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

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

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

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

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

Indications and Usage (1)	6/2023
Dosage and Administration (2.2)	2/2023
Dosage and Administration (2.3, 2.7)	6/2023
Dosage and Administration (2.6)	10/2023
Warnings and Precautions (5.2, 5.8)	10/2023
Warnings and Precautions (5.5)	6/2023

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

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

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

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

- Cardiovascular death in adults with established cardiovascular disease. (1)
- Cardiovascular death and hospitalization for heart failure in adults with heart failure. (1)

Limitations of Use:

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. (1)
- Because of the metformin component, the use of SYNJARDY or SYNJARDY XR is limited to patients with type 2 diabetes mellitus for all indications. (1)

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

- Assess renal function before initiating and as clinically indicated. Assess volume status and correct volume depletion before initiating. (2.1)
- Individualize the starting dosage based on the patient's current regimen and renal function. (2.2, 2.3, 2.4)
- The maximum recommended dosage is 25 mg/day of empagliflozin and 2,000 mg/day of metformin HCl. (2.2, 2.3)
- Initiation of SYNJARDY or SYNJARDY XR is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2, due to the metformin component. (2.4)
- SYNJARDY: take orally twice daily with meals, with gradual dosage escalation to reduce the gastrointestinal side effects due to metformin. (2.2, 2.3)
- SYNJARDY XR: take orally once daily with a meal in the morning, with gradual dosage escalation to reduce the gastrointestinal side effects due to metformin. Swallow whole; do not split, crush, dissolve, or chew. (2.2)
- SYNJARDY or SYNJARDY XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.5)
- Withhold SYNJARDY or SYNJARDY XR at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting. (2.6)

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

SYNJARDY Tablets:

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

SYNJARDY XR Tablets:

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

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

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

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

- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:* Consider monitoring in patients at risk of ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue SYNJARDY or SYNJARDY XR if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.2)
- *Volume Depletion:* Before initiating SYNJARDY or SYNJARDY XR, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy. (5.3)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Hypoglycemia:* Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher regardless of insulin use. Consider lowering the dosage of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating SYNJARDY or SYNJARDY XR. (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.6)
- *Genital Mycotic Infections:* Monitor and treat as appropriate. (5.7)
- *Lower Limb Amputation:* Monitor patients for infections or ulcers of lower limbs, and institute appropriate treatment. (5.8)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., angioedema) have occurred with empagliflozin. If hypersensitivity reactions occur, discontinue SYNJARDY or SYNJARDY XR, treat promptly, and monitor until signs and symptoms resolve. (5.9)
- *Vitamin B_{12} Deficiency:* Metformin may lower vitamin B_{12} levels. Measure hematologic parameters annually and vitamin B_{12} at 2 to 3 year intervals and manage any abnormalities. (5.10)

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

- Most common adverse reactions associated with empagliflozin (5% or greater incidence) were urinary tract infections and female genital mycotic infections. (6.1)

- Most common adverse reactions associated with metformin (>5%) are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. (6.1)

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

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

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

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

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

1 INDICATIONS AND USAGE

SYNJARDY

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

SYNJARDY XR

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

Empagliflozin

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

- Cardiovascular death in adults with established cardiovascular disease.
- Cardiovascular death and hospitalization for heart failure in adults with heart failure.

Limitations of Use

- SYNJARDY and SYNJARDY XR are not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.2)]*.
- Because of the metformin component, the use of SYNJARDY or SYNJARDY XR is limited to patients with type 2 diabetes mellitus for all indications.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of SYNJARDY or SYNJARDY XR

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

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

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

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

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

2.4 Dosage Recommendations in Patients with Renal Impairment

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

2.5 Discontinuation for Iodinated Contrast Imaging Procedures

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

2.6 Temporary Interruption for Surgery

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

2.7 Recommendations Regarding Missed Dose

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

3 DOSAGE FORMS AND STRENGTHS

SYNJARDY Tablets:

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

SYNJARDY XR Tablets:

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

4 CONTRAINDICATIONS

SYNJARDY and SYNJARDY XR are contraindicated in patients with:

- severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease, or dialysis *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.
- acute or chronic metabolic acidosis, including diabetic ketoacidosis *[see Warnings and Precautions (5.1)]*.
- hypersensitivity to empagliflozin, metformin or any of the excipients in SYNJARDY or SYNJARDY XR, reactions such as angioedema have occurred *[see Warnings and Precautions (5.9)]*.

5 WARNINGS AND PRECAUTIONS

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.