APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

Synjardy® 5/500 mg
Synjardy® 5/850 mg
Synjardy® 5/1000 mg
Synjardy® 12,5/500 mg
Synjardy® 12,5/850 mg
Synjardy® 12,5/1000 mg
film-coated tablets

SYNJARDY IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES.
SYNJARDY IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES.
There have been reports of metabolic acidosis, including ketoacidosis, which were serious, life threatening or fatal, in patients taking SYNJARDY.
Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/L. SYNJARDY should be discontinued and the patient should be promptly evaluated and managed accordingly.
Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with SYNJARDY.
Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. SYNJARDY is contraindicated in these patients.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- SYNJARDY 5/500 mg contains 5 mg empagliflozin and 500 mg metformin hydrochloride
- SYNJARDY 5/850 mg contains 5 mg empagliflozin and 850 mg metformin hydrochloride
- SYNJARDY 5/1000 mg contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride
- SYNJARDY 12,5/500 mg contains 12,5 mg empagliflozin and 500 mg metformin hydrochloride
- SYNJARDY 12,5/850 mg contains 12,5 mg empagliflozin and 850 mg metformin hydrochloride
- SYNJARDY 12,5/1000 mg contains 12,5 mg empagliflozin and 1 000 mg metformin hydrochloride.

Sugar free.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

SYNJARDY are film-coated tablets for oral administration.
SYNJARDY 5/500 mg – 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'.
SYNJARDY 5/850 mg – yellowish white, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and 'S5', the other side is debossed with '850'.
SYNJARDY 5/1000 mg – brownish yellow, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and 'S5', the other side is debossed with '1000'.
SYNJARDY 12,5/500 mg – pale brownish purple, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and 'S12', the other side is debossed with '500'.
SYNJARDY 12,5/850 mg – pinkish white, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and 'S12', the other side is debossed with '850'.
SYNJARDY 12,5/1000 mg – dark brownish purple, oval, biconvex film-coated tablets. One side is debossed with Boehringer Ingelheim company symbol and 'S12', the other side is debossed with '1000'.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Glycaemic control
SYNJARDY is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus who have been stabilised on co-administration of the two component medicines. (See Sections 4.2 and 5.1 Clinical trials.)

Prevention of cardiovascular events
SYNJARDY is indicated in patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of cardiovascular death or hospitalisation for heart failure. (See Section 5.1 Clinical trials.)

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. Risk factors include renal impairment, old age and the use of high doses of metformin above 2 000 mg per day. Empagliflozin may also induce metabolic acidosis including ketoacidosis. It is not known if the combination of metformin and empagliflozin increases this risk.

The recommended dose is one SYNJARDY tablet twice daily.

Adults with normal renal function (GFR ≥90 mL/min)

The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability. The maximum recommended daily dose of SYNJARDY is 25 mg of empagliflozin and 2 000 mg of metformin (see Table 1 for additional dosing information).

SYNJARDY should be given with meals to reduce the gastrointestinal undesirable effects associated with metformin.

Treatment naïve patients

The recommended starting dose is 5/500 mg twice daily. If additional glycaemic control is required, adjust dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 25 mg empagliflozin and 2 000 mg metformin.

Patients switching from separate tablets of empagliflozin and metformin

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 empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Patients not adequately controlled on the maximal tolerated dose of metformin alone or in combination with other medicines, including insulin

The recommended starting dose of SYNJARDY should provide empagliflozin 5 mg twice daily (10 mg total 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, the dose can be increased to a total daily dose of empagliflozin 25 mg.

Combination use

When SYNJARDY is used in combination with a sulphonylurea and/or insulin, a lower dose of sulphonylurea and/or insulin may be required to reduce the risk of hypoglycaemia (see Sections 4.5 and 4.8).

Renal impairment

No dose adjustment is recommended for patients with mild renal impairment. SYNJARDY is contraindicated for use in patients with severe renal impairment (creatinine clearance <30 mL/min) (see Section 4.3).
Renal function should be assessed before initiation of treatment with SYNJARDY and at least annually thereafter.
In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months (see Section 4.4).

Table 1 Posology for renally impaired patients*

eGFR mL/min	Metformin	Empagliflozin
60 - 89	Maximum daily dose is 3 000 mg.* Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 25 mg. No dose adjustment is required.
45 - 59	Maximum daily dose is 2 000 mg. The starting dose is at most half of the maximum dose.	No dose adjustment is required.**
30 - 44	Maximum daily dose is 1 000 mg.*	No dose adjustment is required.**

	The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	Empagliflozin is contraindicated

* If no adequate strength of SYNJARDY is available, individual monocomponents should be used instead of the fixed dose combination.
** More intensive monitoring of renal function is recommended.

Hepatic impairment
SYNJARDY is contraindicated in patients with hepatic impairment due to the metformin component (see Section 4.3).

Elderly patients
Patients aged 75 years and older may be at an increased risk of volume depletion, therefore, SYNJARDY should be prescribed with caution in these patients. Therapeutic experience in patients aged 85 years and older is limited. Initiation of treatment in this population is not recommended (see Section 4.4 Use in the elderly).

Paediatric population
SYNJARDY is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

4.3 CONTRAINDICATIONS

- Hypersensitivity to active ingredients empagliflozin and/or metformin hydrochloride or to any of the excipients.
- Type 1 Diabetes Mellitus.
- Any type of metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).
- Diabetic pre-coma.
- Severe renal failure (creatinine clearance <30 mL/min or eGFR <30 mL/min/1,73m2), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia (see Section 4.4).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see Section 4.4).
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock, pulmonary embolism, acute significant blood loss, sepsis, gangrene, pancreatitis (see Section 4.4).
- During or immediately following surgery where insulin is essential, elective major surgery.
- Hepatic impairment, acute alcohol intoxication, alcoholism (due to the metformin component).
- Pregnancy and lactation (see Section 4.6).

SYNJARDY must be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function (see Section 4.4 'Administration of iodinated contrast agent').

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General
SYNJARDY should not be used in patients with type 1 diabetes (see Section 4.3).

Diabetic ketoacidosis
SYNJARDY should not be used for the treatment of diabetic ketoacidosis.
Cases of diabetic ketoacidosis (DKA), a serious life threatening condition requiring urgent hospitalisation, have been reported in post-marketing surveillance in patients treated with SGLT2 inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in patients taking empagliflozin.
Patients treated with SYNJARDY who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with SYNJARDY may be present even if blood glucose levels are less than 13,8 mmol/L.
Signs and symptoms of ketoacidosis may include excessive thirst, nausea, vomiting, abdominal pain, generalised malaise, and shortness of breath. If ketoacidosis is suspected, SYNJARDY should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement.
Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.
Before initiating SYNJARDY, consider factors in the patient history that may predispose to ketoacidosis.
Factors that predispose patients to ketoacidosis include a low carbohydrate diet, dehydration, acute illness, surgery (see Section 'Surgery'), a previous ketoacidosis, insulin deficiency from any cause (including insulin pump failure, history of pancreatitis, or pancreatic surgery), malnourishment/reduced caloric intake or increased insulin requirements due to infections, and alcohol abuse. SYNJARDY should be used with caution in these patients. When reducing the insulin dose in patients requiring insulin, caution should be taken (see Section 4.2). Consider monitoring for ketoacidosis and temporarily discontinuing SYNJARDY in clinical situations known to predispose to ketoacidosis. In these situations, consider monitoring of ketones, even if SYNJARDY treatment has been interrupted.
Treatment should be interrupted in patients who are hospitalised for acute serious medical illnesses.

Lactic acidosis
Lactic acidosis a serious metabolic complication, that most often occurs at in association with acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin, as contained in SYNJARDY should be temporarily discontinued.
Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients.
Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting, and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see Sections 4.3 and 4.5).

