Prescribing Information (UK) SYNJARDY® (empagliflozin and metformin hydrochloride)

Film-coated tablets containing 5 mg empagliflozin and 850 mg metformin hydrochloride, 5 mg empagliflozin and 1000 mg metformin hydrochloride, 12.5 mg empagliflozin and 850 mg metformin hydrochloride or 12.5 mg empagliflozin and 1000 mg metformin hydrochloride. **Indication:** Synjardy is indicated for the treatment of adults with type 2 diabetes mellitus as an adjunct to diet and exercise: in patients insufficiently controlled on their maximally tolerated dose of metformin alone; in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products; in patients already being treated with the combination of empagliflozin and metformin as separate tablets. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the population studied, refer to the Summary of Product Characteristics. **Dose and Administration:** Adults with normal renal function (GFR ≥90 ml/min). Recommended dose: one tablet twice daily. The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability using the recommended daily dose of 10 mg or 25 mg of empagliflozin, while not exceeding the maximum recommended daily dose of metformin. For patients insufficiently controlled on metformin (either alone or in combination with other medicinal products for the treatment of diabetes), the recommended starting dose of Synjardy should provide empagliflozin 5 mg twice daily (10 mg daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10 mg and who need tighter glycaemic control, the dose can be increased to a total daily dose of empagliflozin 25 mg. When used in combination with insulin and/or an insulin secretagogue such as sulphonylurea, a lower dose of the insulin and/or insulin secretagogue may be required. Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin to Synjardy should receive the same daily dose of these already being taken or the nearest therapeutically appropriate dose of metformin. If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time. In that case, the missed dose should be skipped. *Hepatic impairment:* Not to be used in patients with hepatic impairment. *Renal impairment:* No dose adjustment is recommended for patients with mild renal impairment. Assess GFR before initiating treatment and at least annually thereafter, or more frequently (e.g. every 3-6 months) in patients at an increased risk of further progression of renal impairment and in the elderly. If no adequate strength of Synjardy is available, individual monocomponents should be used instead of the fixed dose combination. For full details prescribers should consult the Summary of Product Characteristics. *Elderly:* Decreased renal function will result in reduced glycaemic efficacy of empagliflozin. Metformin is excreted by the kidney and therefore caution should be used in elderly patients due to decreased renal function in the elderly population. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients. In patients 75 years and older, an increased risk for volume depletion should be taken into account. Not recommended in patients 85 years or older. *Paediatric population:* No data are available. *Method of administration:* Synjardy should be taken twice daily with meals. The tablets should be swallowed whole with water. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients; any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis); diabetic pre coma; severe renal failure (GFR <30 ml/min; acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock; disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock; hepatic impairment, acute alcohol intoxication, alcoholism. **Warnings and Precautions:** Not to be used in patients with type 1 diabetes or in paediatric populations. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis. Temporarily discontinued treatment in case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake). Initiate products that can acutely impair renal function (e.g. antihypertensives, diuretics and non-steroidal anti-inflammatory drugs (NSAIDs)) with caution. Inform patients and/or care givers of the risk of lactic acidosis. If lactic acidosis is suspected the patient should stop taking metformin and seek immediate medical attention. Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. Consider the risk of DKA in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness and assess patients for ketoacidosis immediately, regardless of blood glucose level. In patients where DKA is suspected or diagnosed, treatment should be discontinued immediately. Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised. Before initiating empagliflozin, consider factors in the patient history that may predispose to ketoacidosis. Use with caution in patients who may be at higher risk of DKA. Intravascular administration of iodinated contrast agents may result in metformin accumulation and increased risk of lactic acidosis. Discontinue treatment prior to or at the time of the imaging procedure. Restart after at least 48 hours, provided that renal function is re-evaluated and found to be stable. Assess GFR before initiating treatment and regularly thereafter (see Dose and Administration). Temporarily discontinue treatment in the presence of conditions that alter renal function. Discontinue treatment at the time of surgery under general, spinal or epidural anaesthesia. Restart therapy no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function is re-evaluated and found to be stable. Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Synjardy may be used with a regular monitoring of cardiac and renal function. Exercise caution in patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or patients aged 75 years and older. In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status and electrolytes is recommended. Temporary interruption of treatment should be considered until the fluid loss is corrected. Patients aged 75 years and older may be at an increased risk of volume depletion. Special attention should be given to their volume intake in case of coadministered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors). Temporary interruption of treatment should be considered in patients with complicated urinary tract infections. Cases of necrotising fasciitis of the perineum (Fournier's gangrene), have been reported in patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment. Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Synjardy should be discontinued and prompt treatment should be instituted. An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor, counsel patients on routine preventative footcare. Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. Haematocrit increase was observed with empagliflozin treatment. Patients taking Synjardy will test positive for glucose in their urine. **Interactions:** No interaction studies have been performed for Synjardy. *Interactions for Empagliflozin:* Use with diuretics may increase the risk of dehydration and hypotension. Insulin and insulin secretagogues may increase the risk of hypoglycaemia therefore, a lower dose of insulin or an insulin secretagogue may be required. The effect of UGT induction (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Synjardy is appropriate. Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide. Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives. Glucocorticoids (given by systemic and local routes), beta 2 agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. *Interactions for Metformin:* Concomitant use not recommended: alcohol; iodinated contrast agents; organic cation transporters: OCT1 and OCT2 inhibitors/inducers such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib and olaparib, use caution especially in patients with renal impairment and consider dose adjustment if needed. For products which may increase the risk of lactic acidosis e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, close monitoring of renal function is necessary. Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. **Fertility, Pregnancy and Lactation:** There are no data from the use of Synjardy or empagliflozin in pregnant women. When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product, but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus. Synjardy should not be used during breast feeding. No studies on the effect on human fertility have been conducted for Synjardy or empagliflozin. **Undesirable effects:** Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Very common: hypoglycaemia (when used with sulphonylurea or insulin), gastrointestinal symptoms. Common: vaginal moniliasis, vulvovaginitis, balanitis and other genital infections, urinary tract infection (including pyelonephritis and urosepsis), thirst, taste disturbance, pruritus (generalised), rash, increased urination, serum lipids increased. Uncommon: volume depletion, urticaria, dysuria, blood creatinine increased/glomerular filtration rate decreased, haematocrit increased. Rare: DKA. Very rare: lactic acidosis, vitamin B12 deficiency, liver function tests abnormalities, hepatitis, erythema. Not known: necrotising fasciitis of the perineum (Fournier's gangrene), angioedema. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 56 x 1 film-coated tablets; 5 mg/850 mg: **£36.59**, 5 mg/1000 mg: **£36.59**, 12.5 mg/850 mg: **£36.59** and 12.5 mg/1000 mg: **£36.59**. **Legal category:** POM. **MA numbers:** 5 mg/850 mg: EU/1/15/1003/004; 5 mg/1000 mg: EU/1/15/1003/013; 12.5 mg/850 mg: EU/1/15/1003/22; 12.5 mg/1000 mg: EU/1/15/1003/031. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Strasse 173, D55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in** July 2020.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Boehringer Ingelheim

Lilly