNJARDY. See the end of this Medication Guide for a list of ingredients in SYNJARDY.

What should I tell my doctor before using SYNJARDY?
Before taking SYNJARDY, tell your healthcare provider about all of your medical conditions, including if you:
- have kidney problems
- have liver problems
- have a history of urinary tract infection or problems with urination
- have heart problems, including congestive heart failure
- drink alcohol very often, or drink a lot of alcohol in short term "binge" drinking
- are going to get an injection of dye or contrast agents for an x-ray procedure. SYNJARDY will need to be stopped for a short time. Talk to your doctor about when you should stop SYNJARDY and when you should start SYNJARDY again. See **"What is the most important information I should know about SYNJARDY?"**
- have a history of urinary tract infections or problems with urination
- have type 1 diabetes. SYNJARDY should not be used to treat people with type 1 diabetes.

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- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if SYNJARDY will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if SYNJARDY passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take SYNJARDY.

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

How should I take SYNJARDY?

- Take SYNJARDY exactly as your doctor tells you to take it.
- Take SYNJARDY by mouth 2 times each day with meals. Taking SYNJARDY with meals may lower your chance of having an upset stomach.
- Your doctor will tell you how much SYNJARDY to take and when to take it.
- Your doctor may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of SYNJARDY at the same time. Talk with your doctor if you have questions about a missed dose.
- Your doctor may tell you to take SYNJARDY along with other diabetes medicines. Low blood sugar can happen more often when SYNJARDY is taken with certain other diabetes medicines. See “What are the possible side effects of SYNJARDY?”
- If you take too much SYNJARDY, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor’s instructions.
- Check your blood sugar as your doctor tells you to.
- When taking SYNJARDY, you may have sugar in your urine, which will show up on a urine test.
- Stay on your prescribed diet and exercise program while taking SYNJARDY.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with SYNJARDY.
- Your doctor may do certain blood tests before you start SYNJARDY and during treatment.

What should I avoid while taking SYNJARDY?

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?

SYNJARDY may cause serious side effects, including:

- See **“What is the most important information I should know about SYNJARDY?”**
- **Dehydration.** SYNJARDY can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). You may be at higher risk of dehydration if you:
  - have low blood pressure
  - have kidney problems
  - are 65 years of age or older
  - are on low sodium (salt) diet
  - take medicines to lower your blood pressure, including diuretics (water pill)
- **low blood sugar (hypoglycemia).** If you take SYNJARDY with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take SYNJARDY. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - irritability
  - hunger
  - fast heartbeat
  - confusion
  - shaking or feeling jittery
  - dizziness
  - sweating
- **kidney problems,** especially in people 75 years of age or older and people who already have kidney problems
- **vaginal yeast infection.** Women who take SYNJARDY may get vaginal yeast infections. Symptoms of a vaginal yeast infection include vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), or vaginal itching.
- **yeast infection of the penis (balanitis).** Men who take SYNJARDY may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include redness, itching, or swelling of the penis, rash of the penis, foul smelling discharge from the penis, or pain in the skin around the penis.

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Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

- **urinary tract infection. Tell your doctor if you have any** signs and symptoms of a urinary tract infection that may include burning feeling when passing urine, urine that looks cloudy, pain in the pelvis, or back pain.
- **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 doctor may do blood tests to check your vitamin B_{12} levels.
- **increased fats in your blood (cholesterol)**

The most common side effects of SYNJARDY include stuffy or runny nose and sore throat.
These are not all the possible side effects of SYNJARDY. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SYNJARDY?
Store SYNJARDY at room temperature between 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of SYNJARDY.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SYNJARDY for a condition for which it was not prescribed. Do not give SYNJARDY 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 that is written for health professionals.

What are the ingredients in SYNJARDY?
Active Ingredients: empagliflozin and metformin hydrochloride
Inactive Ingredients: copovidone, corn starch, colloidal silicon dioxide, magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, and polyethylene glycol 400. 5 mg/500 mg and 5 mg/1000 mg tablets also contain yellow ferric oxide;12.5 mg/500 mg and 12.5 mg/1000 mg tablets also contain red ferric oxide and black ferrosoferric oxide

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

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