Patients and/or caregivers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin, as contained in SYNJARDY and be hospitalised immediately.
Diagnostic laboratory findings are decreased blood pH (<7,35), increased plasma lactate levels (>5 mmol/L), and an increased anion gap and lactate/pyruvate ratio.

Cardiac function
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.
For patients with acute and unstable heart failure, SYNJARDY is contraindicated due to the metformin component (see Section 4.3).

Use in patients at risk for volume depletion
Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as 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 (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with SYNJARDY should be considered until the fluid loss is corrected.

Urosepsis and Pyelonephritis
There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see Section 4.8).
Discontinuation of SYNJARDY may be considered in cases of recurrent urinary tract infections.

Genital infections including life threatening necrotising fasciitis
SGLT2 inhibitors, such as contained in SYNJARDY, have been associated with an increased risk of genital infection in both males and females caused by bacteria and/or fungi. Genital fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis.

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene), a serious and life threatening necrotising infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalisation, multiple surgeries, and death.
Patients treated with SYNJARDY who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotising fasciitis. If suspected, SYNJARDY should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in a long-term clinical study with another SGLT2 inhibitor. The medicine in that study is not empagliflozin. However, it is unknown whether this constitutes a class effect. In a pooled safety analysis of 12 620 patients with T2DM the frequency of patients with lower limb amputations was similar between empagliflozin and placebo. In the largest placebo controlled trial in 7 020 patients (EMPA-REG OUTCOME trial), in which 88 % of all the cases of amputations were reported, lower limb amputations occurred in 1,8 % of patients treated with empagliflozin 10 mg, in 2,0 % of patients treated with empagliflozin 25 mg, and in 1,8 % of patients in the placebo arm. It is important to regularly examine the feet and counsel all diabetic patients on routine preventative foot care.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin as contained in SYNJARDY, should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see Sections 4.2 and 4.5).

Surgery

Treatment with SYNJARDY should be ceased at least 48 hours prior to major surgery (see Sections 'Diabetic ketoacidosis' and 'Lactic acidosis'). An increase in other glucose lowering agents may be required during this time.

Patients scheduled for non-urgent surgery who have not ceased SYNJARDY should be assessed and consideration should be given to postponing the procedure.

Treatment with SYNJARDY may be restarted not earlier than 48 hours following surgery once the patient's condition has stabilised, oral intake is normal and only after renal function has been re-evaluated and found to be normal.

Vitamin B12 levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7 % of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of haematologic 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 B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Use in patients with renal impairment

Empagliflozin increases serum creatinine and decreases eGFR (see Section 4.8). Renal function abnormalities can occur after initiating empagliflozin. Patients with hypovolaemia may be more susceptible to these changes.

There have been post-marketing reports of acute kidney injury, some requiring hospitalisation and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

Due to the mechanism of action, decreased renal function will result in reduced efficacy

of empagliflozin.
GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2.
Patients treated with empagliflozin can experience an initial fall in eGFR. More intensive monitoring of renal function is recommended, particularly following treatment initiation, if empagliflozin is used in patients with an eGFR <60 mL/min/1,73 m^2, especially if the eGFR is <45 mL/min/1,73 m^2.
SYNJARDY is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section 4.3.

Hypoglycaemia
SYNJARDY alone does not cause hypoglycaemia under usual circumstances of use, but hypoglycaemia 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 sulphonylureas and insulin) or ethanol.

Use in the elderly
Patients aged 75 years and older may be at an increased risk of volume depletion, therefore, SYNJARDY should be prescribed with caution in these patients (see Section 4.8). Therapeutic experience in patients aged 85 years and older is limited. Initiation of treatment in this population is not recommended.
As metformin is excreted by the kidney, SYNJARDY should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients.

Paediatric Use
Safety and effectiveness of SYNJARDY in paediatric patients under 18 years have not been established.

Effects on laboratory tests
Urine will test positive for glucose while patients are taking SYNJARDY due to the nature of the mechanism of action of the SGLT2 inhibitors (see Section 5.1 Pharmacodynamic properties).

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

General
Co-administration of multiple doses of empagliflozin (50 mg once daily) and metformin hydrochloride (1 000 mg twice daily) did not meaningfully alter the pharmacokinetics of either empagliflozin or metformin in healthy volunteers.
Pharmacokinetic interaction studies with SYNJARDY have not been performed; however, such studies have been conducted with empagliflozin and metformin alone.

Empagliflozin
Pharmacodynamic Interactions

Diuretics
Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin (see Sections 4.2 and 4.8).

Pharmacokinetic Interactions
Lithium
Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

In vitro assessment of medicine interactions
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not notably inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. At therapeutic doses, the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 and UGT isoforms is remote. Interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.
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 medicines 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, as such, interactions with substrates of these uptake transporters are considered unlikely.

In vivo assessment of medicine interactions
No clinically meaningful pharmacokinetic interactions were observed when empagliflozin was co-administered with other commonly used medicines. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co-administered with commonly prescribed medicines.
Empagliflozin pharmacokinetics were similar with and without co-administration of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, in healthy volunteers and with or without co-administration of torasemide and hydrochlorothiazide in patients with T2DM. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59 %), rifampicin (35 %), or probenecid (53 %). These changes were not considered to be clinically meaningful.
Empagliflozin had no clinically relevant effect on the pharmacokinetics of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

Metformin hydrochloride

Contraindicated combinations

Iodinated contrast materials

SYNJARDY must be discontinued prior to, or at the time of the imaging procedure and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable. (see Sections 4.3 and 4.4).

Inadvisable combinations

Alcohol

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin component of SYNJARDY (see Section 4.4 'Lactic acidosis'). Consumption of alcohol and medicines containing alcohol should be avoided. Alcohol may make the signs of hypoglycaemia less clear, and delayed hypoglycaemia can occur. The CNS depressant effects of alcohol plus hypoglycaemia can make driving or the operation of dangerous machinery much more hazardous.

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function 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, especially loop diuretics. When starting or using such products in combination with metformin as contained in SYNJARDY, close monitoring of renal function is necessary.

Medicines with intrinsic hyperglycaemic activity

e.g. glucocorticoids and tetracosactides (systemic and local routes), beta-2-agonists, danazol, chlorpromazine at high dosages of 100 mg per day and diuretics

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon discontinuation.

Diuretics, especially loop diuretics

May increase the risk of lactic acidosis due to their potential to decrease renal function.

ACE-inhibitors

ACE-inhibitors may decrease the blood glucose levels. Therefore, dose adjustment of SYNJARDY may be necessary when such medicines are added or discontinued.

Calcium channel blockers

Calcium channel blockers may affect glucose control in diabetic patients; regular monitoring of glycaemic control is recommended.

Beta-blockers

Co-administration of metformin and beta-blockers may result in a potentiation of the anti-hyperglycaemic action. In addition, some of the premonitory signs of hypoglycaemia, in particular tachycardia, may be masked. Monitoring of blood glucose should be undertaken during dosage adjustment of either medicine.

Cimetidine

Reduced clearance of metformin has been reported during cimetidine therapy, so a dose

reduction should be considered.

Anticoagulants
Metformin increases the elimination rate of vitamin K antagonists. Consequently, the prothrombin time should be closely monitored in patients in whom metformin and vitamin K antagonists are being co-administered. Cessation of metformin in patients receiving vitamin K antagonists can cause marked increases in the prothrombin time.

Nifedipine
A single-dose, metformin-nifedipine medicine interaction study in normal healthy volunteers demonstrated that co-administration of metformin and nifedipine increased plasma metformin C_{max} and AUC by 20 % and 9 %, respectively, and increased the amount of metformin excreted in the urine. T_{max} and half-life of metformin were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on the pharmacokinetics of nifedipine.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2.
Co-administration of metformin with:
- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy.
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, crizotinib, olaparib, daclatasvir, vandetanib) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.

