

**Jardiance® Duo**  
**Empagliflozin and Metformin hydrochloride**

**DESCRIPTION**

Jardiance Duo 5/500: Orange yellow, oval, biconvex film-coated tablets, one side debossed with Boehringer Ingelheim company symbol and "S5", the other side is debossed with "500".

Jardiance Duo 12.5/500: Pale brownish purple, oval, biconvex film-coated tablets, one side debossed with Boehringer Ingelheim company symbol and "S12", the other side is debossed with "500".

Jardiance Duo 12.5/850: Pinkish white, oval, biconvex film-coated tablets, one side debossed with Boehringer Ingelheim company symbol and "S12", the other side is debossed with "850".

Jardiance Duo 12.5/1.000: Dark brownish purple, oval, biconvex film-coated tablets, one side debossed with Boehringer Ingelheim company symbol and "S12", the other side is debossed with "1000".

**COMPOSITION**

1 film-coated tablet contains:

D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S) (= empagliflozin) 5 or 12.5 mg  
and

N,N-dimethylimidodicarbonimidic diamide hydrochloride (= metformin hydrochloride) 500 mg, 850 mg, or 1000 mg

Excipient List :

- Core Tablet : Maize starch, Copovidone, Colloidal anhydrous silica, Magnesium stearate
- Film Coated : Hypromellose, Macrogol 400, Titanium dioxide, Talc
- Iron oxide yellow for Jardiance Duo 5 mg/500 mg film-coated tablets
- Iron oxide black for Jardiance Duo 12,5 mg/500 mg, Jardiance Duo 12,5 mg/850 mg and Jardiance Duo 12,5 mg/1000 mg film-coated tablets
- Iron oxide red for Jardiance Duo 12,5 mg/500 mg, Jardiance Duo 12,5 mg/850 mg and Jardiance Duo 12,5 mg/1000 mg film-coated tablets

**INDICATIONS**

Jardiance Duo is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control

- in patients inadequately controlled on their maximally tolerated dose of metformin alone
- 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 Special warnings and precautions, Interactions, and Pharmacological Properties

## **DOSAGE AND ADMINISTRATION**

Adults with normal renal function ( $\text{GFR} \geq 90\text{ml/min}$ )

The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability. The maximum recommended daily dose of Jardiance Duo 25 mg of empagliflozin and 2000 mg of metformin.

In patients not adequately controlled on metformin alone, the recommended starting dose of Jardiance Duo should provide empagliflozin 5 mg twice daily (10 mg total daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10 mg, the dose can be increased to a total daily dose of empagliflozin 25 mg.

- Patients already treated with empagliflozin should continue to take the same daily dose of empagliflozin.
- Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin to Jardiance Duo should receive the same daily dose of empagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

The recommended dose is one tablet twice daily.

For the different doses of metformin, Jardiance Duo is available in strengths of 5 mg empagliflozin plus 500 mg metformin hydrochloride or 12.5 mg empagliflozin plus 500 mg, 850 mg or 1000 mg metformin hydrochloride.

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

### Renal impairment

No dose adjustment is recommended for patients with mild renal impairment.

A GFR 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.

### 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 at the same time. In that case, the missed dose should be skipped.

#### Paediatric population

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

### **CONTRAINDICATIONS**

- Hypersensitivity to active ingredients empagliflozin and/or metformin or to any of the excipients (see section Composition)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Renally impaired patients with eGFR less than 45 mL/min/1,73m<sup>2</sup>, severe renal impairment, end-stage renal disease and patients on dialysis
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section Special warnings and precautions)
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (see section Interactions)
- Major surgery

### **SPECIAL WARNINGS AND PRECAUTIONS**

#### General

Jardiance Duo should not be used in patients with type 1 diabetes.

#### Diabetic ketoacidosis

Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 mg/dl).

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. If ketoacidosis is suspected, Jardiance Duo should be discontinued, patient should be evaluated, and prompt treatment should be instituted.

Diabetic ketoacidosis and glucosuria may be prolonged after discontinuation of Jardiance Duo in some patients, i.e. it may last longer than expected from 5 plasma half-lives of empagliflozin (see Pharmacokinetics)

Patients who may be at higher risk of ketoacidosis while taking Jardiance Duo include patients on a very low carbohydrate diet (as the combination may further increase ketone

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body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration, and patients with a history of ketoacidosis. Jardiance Duo should be used with caution in these patients. When reducing the insulin dose caution should be taken. In patients treated with Jardiance Duo consider monitoring for ketoacidosis and temporarily discontinuing Jardiance Duo in clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if Jardiance Duo treatment has been interrupted.

#### 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 section Contraindications and Interactions).

Patients and/or care-givers should be informed of the risk of lactic acidosis.

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin 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.

#### 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 Posology and Interactions.

#### Necrotizing fasciitis of the perineum (Fournier's gangrene)

Cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients treated

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with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Jardiance Duo who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, Jardiance Duo should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

#### Renal function

Due to the mechanism of action, the efficacy of empagliflozin is dependent on renal function. GFR should be assessed before treatment initiation and regularly thereafter, see section Posology. Jardiance Duo is contraindicated in patients with GFR<45 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section Contraindications.

#### Cardiac function

Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, Jardiance Duo may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, Jardiance Duo is contraindicated due to the metformin component (see section Contraindications).

#### Elderly patients

Patients aged 75 years and older may be at an increased risk of volume depletion, therefore, Jardiance Duo should be prescribed with caution in these patients (see section Side effects).

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Jardiance Duo should have their renal function monitored regularly.

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status.

#### Use in patients at risk for volume depletion

Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on 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 empagliflozin. Temporary interruption of treatment with Jardiance Duo should be considered until the fluid loss is corrected.

#### Urinary tract infections

In the pooled placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was higher in patients treated with empagliflozin 10 mg plus metformin as compared to patients treated with placebo plus metformin or empagliflozin 25 mg plus metformin (see section Side Effects).

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

#### Surgery

Jardiance Duo 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.

#### Elevated haematocrit

Haematocrit increase was observed with empagliflozin treatment

#### Urine laboratory assessments

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

#### Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. Discontinuation of Jardiance Duo may be considered in cases of recurrent urinary tract infections.

#### Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in a long-term clinical study with another SGLT2 inhibitor. The medicine in that study is not empagliflozin. However, it is unknown whether this constitutes a class effect. In a pooled safety analysis of 12,620 patients with T2DM the frequency of patients with lower limb amputations was similar between empagliflozin and placebo. In the largest placebo-controlled trial in 7020 patients (EMPA-REG OUTCOME trial), in which 88% of all the cases of amputations were reported, lower limb amputations occurred in 1.8% of patients treated with empagliflozin 10 mg, in 2.0% of patients treated with empagliflozin 25 mg, and in 1.8% of patients in the placebo arm. It is important to regularly examine the feet and counsel all diabetic patients on routine preventative footcare.

#### 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.

### Cardiac Failure

Experience in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV. In the EMPA-REG OUTCOME study, 10.1% of the patients were reported with cardiac failure at baseline. The reduction of cardiovascular death in these patients was consistent with the overall study population

### Vitamin B12 levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B12 supplementation. Measurement of haematologic parameters on an annual basis is advised in patients on Jardiance Duo and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

#### **Vitamin B12**

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.

### **USE IN SPECIFIC POPULATIONS**

#### 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. When the patient plans to become pregnant, and during pregnancy, it is recommended that diabetes is not treated with this medicinal product.

##### **Lactation**

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. It is unknown whether empagliflozin is excreted in human milk.

Available nonclinical data in animals have shown excretion of empagliflozin in milk. A risk to human newborns/infants cannot be excluded. It is recommended to discontinue breast feeding during treatment with Jardiance Duo.

### **Fertility**

No studies on the effect on human fertility have been conducted with Jardiance Duo or its individual components.

Non-clinical studies in animals with the individual components do not indicate direct or indirect harmful effects with respect to fertility.

### Driving and Using Machines

No studies on the effects on the ability to drive and use machines have been performed. Jardiance duo 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 Jardiance Duo is used in combination with a sulphonylurea and/or insulin.

## **INTERACTIONS**

### Empagliflozin

#### Pharmacodynamic Interactions

##### *Diuretics*

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

##### *Insulin Secretagogues*

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 Side effects). However, combination of Jardiance Duo with insulin or an insulin secretagogue is not indicated.

##### *Interference with 1,5-anhydroglucitol (1,5-AG) Assay*

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

#### Pharmacokinetic Interactions

##### *Lithium*

Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

#### *In vitro assessment of drug interactions*

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

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

#### *In vivo assessment of drug interactions*

No clinically meaningful pharmacokinetic interactions were observed when empagliflozin was coadministered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co-administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics were similar with and without co-administration of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, in healthy volunteers and with or without co-administration of torasemide and hydrochlorothiazide in patients with T2DM. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59%), rifampicin (35%), or probenecid (53%). These changes were not considered to be clinically meaningful

Empagliflozin had no clinically relevant effect on the pharmacokinetics of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

#### Metformin

Concomitant use not recommended

#### *Alcohol*

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

#### *Iodinated contrast agents*

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Jardiance Duo must be discontinued prior to or at the time of the imaging procedure and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see section Posology and Special warnings and precautions).

