ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/850 mg film-coated tablets
Synjardy 5 mg/1 000 mg film-coated tablets
Synjardy 12.5 mg/850 mg film-coated tablets
Synjardy 12.5 mg/1 000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Synjardy 5 mg/850 mg film-coated tablets

Each tablet contains 5 mg empagliflozin and 850 mg metformin hydrochloride.

Synjardy 5 mg/1 000 mg film-coated tablets

Each tablet contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride.

Synjardy 12.5 mg/850 mg film-coated tablets

Each tablet contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.

Synjardy 12.5 mg/1 000 mg film-coated tablets

Each tablet contains 12.5 mg empagliflozin and 1 000 mg metformin hydrochloride.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Synjardy 5 mg/850 mg film-coated tablets

Yellowish white, oval, biconvex film coated tablets debossed with “S5” and the Boehringer Ingelheim logo on one side and “850” on the other side (tablet length: 19.2 mm, tablet width: 9.4 mm).

Synjardy 5 mg/1 000 mg film-coated tablets

Brownish yellow, oval, biconvex film coated tablets debossed with “S5” and the Boehringer Ingelheim logo on one side and “1 000” on the other side (tablet length: 21.1 mm, tablet width: 9.7 mm).

Synjardy 12.5 mg/850 mg film-coated tablets

Pinkish white, oval, biconvex film coated tablets debossed with “S12” and the Boehringer Ingelheim logo on one side and “850” on the other side (tablet length: 19.2 mm, tablet width: 9.4 mm).

Synjardy 12.5 mg/1 000 mg film-coated tablets

Dark brownish purple, oval, biconvex film coated tablets debossed with “S12” and the Boehringer Ingelheim logo on one side and “1 000” on the other side (tablet length: 21.1 mm, tablet width: 9.7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Synjardy is indicated in adults and children aged 10 years and above for the treatment of 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, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

Adults with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2)

The recommended dose is 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)

In patients insufficiently controlled on metformin 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 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 hypoglycemia (see sections 4.5 and 4.8).

For 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 (for available strengths see section 2).

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same time. In that case, the missed dose should be skipped.

Special populations

Renal impairment
The glycaemic efficacy of empagliflozin is dependent on renal function. For cardiovascular risk reduction as add on to standard of care, a dose of 10 mg empagliflozin daily should be used in patients with an eGFR below 60 mL/min/1.73 m^2 (see Table 1). Because the glycaemic lowering efficacy of empagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with

severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered.
For dose adjustment recommendations according to eGFR or CrCL refer to Table 1.

A eGFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at 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.

If no adequate strength of Synjardy is available, individual monocomponents should be used instead of the fixed dose combination.

For dosing recommendations in the paediatric population see subsection paediatric patients below.

Table 1: Posology for renally impaired adult patients[a]

eGFR [mL/min/1.73 m²] or CrCL [mL/min]	**Metformin**	**Empagliflozin**
≥ 60	Maximum daily dose is 3 000 mg. Dose reduction may be considered in relation to declining renal function.	Initiate with 10 mg. In patients tolerating 10 mg and requiring additional glycaemic control, the dose can be increased to 25 mg.
45 to < 60	Maximum daily dose is 2 000 mg. The starting dose is at most half of the maximum dose.	Initiate with 10 mg.[b] Continue with 10 mg in patients already taking empagliflozin.
30 to < 45	Maximum daily dose is 1 000 mg. The starting dose is at most half of the maximum dose.	Initiate with 10 mg.[b] Continue with 10 mg in patients already taking empagliflozin.[b]
< 30	Metformin is contraindicated.	Empagliflozin is not recommended.

[a] See sections 4.4, 4.8, 5.1 and 5.2
[b] patients with type 2 diabetes mellitus and established cardiovascular disease

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin. Because metformin is excreted by the kidney and elderly patients are more likely to have decreased renal function, Synjardy should be used with caution in these patients. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients (see sections 4.3 and 4.4). In patients 75 years and older, an increased risk for volume depletion should be taken into account (see sections 4.4 and 4.8).

Paediatric population
The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability.
If empagliflozin is added in patients already receiving metformin, the metformin dose should remain the same as the patient is already taking. The recommended empagliflozin starting dose is 5 mg twice daily (10 mg total daily doses). In patients tolerating empagliflozin 5 mg twice daily and requiring additional glycaemic control, the dose can be increased to 12.5 mg twice daily (25 mg total daily dose).
If patients switching from separate tablets of empagliflozin and metformin to Synjardy the same daily dose of empagliflozin and metformin should remain as already being taken or the nearest therapeutically appropriate dose of metformin.

The maximum recommended daily dose of Synjardy is 25 mg of empagliflozin and 2 000 mg of metformin (see general information above in section 4.2).
No data are available for children with eGFR < 60 mL/min/1.73 m² and children below 10 years of age.

Method of administration

Synjardy should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin. The tablets should be swallowed whole with water. All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis) (see section 4.4).
- Diabetic pre-coma.
- Severe renal failure (eGFR < 30 mL/min/1.73 m^2) (see sections 4.2 and 4.4).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock (see sections 4.4 and 4.8).
- 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 (see section 4.4).
- Hepatic impairment, acute alcohol intoxication, alcoholism (see sections 4.2 and 4.5).

4.4 Special warnings and precautions for use

General

Empagliflozin should not be used in patients with type 1 diabetes mellitus (see “Diabetic ketoacidosis” in section 4.4).

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at 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 should be temporarily discontinued and contact with a health care professional is recommended.

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 care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. 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.

Patients with known or suspected mitochondrial diseases

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including empagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of empagliflozin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with empagliflozin 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, factors in the patient history that may predispose to ketoacidosis should be considered.

Prolonged diabetic ketoacidosis and prolonged glucosuria have been observed with empagliflozin. Diabetic ketoacidosis may last longer after discontinuation of empagliflozin than expected from the plasma half-life (see section 5.2). Empagliflozin-independent factors, such as insulin deficiency, might be involved in prolonged periods of diabetic ketoacidosis.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

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.

Synjardy should not be used in patients with type 1 diabetes. Data from a clinical trial program in patients with type 1 diabetes showed increased DKA occurrence with common frequency in patients treated with empagliflozin 10 mg and 25 mg as an adjunct to insulin compared to placebo.

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 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).

Renal impairment

Due to the mechanism of action, decreased renal function will result in reduced glycaemic efficacy of empagliflozin. Empagliflozin/metformin is contraindicated in patients with eGFR< 30 mL/min/1.73 m^2 and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

Monitoring of renal function
Assessment of renal function is recommended as follows:
- Prior to empagliflozin/metformin initiation and periodically during treatment, i.e. at least yearly (see section 4.2).
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

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).

Surgery

Metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

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 (see section 5.1). Therefore, caution should be exercised in patients for whom a empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive 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 Synjardy. Temporary interruption of treatment with Synjardy should be considered until the fluid loss is corrected.

Elderly

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

Urinary tract infections

Post marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see section 4.8). Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors, including empagliflozin. 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 (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.

Hepatic injury

Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment (see section 4.8). Patients with pronounced elevations in haematocrit should be monitored and investigated for underlying haematological disease.

Chronic kidney disease

There is experience with empagliflozin for the treatment of diabetes in patients with chronic kidney disease (eGFR $\geq$ 30 mL/min/1.73 m^2) both with and without albuminuria. Patients with albuminuria may benefit more from treatment with empagliflozin.

Urine laboratory assessments

Due to its mechanism of action, patients taking Synjardy will test positive for glucose in their urine.

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 of alternative methods to monitor glycaemic control is advised.

Vitamin B12

Metformin may reduce vitamin B12 levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or

neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Paediatric population

In the DINAMO trial (see section 5.1), the overall safety profile in children and adolescents was similar with the known safety profile seen in adult patients and there were no relevant differences between placebo and empagliflozin regarding growth assessments or concerning the sexual maturation after 26 weeks of treatment.
No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12
In metformin studies, only 15 patients aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents.
The DINAMO trial included 157 patients and 91% were on metformin as background therapy, 25 of these patients were between 10 and 12 years old.
Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of empagliflozin and metformin does not meaningfully alter the pharmacokinetics of either empagliflozin or metformin in healthy subjects.

No interaction studies have been performed for Synjardy. The following statements reflect the information available on the individual active substances.