Carbonic anhydrase inhibitors
Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloraemic metabolic acidosis. Concomitant use of these medicines with metformin as contained in SYNJARDY may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

NSAID
May increase the risk of lactic acidosis and adversely affect renal function.
Therefore, caution is advised when these medicines are co-administered with metformin and a dose adjustment may be considered, particularly in patients with renal impairment.

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility
No studies on the effect on human fertility have been conducted with SYNJARDY or its individual components.
Nonclinical studies in animals with the individual components do not indicate direct or indirect harmful effects with respect to fertility.

Pregnancy
SYNJARDY is contraindicated in pregnancy (see Section 4.3).
In animal reproductive studies, both component medicines have shown foeto-toxicity at

higher doses.

Breastfeeding
SYNJARDY is contraindicated in women who are breastfeeding their infants.
Both component medicines are excreted in milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Hypoglycaemia may impair driving and machinery use capabilities.
Low blood sugar may occur in patients who already take another medication to treat diabetes such as a sulphonylurea or insulin while taking SYNJARDY. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance e.g. driving a car or operating machinery. People should be advised to take precautions to avoid hypoglycaemia whilst driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

Adverse Reactions in Clinical Trials
A total of 12 245 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin plus metformin, of which 8 199 patients were treated with empagliflozin plus metformin, either alone, or in addition to a sulphonylurea, pioglitazone, DPP4 inhibitors, or insulin. In these trials 2 910 patients received treatment with empagliflozin 10 mg plus metformin and 3 699 patients treatment with empagliflozin 25 mg plus metformin for at least 24 weeks and 2 151 or 2 807 patients for at least 76 weeks.
The overall safety profile of empagliflozin plus metformin for patients enrolled in the EMPA-REG OUTCOME study was comparable to the previously known safety profile.

Placebo controlled double-blind trials of 18 to 24 weeks of exposure included 3 456 patients, of which 1 271 were treated with empagliflozin 10 mg plus metformin and 1 259 with empagliflozin 25 mg plus metformin.

The most frequently reported adverse event in clinical trials was hypoglycaemia, which depended on the type of background therapy used in the respective studies (Table 2).

No additional side effects were identified in clinical trials with empagliflozin plus metformin compared to the side effects of the single components.

Tabulated list of adverse reactions
The adverse reactions are listed by absolute frequency. 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), or very rare (<1/10 000), and not known (cannot be estimated from the available data).

Table 2 Adverse reactions reported in placebo controlled studies

System organ class	Very common	Common	Uncommon	Very rare
Infections and infestations		Vaginal moniliasis,		

System organ class	Very common	Common	Uncommon	Very rare
		vulvovaginitis, balanitis and other genital infection[1, 2] Urinary tract infection[1, 2]		
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[1]	Vitamin B12 decrease/ deficiency[3, 4]		Lactic acidosis[3]
Nervous system disorders		Taste disturbance[3]		
Vascular disorders			Volume depletion[1, 2]	
Gastro-intestinal disorders	Gastro-intestinal symptoms[3, 5]	Constipation		
Hepatobiliary disorders				Liver function tests abnormalities[3, 6] Hepatitis[3, 6]
Skin and sub-cutaneous tissue disorders		Pruritus[2,3] (generalised)		Erythema[3] Urticaria[3]
Renal and urinary disorders		Increased urination[1, 2]	Dysuria[2]	
General disorders and administration site conditions		Thirst[2]		
Investigations		Serum lipids increased[1,2]	Glomerular filtration rate decreased[1] Blood creatinine increased[1] Haematocrit increased[1,2]	

[1] See subsections below for additional information

[2] Identified adverse reactions of empagliflozin monotherapy
[3] Identified adverse reactions of metformin monotherapy
[4] Decrease of vitamin B12 absorption with a decrease in serum levels has been observed in patients treated long-term with metformin. Consideration of such an aetiology is recommended if a patient presents with megaloblastic anaemia. Therefore, serum B12 levels should be appropriately monitored or periodic parenteral B12 supplementation should be considered (see Section 4.4 Vitamin B12 levels)
[5] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
[6] Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

Post-marketing experience

The following post-marketing case reports have been reported during post-approval use of empagliflozin. Because these cases are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.
Metabolism and nutrition disorders – Ketoacidosis.
Infections and infestations - Pyelonephritis, urosepsis, necrotising fasciitis of the perineum (Fournier's gangrene).
Immune system disorders - Allergic skin reactions (e.g. rash, urticaria), angioedema.
Reproductive system and breast disorders – Phimosis has been reported with the use of SGLT2 inhibitors such as SYNJARDY.

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar to placebo for empagliflozin as add-on to metformin and as add-on to pioglitazone +/- metformin, and as add-on with linagliptin + metformin. The frequency of patients with hypoglycaemia was increased in patients treated with empagliflozin compared to placebo when given as add-on to metformin plus sulphonylurea, and as add-on to insulin +/- metformin and +/- sulphonylurea. (See Section 4.2, and Table 3 below.)

Major hypoglycaemia (events requiring assistance)
The overall frequency of patients with major hypoglycaemic events was low (<1 %) and similar for empagliflozin and placebo on a background of metformin. The frequency of major hypoglycaemia depended on the background therapy in the respective studies (see Section 4.2; and Table 3 below).

Table 3 Frequency of patients with confirmed hypoglycaemic events per trial and indication (1245.19, 1245.23$_{(met)}$, 1245.23$_{(met+SU)}$, 1245.33, 1245.49, 1276.1, 1276.10, 1276.9 and 1245.25 – Treated Set[1])

Treatment group	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
In Combination with Metformin (1245.23 $_{(met)}$) (24 weeks)			
N	206	217	214
Overall confirmed (%)	0,5 %	1,8 %	1,4 %
Major (%)	0 %	0 %	0 %
In Combination with Metformin + Sulphonylurea (1245.23 $_{(met + SU)}$) (24 weeks)			
N	225	224	217
Overall confirmed (%)	8,4 %	16,1 %	11,5 %
Major (%)	0 %	0 %	0 %
In Combination with Pioglitazone +/- Metformin (1245.19) (24 weeks)			
N	165	165	168
Overall confirmed (%)	1,8 %	1,2 %	2,4 %

Major (%)	0 %	0 %	0 %
In Combination with Basal Insulin +/- Metformin (1245.33) (18 weeks[2] / 78 weeks)			
N	170	169	155
Overall confirmed (%)	20,6 % / 35,3 %	19,5 % / 36,1 %	28,4 % / 36,1 %
Major (%)	0 % / 0 %	0 % / 0 %	1,3 % / 1,3 %
In Combination with MDI Insulin +/- Metformin (1245.49) (18 weeks[2] / 52 weeks)			
N	188	186	189
Overall confirmed (%)	37,2 % / 58,0 %	39,8 % / 51,1 %	41,3 % / 57,7 %
Major (%)	0,5 % / 1,6 %	0,5 % / 1,6 %	0,5 % / 0,5 %
Empagliflozin bid versus qd as add-on to Metformin (1276.10) (16 weeks)			
	Placebo	Empa 10 mg	Empa 25 mg
N	107	439	437
Overall confirmed (%)	0,9 %	0,5 %	0,2 %
Major (%)	0 %	0 %	0 %
In Combination with Metformin in drug-naïve patients (1276.1[3]) (24 weeks)			
	Met 500/ 1 000 mg bid	Empa 10/25 mg qd	Empa (5/12,5 mg) + Met (500/1 000 mg) bid
N	341	339	680
Overall confirmed (%)	0,6 %	0,6 %	1,0 %
Major (%)	0 %	0 %	0 %
In Combination with Metformin and Linagliptin (1275.9) (24 weeks)[4]			
N	110	112	110
Overall confirmed (%)	0,9 %	0,0 %	2,7 %
Major (%)	0 %	0 %	0,9 %
EMPA-REG OUTCOME (1245.25)			
	Placebo	Empa 10 mg	Empa 25 mg
N	2 333	2 345	2 342
Overall confirmed (%)	27,9 %	28 %	27,6 %
Major (%)	1,5 %	1,4 %	1,3 %

Confirmed: blood glucose ≤3,9 mmol/L or required assistance; Major: required assistance
MDI = multiple daily injections; qd = once daily; bid = Twice daily
[1] i.e. patients who received at least one dose of study medicine
[2] The dose of insulin as background medicine was to be stable for the first 18 weeks
[3] Eight treatment arms: 4 combination treatments of empagliflozin (5 mg or 12,5 mg bid) and metformin (500 or 1 000 mg bid) and treatment with the individual components of empagliflozin (10 mg or 25 mg qd) or metformin (500 mg or 1 000 mg bid).
[4] This was a fixed-dose combination of empagliflozin with linagliptin 5 mg with a background treatment with metformin.