#### *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

#### *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, trimethoprim, 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.

#### **SIDE EFFECTS**

A total of 12245 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin plus metformin. In these trials 2910 patients received treatment with empagliflozin 10 mg plus metformin and 3699 patients treatment with empagliflozin 25 mg plus metformin for at least 24 weeks and 2151 or 2807 patients for at least 76 weeks. The overall safety profile of empagliflozin plus metformin for patients enrolled in the EMPA-REG OUTCOME study was comparable to the previously known safety profile.

Placebo-controlled, double-blind trials of 18 to 24 weeks of exposure included 3456 patients, of which 1271 were treated with empagliflozin 10 mg plus metformin and 1259 with empagliflozin 25 mg plus metformin.

The most frequently reported adverse event in clinical trials was hypoglycaemia, which depended on the type of background therapy used in the respective studies (see description of selected side effects).

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

**Table 1** Side effects reported in patients who received empagliflozin monotherapy or combination therapy of empagliflozin and metformin in placebo controlled double-blind studies of up to 24 weeks (regardless of investigator reported causality assessment), and side effects derived from postmarketing experience with empagliflozin monotherapy or combination therapy of empagliflozin and metformin, classified by MedDRA System organ class and MedDRA Preferred terms

| <u>System Organ class</u>               | Very Common                                                          | Common                                                                                                                                                                        | Uncommon                                                                                                                  | Rare                               | Very Rare                                                                | Not Known                                                                  |
|-----------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Infections and infestations             |                                                                      | Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection <sup>1, 2</sup><br>Urinary tract infection (including pyelonephritis and urosepsis) <sup>1, 2</sup> |                                                                                                                           |                                    |                                                                          | Necrotizing fasciitis of the perineum (Fournier's gangrene) <sup>2,6</sup> |
| Metabolism and nutrition disorders      | Hypoglycaemia (when used with sulphonylurea or insulin) <sup>1</sup> | Thirst <sup>2</sup><br>Vitamin B12 deficiency <sup>3, 4</sup>                                                                                                                 |                                                                                                                           | Diabetic Ketoacidosis <sup>a</sup> | Lactic acidosis <sup>3</sup>                                             |                                                                            |
| Nervous system disorders                |                                                                      | Taste disturbance <sup>3</sup>                                                                                                                                                |                                                                                                                           |                                    |                                                                          |                                                                            |
| Vascular disorders                      |                                                                      |                                                                                                                                                                               | Volume depletion <sup>1,2</sup>                                                                                           |                                    |                                                                          |                                                                            |
| Gastrointestinal disorders <sup>5</sup> | Gastrointestinal symptoms <sup>3, 5</sup>                            | Constipation                                                                                                                                                                  |                                                                                                                           |                                    |                                                                          |                                                                            |
| Hepatobiliary disorders                 |                                                                      |                                                                                                                                                                               |                                                                                                                           |                                    | Liver function tests abnormalities <sup>3</sup> , Hepatitis <sup>3</sup> |                                                                            |
| Skin and subcutaneous tissue disorders  |                                                                      | Pruritus (generalised) <sup>2, 3</sup><br>Rash                                                                                                                                | Urticaria                                                                                                                 |                                    | Erythema <sup>3</sup>                                                    | Angioedema                                                                 |
| Renal and urinary disorders             |                                                                      | Increased urination <sup>1,2</sup>                                                                                                                                            | Dysuria <sup>2</sup>                                                                                                      |                                    |                                                                          |                                                                            |
| Investigations                          |                                                                      | Serum lipids increased <sup>2,b</sup>                                                                                                                                         | Blood creatinine increased/<br>Glomerular filtration rate decreased <sup>1</sup><br>Haematocrit increased <sup>2, c</sup> |                                    |                                                                          |                                                                            |

1 See subsections below for additional information

2 Identified side effect of empagliflozin monotherapy

3 Identified side effect of metformin monotherapy

4 Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia)

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5 Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

6 Identified adverse reactions from postmarketing experience

a See section Special warning and precautions

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.

### Description of selected side effects

The frequencies below are calculated for side effects regardless of causality.

#### Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar to placebo for empagliflozin as add-on to metformin and as add-on to pioglitazone +/- metformin, and as add-on with linagliptin + metformin. The frequency of patients with hypoglycaemia was increased in patients treated with empagliflozin compared to placebo when given as add-on to metformin plus sulfonylurea, and as add-on to insulin +/- metformin and +/-sulfonylurea. (see Table 2 below)

#### 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 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 10mg, empagliflozin 25mg and placebo when added on to metformin and insulin, respectively. (see Table 2 below)

Table 2      Frequency of patients with confirmed hypoglycaemic events per trial and indication (1245.19, 1245.23(met), 1245.23(met+SU), 1245.33, 1245.49, 1276.1, 1276.10, 1275.9, and 1245.25 – TS<sup>1</sup>)

| Treatment group                                                                                                    | Placebo                        | Empagliflozin 10 mg     | Empagliflozin 25 mg                                     |
|--------------------------------------------------------------------------------------------------------------------|--------------------------------|-------------------------|---------------------------------------------------------|
| <b>In combination with metformin (1245.23 (met)) (24 weeks)</b>                                                    |                                |                         |                                                         |
| N                                                                                                                  | <b>206</b>                     | <b>217</b>              | <b>214</b>                                              |
| Overall confirmed (%)                                                                                              | 0.5%                           | 1.8%                    | 1.4%                                                    |
| Major (%)                                                                                                          | 0%                             | 0%                      | 0%                                                      |
| <b>In Combination with Metformin + Sulfonylurea (1245.23 (met + SU)) (24 weeks)</b>                                |                                |                         |                                                         |
| N                                                                                                                  | <b>225</b>                     | <b>224</b>              | <b>217</b>                                              |
| Overall confirmed (%)                                                                                              | 8.4%                           | 16.1%                   | 11.5%                                                   |
| Major (%)                                                                                                          | 0%                             | 0%                      | 0%                                                      |
| <b>In Combination with Pioglitazone +/- Metformin (1245.19) (24 weeks)</b>                                         |                                |                         |                                                         |
| N                                                                                                                  | <b>165</b>                     | <b>165</b>              | <b>168</b>                                              |
| Overall confirmed (%)                                                                                              | 1.8%                           | 1.2%                    | 2.4%                                                    |
| Major (%)                                                                                                          | 0%                             | 0%                      | 0%                                                      |
| <b>In Combination with Basal Insulin +/- Metformin +/-sulfonylurea (1245.33) (18 weeks<sup>2</sup> / 78 weeks)</b> |                                |                         |                                                         |
| N                                                                                                                  | <b>170</b>                     | <b>169</b>              | <b>155</b>                                              |
| Overall confirmed (%)                                                                                              | 20.6% / 35.3%                  | 19.5% / 36.1%           | 28.4% / 36.1%                                           |
| Major (%)                                                                                                          | 0% / 0%                        | 0% / 0%                 | 1.3% / 1.3%                                             |
| <b>In Combination with MDI Insulin +/-Metformin (1245.49) (18 weeks<sup>2</sup> / 52 weeks)</b>                    |                                |                         |                                                         |
| N                                                                                                                  | <b>188</b>                     | <b>186</b>              | <b>189</b>                                              |
| Overall confirmed (%)                                                                                              | 37.2% / 58.0%                  | 39.8% / 51.1%           | 41.3% / 57.7%                                           |
| Major (%)                                                                                                          | 0.5% / 1.6%                    | 0.5% / 1.6%             | 0.5% / 0.5%                                             |
| <b>Empagliflozin BID versus QD as add on to metformin (1276.10) (16 weeks)</b>                                     |                                |                         |                                                         |
|                                                                                                                    | <b>Placebo</b>                 | <b>Empa 10 mg</b>       | <b>Empa 25 mg</b>                                       |
| N                                                                                                                  | <b>107</b>                     | <b>439</b>              | <b>437</b>                                              |
| Overall confirmed (%)                                                                                              | 0.9%                           | 0.5%                    | 0.2%                                                    |
| Major (%)                                                                                                          | 0%                             | 0%                      | 0%                                                      |
| <b>In Combination with metformin in drug-naïve patients (1276.1<sup>3</sup>) (24 weeks)</b>                        |                                |                         |                                                         |
|                                                                                                                    | <b>Met 500/1000 mg<br/>BID</b> | <b>Empa 10/25 mg QD</b> | <b>Empa (5/12.5 mg) +<br/>Met (500/1000 mg)<br/>BID</b> |
| N                                                                                                                  | <b>341</b>                     | <b>339</b>              | <b>680</b>                                              |
| Overall confirmed (%)                                                                                              | 0.6%                           | 0.6%                    | 1.0%                                                    |
| Major (%)                                                                                                          | 0%                             | 0%                      | 0%                                                      |
| <b>In Combination with metformin and linagliptin (1275.9) (24 weeks)<sup>3</sup></b>                               |                                |                         |                                                         |
| N                                                                                                                  | <b>110</b>                     | <b>112</b>              | <b>110</b>                                              |
| Overall confirmed (%)                                                                                              | 0.9%                           | 0.0%                    | 2.7%                                                    |
| Major (%)                                                                                                          | 0%                             | 0%                      | 0.9%                                                    |
| <b>EMPA REG OUTCOME Study (1245.25)</b>                                                                            |                                |                         |                                                         |
|                                                                                                                    | <b>Placebo</b>                 | <b>Empa 10 mg</b>       | <b>Empa 25 mg</b>                                       |
| N                                                                                                                  | <b>2333</b>                    | <b>2345</b>             | <b>2342</b>                                             |
| Overall confirmed (%)                                                                                              | 27.9%                          | 28%                     | 27.6%                                                   |

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|           |      |      |      |
|-----------|------|------|------|
| Major (%) | 1.5% | 1.4% | 1.3% |
|-----------|------|------|------|

Confirmed: blood glucose  $\leq 70$  ml/dL or required assistance

Major: required assistance

<sup>1</sup>i.e. patients who had received at least one dose of study drug

<sup>2</sup>The dose of insulin as background medication was to be stable for the first 18 weeks

<sup>3</sup>Eight treatment arms: 4 combination treatments of empagliflozin (5 mg or 12.5 mg BID) and metformin (500 or 1000 mg BID) and treatment with the individual components of empagliflozin (10 mg or 25 mg QD) or metformin (500 mg or 1000 mg BID).