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 (see section 4.4).

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

Effects of other medicinal products on empagliflozin
In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (C_{max}) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.

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.

An interaction study with gemfibrozil, an *in vitro* inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C_{max} increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful.

Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in C_{max} and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.

Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor, indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.

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.

Effects of empagliflozin on other medicinal products
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.

Based on *in vitro* studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with active substances that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in C_{max} of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 *in vitro* at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

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.

<u>Metformin</u>

<u>Concomitant use not recommended</u>

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Organic cation transporters (OCT)
Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin (see sections 4.2 and 4.4).

Iodinated contrast agents
Metformin must 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 4.4).

Combination 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, close monitoring of renal function is necessary.

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. If necessary, the dose of the anti hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

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 metformin (see sections 4.2 and 4.8).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of this medicinal product or empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development. A limited amount of data suggests that the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with the combination of empagliflozin and metformin or with metformin alone have shown reproductive toxicity at higher doses of metformin only (see section 5.3).

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 associated with abnormal blood glucose levels.

Breast-feeding

Metformin is excreted into human milk. No effects have been shown in breastfed newborns/infants of treated women. No data in humans are available on excretion of empagliflozin into milk. Available animal data have shown excretion of empagliflozin and metformin in milk. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used during breast feeding.

Fertility

No studies on the effect on human fertility have been conducted for this medicinal product or empagliflozin. Animal studies with empagliflozin and metformin do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Synjardy has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Synjardy is used in combination with a sulphonylurea and/or insulin.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in clinical trials were hypoglycaemia in combination with insulin and/or sulphonylurea and gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain and loss of appetite). No additional adverse reactions were identified in clinical trials with empagliflozin as add-on to 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: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies and from post-marketing experience

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[1, 2] Urinary tract infection (including pyelonephritis and urosepsis)[1, 2]		Necrotising fasciitis of the perineum (Fournier´s gangrene) [a]	
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[1]	Thirst[2] Vitamin B12 decrease/deficiency[3,a]		Diabetic ketoacidosis[a]	Lactic acidosis[3]
Nervous system disorders		Taste disturbance[3]			
Vascular disorders			Volume depletion[1, 2, d]		
Gastrointestinal disorders	Gastrointestinal symptoms[3, 4]	Constipation			
Hepatobiliary disorders					Liver function tests abnormalities[3] Hepatitis[3]
Skin and subcutaneous tissue disorders		Pruritus (generalised)[2, 3] Rash	Urticaria Angioedema		Erythema[3]
Renal and urinary disorders		Increased urination[1, 2]	Dysuria[2]		Tubulointerstitial nephritis
Investigations		Serum lipids increased[2, b]	Blood creatinine increased/ Glomerular filtration rate decreased[1] Haematocrit increased[2, c]		

[1] See subsections below for additional information
[2] Identified adverse reactions of empagliflozin monotherapy
[3] Identified adverse reactions of metformin monotherapy
[4] 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.
[a] See section 4.4
[b] 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%.
[c] 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.
[d] Pooled data of empagliflozin trials in patients with heart failure (where half of the patients had type 2 diabetes mellitus) showed a higher frequency of volume depletion (“very common”: 11.4% for empagliflozin versus 9.7% for placebo).

Description of selected adverse reactions

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as add-on to metformin, as add-on to linagliptin and metformin, for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy. An increased frequency was noted when empagliflozin given as add-on to metformin and a sulfonylurea (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5% and placebo: 8.4%), or as add-on to metformin and insulin (empagliflozin 10 mg: 31.3%, empagliflozin 25 mg: 36.2% and placebo: 34.7%).

Major hypoglycaemia (events requiring assistance)
The overall frequency of patients with major hypoglycaemic events was low (< 1%) and similar for empagliflozin and placebo as add-on to metformin, and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components, and as adjunct to standard care therapy. Major hypoglycaemic events occurred in 0.5%, 0% and 0.5% of patients treated with empagliflozin 10 mg, empagliflozin 25 mg and placebo when added on to metformin and insulin, respectively. No patient had a major hypoglycaemic event in the combination with metformin and a sulphonylurea and as add-on to linagliptin and metformin.

Urinary tract infection

The overall frequency of urinary tract infection adverse events was higher in metformin-treated patients who received empagliflozin 10 mg (8.8%) compared to empagliflozin 25 mg (6.6%) or placebo (7.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections (i.e. mild/moderate/severe) was similar to placebo. Urinary tract infection events were reported more frequently for empagliflozin 10 mg compared with placebo in female patients, but not for empagliflozin 25 mg. The frequencies of urinary tract infections were low for male patients and were balanced across treatment groups.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in metformin-treated patients who received empagliflozin 10 mg (4.0%) and empagliflozin 25 mg (3.9%) compared to placebo (1.3%), and were reported more frequently for empagliflozin 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.

Cases of phimosis/acquired phimosis have been reported concurrent with genital infections and in some cases, circumcision was required.

Increased urination

As expected from the mechanism of action, increased urination (as assessed by PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in metformin-treated patients who received empagliflozin 10 mg (3.0%) and empagliflozin 25 mg (2.9%) compared to placebo (1.4%) as add-on to metformin therapy. Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin (< 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) in metformin-treated patients who received empagliflozin was

low: 0.6% for empagliflozin 10 mg, 0.3% for empagliflozin 25 mg and 0.1% for placebo. The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients age 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 as add-on to metformin therapy.

Blood creatinine increased/Glomerular filtration rate decreased

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were 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%).
Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with empagliflozin as add-on to metformin therapy were generally transient during continuous treatment or reversible after drug discontinuation of treatment.
Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 mL/min/1.73 m^2). Thereafter, eGFR was maintained during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting acute haemodynamic changes may play a role in these renal function changes.

Paediatric population

In the DINAMO trial 157 children aged 10 years and above with type 2 diabetes were treated, in which 52 patients received empagliflozin, 52 linagliptin and 53 placebo (see section 5.1). During the placebo-controlled phase, the most frequent adverse drug reaction was hypoglycaemia (empagliflozin 10 mg and 25 mg, pooled: 23.1%, placebo: 9.4%). None of these events was severe or required assistance.

Overall, the safety profile in children was similar to the safety profile in adults with type 2 diabetes mellitus.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

Empagliflozin

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32-times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4-times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful. There is no experience with doses above 800 mg in humans.

Metformin

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital (see sections 4.4 and 4.5).

Therapy

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD20

Mechanism of action

Synjardy combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2), and metformin hydrochloride, a member of the biguanide class.

Empagliflozin

Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5 000-times more selective for SGLT2 versus SGLT1, the major transporter 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 the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine. In addition, initiation of empagliflozin increases excretion of sodium resulting in osmotic diuresis and reduced intravascular volume.

In patients with type 2 diabetes, 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 the 4-week treatment period, averaging approximately 78 g/day with empagliflozin 25 mg. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was 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. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Metformin

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

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis,
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization,
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

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

Clinical efficacy and safety

Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Glycaemic efficacy and cardiovascular outcomes have been assessed in a total of 10 366 patients with type 2 diabetes who were treated in 9 double-blind, placebo or active-controlled clinical studies of at least 24 weeks duration, of which 2 950 patients received empagliflozin 10 mg and 3 701 received empagliflozin 25 mg as add-on to metformin therapy. Of these, 266 or 264 patients were treated with empagliflozin 10 mg or 25 mg as add-on to metformin plus insulin, respectively.

Treatment with empagliflozin in combination with metformin with or without other antidiabetic medicinal products (pioglitazone, sulfonylurea, DPP-4 inhibitors, and insulin) led to clinically relevant improvements in HbA_{1c}, fasting plasma glucose (FPG), body weight, systolic and diastolic blood pressure. Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA_{1c} goal of less than 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. In patients age 75 years and older, numerically lower reductions in HbA_{1c} were observed with empagliflozin treatment. Higher baseline HbA_{1c} was associated with a greater reduction in HbA_{1c}. In addition, empagliflozin as adjunct to standard care therapy reduced cardiovascular mortality in patients with type 2 diabetes and established cardiovascular disease.