Urinary tract infection

The overall frequency of urinary tract infection adverse events was higher in patients treated with empagliflozin 10 mg plus metformin (8,8 %) as compared to empagliflozin 25 mg plus metformin (6,6 %) or placebo plus metformin (7,8 %). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin plus metformin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo. Urinary tract infection events were reported more frequently for empagliflozin 10 mg plus metformin compared with placebo in female patients, but not for empagliflozin 25 mg plus metformin. The frequencies of urinary tract infections were low for male patients and were balanced across treatment groups.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg plus metformin (4,0 %) and empagliflozin 25 mg plus metformin (3,9 %) compared to placebo plus metformin (1,3 %), and were reported more frequently for empagliflozin plus metformin compared to placebo in female patients. The difference in frequency was less pronounced in male patients. Genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination

As expected via its mechanism of action, increased urination (as assessed by preferred term search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin 10 mg plus metformin (3,0 %) and empagliflozin 25 mg plus metformin (2,9 %) compared to placebo plus metformin (1,4 %). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin, both on a background of metformin (<1 %).

Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was low and comparable to placebo (empagliflozin 10 mg plus metformin (0,6 %), empagliflozin 25 mg plus metformin (0,3 %) and placebo plus metformin (0,1 %)). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status of patients aged 75 years and older. In patients ≥75 years of age volume depletion events have been reported in a single patient treated with empagliflozin 25 mg plus metformin.

Blood creatinine increased and glomerular filtration rate decreased

Use of empagliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes play a role in the renal function abnormalities observed with empagliflozin.

Renal-related adverse reactions (e.g. acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with empagliflozin.

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between empagliflozin and placebo as add-on to metformin (blood creatinine increased: empagliflozin 10 mg 0,5 %, empagliflozin 25 mg 0,1 %, placebo 0,4 %; glomerular filtration rate decreased: empagliflozin 10 mg 0,1 %, empagliflozin 25 mg 0 %, placebo 0,2 %).

In these placebo controlled, double-blind studies up to 24 weeks, initial transient increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0,001 mmol/L, empagliflozin 25 mg 0,001 mmol/L) and initial transient decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: empagliflozin 10 mg -1,46 mL/min/1,73 m^2, empagliflozin 25 mg -2,05 mL/ min/1,73 m^2) have been observed. In the long-term studies, these changes were generally reversible during continuous treatment or after medicine discontinuation (see Section 5.1 Clinical Trials Figure 4 for the eGFR course in the EMPA-REG OUTCOME study).

Laboratory parameters

Haematocrit increased

In a pooled safety analysis of all trials with metformin background treatment, mean changes from baseline in haematocrit were 3,6 % and 4,0 % for empagliflozin 10 mg and 25 mg, respectively, compared to 0 % for placebo. In the EMPA-REG OUTCOME study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

Serum lipids increased
In a pooled safety analysis of all trials with metformin background treatment, mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 5,0 % and 5,2 % versus 3,7 %; HDL-cholesterol 4,6 % and 2,7 % versus -0,5 %; LDL-cholesterol 9,1 % and 8,7 % versus 7,8 %; triglycerides 5,4 % and 10,8 % versus 12,1 %.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 OVERDOSE

For information on the management of overdose, contact the nearest poisons control centre or hospital.

Symptoms
An overdose may exacerbate and exaggerate the adverse events signs and symptoms of section 4.8.
Hypoglycaemia has not been seen with the component medicines of SYNJARDY given alone, however co-administration with other antidiabetic medicines may cause hypoglycaemia. Hypoglycaemia must always be monitored for and treated appropriately. SYNJARDY may result in lactic acidosis and appropriate monitoring is required, with appropriate treatment. Potential pathology precipitating the lactic acidosis should be sought. Lactic acidosis is a medical emergency and must be treated in hospital.

Therapy
In the event of an overdose, supportive treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin hydrochloride is haemodialysis whereas removal of empagliflozin by haemodialysis has not been studied.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacological Classification: A 21.2 Oral hypoglycaemics

Mechanism of action

Empagliflozin

Empagliflozin is a reversible competitive inhibitor of SGLT2 with an IC_{50} of 1,3 nM. It has a 5 000-fold selectivity over human SGLT1 (IC_{50} of 6 278 nM), responsible for glucose absorption in the gut.

SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose re-absorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

In patients with T2DM, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 hour dosing interval. Increased urinary glucose excretion was maintained at the end of 4-week treatment period, averaging approximately 78 g/day with 25 mg empagliflozin once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM.

Empagliflozin improves both fasting and post-prandial plasma glucose levels.

The insulin independent mechanism of action of empagliflozin contributes to a low risk of hypoglycaemia.

The effect of empagliflozin in lowering blood glucose is independent of beta cell function and insulin pathway. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) and proinsulin to insulin ratio were noted. In addition urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction.

The glucosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure (BP).

Metformin hydrochloride

Metformin hydrochloride is a biguanide with antihyperglycaemic effects, lowering both basal and post-prandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin hydrochloride may act via 3 mechanisms:

1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium or long-term clinical studies: metformin hydrochloride reduces total

cholesterol, LDL cholesterol and triglyceride levels.

Clinical trials

A total of 10 224 patients with type 2 diabetes were treated in 9 double-blind, placebo or active-controlled clinical studies, of at least 24 weeks duration, of which 2 947 patients received empagliflozin 10 mg and 3 703 received empagliflozin 25 mg as add-on to metformin therapy.

Treatment with empagliflozin in combination with metformin with or without other background (pioglitazone, sulphonylurea, DPP-4 inhibitors, and insulin) led to clinically relevant reductions in HbA1c, fasting plasma glucose (FPG), body weight, systolic and diastolic blood pressure (BP). Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA1c goal of <7 % and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. There was a clinically meaningful reduction in HbA1c in all subgroups of gender, race, geographic region, time since diagnosis of type 2 diabetes mellitus (T2DM) and body mass index (BMI). In patients aged 75 years and older, numerically lower reductions in HbA1c were observed with empagliflozin treatment. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Empagliflozin in combination with metformin in drug-naïve patients led to clinically meaningful reductions in HbA1c, FPG, body weight and BP.

Empagliflozin as add-on to metformin therapy

A double-blind, placebo controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients not sufficiently treated with metformin. Treatment with empagliflozin resulted in statistically significant reductions in HbA1c and body weight, and clinically meaningful reductions in FPG and BP compared to placebo.
In the double-blind placebo controlled extension of this study, reductions of HbA1c (change from baseline of -0,62 % for empagliflozin 10 mg, -0,74 % for empagliflozin 25 mg and -0,01 % for placebo), body weight (change from baseline of -2,39 kg for empagliflozin 10 mg, -2,65 kg for empagliflozin 25 mg and -0,46 kg for placebo) and BP (systolic BP: change from baseline of -5,2 mmHg for empagliflozin 10 mg, -4,5 mmHg for empagliflozin 25 mg and -0,8 mmHg for placebo, diastolic BP: change from baseline of -2,5 mmHg for empagliflozin 10 mg, -1,9 mmHg for empagliflozin 25 mg and -0,5 mmHg for placebo) were sustained up to Week 76.