<sup>3</sup> This was a fixed-dose combination of empagliflozin with linagliptin 5 mg with a background treatment with metformin. (see also Clinical Trials section).

### Urinary tract infection

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

### Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg plus metformin (4.0%) and empagliflozin 25 mg plus metformin (3.9%) compared to placebo plus metformin (1.3%), and were reported more frequently for empagliflozin plus metformin compared to placebo in female patients. The difference in frequency was less pronounced in male patients. Genital tract infections were mild and moderate in intensity, none was severe in intensity.

Cases of phimosis/acquired phimosis have been reported concurrent with genital infections.

### Increased urination

As expected via its mechanism of action, increased urination (as assessed by PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin 10 mg plus metformin (3.0%) and empagliflozin 25 mg plus metformin (2.9%) compared to placebo plus metformin (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin, both on a background of metformin (<1%).

### Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was low and comparable to placebo (empagliflozin 10 mg plus metformin (0.6%), empagliflozin 25 mg plus metformin (0.3%) and placebo plus metformin (0.1%). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status of patients aged 75 years and older. In patients  $\geq 75$  years of age, volume

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depletion events have been reported in a single patient treated with empagliflozin 25 mg plus metformin.

#### Blood creatinine increased and glomerular filtration rate decreased

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between empagliflozin and placebo as add-on to metformin (blood creatinine increased: empagliflozin 10 mg 0.5%, empagliflozin 25 mg 0.1%, placebo 0.4%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.2%).

In these placebo-controlled, double-blind studies up to 24 weeks, initial transient increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0.02 mg/dL, empagliflozin 25 mg 0.02 mg/dL) and initial transient decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: empagliflozin 10 mg -1.46 mL/min/1.73m<sup>2</sup>, empagliflozin 25 mg -2.05 mL/min/1.73m<sup>2</sup>) have been observed. In the long term studies, these changes were generally reversible during continuous treatment or after drug discontinuation (see section Clinical Trials figure 6 for the eGFR course in the EMPA-REG outcome study).

#### **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 following contact: Telephone: +62 21 21684084 Or Email: [IDSafety@zelligpharma.com](mailto:IDSafety@zelligpharma.com)

#### **OVERDOSE**

During controlled clinical trials in healthy subjects, single doses of up to 800 mg empagliflozin, equivalent to 32 times the maximum recommended daily dose, were well tolerated.

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

#### Therapy

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

#### **PHARMACOLOGICAL PROPERTIES**

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD20

### Mode of Action

Jardiance Duo 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 is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an  $IC_{50}$  of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 ( $IC_{50}$  of 6278 nM), responsible for glucose absorption in the gut. Furthermore high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues.

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

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR. Through inhibition of SGLT-2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

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

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

The 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-B (HOMA- $\beta$ ) and proinsulin to insulin ratio were noted. In addition urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction.

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

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 hydrochloride may act via 3 mechanisms:

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

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

Metformin hydrochloride increases the transport capacity of all types of membrane GLUTs known to date.

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

### **Clinical Trials**

A total of 10224 patients with type 2 diabetes were treated in 9 double-blind, placebo- or active-controlled clinical studies of at least 24 weeks duration, of which 2947 patients received empagliflozin 10 mg and 3703 received empagliflozin 25 mg as add-on to metformin therapy.

Treatment with empagliflozin in combination with metformin with or without other background (pioglitazone, sulfonylurea, DPP-4 inhibitors, and insulin) led to clinically relevant improvements in HbA<sub>1c</sub>, fasting plasma glucose, body weight, systolic and diastolic blood pressure. Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA<sub>1c</sub> goal of < 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. There was a clinically meaningful improvement in HbA<sub>1c</sub> in all subgroups of gender, race, geographic region, time since diagnosis of T2DM and body mass index (BMI). In patients aged 75 years and older, numerically lower reductions in HbA<sub>1c</sub> were observed with empagliflozin treatment. Higher baseline HbA<sub>1c</sub> was associated with a greater reduction in HbA<sub>1c</sub>. Empagliflozin in combination with metformin in drug-naïve patients led to clinically meaningful reductions in HbA<sub>1c</sub>, FPG, body weight and BP.

### ***Empagliflozin as add on to metformin therapy***

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients not sufficiently treated with metformin. Treatment with empagliflozin resulted in statistically significant improvements in HbA<sub>1c</sub> and body weight, and clinically meaningful reductions in FPG and blood pressure compared to placebo (Table 3).

In the double-blind placebo-controlled extension of this study, reductions of HbA<sub>1c</sub> (change from baseline of -0.62% for empagliflozin 10 mg, -0.74% for empagliflozin 25 mg and -0.01% for placebo), body weight (change from baseline of -2.39 kg for empagliflozin 10 mg, -2.65 kg for empagliflozin 25 mg and -0.46 kg for placebo) and blood pressure (SBP: change from baseline of -5.2 mmHg for empagliflozin 10 mg, -4.5 mmHg for empagliflozin 25 mg and -0.8

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mmHg for placebo, DBP: change from baseline of -2.5 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg and -0.5 mmHg for placebo) were sustained up to Week 76.

Table 3 Results of a 24-week (LOCF)<sup>3</sup> placebo-controlled study of empagliflozin as add-on to metformin (Full Analysis Set)

| <b>Empagliflozin as add-on to metformin therapy</b>                            | <b>Placebo</b> | <b>Empagliflozin 10 mg</b>                    | <b>Empagliflozin 25 mg</b>                    |
|--------------------------------------------------------------------------------|----------------|-----------------------------------------------|-----------------------------------------------|
| N                                                                              | 207            | 217                                           | 213                                           |
| <b>HbA1c (%)</b>                                                               |                |                                               |                                               |
| Baseline (mean)                                                                | 7.90           | 7.94                                          | 7.86                                          |
| Change from baseline <sup>1</sup>                                              | -0.13          | -0.70                                         | -0.77                                         |
| Difference from placebo <sup>1</sup> (97.5% CI)                                |                | -0.57* (-0.72, -0.42)                         | -0.64* (-0.79, -0.48)                         |
| N                                                                              | 184            | 199                                           | 191                                           |
| <b>Patients (%) achieving HbA1c &lt;7% with baseline HbA1c ≥7%<sup>2</sup></b> | 12.5           | 37.7                                          | 38.7                                          |
| N                                                                              | 207            | 216                                           | 213                                           |
| <b>FPG (mg/dL) [mmol/l]<sup>2</sup></b>                                        |                |                                               |                                               |
| Baseline (mean)                                                                | 156.0 [8.66]   | 154.6 [8.58]                                  | 149.4 [8.29]                                  |
| Change from baseline <sup>1</sup>                                              | 6.4 [0.35]     | -20.0 [-1.11]                                 | -22.3 [-1.24]                                 |
| Difference from placebo <sup>1</sup> (95% CI)                                  |                | -26.4* (-31.3, -21.6) [-1.47* (-1.74, -1.20)] | -28.7* (-33.6, -23.8) [-1.59* (-1.86, -1.32)] |
| N                                                                              | 207            | 217                                           | 213                                           |
| <b>Body Weight (kg)</b>                                                        |                |                                               |                                               |
| Baseline (mean)                                                                | 79.73          | 81.59                                         | 82.21                                         |
| Change from baseline <sup>1</sup>                                              | -0.45          | -2.08                                         | -2.46                                         |
| Difference from placebo <sup>1</sup> (97.5% CI)                                |                | -1.63* (-2.17, -1.08)                         | -2.01* (-2.56, -1.46)                         |
| N                                                                              | 207            | 217                                           | 213                                           |
| <b>Patients (%) achieving weight loss of &gt;5%<sup>2</sup></b>                | 4.8            | 21.2                                          | 23.0                                          |
| N                                                                              | 207            | 217                                           | 213                                           |
| <b>SBP (mmHg)<sup>2</sup></b>                                                  |                |                                               |                                               |
| Baseline (mean)                                                                | 128.6          | 129.6                                         | 130.0                                         |
| Change from baseline <sup>1</sup>                                              | -0.4           | -4.5                                          | -5.2                                          |
| Difference from placebo <sup>1</sup> (95% CI)                                  |                | -4.1* (-6.2, -2.1)                            | -4.8* (-6.9, -2.7)                            |

<sup>1</sup> mean adjusted for baseline value and stratification

<sup>2</sup> not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

<sup>3</sup> Last observation (prior to glycaemic rescue) carried forward (LOCF)

\*p-value <0.0001

#### ***Empagliflozin 2-year data, as add on to metformin in comparison to glimepiride***

In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (4 mg) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA<sub>1c</sub>, and a clinically meaningful reduction in FPG, compared to glimepiride (Table 4). Empagliflozin daily resulted in a

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statistically significant reduction in body weight, systolic and diastolic blood pressure (change from baseline in DBP of -1.8 mmHg for empagliflozin and +0.9 mmHg for glimepiride,  $p < 0.0001$ ).