Empagliflozin as add-on to metformin, sulphonylurea, pioglitazone

Empagliflozin as add-on to metformin, metformin and a sulphonylurea, or pioglitazone and metformin resulted in statistically significant ($p < 0.0001$) reductions in HbA_{1c} and body weight compared to placebo (Table 3). In addition it resulted in a clinically meaningful reduction in FPG, systolic and diastolic blood pressure compared to placebo.
In the double-blind placebo-controlled extension of these studies, reduction of HbA_{1c}, body weight and blood pressure were sustained up to Week 76.

Table 3: Efficacy results of 24 week placebo-controlled studies

Add-on to metformin therapy[a]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	207	217	213
HbA_{1c} (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline[1]	-0.13	-0.70	-0.77
Difference from placebo[1] (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	12.5	37.7	38.7
N	207	217	213
Body Weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1] (97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)
N	207	217	213
SBP (mmHg)[2]			
Baseline (mean)	128.6	129.6	130.0
Change from baseline[1]	-0.4	-4.5	-5.2
Difference from placebo[1] (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)
Add-on to metformin and a sulphonylurea therapy[a]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	225	225	216
HbA_{1c} (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.17	-0.82	-0.77
Difference from placebo[1] (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	9.3	26.3	32.2
N	225	225	216
Body Weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline[1]	-0.39	-2.16	-2.39
Difference from placebo[1] (97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)
N	225	225	216
SBP (mmHg)[2]			
Baseline (mean)	128.8	128.7	129.3
Change from baseline[1]	-1.4	-4.1	-3.5
Difference from placebo[1] (95% CI)		-2.7 (-4.6, -0.8)	-2.1 (-4.0, -0.2)

Add-on to pioglitazone + metformin therapy[b]			
	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
N	124	125	127
HbA_{1c} (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.11	-0.55	-0.70
Difference from placebo[1] (97.5% CI)		-0.45* (-0.69, -0.21)	-0.60* (-0.83, -0.36)
N	118	116	123
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	8.5	22.4	28.5
N	124	125	127
Body Weight (kg)			
Baseline (mean)	79.45	79.44	80.98
Change from baseline[1]	0.40	-1.74	-1.59
Difference from placebo[1] (97.5% CI)		-2.14* (-2.93, -1.35)	-2.00* (-2.78, -1.21)
N	124	125	127
SBP (mmHg)[2, 3]			
Baseline (mean)	125.5	126.3	126.3
Change from baseline[1]	0.8	-3.5	-3.3
Difference from placebo[1] (95% CI)		-4.2** (-6.94, -1.53)	-4.1** (-6.76, -1.37)

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[b] Subgroup analysis for patients on additional background of metformin (FAS, LOCF)
[1] Mean adjusted for baseline value
[2] Not evaluated for statistical significance as a part of the sequential confirmatory testing procedure
[3] LOCF, values after antihypertensive rescue censored
[*] p-value < 0.0001
[**] p-value < 0.01

Empagliflozin in combination with metformin in drug-naïve patients

A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin 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 improvements in HbA_{1c} (Table 4) and led to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin).

Table 4: Efficacy results at 24 week comparing empagliflozin in combination with metformin to the individual components[a]

	Empagliflozin 10 mg[b]			Empagliflozin 25 mg[b]			Metformin[c]	
	+ Met 1 000 mg [c]	+ Met 2 000 mg [c]	No Met	+ Met 1 000 mg [c]	+ Met 2 000 mg [c]	No Met	1 000 mg	2 000 mg
N	161	167	169	165	169	163	167	162
HbA_{1c} (%)								
Baseline (mean)	8.68	8.65	8.62	8.84	8.66	8.86	8.69	8.55
Change from baseline[1]	-1.98	-2.07	-1.35	-1.93	-2.08	-1.36	-1.18	-1.75
Comparison vs. empa (95% CI)[1]	-0.63* (-0.86, -0.40)	-0.72* (-0.96, -0.49)		-0.57* (-0.81, -0.34)	-0.72* (-0.95, -0.48)			
Comparison vs. met (95% CI)[1]	-0.79* (-1.03, -0.56)	-0.33* (-0.56, -0.09)		-0.75* (-0.98 -0.51)	-0.33* (-0.56, -0.10)			

Met = metformin; empa = empagliflozin

[1] mean adjusted for baseline value

[a] Analyses were performed on the full analysis set (FAS) using an observed cases (OC) approach

[b] Given in two equally divided doses per day when given together with metformin

[c] Given in two equally divided doses per day

* $p \leq 0.0062$ for HbA_{1c}

Empagliflozin in patients inadequately controlled with metformin and linagliptin

In patients inadequately controlled with metformin and linagliptin 5 mg, treatment with both empagliflozin 10 mg or 25 mg resulted in statistically significant ($p < 0.0001$) reductions in HbA_{1c} and body weight compared to placebo (Table 5). In addition it resulted in clinically meaningful reductions in FPG, systolic and diastolic blood pressure compared to placebo.

Table 5: Efficacy results of a 24 week placebo-controlled study in patients inadequately controlled with metformin and linagliptin 5 mg

Add-on to metformin and linagliptin 5 mg			
	Placebo[5]	**Empagliflozin[6]**	
		10 mg	**25 mg**
N	106	109	110
HbA_{1c} (%)[3]			
Baseline (mean)	7.96	7.97	7.97
Change from baseline[1]	0.14	-0.65	-0.56
Difference from placebo (95% CI)		-0.79* (-1.02, -0.55)	-0.70* (-0.93, -0.46)
N	100	100	107
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	17.0	37.0	32.7
N	106	109	110
Body Weight (kg)[3]			
Baseline (mean)	82.3	88.4	84.4
Change from baseline[1]	-0.3	-3.1	-2.5
Difference from placebo (95% CI)		-2.8* (-3.5, -2.1)	-2.2* (-2.9, -1.5)
N	106	109	110
SBP (mmHg)[4]			
Baseline (mean)	130.1	130.4	131.0
Change from baseline[1]	-1.7	-3.0	-4.3
Difference from placebo (95% CI)		-1.3 (-4.2, 1.7)	-2.6 (-5.5, 0.4)

1 Mean adjusted for baseline value
2 Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
3 MMRM model on FAS (OC) included baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, visit, treatment, and treatment by visit interaction. For weight, baseline weight was included.
4 MMRM model included baseline SBP and baseline HbA_{1c} as linear covariate(s), and baseline eGFR, geographical region, treatment, visit, and visit by treatment interaction as fixed effects.
5 Patients randomized to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin
6 Patients randomized to the empagliflozin 10 mg or 25 mg groups were receiving empagliflozin 10 mg or 25 mg and linagliptin 5 mg with background metformin
* p-value < 0.0001

In a prespecified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5% the reduction from baseline in HbA_{1c} was -1.3% with empagliflozin 10 mg or 25 mg at 24 weeks ($p < 0.0001$) compared to placebo.

Empagliflozin 24 months data, as add-on to metformin in comparison to glimepiride

In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (up to 4 mg per day) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA_{1c} (Table 6), and a clinically meaningful reduction in FPG, compared to glimepiride. Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure and a statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, $p < 0.0001$).

Table 6: Efficacy results at 104 week in an active controlled study comparing empagliflozin to glimepiride as add on to metformin[a]

	Empagliflozin 25 mg	**Glimepiride[b]**
N	765	780
HbA_{1c} (%)		
Baseline (mean)	7.92	7.92
Change from baseline[1]	-0.66	-0.55
Difference from glimepiride[1] (97.5% CI)	-0.11* (-0.20, -0.01)	
N	690	715
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	33.6	30.9
N	765	780
Body Weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline[1]	-3.12	1.34
Difference from glimepiride[1] (97.5% CI)	-4.46** (-4.87, -4.05)	
N	765	780
SBP (mmHg)[3]		
Baseline (mean)	133.4	133.5
Change from baseline[1]	-3.1	2.5
Difference from glimepiride[1] (97.5% CI)	-5.6** (-7.0, -4.2)	

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[b] Up to 4 mg glimepiride
[1] Mean adjusted for baseline value
[2] Not evaluated for statistical significance as a part of the sequential confirmatory testing procedure
[3] LOCF, values after antihypertensive rescue censored
* p-value < 0.0001 for non-inferiority, and p-value = 0.0153 for superiority
** p-value < 0.0001

Add-on to insulin therapy

Empagliflozin as add-on to multiple daily insulin
The efficacy and safety of empagliflozin as add-on to multiple daily insulin with concomitant metformin therapy 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 (< 100 mg/dL), and post-prandial glucose levels < 7.8 mmol/L (< 140 mg/dL) between Weeks 19 and 40.
At Week 18, empagliflozin provided statistically significant improvement in HbA_{1c} compared with placebo (Table 7).
At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA_{1c} and insulin sparing compared with placebo and a reduction in body weight.