Empagliflozin and metformin combination therapy in drug-naïve patients

A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in combination with metformin vs. individual monotherapies of empagliflozin and metformin in drug-naïve patients. Treatment with empagliflozin in combination with metformin (5 mg and 500 mg; 5 mg and 1 000 mg; 12,5 mg and 500 mg, and 12,5 mg and 1 000 mg given twice daily) provided statistically significant reductions in HbA1c, FPG and body weight compared to the individual components. A greater proportion of patients with a baseline HbA1c ≥7,0 % and treated with empagliflozin in combination with metformin achieved a target HbA1c <7 % compared to the individual components.

Empagliflozin as add-on to a combination of metformin and sulphonylurea therapy

A double-blind, placebo controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients not sufficiently treated with a combination of metformin and a sulphonylurea. Treatment with empagliflozin resulted in

statistically significant improvements in HbA1c and body weight and clinically meaningful reductions in FPG and BP compared to placebo.
In the double-blind placebo controlled extension of this study, reductions of HbA1c (change from baseline of -0,74 % for empagliflozin 10 mg, -0,72 % for empagliflozin 25 mg and -0,03 % for placebo), body weight (change from baseline of -2,44 kg for empagliflozin 10 mg, -2,28 kg for empagliflozin 25 mg and -0,63 kg for placebo) and BP (systolic BP: change from baseline of -3,8 mmHg for empagliflozin 10 mg, -3,7 mmHg for empagliflozin 25 mg and -1,6 mmHg for placebo, diastolic BP: change from baseline of -2,6 mmHg for empagliflozin 10 mg, -2,3 mmHg for empagliflozin 25 mg and -1,4 mmHg for placebo) were sustained up to Week 76.

2 hour post-prandial glucose
Treatment with empagliflozin as add-on to metformin or metformin plus sulphonylurea resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin: -2,55 mmol/L for empagliflozin 10 mg (n=52), -2,48 mmol/L for empagliflozin 25 mg (n=58), 0,33 mmol/L for placebo (n=57); add-on to metformin plus sulphonylurea: -1,98 mmol/L for empagliflozin 10 mg (n=44), -2,03 mmol/L for empagliflozin 25 mg (n=46), -0,13 mmol/L for placebo (n=35)).

Empagliflozin as add-on to a combination of pioglitazone therapy (+/- metformin)
The efficacy and safety of empagliflozin in combination with pioglitazone, with or without metformin (75,5 % of all patients were on metformin background) was evaluated in a double-blind, placebo controlled study of 24 weeks duration. Empagliflozin in combination with pioglitazone (mean dose ≥30 mg) with or without metformin resulted in statistically significant reductions in HbA1c, fasting plasma glucose, and body weight and clinically meaningful reductions in BP compared to placebo.
In the double-blind placebo controlled extension of this study, reductions of HbA1c (change from baseline of -0,61 % for empagliflozin 10 mg, -0,70 % for empagliflozin 25 mg and -0,01 % for placebo), body weight (change from baseline of -1,47 kg for empagliflozin 10 mg, -1,21 kg for empagliflozin 25 mg and +0,50 kg for placebo) and BP (systolic BP: change from baseline of -1,7 mmHg for empagliflozin 10 mg, -3,4 mmHg for empagliflozin 25 mg and +0,3 mmHg for placebo, diastolic BP: change from baseline of -1,43 mmHg for empagliflozin 10 mg, -2,0 mmHg for empagliflozin 25 mg and +0,2 mmHg for placebo) were sustained up to Week 76.

Empagliflozin and linagliptin as add-on therapy to metformin
In a factorial design study, patients inadequately controlled on metformin, 24-weeks treatment with both doses of empagliflozin 10 mg and 25 mg administered together with linagliptin 5 mg provided statistically significant improvements in HbA1c and FPG compared to linagliptin 5 mg and also compared to empagliflozin 10 or 25 mg. Compared to linagliptin 5 mg, both doses of empagliflozin plus linagliptin 5 mg provided statistically significant reductions in body weight and blood pressure. A greater proportion of patients with a baseline HbA1c ≥7,0 % and treated with empagliflozin plus linagliptin achieved a target HbA1c of <7 % compared to linagliptin 5 mg.
After 24 weeks treatment with empagliflozin+linagliptin, both systolic and diastolic blood pressures were reduced, -5,6/-3,6 mmHg (p<0,001 versus linagliptin 5 mg for SBP and DBP) for empagliflozin 25 mg+linagliptin 5 mg and -4,1/-2,6 mmHg (p<0,05 versus linagliptin 5 mg for SBP, n.s. for DBP) for empagliflozin 10 mg+linagliptin 5 mg. Clinically meaningful reductions in blood pressure were maintained for 52 weeks, -3,8/-1,6 mmHg (p<0,05 versus linagliptin 5 mg for SBP and DBP) for empagliflozin 25 mg/linagliptin 5 mg

and -3,1/-1,6 mmHg (p<0,05 versus linagliptin 5 mg for SBP, n.s. for DBP) for empagliflozin 10 mg/linagliptin 5 mg.
After 24 weeks, rescue therapy was used in 1 (0,7 %) patient treated with empagliflozin 25 mg/linagliptin 5 mg and in 3 (2,2 %) patients treated with empagliflozin 10 mg/linagliptin 5 mg, compared to 4 (3,1 %) patients treated with linagliptin 5 mg and 6 (4,3 %) patients treated with empagliflozin 25 mg and 1 (0,7 %) patient treated with empagliflozin 10 mg.

Empagliflozin in patients inadequately controlled on metformin and linagliptin
In patients inadequately controlled on metformin and linagliptin 5 mg, 24-weeks treatment with both empagliflozin/linagliptin 10 mg/5 mg and empagliflozin/linagliptin 25 mg/5 mg provided statistically significant improvements in HbA1c, FPG and body weight compared to placebo+linagliptin 5 mg. A statistically significantly greater number of patients with a baseline HbA1c ≥7,0 % and treated with both doses of empagliflozin achieved a target HbA1c of <7 % compared to placebo+linagliptin 5 mg. After 24 weeks treatment with empagliflozin, both systolic and diastolic blood pressures were reduced, -2,6/-1,1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 25 mg+linagliptin 5 mg and -1,3/-0,1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 10 mg+linagliptin 5 mg.
After 24 weeks, rescue therapy was used in 4 (3,6 %) patients treated with empagliflozin 25 mg+linagliptin 5 mg and in 2 (1,8 %) patients treated with empagliflozin 10 mg+linagliptin 5 mg, compared to 13 (12,0 %) patients treated with placebo+linagliptin 5 mg.

In a prespecified subgroup of patients with baseline HbA1c greater or equal than 8,5 % the reduction from baseline in HbA1c with empagliflozin 25 mg+linagliptin 5 mg was -1,3 % at 24 weeks (p<0,0001 versus placebo+linagliptin 5 mg) and with empagliflozin 10 mg+linagliptin 5 mg -1,3 % at 24 weeks (p<0,0001 versus placebo+linagliptin 5 mg).

Empagliflozin 2-year data, as add-on to metformin in comparison to glimepiride
In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (1-4 mg) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA1c, and a clinically meaningful reduction in FPG, compared to glimepiride. Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic BP (change from baseline in diastolic BP of -1,8 mmHg for empagliflozin and +0,9 mmHg for glimepiride, p<0,0001).
Treatment with empagliflozin resulted in statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2,5 % for empagliflozin, 24,2 % for glimepiride, p<0,0001).