Treatment with empagliflozin resulted in statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride,  $p < 0.0001$ ).

Table 4 Results at 104 week (LOCF)<sup>4</sup> in an active controlled study comparing empagliflozin to glimepiride as add on to metformin (Full Analysis Set)

| <b>Empagliflozin as add-on to metformin therapy in comparison to glimepiride</b> | <b>Empagliflozin 25 mg</b> | <b>Glimepiride (up to 4 mg)</b> |
|----------------------------------------------------------------------------------|----------------------------|---------------------------------|
| N                                                                                | 765                        | 780                             |
| <b>HbA1c (%)</b>                                                                 |                            |                                 |
| Baseline (mean)                                                                  | 7.92                       | 7.92                            |
| Change from baseline <sup>1</sup>                                                | -0.66                      | -0.55                           |
| Difference from glimepiride <sup>1</sup> (97.5% CI)                              | -0.11* (-0.20, -0.01)      |                                 |
| N                                                                                | 690                        | 715                             |
| <b>Patients (%) achieving HbA1c &lt;7% with baseline HbA1c ≥7%<sup>2</sup></b>   | 33.6                       | 30.9                            |
| N                                                                                | 764                        | 779                             |
| <b>FPG (mg/dL)<sup>2</sup></b>                                                   |                            |                                 |
| Baseline (mean)                                                                  | 150.00                     | 149.82                          |
| Change from baseline <sup>1</sup>                                                | -15.36                     | -2.98                           |
| Difference from glimepiride <sup>1</sup> (95% CI)                                | -12.37** (-15.47,-9.27)    |                                 |
| N                                                                                | 765                        | 780                             |
| <b>Body Weight (kg)</b>                                                          |                            |                                 |
| Baseline (mean)                                                                  | 82.52                      | 83.03                           |
| Change from baseline <sup>1</sup>                                                | -3.12                      | 1.34                            |
| Difference from glimepiride <sup>1</sup> (97.5% CI)                              | -4.46** (-4.87, -4.05)     |                                 |
| N                                                                                | 765                        | 780                             |
| <b>Patients(%) achieving weight loss of &gt;5%<sup>2</sup></b>                   | 27.5                       | 3.8%                            |
| N                                                                                | 765                        | 780                             |
| <b>SBP (mmHg)<sup>3</sup></b>                                                    |                            |                                 |
| Baseline (mean)                                                                  | 133.4                      | 133.5                           |
| Change from baseline <sup>1</sup>                                                | -3.1                       | 2.5                             |
| Difference from glimepiride <sup>1</sup> (97.5% CI)                              | -5.6** (-7.0,-4.2)         |                                 |

<sup>1</sup> Mean adjusted for baseline value and stratification

<sup>2</sup> Not evaluated for statistical significance; not part of the sequential testing procedure for the secondary endpoints

<sup>3</sup> LOCF, values after antihypertensive rescue censored

<sup>4</sup> Last observation (prior to glycaemic rescue) carried forward (LOCF)

\* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority

\*\* p-value <0.0001

#### ***Empagliflozin twice daily versus once daily as add on to metformin therapy***

The efficacy and safety of empagliflozin twice daily versus once daily (daily dose of 10 mg and 25 mg) as add-on therapy in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo-controlled study of 16 weeks

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duration. All treatments with empagliflozin resulted in significant reductions in HbA<sub>1c</sub> from baseline (total mean 7.8%) after 16 weeks of treatment compared with placebo. Empagliflozin twice daily dose regimens led to comparable reductions in HbA<sub>1c</sub> versus once daily dose regimens with a treatment difference in HbA<sub>1c</sub> reductions from baseline to week 16 of -0.02% (95% CI -0.16, 0.13) for empagliflozin 5 mg twice daily vs. 10 mg once daily, and -0.11% (95% CI -0.26, 0.03) for empagliflozin 12.5 mg twice daily vs. 25 mg once daily.

#### 2-hour postprandial glucose

Treatment with empagliflozin as add-on to metformin resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin, placebo (n=57): +5.9 mg/dL, empagliflozin 10 mg (n=52): -46.0 mg/dl, empagliflozin 25 mg (n=58): -44.6 mg/dL.

#### Patients with baseline HbA<sub>1c</sub> ≥9%

In a pre-specified analysis of subjects with baseline HbA<sub>1c</sub> ≥9.0%, treatment with empagliflozin 10 mg or 25 mg as add-on to metformin resulted in statistically significant reductions in HbA<sub>1c</sub> at Week 24 (adjusted mean change from baseline of -1.49% for empagliflozin 25 mg, -1.40% for empagliflozin 10 mg, and -0.44% for placebo).

#### Body weight

In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin (68% of all patients were on metformin background) resulted in body weight reduction compared to placebo at week 24 (-2.04 kg for empagliflozin 10 mg, -2.26 kg for empagliflozin 25 mg and -0.24 kg for placebo) that was maintained up to week 52 (-1.96 kg for empagliflozin 10 mg, -2.25 kg for empagliflozin 25 mg and -0.16 kg for placebo).

#### Blood pressure

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo-controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic (67.8% treated with metformin with or without other antidiabetic drugs including insulin) and up to 2 antihypertensive therapies (Table 5). Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA<sub>1c</sub>, 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin provided reductions in seated SBP (change from baseline of -0.67 mmHg for placebo, -4.60 mmHg for empagliflozin 10 mg and -5.47 mmHg for empagliflozin 25 mg) and seated DBP (change from baseline of -1.13 mmHg for placebo, -3.06 mmHg for empagliflozin 10 mg and -3.02 mmHg for empagliflozin 25 mg).

Table 5 Results at 12 week (LOCF)<sup>3</sup> in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)

|                                        | Placebo | Empagliflozin<br>10 mg | Empagliflozin 25<br>mg |
|----------------------------------------|---------|------------------------|------------------------|
| N                                      | 271     | 276                    | 276                    |
| <b>HbA<sub>1c</sub> (%) at week 12</b> |         |                        |                        |
| Baseline (mean)                        | 7.90    | 7.87                   | 7.92                   |
| Change from baseline <sup>1</sup>      | 0.03    | -0.59                  | -0.62                  |

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|                                                  |        |                             |                            |
|--------------------------------------------------|--------|-----------------------------|----------------------------|
| Difference from placebo <sup>1</sup><br>(95% CI) |        | -0.62* (-0.72, -<br>0.52)   | -0.65* (-0.75, -<br>0.55)  |
| <b>24 hour SBP at week 12<sup>2</sup></b>        |        |                             |                            |
| Baseline (mean)                                  | 131.72 | 131.34                      | 131.18                     |
| Change from baseline <sup>1</sup>                | 0.48   | -2.95                       | -3.68                      |
| Difference from placebo <sup>1</sup><br>(95% CI) |        | -3.44* (-4.78, -<br>2.09)   | -4.16* (-5.50, -<br>2.83)  |
| <b>24 hour DBP at week 12<sup>2</sup></b>        |        |                             |                            |
| Baseline (mean)                                  | 75.16  | 75.13                       | 74.64                      |
| Change from baseline <sup>1</sup>                | 0.32   | -1.04                       | -1.40                      |
| Difference from placebo <sup>1</sup><br>(95% CI) |        | -1.36** (-2.15, -<br>-0.56) | -1.72* (-2.51, -<br>-0.93) |

<sup>1</sup> Mean adjusted for baseline value and stratification

<sup>2</sup> Last observation (prior to antihypertensive rescue ) carried forward (LOCF) LOCF, values after antihypertensive rescue censored value

<sup>3</sup> Last observation (prior to glycaemic rescue ) carried forward (LOCF)

\* p-value <0.0001

\*\* p-value =0.0008

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 76.

### **Cardiovascular outcome**

The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomized, double-blind, placebo-controlled trial investigating the effect of empagliflozin as adjunct to standard care therapy in reducing cardiovascular events in patients with type 2 diabetes and one or more cardiovascular risk factors, including coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), or history of stroke. The primary endpoint was the time to first event in the composite of CV death, nonfatal MI, or non-fatal stroke (Major Adverse Cardiovascular Events (MACE-3). Additional pre-specified endpoints addressing clinically relevant outcomes tested in an exploratory manner included CV death, the composite of heart failure requiring hospitalization or CV death, all-cause mortality and the composite of new or worsening nephropathy.