Table 7: Efficacy results at 18 and 52 weeks in a placebo-controlled study of empagliflozin as add-on to multiple daily doses of insulin with concomitant metformin therapy

	Placebo	**empagliflozin**	
		10 mg	**25 mg**
N	135	128	137
HbA_{1c} (%) at week 18[a]			
Baseline (mean)	8.29	8.42	8.29
Change from baseline[1]	-0.58	-0.99	-1.03
Difference from placebo[1] (97.5% CI)		-0.41* (-0.61, -0.21)	-0.45* (-0.65, -0.25)
N	86	84	87
HbA_{1c} (%) at week 52[b]			
Baseline (mean)	8.26	8.43	8.38
Change from baseline[1]	-0.86	-1.23	-1.31
Difference from placebo[1] (97.5% CI)		-0.37** (-0.67, -0.08)	-0.45* (-0.74, -0.16)
N	84	84	87
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7% at week 52[b, 2]	27.4	41.7	48.3
N	86	83	86
Insulin dose (IU/day) at week 52[b, 3]			
Baseline (mean)	91.01	91.77	90.22
Change from baseline[1]	12.84	0.22	-2.25
Difference from placebo[1] (97.5% CI)		-12.61** (-21.43, -3.80)	-15.09** (-23.79, -6.40)
N	86	84	87
Body Weight (kg) at week 52[b]			
Baseline (mean)	97.78	98.86	94.93
Change from baseline[1]	0.42	-2.47	-1.94
Difference from placebo[1] (97.5% CI)		-2.89* (-4.29, -1.49)	-2.37* (-3.75, -0.98)

[a] Subgroup analysis for patients on additional background of metformin (FAS, LOCF)
[b] Subgroup analysis for patients on additional background of metformin (PPS-Completers, LOCF)
[1] Mean adjusted for baseline value
[2] not evaluated for statistical significance as a part of the sequential confirmatory testing procedure
[3] Week 19-40: treat-to-target regimen for insulin dose adjustment to achieve pre-defined glucose target levels (pre-prandial < 5.5 mmol/L (< 100 mg/dL), post-prandial < 7.8 mmol/L (< 140 mg/dL)
[*] p-value ≤ 0.0005
[**] p-value < 0.005

Empagliflozin as add on to basal insulin

The efficacy and safety of empagliflozin as add on to basal insulin with concomitant metformin therapy was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. During the initial 18 weeks the insulin dose was kept stable, but was adjusted to achieve a FPG < 110 mg/dL in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA_{1c}. A greater proportion of patients treated with empagliflozin and with a baseline HbA_{1c} ≥ 7.0% achieved a target HbA1c of < 7% compared to placebo (Table 8).

At 78 weeks, the decrease in HbA_{1c} and insulin sparing effect of empagliflozin was maintained. Furthermore, empagliflozin resulted in a reduction in FPG, body weight and blood pressure.

Table 8: Efficacy results at 18 and 78 weeks in a placebo-controlled study of empagliflozin as add on to basal insulin with metformin[a]

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	96	107	99
HbA_{1c} (%) at week 18			
Baseline (mean)	8.02	8.21	8.35
Change from baseline[1]	-0.09	-0.62	-0.72
Difference from placebo[1] (97.5% CI)		-0.54* (-0.77, -0.30)	-0.63* (-0.88, -0.39)
N	89	105	94
HbA_{1c} (%) at week 78			
Baseline (mean)	8.03	8.24	8.29
Change from baseline[1]	-0.08	-0.42	-0.71
Difference from placebo[1] (97.5% CI)		-0.34** (-0.64, -0.05)	-0.63* (-0.93, -0.33)
N	89	105	94
Basal insulin dose (IU/day) at week 78			
Baseline (mean)	49.61	47.25	49.37
Change from baseline[1]	4.14	-2.07	-0.28
Difference from placebo[1] (97.5% CI)		-6.21** (-11.81, -0.61)	-4.42 (-10.18, 1.34)

[a] Subgroup analysis of full analysis set (FAS) for patients on additional background of metformin - Completers using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[1] mean adjusted for baseline value
[*] p-value < 0.0001
[**] p-value ≤ 0.025

Empagliflozin and linagliptin as add-on therapy to metformin

In a double-blind trial in patients with inadequate glycemic control, 24-weeks treatment with both doses of empagliflozin plus linagliptin as add-on to metformin therapy provided statistically significant ($p < 0.0001$) reductions in HbA_{1c} (change from baseline of -1.08% for empagliflozin 10 mg plus linagliptin 5 mg, -1.19% for empagliflozin 25 mg plus linagliptin 5 mg, -0.70% for linagliptin 5 mg). Compared to linagliptin 5 mg, both doses of empagliflozin plus linagliptin 5 mg provided statistically significant reductions in FPG and blood pressure. Both doses provided similar statistically significant reductions in body weight, expressed as kg and percentage change. A greater proportion of patients with a baseline $HbA_{1c} \geq 7.0\%$ and treated with empagliflozin plus linagliptin achieved a target HbA_{1c} of < 7% compared to linagliptin 5 mg. Clinically meaningful reductions in HbA_{1c} were maintained for 52 weeks.

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 in sufficient glycemic 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 HbA_{1c} from baseline (total mean 7.8%) after 16 weeks of treatment compared with placebo. Empagliflozin twice daily dose regimens on a background of metformin led to comparable reductions in HbA_{1c} versus once daily dose regimens with a treatment difference in HbA_{1c} reductions from baseline to week 16 of -0.02% (95% CI -0.16, 0.13) for empagliflozin 5 mg twice daily versus 10 mg once daily, and -0.11% (95% CI -0.26, 0.03) for empagliflozin 12.5 mg twice daily versus 25 mg once daily.

Cardiovascular outcome

The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with type 2 diabetes and established cardiovascular disease. A total of 7 020 patients were treated (empagliflozin 10 mg: 2 345, empagliflozin 25 mg: 2 342, placebo: 2 333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA_{1c} was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a sulfonylurea. 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.

At week 12, an adjusted mean (SE) improvement in HbA_{1c} when compared to baseline of 0.11% (0.02) in the placebo group, 0.65% (0.02) and 0.71% (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA_{1c} of 0.08% (0.02) in the placebo group, 0.50% (0.02) and 0.55% (0.02) in the empagliflozin 10 and 25 mg groups.

Empagliflozin was superior in preventing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg (see Figure 1) and confirmed by an improved overall survival (Table 9). The effect of empagliflozin on the primary combined endpoint of CV death, non-fatal MI, or non-fatal stroke was largely independent of glycaemic control or renal function (eGFR) and generally consistent across eGFR categories down to an eGFR of 30 mL/min/1.73 m^2 in the EMPA-REG OUTCOME study.

The efficacy for preventing cardiovascular mortality has not been conclusively established in patients using empagliflozin concomitantly with DPP-4 inhibitors or in Black patients because the representation of these groups in the EMPA-REG OUTCOME study was limited.