Empagliflozin as add-on to basal insulin therapy
The efficacy and safety of empagliflozin as add-on to basal insulin with or without concomitant metformin and/or sulphonylurea therapy (79,8 % of all patients were on metformin background) was evaluated in a double-blind, placebo controlled trial of 78 weeks duration. During the initial 18 weeks the insulin dose was to be kept stable, but was adjusted to achieve a FPG <6,10 mmol/L in the following 60 weeks.
At week 18, empagliflozin provided statistically significant improvement in HbA1c compared to placebo. A greater proportion of patients with a baseline HbA1c ≥7,0 % achieved a target HbA1c of <7 % compared to placebo. At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared to placebo.

At week 78, empagliflozin resulted in a reduction in FPG (-0,58 mmol/L for empagliflozin 10 mg, -0,97 mmol/L for empagliflozin 25 mg and -0,30 mmol/L for placebo), body weight (-2,47 kg for empagliflozin 10 mg, -1,96 kg for empagliflozin 25 mg and +1,16 kg for placebo, p<0,0001), BP (systolic BP: -4,1 mmHg for empagliflozin 10 mg, -2,4 mmHg for empagliflozin 25 mg and 0,1 mmHg for placebo, diastolic BP: -2,9 mmHg for empagliflozin 10 mg, -1,5 mmHg for empagliflozin 25 mg and -0,3 mmHg for placebo).

Empagliflozin as add-on to MDI insulin therapy and metformin

The efficacy and safety of empagliflozin as add-on to multiple daily insulin with or without concomitant metformin therapy (71,0 % of all patients were on metformin background) was evaluated in a double-blind, placebo controlled trial of 52 weeks duration. During the initial 18 weeks and the last 12 weeks, the insulin dose was kept stable, but was adjusted to achieve pre-prandial glucose levels <5,5 mmol/L, and post-prandial glucose levels <7,8 mmol/L between weeks 19 and 40.

At week 18, empagliflozin provided statistically significant improvement in HbA1c compared with placebo. A greater proportion of patients with a baseline HbA1c ≥7,0 % (19,5 % empagliflozin 10 mg, 31,0 % empagliflozin 25 mg) achieved a target HbA1c of <7 % compared with placebo (15,1 %).

At week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared with placebo and a reduction in FPG (change from baseline of -0,02 mmol/L for placebo, -1,09 mmol/L for empagliflozin 10 mg, and -1,31 mmol/L for empagliflozin 25 mg), body weight, and BP (systolic BP: change from baseline of -2,6 mmHg for placebo, -3,9 mmHg for empagliflozin 10 mg and -4,0 mmHg for empagliflozin 25 mg, diastolic BP: change from baseline of -1,0 mmHg for placebo, -1,4 mmHg for empagliflozin 10 mg and-2,6 mmHg for empagliflozin 25 mg).

Empagliflozin twice daily versus once daily as add-on to metformin therapy

The efficacy and safety of empagliflozin twice daily versus once daily (daily dose of 10 mg and 25 mg) as add-on therapy in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double-blind placebo controlled study of 16 weeks duration. All treatments with empagliflozin resulted in significant reductions in HbA1c from baseline (total mean 7,8 %) after 16 weeks of treatment compared with placebo. Empagliflozin twice daily dose regimens led to comparable reductions in HbA1c versus once daily dose regimens with a treatment difference in HbA1c reductions from baseline to week 16 of -0,02 % (95 % CI -0,16, 0,13) for empagliflozin 5 mg twice daily vs. 10 mg once daily, and -0,11 % (95 % CI -0,26, 0,03) for empagliflozin 12,5 mg twice daily vs. 25 mg once daily.

Patients with baseline HbA1c ≥9 %

In a pre-specified analysis of subjects with baseline HbA1c ≥ 9,0 %, treatment with empagliflozin 10 mg or 25 mg as add-on to metformin resulted in statistically significant reductions in HbA1c at Week 24 (adjusted mean change from baseline of -1,49 % for empagliflozin 25 mg, -1,40 % for empagliflozin 10 mg, and -0,44 % for placebo).

Body weight

In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin (68 % of all patients were on metformin background) resulted in body weight reduction compared to placebo at week 24 (-2,04 kg for empagliflozin 10 mg, -2,26 kg for empagliflozin 25 mg and -0,24 kg for placebo) that was maintained up to week 52 (-1,96 kg for empagliflozin 10 mg, -2,25 kg for empagliflozin 25 mg and -0,16 kg for placebo).

Blood pressure
The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic (67,8 % treated with metformin with or without other antidiabetic medicines including insulin) and up to 2 antihypertensive therapies. Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, 24 hour mean systolic and diastolic blood pressure as determined by ambulatory BP monitoring. Treatment with empagliflozin provided reductions in seated systolic BP (change from baseline of -0,67 mmHg for placebo, -4,60 mmHg for empagliflozin 10 mg and -5,47 mmHg for empagliflozin 25 mg) and seated diastolic BP (change from baseline of -1,13 mmHg for placebo, -3,06 mmHg for empagliflozin 10 mg and -3,02 mmHg for empagliflozin 25 mg).

In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin (68 % of all patients were on metformin background) resulted in a reduction in systolic blood pressure (empagliflozin 10 mg -3,9 mmHg, empagliflozin 25 mg -4,3 mmHg) compared with placebo (-0,5 mmHg), and in diastolic blood pressure (empagliflozin 10 mg -1,8 mmHg, empagliflozin 25 mg -2,0 mmHg) compared with placebo (-0,5 mmHg), at week 24, that were maintained up to week 52.

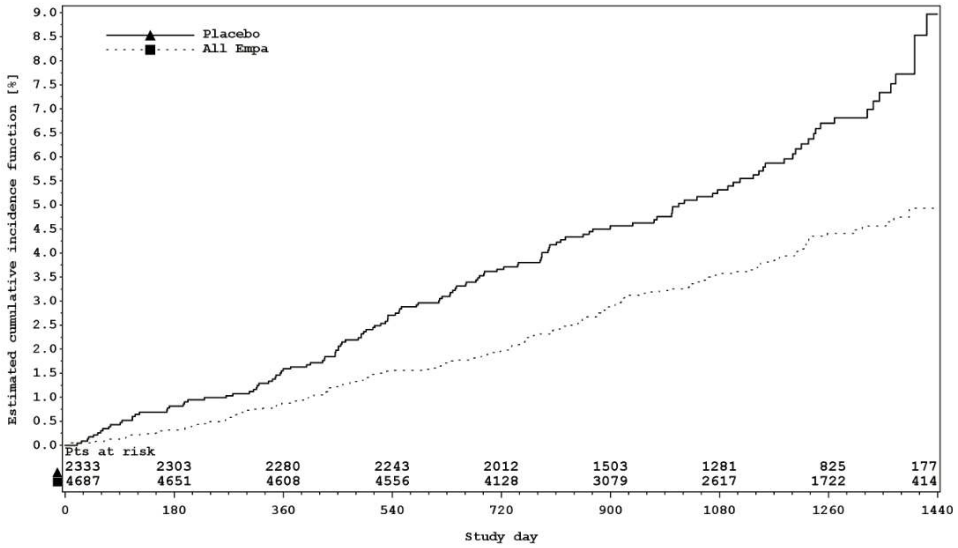
Cardiovascular outcome
Empagliflozin is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death. However, the effectiveness of SYNJARDY on reducing the risk of cardiovascular death in adults with type 2 diabetes mellitus and cardiovascular disease has not been established. The effect of empagliflozin on cardiovascular risk in adult patients with type 2 diabetes and established cardiovascular disease is presented below.
The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomised, double-blind, placebo controlled trial investigating the effect of empagliflozin as adjunct to standard care therapy in reducing cardiovascular events in patients with type 2 diabetes and one or more cardiovascular risk factors, including coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), or history of stroke. The primary endpoint was the time to first event in the composite of CV death, non-fatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events (MACE-3)). Additional pre-specified endpoints addressing clinically relevant outcomes tested in an exploratory manner included CV death, the composite of heart failure requiring hospitalisation or CV death, all-cause mortality and the composite of new or worsening nephropathy.
A total of 7 020 patients were treated with empagliflozin (empagliflozin 10 mg: 2 345, empagliflozin 25 mg: 2 342, placebo: 2 333) and followed for a median of 3,1 years. Approximately 74 % of patients were being treated with metformin at baseline, 48 % with insulin and 43 % with sulphonylurea.
The population was 72,4 % Caucasian, 21,6 % Asian, and 5,1 % Black. The mean age was 63 years and 71,5 % were male. At baseline, approximately 81 % of patients were being treated with renin angiotensin system inhibitors, 65 % with beta-blockers, 43 % with diuretics, 89 % with anticoagulants, and 81 % with lipid lowering medication.
About half of the patients (52,2 %) had an eGFR of 60-90 mL/min/1,73 m^2, 17,8 % of 45-60 mL/min/1,73 m^2 and 7,7 % of 30-45 mL/min/1,73 m^2. Mean systolic BP was 136 mmHg, diastolic BP 76 mmHg, low density lipoprotein (LDL) 2,2 mmol/L, high density lipoprotein (HDL) 1,1 mmol/L, and urinary albumin to creatinine ratio (UACR) 19,8 mg/mmol at baseline.