A total of 7020 patients were treated with empagliflozin (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years.

The population was 72.4% Caucasian, 21.6% Asian, and 5.1% Black. The mean age was 63 years and 71.5% were male. At baseline, approximately 81% of patients were being treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 89% with anticoagulants, and 81% with lipid lowering medication. Approximately 74% of patients were being treated with metformin at baseline, 48% with insulin and 43% with sulphonylurea.

About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m<sup>2</sup>, 17.8% of 45-60 ml/min/1.73 m<sup>2</sup> and 7.7% of 30-45 ml/min/1.73 m<sup>2</sup>. Mean systolic BP was 136 mmHg, diastolic BP 76 mmHg, LDL 86 mg/dL, HDL 44 mg/dL, and urinary albumin to creatinine ratio (UACR) 175 mg/g at baseline.

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**Reductions in risk of CV death and overall mortality**

Empagliflozin is superior in reducing the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke compared to placebo. The treatment effect reflected a reduction in cardiovascular death with no significant change in non-fatal MI, or non-fatal stroke (Table 6 and Figure 1).

Empagliflozin also improved overall survival (Table 6 and Figure 2), which was driven by a reduction in cardiovascular death with empagliflozin. There was no statistically significant difference between empagliflozin and placebo in non-cardiovascular mortality.

Table 6 Treatment effect for the primary composite endpoint, its components and mortality (Treated Set\*)

|                                                                                                  | Placebo    | Empagliflozin<br>(10 and 25 mg,<br>pooled) |
|--------------------------------------------------------------------------------------------------|------------|--------------------------------------------|
| N                                                                                                | 2333       | 4687                                       |
| <b><u>Time to first occurrence of CV death,<br/>non-fatal MI, or non-fatal stroke) N (%)</u></b> | 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                                     |
| <b><u>CV Death N (%)</u></b>                                                                     | 137 (5.9)  | 172 (3.7)                                  |
| Hazard ratio vs. placebo (95% CI)                                                                |            | 0.62 (0.49, 0.77)                          |
| p-value                                                                                          |            | <0.0001                                    |
| <b><u>Non-fatal MI N (%)</u></b>                                                                 | 121 (5.2)  | 213 (4.5)                                  |
| Hazard ratio vs. placebo (95% CI)                                                                |            | 0.87 (0.70, 1.09)                          |
| p-value                                                                                          |            | 0.2189                                     |
| <b><u>Non-fatal stroke N (%)</u></b>                                                             | 60 (2.6)   | 150 (3.2)                                  |
| Hazard ratio vs. placebo (95% CI)                                                                |            | 1.24 (0.92, 1.67)                          |
| p-value                                                                                          |            | 0.1638                                     |
| <b><u>All-cause mortality N (%)</u></b>                                                          | 194 (8.3)  | 269 (5.7)                                  |
| Hazard ratio vs. placebo (95% CI)                                                                |            | 0.68 (0.57, 0.82)                          |
| p-value                                                                                          |            | <0.0001                                    |
| <b><u>Non-CV mortality N (%)</u></b>                                                             | 57 (2.4)   | 97 (2.1)                                   |
| Hazard ratio vs. placebo (95% CI)                                                                |            | 0.84 (0.60, 1.16)                          |

\* i.e. patients who had received at least one dose of study drug

\*\*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 CV death

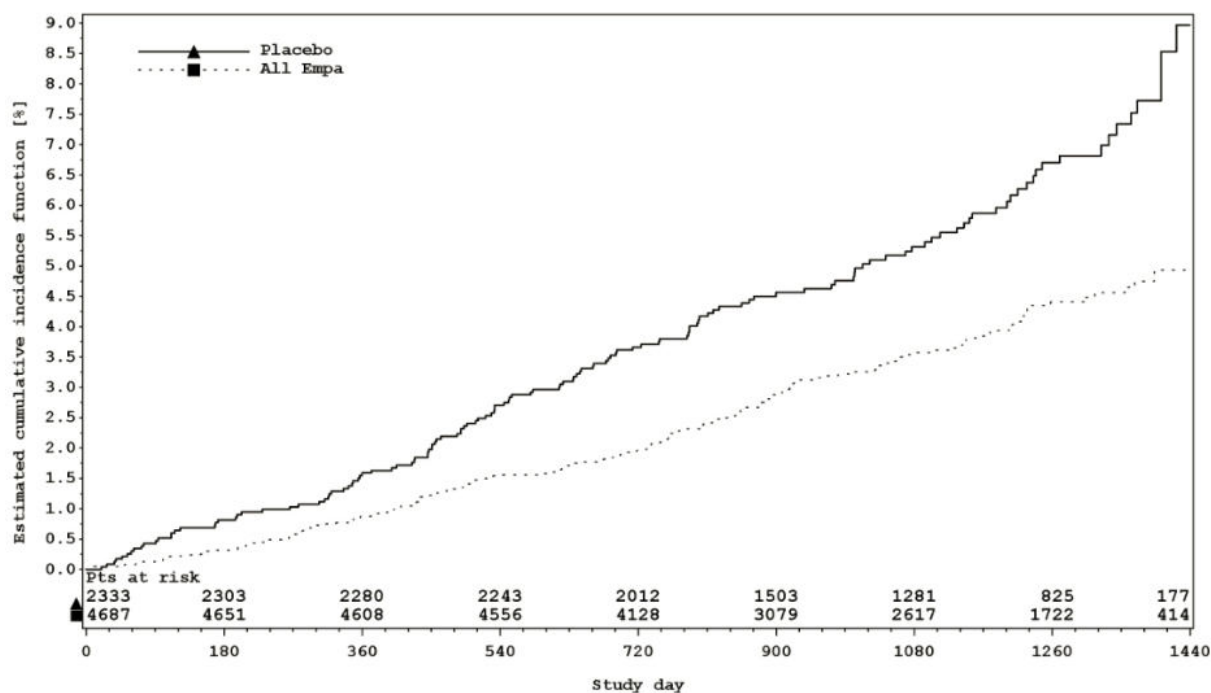
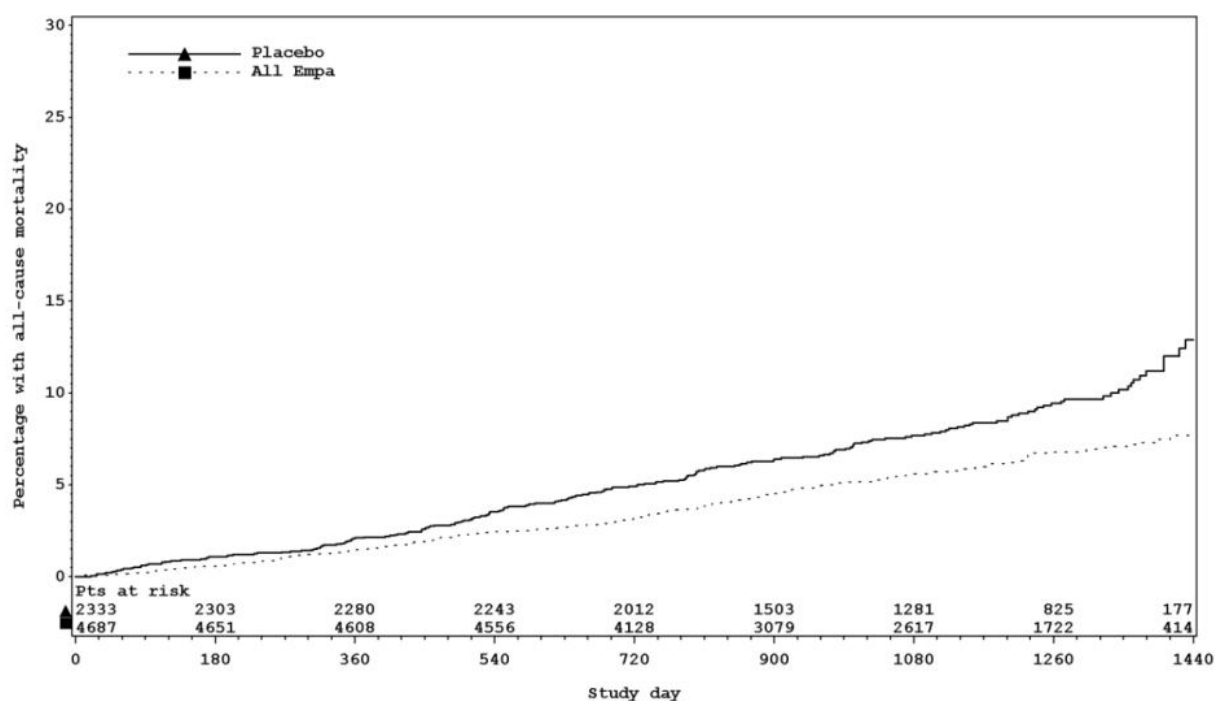


Figure 2 Time to occurrence of all-cause mortality\*



\*Kaplan-Meier estimate of time to all cause-mortality, pooled empagliflozin vs. placebo – treated set

**Reductions in risk of heart failure requiring hospitalization or CV death**

Empagliflozin is superior in reducing the risk of hospitalization for heart failure and cardiovascular death or hospitalization for heart failure compared with placebo (Table 7 and Figure 3).