Table 9: Treatment effect for the primary composite endpoint, its components and mortality[a]

	Placebo	**Empagliflozin[b]**
N	2333	4687
Time to first event of CV death, non-fatal MI, or non-fatal stroke N (%)	282 (12.1)	490 (10.5)
Hazard ratio vs. placebo (95.02% CI)*		0.86 (0.74, 0.99)
p−value for superiority		0.0382
CV Death N (%)	137 (5.9)	172 (3.7)
Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		< 0.0001
Non-fatal MI N (%)	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p−value		0.2189
Non-fatal stroke N (%)	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p−value		0.1638
All-cause mortality N (%)	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		< 0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

CV = cardiovascular, MI = myocardial infarction

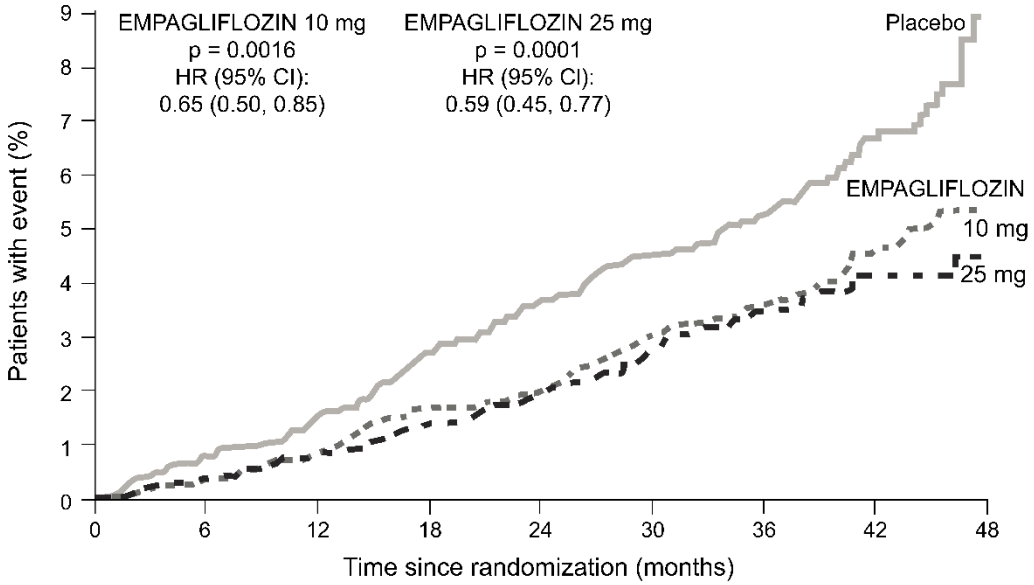
[a] Treated set (TS), i.e. patients who had received at least one dose of study drug

[b] Pooled doses of empagliflozin 10 mg and 25 mg

* Since data from the trial were included in an interim analysis, a two-sided 95.02% confidence interval applied which corresponds to a p-value of less than 0.0498 for significance.

Figure 1 Time to occurrence of cardiovascular death in the EMPA-REG OUTCOME study

Individual Empagliflozin Doses versus Placebo



No. at Risk									
EMPAGLIFLOZIN 10 mg	2 345	2 327	2 305	2 274	2 055	1 542	1 303	847	201
EMPAGLIFLOZIN 25 mg	2 342	2 324	2 303	2 282	2 073	1 537	1 314	875	213
Placebo	2 333	2 303	2 280	2 243	2 012	1 503	1 281	825	177

Heart failure requiring hospitalization
In the EMPA-REG OUTCOME study, empagliflozin reduced the risk of heart failure requiring hospitalization compared with placebo (empagliflozin 2.7%; placebo 4.1%; HR 0.65, 95% CI 0.50, 0.85).

Nephropathy
In the EMPA-REG OUTCOME study, for time to first nephropathy event, the HR was 0.61 (95% CI 0.53, 0.70) for empagliflozin (12.7%) vs placebo (18.8%).

In addition, empagliflozin showed a higher (HR 1.82, 95% CI 1.40, 2.37) occurrence of sustained normo- or micro-albuminuria (49.7%) in patients with baseline macro-albuminuria compared with placebo (28.8%).

2 hour post-prandial glucose

Treatment with empagliflozin as add-on to metformin or metformin plus sulfonylurea resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin, placebo: +5.9 mg/dL, empagliflozin 10 mg: -46.0 mg/dL, empagliflozin 25 mg: -44.6 mg/dL; add-on to metformin plus sulphonylurea, placebo: -2.3 mg/dL, empagliflozin 10 mg: -35.7 mg/dL, empagliflozin 25 mg: -36.6 mg/dL).

Patients with baseline $HbA_{1c} \geq 9\%$

In a pre-specified analysis of subjects with baseline $HbA_{1c} \geq 9.0\%$, treatment with empagliflozin 10 mg or 25 mg as add-on to metformin resulted in statistically significant reductions in HbA_{1c} 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 and up to 2 antihypertensive therapies. Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA_{1c}, and 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (Table 10). Treatment with empagliflozin provided reductions in seated SBP and DBP.

Table 10: Efficacy results at 12 week in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure[a]

	Placebo	**empagliflozin**	
		10 mg	**25 mg**
N	271	276	276
HbA_{1c} (%) at week 12[1]			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[2]	0.03	-0.59	-0.62
Difference from placebo[1] (95% CI)[2]		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 12[3]			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[4]	0.48	-2.95	-3.68
Difference from placebo[4] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 12[3]			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[5]	0.32	-1.04	-1.40
Difference from placebo[5] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

[a] Full analysis set (FAS)
[1] LOCF, values after taking antidiabetic rescue therapy censored
[2] Mean adjusted for baseline HbA_{1c}, baseline eGFR, geographical region and number of antihypertensive medicinal products
[3] LOCF, values after taking antidiabetic rescue therapy or changing antihypertensive rescue therapy censored
[4] Mean adjusted for baseline SBP, baseline HbA_{1c}, baseline eGFR, geographical region and number of antihypertensive medicinal products
[5] Mean adjusted for baseline DBP, baseline HbA_{1c}, baseline eGFR, geographical region and number of antihypertensive medicinal products
[*] p-value < 0.0001
[**] p-value < 0.001

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.

Metformin

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1 000 patient-years) *versus* diet alone (43.3 events/1 000 patient-years), p = 0.0023, and *versus* the combined sulphonylurea and insulin monotherapy groups (40.1 events/1 000 patient-years), p = 0.0034,
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1 000 patient-years, diet alone 12.7 events/1 000 patient-years, p = 0.017,
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1 000 patient-years *versus* diet alone 20.6 events/1 000 patient-years, (p = 0.011), and *versus* the combined sulphonylurea and insulin monotherapy groups 18.9 events/1 000 patient-years (p = 0.021),
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1 000 patient-years, diet alone 18 events/1 000 patient-years, (p = 0.01).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Synjardy in all subsets of the paediatric population from birth to less than 10 years of age in type 2 diabetes (see section 4.2 for information on paediatric use).
The clinical efficacy and safety of empagliflozin (10 mg with a possible dose-increase to 25 mg) and linagliptin (5 mg) once daily has been studied in children and adolescents from 10 to 17 years of age with type 2 diabetes mellitus in a placebo-controlled study (DINAMO) over 26 weeks, with a safety extension period up to 52 weeks. Background therapies as adjunct to diet and exercise included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The adjusted mean changes in HbA1c at week 26 between empagliflozin (N = 52) and placebo (N = 53) of -0.84% was clinically meaningful and statistically significant (95% CI: -1.50, -0.19; p = 0.0116). In addition, treatment with empagliflozin versus placebo resulted in a clinically meaningful adjusted mean change in FPG of -1.95 mmol/L (95% CI: -3.25 to -0.65) (-35.2 mg/dL (95% CI: -58.6, -11.7)). These were -0.76% (95% CI: -1.45%, -0.08%) for HbA1c and -2.12 mmol/L (95% CI: -3.36 to -0.89) (-38.28 mg/dL (95% CI: -60.47 to -16.10)) for FPG in the metformin subgroup (N = 48 empagliflozin, N = 47 placebo).

5.2 Pharmacokinetic properties

Synjardy

The results of bioequivalence studies in healthy subjects demonstrated that Synjardy (empagliflozin/metformin hydrochloride) 5 mg/850 mg, 5 mg/1 000 mg, 12.5 mg/850 mg, and 12.5 mg/1 000 mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of empagliflozin/metformin 12.5 mg/1 000 mg under fed conditions resulted in 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 type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 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. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic 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 type 2 diabetes.

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 empagliflozin 5 mg administered twice daily was similar to empagliflozin 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 empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} 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. Similar results were obtained when Synjardy (empagliflozin/metformin) combination tablets were administered with high-fat and high calorie meal.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Biotransformation

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

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 L/hour. 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 volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). 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.

Special populations

Renal impairment
In patients with mild, moderate or severe renal impairment (creatinine clearance < 30 - < 90 mL/min) and patients with kidney failure/end stage renal disease (ESRD), 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. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in creatinine clearance leading to an increase in drug exposure.

Hepatic impairment
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.

Body Mass Index
Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m^2, respectively, compared to subjects with a body mass index of 25 kg/m^2.