Reductions in risk of CV death and overall mortality

Empagliflozin is superior in reducing the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke compared to placebo. The treatment effect reflected a reduction in cardiovascular death with no significant change in non-fatal MI, or non-fatal stroke (Figure 1).

Empagliflozin also improved overall survival, which was driven by a reduction in cardiovascular death with empagliflozin. There was no statistically significant difference between empagliflozin and placebo in non-cardiovascular mortality.

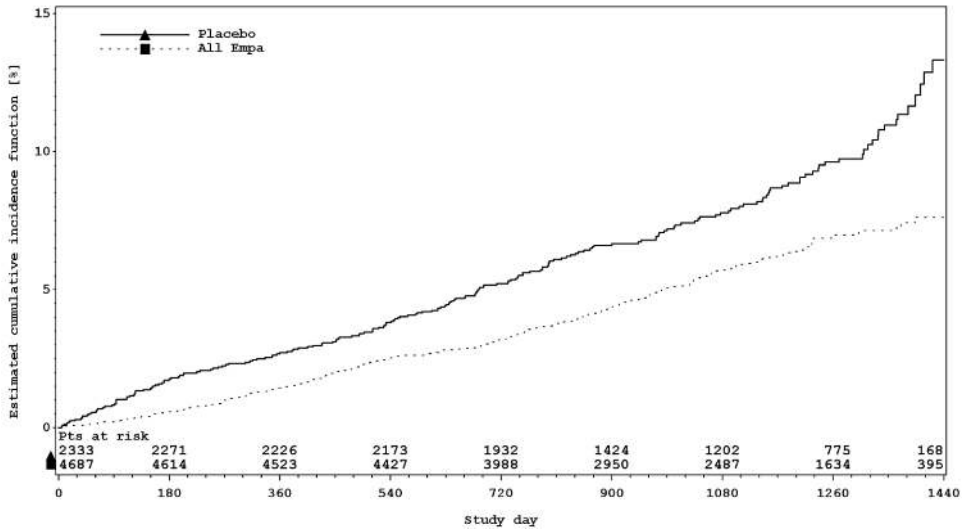
Figure 1 Time to occurrence of CV death



Reductions in risk of heart failure requiring hospitalisation or CV death

Empagliflozin is superior in reducing the risk of hospitalisation for heart failure and cardiovascular death or hospitalisation for heart failure compared with placebo (Figure 2).

Figure 2 Time to first occurrence of first heart failure hospitalisation or CV death*



***Estimated cumulative incidence function for time to first occurrence of first heart failure hospitalisation or CV death, pooled empagliflozin vs placebo – treated set**

The cardiovascular benefits (CV death and hospitalisation for heart failure or CV death) of empagliflozin observed were consistent across the major demographic and disease subgroups.

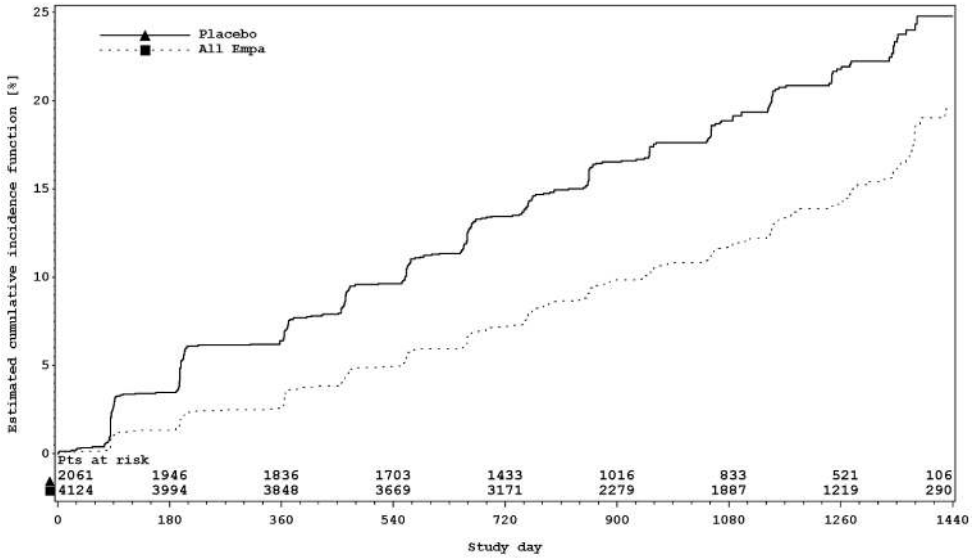
In the subgroup of patients who were on metformin at baseline, the effects on CV outcomes were consistent with the results observed in the entire study population of EMPA-REG OUTCOME.

Diabetic kidney disease

In the EMPA-REG OUTCOME study population, the risk of new or worsening nephropathy (defined as onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e. haemodialysis)) was significantly reduced in empagliflozin group compared to placebo (Figure 3).

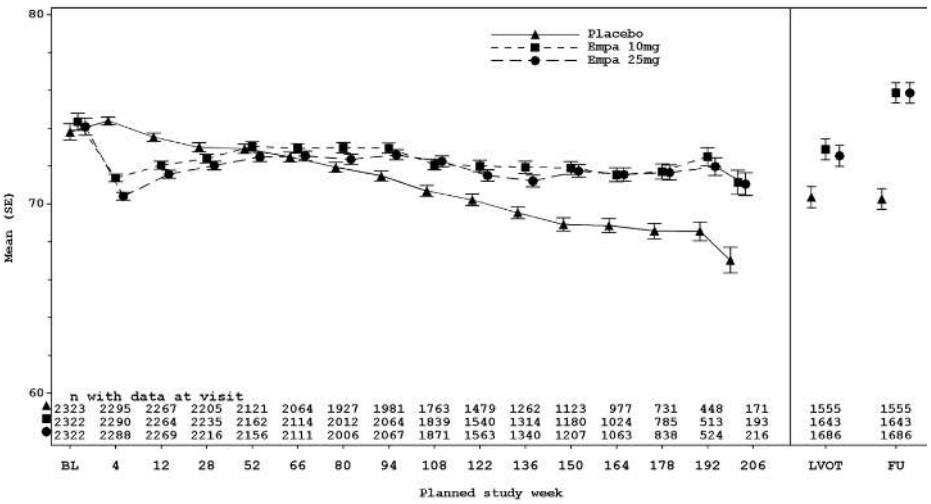
Empagliflozin compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1,82, 95 % CI 1.40, 2.37).