Table 7 Treatment effect for hospitalization for heart failure or cardiovascular death (excluding fatal stroke) (Treated Set\*)

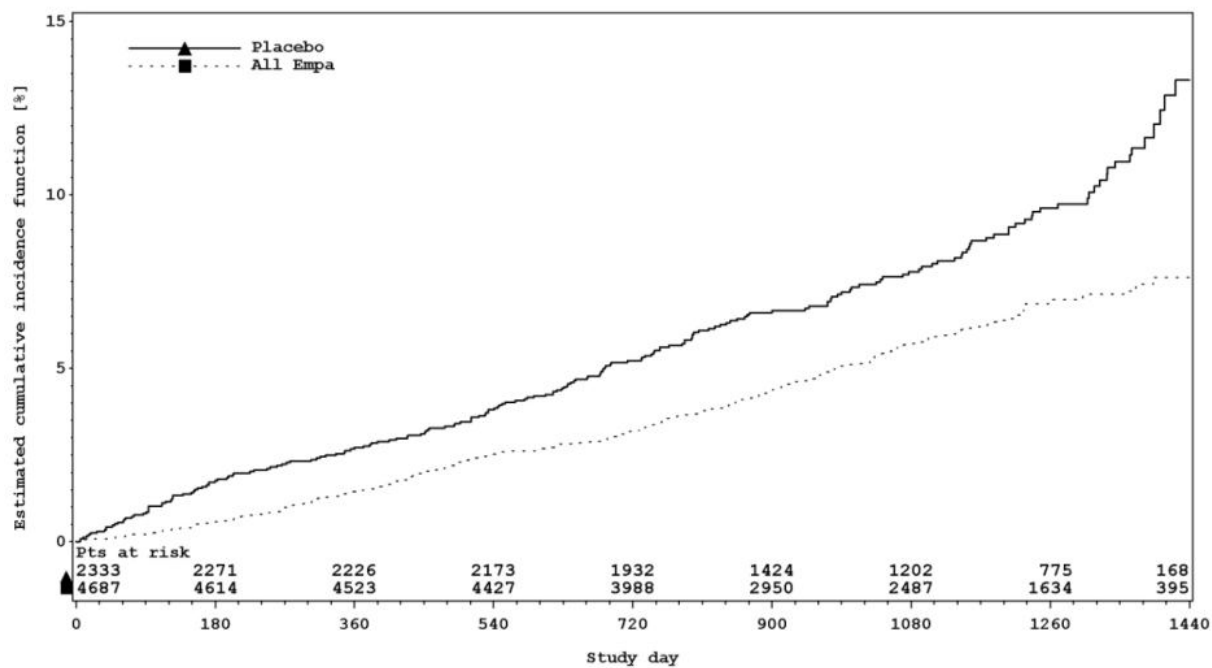
|                                                                                                  | Placebo   | Empagliflozin**<br>(10 and 25 mg,<br>pooled) |
|--------------------------------------------------------------------------------------------------|-----------|----------------------------------------------|
| N                                                                                                | 2333      | 4687                                         |
| <b>Heart failure requiring hospitalisation or<br/>CV death (excluding fatal stroke) N (%)***</b> | 198 (8.5) | 265 (5.7)                                    |
| HR (95% CI)                                                                                      |           | 0.66 (0.55, 0.79)                            |
| p-value                                                                                          |           | <0.0001                                      |
| <b>Heart failure requiring hospitalization N<br/>(%)</b>                                         | 95 (4.1)  | 126 (2.7)                                    |
| HR (95% CI)                                                                                      |           | 0.65 (0.50, 0.85)                            |
| p-value                                                                                          |           | 0.0017                                       |
| <b>CV death (excluding fatal stroke) N (%)</b>                                                   | 126 (5.4) | 156 (3.3)                                    |
| HR (95% CI)                                                                                      |           | 0.61 (0.48, 0.77)                            |
| p-value                                                                                          |           | <0.0001                                      |

\*i.e. patients who had received at least one dose of study drug

\*\*empagliflozin 10 mg and 25 mg showed consistent results

\*\*\* time to first event

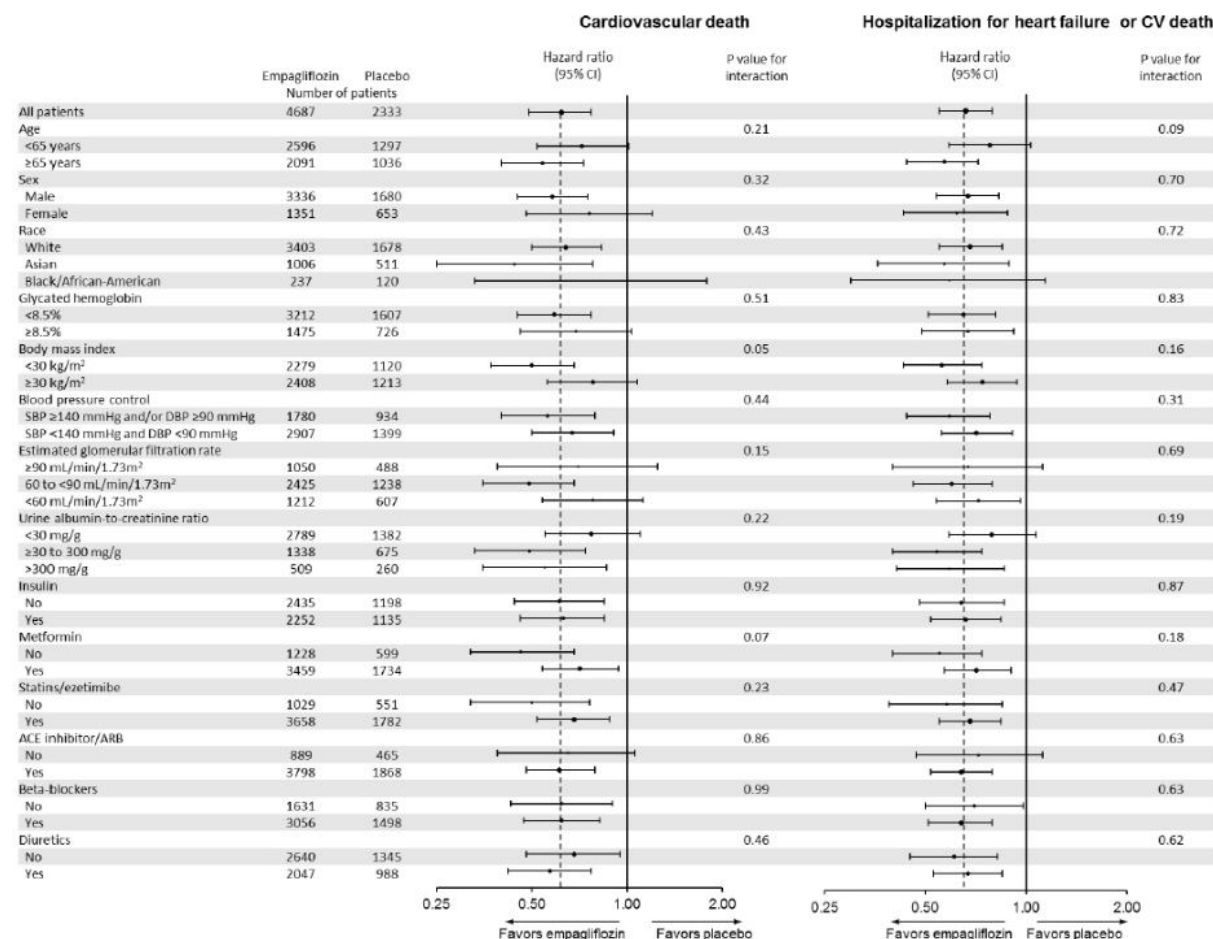
Figure 3 Time to first occurrence of first heart failure hospitalization or CV death\*



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

The cardiovascular benefits of empagliflozin observed were consistent across the subgroups depicted in Figure 4.

Figure 4 Subgroup analyses for CV death and hospitalization for heart failure or CV death\*,\*\*



\* Hospitalization for heart failure or CV death excludes fatal stroke

\*\*p-value is for test of homogeneity of treatment group difference among subgroups (test for group by covariate interaction) with no adjustment for multiple tests and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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

### Diabetic kidney disease

In the EMPA-REG OUTCOME study population, the risk of new or worsening nephropathy (defined as onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e. hemodialysis)) was significantly reduced in empagliflozin group compared to placebo (Table 8 and Figure 5).

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Empagliflozin compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1.82, 95% CI 1.40, 2.37).