Gender
Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race
In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

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

Paediatric population
A paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin (5 mg, 10 mg and 25 mg) in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

A paediatric Phase 3 study examined the pharmacokinetics and pharmacodynamics (HbA1c change from baseline) of empagliflozin 10 mg with a possible dose-increase to 25 mg in children and adolescents 10 to 17 years of age with type 2 diabetes mellitus. The observed exposure-response relationship was overall comparable in adults and children and adolescents. Oral administration of empagliflozin resulted in an exposure within the range observed in adult patients.
The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 26.6 nmol/L and 308 nmol/L with empagliflozin 10 mg once daily and 67.0 nmol/L and 525 nmol/L with empagliflozin 25 mg once daily.

Metformin

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 absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear. At the recommended metformin 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 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. Following administration of a dose of 850 mg metformin hydrochloride, a 40% lower plasma peak concentration, a 25% decrease in AUC 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 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.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 mL/min, indicating that metformin 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 in plasma.

Special populations

Paediatric population
Single dose study: after single doses of metformin hydrochloride 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple-dose 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 approximately 33% and 40% lower, 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.

5.3 Preclinical safety data

Empagliflozin and metformin

General toxicity studies in rats of up to 13 weeks were performed with the combination of empagliflozin and metformin and did not reveal any additional target organs when compared to empagliflozin or metformin alone. Some responses were increased by the combination treatment, such as effects on renal physiology, electrolyte balance and acid/base state. However, only hypochloremia was considered adverse at exposures of approximately 9- and 3-times the clinical AUC exposure of the maximum recommended dose of empagliflozin and metformin, respectively.

An embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of empagliflozin and metformin at exposures of approximately 14-times the

clinical AUC exposure of empagliflozin associated with the highest dose, and 4-times the clinical AUC exposure of metformin associated with the 2 000 mg dose.

Empagliflozin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.

In a 2-year carcinogenicity study, empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72-times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1 000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1 000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period.

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential or reproductive toxicity. At dose levels of 500 mg/kg/day administered to Wistar Hannover rats, associated with 7-times the maximum recommended human dose (MRHD) of metformin, teratogenicity of metformin was observed, mostly evident as an increase in the number of skeletal malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Synjardy 5 mg/850 mg film-coated tablets and Synjardy 5 mg/1 000 mg film-coated tablets

Tablet core

Maize starch
Copovidone (K-value nominally 28)
Colloidal anhydrous silica
Magnesium stearate

Film-coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Talc
Iron oxide yellow (E172)

Synjardy 12.5 mg/850 mg film-coated tablets and Synjardy 12.5 mg/1 000 mg film-coated tablets

Tablet core

Maize starch
Copovidone (K-value nominally 28)
Colloidal anhydrous silica
Magnesium stearate

Film-coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Talc
Iron oxide black (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/aluminium perforated unit dose blisters.
Pack sizes of 10 × 1, 14 × 1, 30 × 1, 56 × 1, 60 × 1, 90 × 1 and 100 × 1 film-coated tablets and multipacks containing 120 (2 packs of 60 × 1), 180 (2 packs of 90 × 1) and 200 (2 packs of 100 × 1) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Synjardy 5 mg/850 mg film-coated tablets

EU/1/15/1003/001
EU/1/15/1003/002
EU/1/15/1003/003
EU/1/15/1003/004
EU/1/15/1003/005
EU/1/15/1003/037
EU/1/15/1003/006
EU/1/15/1003/007
EU/1/15/1003/008
EU/1/15/1003/009

Synjardy 5 mg/1 000 mg film-coated tablets

EU/1/15/1003/010
EU/1/15/1003/011
EU/1/15/1003/012
EU/1/15/1003/013
EU/1/15/1003/014
EU/1/15/1003/038
EU/1/15/1003/015
EU/1/15/1003/016
EU/1/15/1003/017
EU/1/15/1003/018

Synjardy 12.5 mg/850 mg film-coated tablets

EU/1/15/1003/019
EU/1/15/1003/020
EU/1/15/1003/021
EU/1/15/1003/022
EU/1/15/1003/023
EU/1/15/1003/039
EU/1/15/1003/024
EU/1/15/1003/025
EU/1/15/1003/026
EU/1/15/1003/027

Synjardy 12.5 mg/1 000 mg film-coated tablets

EU/1/15/1003/028
EU/1/15/1003/029
EU/1/15/1003/030
EU/1/15/1003/031
EU/1/15/1003/032
EU/1/15/1003/040
EU/1/15/1003/033
EU/1/15/1003/034
EU/1/15/1003/035
EU/1/15/1003/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 2015
Date of latest renewal: 01 April 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co.KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Boehringer Ingelheim Hellas Single Member S.A.
5th km Paiania – Markopoulo
Koropi Attiki, 19441
Greece

Patheon France
40 boulevard de Champaret
Bourgoin Jallieu, 38300
France

Boehringer Ingelheim France
100-104 Avenue de France
75013 Paris
France

Dragenopharm Apotheker Püschl GmbH
Göllstraße 1
84529 Tittmoning
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/850 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg empagliflozin and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 × 1 film-coated tablets
14 × 1 film-coated tablets
30 × 1 film-coated tablets
56 × 1 film-coated tablets
60 × 1 film-coated tablets
90 × 1 film-coated tablets
100 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/001 10 × 1 film-coated tablets
EU/1/15/1003/002 14 × 1 film-coated tablets
EU/1/15/1003/003 30 × 1 film-coated tablets
EU/1/15/1003/004 56 × 1 film-coated tablets
EU/1/15/1003/005 60 × 1 film-coated tablets
EU/1/15/1003/037 90 × 1 film-coated tablets
EU/1/15/1003/006 100 × 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (perforated)

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/850 mg tablets
empagliflozin/metformin HCL

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS – INCLUDING THE BLUE BOX – 5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/850 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg empagliflozin and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 120 (2 packs of 60 × 1) film-coated tablets.
Multipack: 180 (2 packs of 90 × 1) film-coated tablets.
Multipack: 200 (2 packs of 100 × 1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/007 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/008180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/009 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – INTERMEDIATE CARTON WITHOUT BLUE BOX – 5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/850 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg empagliflozin and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
90 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
100 × 1 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/007 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/008 180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/009 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 × 1 film-coated tablets
14 × 1 film-coated tablets
30 × 1 film-coated tablets
56 × 1 film-coated tablets
60 × 1 film-coated tablets
90 × 1 film-coated tablets
100 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/010 10 × 1 film-coated tablets
EU/1/15/1003/011 14 × 1 film-coated tablets
EU/1/15/1003/012 30 × 1 film-coated tablets
EU/1/15/1003/013 56 × 1 film-coated tablets
EU/1/15/1003/014 60 × 1 film-coated tablets
EU/1/15/1003/038 90 × 1 film-coated tablets
EU/1/15/1003/015 100 × 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (perforated)

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/1 000 mg tablets
empagliflozin/metformin HCL

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS – INCLUDING THE BLUE BOX – 5 mg/1 000 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 120 (2 packs of 60 × 1) film-coated tablets.
Multipack: 180 (2 packs of 90 × 1) film-coated tablets.
Multipack: 200 (2 packs of 100 × 1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/016 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/017 180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/018 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – INTERMEDIATE CARTON WITHOUT BLUE BOX – 5 mg/1 000 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
90 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
100 × 1 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/016 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/017 180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/018 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/850 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 × 1 film-coated tablets
14 × 1 film-coated tablets
30 × 1 film-coated tablets
56 × 1 film-coated tablets
60 × 1 film-coated tablets
90 × 1 film-coated tablets
100 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/019 10 × 1 film-coated tablets
EU/1/15/1003/020 14 × 1 film-coated tablets
EU/1/15/1003/021 30 × 1 film-coated tablets
EU/1/15/1003/022 56 × 1 film-coated tablets
EU/1/15/1003/023 60 × 1 film-coated tablets
EU/1/15/1003/039 90 × 1 film-coated tablets
EU/1/15/1003/024 100 × 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 12.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (perforated)

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/850 mg tablets
empagliflozin/metformin HCL