Figure 3 Time to first new or worsening of nephropathy



Treatment with empagliflozin preserved eGFR and eGFR increased during the post treatment 4-week follow up. However, the placebo group showed a gradual decline in eGFR during the course of the study with no further change during 4-week follow up (see Figure 4).

Figure 4 eGFR over time*



*eGFR (MDRD) (mL/min/1,73 m^2) MMRM results over time, unadjusted last value on treatment and follow-up value - treated set – right side based on patients with available last value on treatment (LVOT) and follow-up (FU).

In the subgroup of patients who were on metformin at baseline, the effects on these renal outcomes were consistent with the results observed in the entire study population of EMPA-REG OUTCOME.

Thorough QTc study
In a randomised, placebo controlled, active-comparator, crossover study of 30 healthy subjects no increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

5.2 PHARMACOKINETIC PROPERTIES

The results of bioequivalence studies in healthy subjects demonstrated that SYNJARDY (empagliflozin/metformin hydrochloride) 5/500 mg, 5/850 mg, 5/1000 mg, 12,5/500 mg, 12,5/850 mg and 12,5/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12,5 mg empagliflozin/1 000 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. However, as metformin is recommended to be given with meals, SYNJARDY is also proposed to be given with food.

The following statements reflect the pharmacokinetic properties of the individual active substances of SYNJARDY.

Empagliflozin
Absorption
The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median T_{max} 1,5 h 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 1 870 nmol·h/L and 259 nmol/L with empagliflozin 10 mg and 4 740 nmol·h/L and 687 nmol/L with empagliflozin 25 mg once daily, respectively. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.
The pharmacokinetics of 5 mg empagliflozin twice daily and 10 mg empagliflozin once daily were compared in healthy subjects. Overall exposure (AUC_{ss}) of empagliflozin over a 24-hour period with 5 mg administered twice daily was similar to 10 mg administered once daily. As expected, empagliflozin 5 mg administered twice daily compared with 10 mg empagliflozin once daily resulted in lower C_{max} and higher trough plasma empagliflozin concentrations (C_{min}).
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, UGT1A3, UGT1A8, UGT1A9, and UGT2B7.

Excretion
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. The inter-subject and residual variabilities for empagliflozin oral clearance were 39,1 % and 35,8 %, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22 % accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95,6 % of the drug related radioactivity was eliminated in faeces (41,2 %) or urine (54,4 %). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Metformin hydrochloride
Absorption
After an oral dose of metformin, T_{max} is reached in 2,5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %. After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption are non-linear.
At the recommended metformin hydrochloride doses and dosing schedules, steady-state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/mL. In controlled clinical trials, maximum metformin hydrochloride plasma levels (C_{max}) did not exceed 5 microgram/mL, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution
Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately

the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

Metabolism
Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism.

Excretion
Renal clearance of metformin hydrochloride is >400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6,5 hours.
When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

Pharmacokinetics in special patient groups

Paediatric

Empagliflozin
Studies characterising the pharmacokinetics of empagliflozin in paediatric patients have not been performed.

Metformin hydrochloride
Single dose study: After single doses of metformin 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.
Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33 % and 40 % respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

Elderly

Empagliflozin
Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Metformin hydrochloride
Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.
SYNJARDY treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Body Mass Index (BMI)

Empagliflozin
No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Gender

Empagliflozin

No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

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

Race
Empagliflozin
No dosage adjustment is necessary based on race. Based on the population pharmacokinetic analysis, AUC was estimated to be 13,5 % higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2.

Metformin hydrochloride
No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with type 2 diabetes, the antihyperglycaemic effect was comparable in White (n=249), Black (n=51) and Hispanic (n=24) patients.

Renal impairment
Empagliflozin
In patients with mild (eGFR: 60 - <90 mL/min/1,73m^2), moderate (eGFR: 30 - <60 mL/min/1,73m^2), severe (eGFR: <30 mL/min/1,73m^2) renal impairment and patients with kidney failure/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. In line with the Phase I study, the population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal impairment.

Metformin hydrochloride
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic impairment
Empagliflozin
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23 %, 47 %, and 75 % and C_{max} by approximately 4 %, 23 %, and 48 %, respectively, compared to subjects with normal hepatic function. Based on pharmacokinetics, no dosage adjustment is recommended in patients with hepatic impairment.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Empagliflozin
Empagliflozin was not mutagenic or clastogenic in a battery of genotoxicity studies, including the Ames bacterial mutagenicity assay (bacterial reverse mutation), *in vitro* mouse lymphoma tk assays and *in vivo* rat bone marrow micronucleus assays.

Metformin hydrochloride
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.

Carcinogenicity
Empagliflozin
Two-year oral carcinogenicity studies were conducted in mice and rats. There was an increase in renal adenomas and carcinomas in male mice given empagliflozin at 1 000 mg/kg/day. No renal tumours were seen at 300 mg/kg/day (11- and 28-times the exposure at the clinical dose of 12,5 and 5 mg twice daily, respectively). These tumours are likely associated with a metabolic pathway not present in humans, and are considered to be irrelevant to patients given clinical doses of empagliflozin. No drug-related tumours were seen in female mice or female rats at doses up to 1 000 and 700 mg/kg/day, respectively, resulting in exposures at least 60 times that expected at the clinical dose of 5 or 12,5 mg empagliflozin twice daily. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node, were observed at 700 mg/kg/day, but not at 300 mg/kg/day (approximately 26- and 65-times the exposure at the clinical dose of 12,5 mg and 5 mg twice daily, respectively). These tumours are common in rats and are unlikely to be relevant to humans.

Metformin hydrochloride
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1 500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2 000 mg 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of SYNJARDY contains the following inactive ingredients: colloidal anhydrous silica, copovidone, hypromellose, iron oxide black (SYNJARDY 12,5/500 mg,

SYNJARDY 12,5/850 mg, SYNJARDY 12,5/1000 mg), iron oxide red (SYNJARDY 12,5/500 mg, SYNJARDY 12,5/850 mg, SYNJARDY 12,5/1000 mg), iron oxide yellow (SYNJARDY 5/500 mg, SYNJARDY 5/850 mg, SYNJARDY 5/1000 mg), macrogol 400, magnesium stearate, maize starch, talc, titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The manufacturing and expiry dates can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

SYNJARDY is available in white PVC/PCTFE/Aluminium blister packs containing 60 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ingelheim Pharmaceuticals (Pty) Limited
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
South Africa
Tel. No.: +27 (0)11 348-2400

8 REGISTRATION NUMBERS

SYNJARDY 5/500 mg: 49/21.2/0915
SYNJARDY 5/850 mg: 49/21.2/0916
SYNJARDY 5/1000 mg: 49/21.2/0917
SYNJARDY 12,5/500 mg: 49/21.2/0918
SYNJARDY 12,5/850 mg: 49/21.2/0919
SYNJARDY 12,5/1000 mg: 49/21.2/0920

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 20 October 2020

10 DATE OF REVISION OF THE TEXT

10 October 2025

NAMIBIA Reg. no.		
SYNJARDY 5/500 mg	16/21.2/0210	NS2
SYNJARDY 5/850 mg	16/21.2/0211	
SYNJARDY 5/1000 mg	16/21.2/0212	
SYNJARDY 12,5/500 mg	16/21.2/0213	
SYNJARDY 12,5/850 mg	16/21.2/0214	
SYNJARDY 12,5/1000 mg	16/21.2/0215	

BOTSWANA Reg. no.		
SYNJARDY 5/500 mg	BOT2203842	S2
SYNJARDY 5/850 mg	BOT2203843	
SYNJARDY 5/1000 mg	BOT2203844	
SYNJARDY 12,5/500 mg	BOT2203845	
SYNJARDY 12,5/850 mg	BOT2203846	
SYNJARDY 12,5/1000 mg	BOT2203847	

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