Table 8 Time to first new or worsening of nephropathy (Treated Set\*)

|                                                                 | Placebo    | Empagliflozin<br>(10 and 25 mg,<br>pooled) |
|-----------------------------------------------------------------|------------|--------------------------------------------|
| N                                                               | 2061       | 4124                                       |
| <b>New or worsening nephropathy N (%)</b>                       | 388 (18.8) | 525 (12.7)                                 |
| HR (95% CI)                                                     |            | 0.61 (0.53, 0.70)                          |
| p-value                                                         |            | <0.0001                                    |
| N                                                               | 2323       | 4645                                       |
| <b>Doubling of serum creatinine level**N (%)</b>                | 60 (2.6)   | 70 (1.5)                                   |
| HR (95% CI)                                                     |            | 0.56 (0.39, 0.79)                          |
| p-value                                                         |            | 0.0009                                     |
| N                                                               | 2033       | 4091                                       |
| <b>New onset of macroalbuminuria*** N (%)</b>                   | 330 (16.2) | 459 (11.2)                                 |
| HR (95% CI)                                                     |            | 0.62 (0.54, 0.72)                          |
| p-value                                                         |            | <0.0001                                    |
| N                                                               | 2333       | 4687                                       |
| <b>Initiation of continuous renal replacement therapy N (%)</b> | 14 (0.6)   | 13 (0.3)                                   |
| HR (95% CI)                                                     |            | 0.45 (0.21, 0.97)                          |
| p-value                                                         |            | 0.0409                                     |
| N                                                               | 2333       | 4687                                       |
| <b>Death due to renal disease N (%)****</b>                     | 0          | 3 (0.1)                                    |

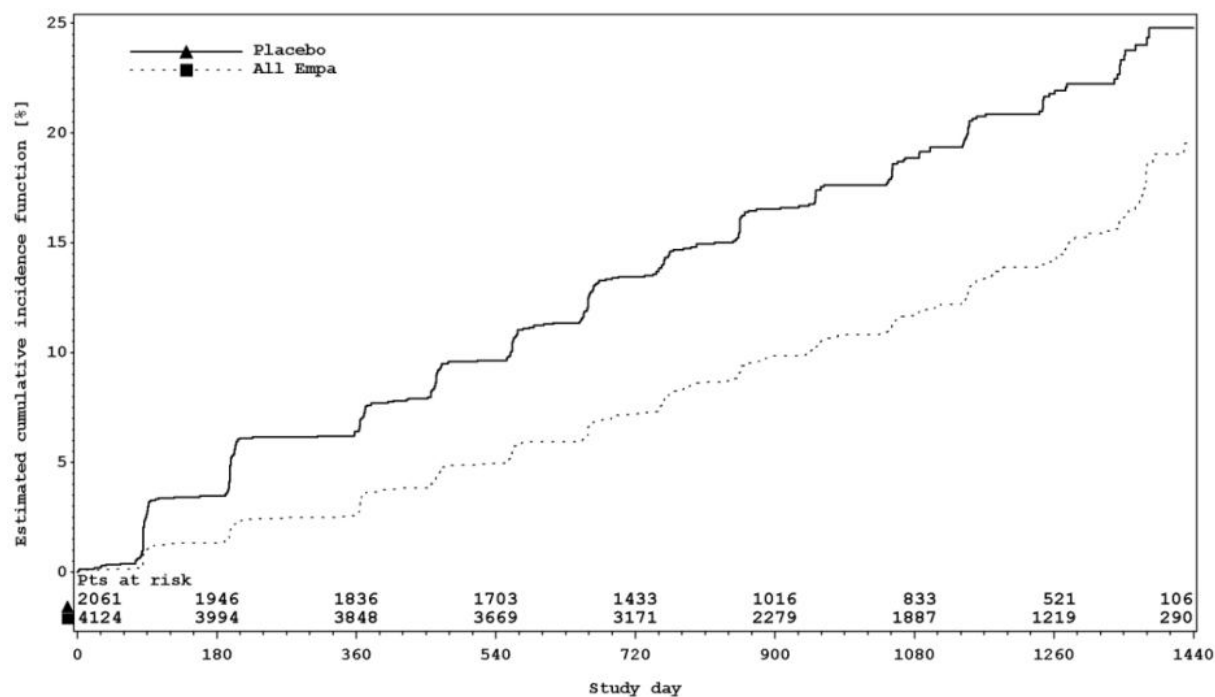
\*i.e. patients who had received at least one dose of study drug

\*\*Accompanied by an eGFR  $\leq 45$  mL/min/1.73m<sup>2</sup>

\*\*\* Urine Albumin Creatinine Ratio >300 mg/g

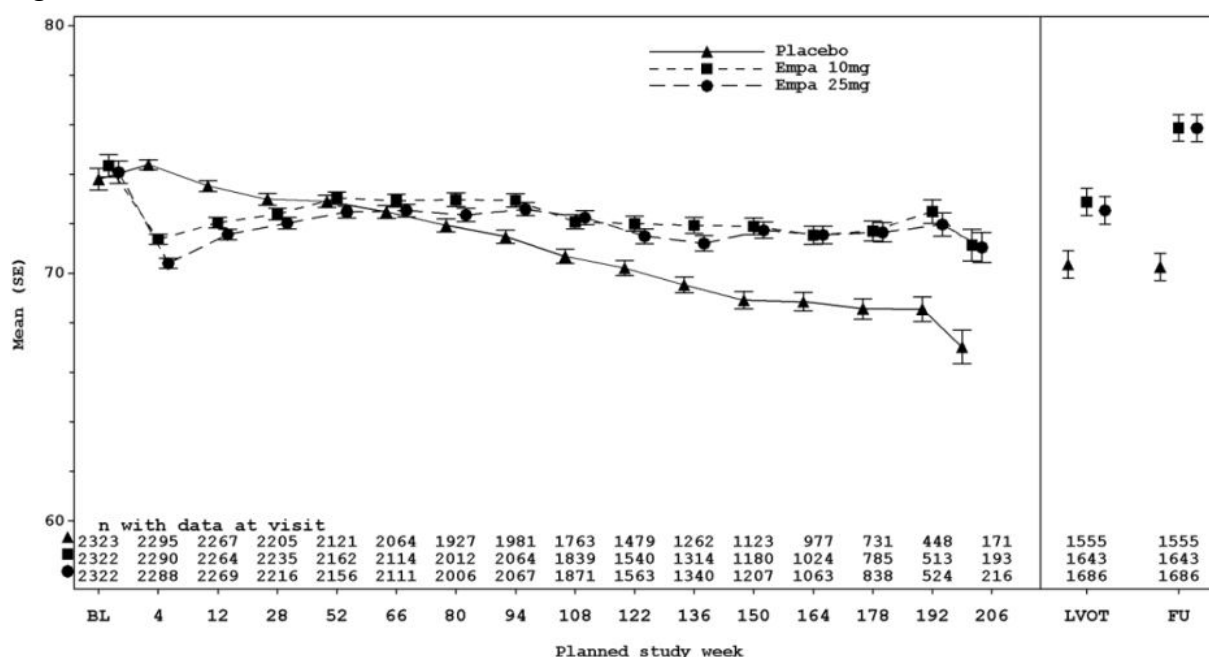
\*\*\* \*Due to low event rate, HR not calculated

Figure 5 Time to first new or worsening of nephropathy



Treatment with empagliflozin preserved eGFR and eGFR increased during the post treatment 4-week follow up. However, the placebo group showed a gradual decline in GFR during the course of the study with no further change during 4-week follow up. (see Figure 6)

Figure 6 eGFR over time\*



\*eGFR (MDRD) (mL/min/1.73m<sup>2</sup>) MMRM results over time, unadjusted last value on treatment and follow-up value - treated set – right side based on patients with available last value on treatment (LVOT) and follow-up (FU).

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

#### Thorough QTc study

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

#### Pharmacokinetics

##### Jardiance Duo

The results of bioequivalence studies in healthy subjects demonstrated that Jardiance Duo (empagliflozin/metformin hydrochloride) 5 mg/500 mg, 5 mg/850 mg, 5 mg/1000 mg, 12.5 mg/500 mg, 12.5 mg/850 mg, and 12.5 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5 mg empagliflozin/1000 mg metformin under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in C<sub>max</sub> for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and C<sub>max</sub> 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, Jardiance Duo is also proposed to be given with food.

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The following data are findings in studies performed with empagliflozin or metformin individually.

### **Empagliflozin**

#### *Absorption*

The pharmacokinetics of empagliflozin have been extensively characterized in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median  $t_{\max}$  1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and  $C_{\max}$  were 1870 nmol.h/L and 259 nmol/L with empagliflozin 10 mg and 4740 nmol.h/L and 687 nmol/L with empagliflozin 25 mg once daily, respectively. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes mellitus.

The pharmacokinetics of 5 mg empagliflozin twice daily and 10 mg empagliflozin once daily were compared in healthy subjects. Overall exposure (AUCss) of empagliflozin over a 24-hour period with 5 mg administered twice daily was similar to 10 mg administered once daily. As expected, empagliflozin 5 mg administered twice daily compared with 10 mg empagliflozin once daily resulted in lower  $C_{\max}$  and higher trough plasma empagliflozin concentrations ( $C_{\min}$ ).