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS – INCLUDING THE BLUE BOX – 12.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/850 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 120 (2 packs of 60 × 1) film-coated tablets.
Multipack: 180 (2 packs of 90 × 1) film-coated tablets.
Multipack: 200 (2 packs of 100 × 1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/025 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/026 180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/027 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 12.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – INTERMEDIATE CARTON WITHOUT BLUE BOX – 12.5 mg/850 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/850 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
90 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
100 × 1 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/025 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/026 180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/027 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 12.5 mg/850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg empagliflozin and 1 000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 × 1 film-coated tablets
14 × 1 film-coated tablets
30 × 1 film-coated tablets
56 × 1 film-coated tablets
60 × 1 film-coated tablets
90 × 1 film-coated tablets
100 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/028 10 × 1 film-coated tablets
EU/1/15/1003/029 14 × 1 film-coated tablets
EU/1/15/1003/030 30 × 1 film-coated tablets
EU/1/15/1003/031 56 × 1 film-coated tablets
EU/1/15/1003/032 60 × 1 film-coated tablets
EU/1/15/1003/040 90 × 1 film-coated tablets
EU/1/15/1003/033 100 × 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 12.5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (perforated)

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/1 000 mg tablets
empagliflozin/metformin HCL

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS – INCLUDING THE BLUE BOX – 12.5 mg/1 000 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg empagliflozin and 1 000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 120 (2 packs of 60 × 1) film-coated tablets.
Multipack: 180 (2 packs of 90 × 1) film-coated tablets.
Multipack: 200 (2 packs of 100 × 1) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1003/034 120 (2 packs of 60 × 1) film-coated tablets
EU/1/15/1003/035 180 (2 packs of 90 × 1) film-coated tablets
EU/1/15/1003/036 200 (2 packs of 100 × 1) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 12.5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

MULTIPACKS – INTERMEDIATE CARTON WITHOUT BLUE BOX – 12.5 mg/1 000 mg

1. NAME OF THE MEDICINAL PRODUCT

Synjardy 12.5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg empagliflozin and 1 000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
90 × 1 film-coated tablets. Component of a multipack, can't be sold separately.
100 × 1 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Synjardy 12.5 mg/1 000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Synjardy 5 mg/850 mg film-coated tablets
Synjardy 5 mg/1 000 mg film-coated tablets
Synjardy 12.5 mg/850 mg film-coated tablets
Synjardy 12.5 mg/1 000 mg film-coated tablets
empagliflozin/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Synjardy is and what it is used for
2. What you need to know before you take Synjardy
3. How to take Synjardy
4. Possible side effects
5. How to store Synjardy
6. Contents of the pack and other information

1. What Synjardy is and what it is used for

What Synjardy is
Synjardy contains two active substances empagliflozin and metformin. Each belongs to a group of medicines called “oral anti-diabetics”. These are medicines taken by mouth to treat type 2 diabetes.

What is type 2 diabetes?
Type 2 diabetes is a disease that comes from both your genes and your lifestyle. If you have type 2 diabetes, your pancreas does not make enough insulin to control the level of glucose in your blood, and your body is unable to use its own insulin effectively. This results in high levels of glucose in your blood which can lead to medical problems like heart disease, kidney disease, blindness, and poor circulation in your limbs.

How Synjardy works
Empagliflozin belongs to a group of medicines called sodium glucose co-transporter-2 (SGLT2) inhibitors. It works by blocking the SGLT2 protein in your kidneys. This causes blood sugar (glucose) to be removed in your urine. Metformin works in a different way to lower blood sugar levels, mainly by blocking glucose production in the liver.

Thereby Synjardy lowers the amount of sugar in your blood. This medicine can also help prevent heart disease.

What Synjardy is used for
- Synjardy is added to diet and exercise to treat type 2 diabetes in adult patients and children aged 10 years and older whose diabetes cannot be controlled by adding metformin alone or metformin with other medicines for diabetes.

- Synjardy can also be combined with other medicines for the treatment of diabetes. These may be medicines taken by mouth or given by injection such as insulin.

- In addition, Synjardy can be used as an alternative to taking both empagliflozin and metformin as single tablets. To avoid overdose, do not continue taking empagliflozin and metformin tablets separately, if you are taking this medicine.

It is important that you continue with your diet and exercise plan as told by your doctor, pharmacist or nurse.

2. What you need to know before you take Synjardy

Do not take Synjardy
- if you are allergic to empagliflozin, metformin or any of the other ingredients of this medicine (listed in section 6);
- if you have uncontrolled diabetes, with, for example, severe hyperglycaemia (very high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see ‘Risk of lactic acidosis’ below) or ketoacidosis. Ketoacidosis is a condition in which substances called ‘ketone bodies’ accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell;
- if you have had a diabetic pre-coma;
- if you have serious kidney problems. Your doctor may limit your daily dose or ask you to take a different medicine (see also section 3, ‘How to take Synjardy’).
- if you have a severe infection such as an infection affecting your lung or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions');
- if you have lost a lot of water from your body (dehydration), e.g. due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see 'Warnings and precautions');
- if you are treated for acute heart failure or have recently had a heart attack, have severe problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see section ‘Warnings and precautions');
- if you have problems with your liver;
- if you drink large amounts of alcohol, either every day or only from time to time (see section “Synjardy with alcohol”).

Warnings and precautions
Risk of lactic acidosis
Synjardy may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart diseases).

If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Synjardy for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Synjardy and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps

- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Talk to your doctor promptly for further instructions
- if you are known to suffer from a genetically inherited disease affecting mitochondria (the energy-producing components within cells) such as MELAS syndrome (Mitochondrial Encephalopathy, myopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).
- if you have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor, pharmacist or nurse before taking this medicine, and during treatment:
- if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, contact a doctor or the nearest hospital straight away and stop taking this medicine until further advice from your doctor. These symptoms could be a sign of "diabetic ketoacidosis" – a rare, but serious, sometines life-threatening problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests. The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness;
- if you have "type 1 diabetes" – this type usually starts when you are young and your body does not produce any insulin. You should not take Synjardy if you have type 1 diabetes;
- might be at risk of dehydration, for example:
  - if you are being sick, have diarrhoea or fever, or if you are not able to eat or drink
  - if you are taking medicines that increase urine production [diuretics] or lower blood pressure
  - if you are 75 years old or older.

  Possible signs are listed in section 4 under 'dehydration'. Your doctor may ask you to stop taking Synjardy until you recover to prevent loss of too much body fluid. Ask about ways to prevent dehydration.
- if you have a serious infection of the kidney or the urinary tract with fever. Your doctor may ask you to stop taking Synjardy until you have recovered;
- if you need to undergo an examination with iodination contrast agents (such as X-ray or scan). More information is given below in "Other medicines and Synjardy".

Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier´s gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.

<u>Surgery</u>
If you need to have major surgery you must stop taking Synjardy during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Synjardy.

<u>Kidney function</u>
During treatment with Synjardy, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Foot care
Like for all diabetic patients it is important to check your feet regularly and adhere to any other advice regarding foot care given by your health care professional.

Urine glucose
Because of how this medicine works, your urine will test positive for sugar while you are taking this medicine.

Children and adolescents
Synjardy can be used in children aged 10 years and older for the treatment of type 2 diabetes mellitus. Due to limited data caution is recommended when used in children aged between 10 and 12 years. No data are available in children below 10 years of age.

Other medicines and Synjardy
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Synjardy before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Synjardy.

Tell your doctor if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Synjardy. It is especially important to mention the following:

- medicines which increase urine production (diuretics), as Synjardy may increase the risk of losing too much fluid. Your doctor may ask you to stop taking Synjardy. Possible signs of losing too much fluid from your body are listed in section 4.
- other medicines that lower the amount of sugar in your blood such as insulin or a "sulphonylurea" medicine. Your doctor may want to lower the dose of these other medicines, to prevent your blood sugar levels from getting too low (hypoglycaemia).
- medicines that may change the amount of metformin in your blood, especially if you have reduced kidney function (such as verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole, crizotinib, olaparib).
- bronchodilators (beta-2 agonists) which are used to treat asthma.
- corticosteroids (given by mouth, as an injection, or inhaled), which are used to treat inflammation in diseases like asthma and arthritis.
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib).
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists).
- medicines that contain alcohol (see section 'Synjardy with alcohol').
- iodinated contrast agents (medicines used during an X-ray, see section 'Warnings and precautions'.
- if you are taking lithium because Synjardy can lower the amount of lithium in your blood.

Synjardy with alcohol
Avoid excessive alcohol intake while taking Synjardy since this may increase the risk of lactic acidosis (see section 'Warnings and precautions').

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take Synjardy if you are pregnant. It is unknown if this medicine is harmful to the unborn child.

Metformin passes into human milk in small amounts. It is not known whether empagliflozin passes into human breast milk. Do not take Synjardy if you are breast-feeding.

Driving and using machines
Synjardy has minor influence on the ability to drive and use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause blood sugar levels to drop too low (hypoglycaemia), which may cause symptoms such as shaking, sweating and change in vision, and may affect your ability to drive and use machines. Do not drive or use any tools or machines if you feel dizzy while taking Synjardy.

3. How to take Synjardy

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The dose of Synjardy varies depending on your condition and the doses of diabetes medicines you currently take. Your doctor will adjust your dose as necessary and tell you exactly which strength of the medicine to take.

The recommended dose is one tablet twice a day. Your doctor will normally start Synjardy treatment by prescribing the strength of tablet that supplies the same dose of metformin you are already taking (850 mg or 1 000 mg twice a day), and the lowest dose of empagliflozin (5 mg twice a day). If you are already taking both medicines separately, your doctor will start treatment with tablets of Synjardy that will supply the same amount of both. If you have reduced kidney function, your doctor may prescribe a lower dose or decide to use an alternative medicine.

Taking this medicine
- Swallow the tablet whole with water.
- Take the tablets with meals to lower your chance of an upset stomach.
- Take the tablet twice daily by mouth.

Your doctor may prescribe Synjardy together with another diabetes medicine. Remember to take all medicines as directed by your doctor to achieve the best results for your health. Your doctor may need to adjust your doses to control your blood sugar.

Appropriate diet and exercise help your body use its blood sugar better. It is important to stay on the diet and exercise program recommended by your doctor while taking Synjardy.

If you take more Synjardy than you should
If you take more Synjardy tablets than you should have, you may experience lactic acidosis. Symptoms of lactic acidosis are non-specific such as feeling or being very sick, vomiting, stomach ache with muscle cramps, a general feeling of not being well with severe tiredness, and difficulty in breathing. Further symptoms are reduced body temperature and heartbeat. **If this happens to you, you may need immediate hospital treatment, as lactic acidosis can lead to coma. Stop taking this medicine immediately and contact a doctor or the nearest hospital straight away (see section 2). Take the medicine pack with you.**

If you forget to take Synjardy
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of this medicine.

If you stop taking Synjardy
Do not stop taking Synjardy without first consulting your doctor, unless you suspect you have diabetic ketoacidosis, lactic acidosis, or if you have a condition that may be associated with dehydration (see

section 2 “warnings and precautions”). Your blood sugar levels may increase when you stop taking Synjardy.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

Severe allergic reaction, seen with uncommon frequency (may affect up to 1 in 100 people)
Possible signs of severe allergic reaction may include:
- swelling of the face, lips, mouth, tongue, or throat that may lead to difficulty breathing or swallowing)

Lactic acidosis, seen very rarely (may affect up to 1 in 10 000 people)
Synjardy may cause a very rare but very serious side effect called lactic acidosis (see section 2). If this happens you must **stop taking Synjardy and contact a doctor or the nearest hospital immediately,** as lactic acidosis may lead to coma.

Diabetic ketoacidosis, seen rarely (may affect up to 1 in 1 000 people)
These are the signs of diabetic ketoacidosis (see section 2):
- increased levels of “ketone bodies” in your urine or blood
- rapid weight loss
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat.

This may occur regardless of blood glucose level. Your doctor may decide to temporarily or permanently stop your treatment with Synjardy.

Contact your doctor as soon as possible if you notice the following side effects:

Low blood sugar (hypoglycaemia), seen very commonly (may affect more than 1 in 10 people)
If you take Synjardy with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is increased. The signs of low blood sugar may include:
- shaking, sweating, feeling very anxious or confused, fast heart beat
- excessive hunger, headache

Your doctor will tell you how to treat low blood sugar levels and what to do if you get any of the signs above. If you have symptoms of low blood sugar, eat glucose tablets, a high sugar snack or drink fruit juice. Measure your blood sugar if possible and rest.

Urinary tract infection, seen commonly (may affect up to 1 in 10 people)
The signs of urinary tract infection are:
- burning sensation when passing urine
- urine that appears cloudy
- pain in the pelvis, or mid-back pain (when kidneys are infected)

An urge to pass urine or more frequent urination may be due to the way Synjardy works, but they can also be signs of urinary tract infection. If you note an increase in such symptoms, you should also contact your doctor.

Dehydration, seen uncommonly (may affect up to 1 in 100 people)
The signs of dehydration are not specific, but may include:
- unusual thirst
- lightheadedness or dizziness upon standing
- fainting or loss of consciousness

Other side effects while taking Synjardy:
Very common
- feeling sick (nausea), vomiting
- diarrhoea or stomach ache
- loss of appetite

Common
- genital yeast infection (thrush)
- passing more urine than usual or needing to pass urine more often
- itching
- rash or red skin – this may be itchy and include raised bumps, oozing fluid or blisters
- changes to the way things taste
- thirst
- blood tests may show an increase in blood fat (cholesterol) levels in your blood
- constipation
- decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.

Uncommon
- hives
- straining or pain when emptying the bladder
- blood tests may show a decrease in kidney function (creatinine or urea)
- blood tests may show increases in the amount of red blood cells in your blood (haematocrit)

Rare
- necrotising fasciitis of the perineum or Fournier´s gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus

Very rare
- abnormalities in liver function tests, inflammation of the liver (hepatitis)
- redness of the skin (erythema)
- inflammation of the kidneys (tubulointerstitial nephritis)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Synjardy

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the packaging is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Synjardy contains
The active substances are empagliflozin and metformin.
Each Synjardy 5 mg/850 mg film-coated tablet (tablet) contains 5 mg empagliflozin and 850 mg metformin hydrochloride.
Each Synjardy 5 mg/1 000 mg film-coated tablet (tablet) contains 5 mg empagliflozin and 1 000 mg metformin hydrochloride.
Each Synjardy 12.5 mg/850 mg film-coated tablet (tablet) contains 12.5 mg empagliflozin and 850 mg metformin hydrochloride.
Each Synjardy 12.5 mg/1 000 mg film-coated tablet (tablet) contains 12.5 mg empagliflozin and 1 000 mg metformin hydrochloride.

The other ingredient(s) are:
- Tablet core: maize starch, copovidone, colloidal anhydrous silica, magnesium stearate.
- Film coating: hypromellose, macrogol 400, titanium dioxide (E171), talc.
  Synjardy 5 mg/850 mg and Synjardy 5 mg/1 000 mg tablets also contain iron oxide yellow (E172). Synjardy 12.5 mg/850 mg and Synjardy 12.5 mg/1 000 mg tablets also contain iron oxide black (E172) and iron oxide red (E172).

What Synjardy looks like and contents of the pack
Synjardy 5 mg/850 mg film-coated tablets are yellowish white, oval, biconvex. They have "S5" and the Boehringer Ingelheim logo on one side and "850" on the other. The tablet is 19.2 mm long and has a width of 9.4 mm.
Synjardy 5 mg/1 000 mg film-coated tablets are brownish yellow, oval, biconvex. They have "S5" and the Boehringer Ingelheim logo on one side and "1 000" on the other. The tablet is 21.1 mm long and has a width of 9.7 mm.
Synjardy 12.5 mg/850 mg film-coated tablets are pinkish white, oval, biconvex. They have "S12" and the Boehringer Ingelheim logo on one side and "850" on the other. The tablet is 19.2 mm long and has a width of 9.4 mm.
Synjardy 12.5 mg/1 000 mg film-coated tablets are dark brownish purple, oval, biconvex. They have "S12" and the Boehringer Ingelheim logo on one side and "1 000" on the other. The tablet is 21.1 mm long and has a width of 9.7 mm.

The tablets are available in PVC/PVDC/aluminium perforated unit dose blisters. The pack sizes are 10 × 1, 14 × 1, 30 × 1, 56 × 1, 60 × 1, 90 × 1 and 100 × 1 film-coated tablets and multipacks containing 120 (2 packs of 60 × 1), 180 (2 packs of 90 × 1) and 200 (2 packs of 100 × 1) film-coated tablets.

Not all pack sizes may be marketed in your country.

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This leaflet was last revised in {**MM/YYYY**}.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.