Administration of 25 mg empagliflozin after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and  $C_{\max}$  decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

#### *Distribution*

The apparent steady-state volume of distribution was estimated to be 73.8 L, based on a population pharmacokinetic analysis. Following administration of an oral [ $^{14}\text{C}$ ]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

#### *Metabolism*

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

### *Elimination*

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. 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 [<sup>14</sup>C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

### Specific Populations

#### *Renal Impairment*

In patients with mild (eGFR: 60 - <90 mL/min/1.73 m<sup>2</sup>), moderate (eGFR: 30 - <60 mL/min/1.73 m<sup>2</sup>), severe (eGFR: <30 mL/min/1.73 m<sup>2</sup>) renal impairment and patients with kidney failure/ESRD patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. In line with the Phase I study, the population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal insufficiency.

#### *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<sub>max</sub> by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function. Based on pharmacokinetics, no dosage adjustment is recommended in patients with hepatic impairment.

#### *Body Mass Index (BMI)*

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

#### *Gender*

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

### *Race*

No dosage adjustment is necessary based on race. Based on the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m<sup>2</sup> compared to non-Asian patients with a BMI of 25 kg/m<sup>2</sup>.

### *Geriatric*

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

### *Paediatric*

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

## **Metformin**

### *Absorption*

After an oral dose of metformin, T<sub>max</sub> is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption are non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin hydrochloride plasma levels (C<sub>max</sub>) did not exceed 5 µg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

### *Distribution*

Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

### *Metabolism*

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

### *Elimination*

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Renal clearance of metformin hydrochloride is >400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

#### Special populations

##### *Renal impairment*

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section Dosage and administration).

##### *Paediatric*

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

Multiple dose study: 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.

## **TOXICOLOGY**

#### Empagliflozin and metformin

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and metformin. In a 13 week combination study with empagliflozin and metformin in rats the No-observed-adverse-effect-level (NOAEL) was based on hypochloremia seen at exposures of approximately 24- and 9-times the clinical AUC exposure of empagliflozin associated with the 10 and 25 mg doses, 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 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose. At dose levels of 600 mg/kg/day, associated with 8-times the maximum recommended human dose (MRHD) of metformin in humans, teratogenicity of metformin was observed.

The following data are findings in studies performed with empagliflozin or metformin individually.

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## Empagliflozin

In general toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of 25 mg. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and included 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, gluconeogenesis and electrolyte imbalances, urinary changes such as polyuria and glucosuria, and microscopic changes in kidney.

### *Carcinogenicity*

Empagliflozin did not increase the incidence of tumours in female rats at doses up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72- and 182- times the clinical AUC exposure associated with the 25 mg and 10 mg doses, respectively. In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node were observed at 700 mg/kg/day, which corresponds to approximately 42- and 105-times the clinical exposure associated with the 25 mg and 10 mg doses, respectively. These 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 1000 mg/kg/day, which corresponds to approximately 62- and 158-times the clinical exposure associated with the 25 mg and 10 mg doses, respectively. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, which corresponds to approximately 45- and 113-times the clinical exposure associated with the 25 mg and 10 mg doses, respectively. 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.

### *Genotoxicity*

Empagliflozin is not genotoxic.

### *Reproduction Toxicity*

Nonclinical 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. Empagliflozin administered during the period of organogenesis was not teratogenic at doses up to 300 mg/kg in the rat or rabbit, which corresponds to approximately 48- and 122- times or 128- and 325- times the clinical dose of empagliflozin based on AUC exposure associated with the 25 mg and 10 mg doses, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155- and 393- times the clinical dose associated with the 25 mg and 10 mg doses, respectively. Maternally toxic doses in the rabbit also caused increased embryofetal loss at doses approximately 139- and 353- times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

In pre- and postnatal toxicity studies in rats, reduced weight gain in offspring was observed at maternal exposures approximately 4- and 11-times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

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**

Non-clinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, genotoxicity, and carcinogenic potential. In a 2 week metformin only study and 2 and 13-week toxicity empagliflozin/metformin studies in rats, metformin related toxicity was seen in heart, liver, kidneys, salivary glands, ovaries, gastrointestinal tract and adrenal glands at dosages associated with a systemic exposure of 5 times the MRHD or higher.

Metformin was not teratogenic in rats at a dose of 200 mg/kg/day associated with a systemic exposure of 4 times the MRHD (2000 mg metformin). At higher doses (500 and 1000 mg/kg/day, associated with 11 and 23 times the MRHD), teratogenicity of metformin was observed in the rat which was mostly evident as an increase in the number of skeletal malformations.

### **Availability :**

Film coated tablet 5/500 mg

Box, 3 blisters @ 10 film coated tablet

Reg. No. DKI2356100217A1

Film coated tablet 12.5/500 mg

Box, 3 blisters @ 10 film coated tablet

Reg. No: DKI2356100217B1

Film coated tablet 12.5/850 mg

Box, 3 blisters @ 10 film coated tablet

Reg. No: DKI2356100217C1

Film coated tablet 12.5/1000mg

Box, 3 blisters @ 10 film coated tablet

Reg. No: DKI2356100217D1

**Only on doctor's prescription**

**Harus dengan resep dokter**

### **Product Shelf life :**

See packaging for expiry date

### **Storage conditions :**

Store below 30°C

Store in a safe place, out of the reach of children

### **Manufactured by :**

Boehringer Ingelheim Hellas Single Member S.A.

Koropi, Greece

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ERE10015512500143

**For :**

Boehringer Ingelheim International GmbH  
Ingelheim am Rhein, Germany

**Registered by :**

PT Tunggal Idaman Abdi  
Jakarta, Indonesia

Version: 20-1025

## Informasi Produk untuk Pasien

### Jardiance® Duo

(Empagliflozin/Metformin hidroklorida)

Tablet salut selaput 5 mg/500 mg

Tablet salut selaput 12.5 mg/500 mg

Tablet salut selaput 12.5 mg/850 mg

Tablet salut selaput 12.5 mg/1000 mg

**Bacalah seluruh lembar informasi ini dengan seksama sebelum mulai mengonsumsi obat ini karena lembar ini berisi informasi yang bermanfaat untuk anda.**

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, bertanyalah kepada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda saja. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka, walau tanda-tanda penyakit mereka sama dengan Anda.
- Bila Anda mengalami efek samping apapun, bicarakan kepada dokter, apoteker atau perawat Anda, termasuk efek samping yang belum tertulis dalam leaflet ini.

### Apa yang ada pada lembar ini

1. Apakah Jardiance Duo dan digunakan untuk apakah obat ini
2. Apa yang perlu Anda ketahui sebelum Anda minum Jardiance Duo
3. Bagaimana cara minum Jardiance Duo
4. Kemungkinan efek samping
5. Bagaimana cara menyimpan Jardiance Duo
6. Isi paket dan informasi lainnya

#### 1. Apa itu Jardiance Duo dan digunakan untuk apakah obat ini

Jardiance Duo adalah obat diabetes yang mengandung dua zat aktif yang disebut empagliflozin dan metformin.

- Empagliflozin bekerja dengan menghambat protein dalam ginjal yang disebut *sodium glucose co transporter 2* (SGLT2). SGLT2 mencegah glukosa diekskresi dalam urin dengan mengabsorpsi kembali glukosa ke dalam aliran darah saat darah difiltrasi dalam ginjal. Dengan menghambat protein ini maka obat ini menyebabkan glukosa (gula darah) dikeluarkan melalui urin. Hal ini membantu untuk menurunkan kadar gula darah yang tinggi pada pasien dengan diabetes tipe 2.
- Metformin bekerja dengan cara yang berbeda untuk menurunkan kadar gula darah, terutama dengan cara menghambat produksi glukosa di hati.

Jardiance Duo digunakan sebagai tambahan diet dan olahraga untuk mengobati diabetes tipe 2 pada pasien dewasa bila diabetes anda tidak dapat dikontrol dengan menambahkan metformin saja

Sebagai tambahan, Jardiance Duo dapat digunakan sebagai alternatif untuk pasien yang telah mengonsumsi empagliflozin dan metformin sebagai sediaan tunggal (telah mengonsumsi

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tablet terpisah). Untuk mencegah overdosis, jangan melanjutkan mengonsumsi tablet sediaan tunggal empagliflozin dan metformin bila anda mengonsumsi obat ini.

Penting bagi anda untuk tetap melanjutkan rencana diet dan olah raga sebagaimana yang diberitahukan oleh dokter, apoteker dan perawat anda.

## **Apakah diabetes tipe 2?**

Diabetes tipe 2 adalah suatu penyakit yang berasal dari gen dan gaya hidup Anda. Bila Anda memiliki diabetes tipe 2, berarti pankreas Anda tidak menghasilkan insulin dalam jumlah yang cukup untuk mengontrol kadar glukosa dalam darah Anda, dan tubuh Anda tidak dapat menggunakan insulinnya sendiri secara efektif. Kadar gula darah yang tinggi dalam darah dapat menyebabkan masalah kesehatan seperti penyakit jantung, penyakit ginjal, kebutaan, dan sirkulasi darah yang buruk pada anggota tubuh

## **2. Apa yang perlu Anda ketahui sebelum mengonsumsi Jardiance Duo**

### **Jangan mengonsumsi Jardiance Duo:**

- bila anda alergi terhadap empagliflozin, metformin atau bahan lainnya yang terkandung dalam obat ini (terdapat dalam bab 6).
- bila anda memiliki diabetes yang tidak terkontrol, misalnya : hiperglikemia parah (glukosa darah tinggi), mual, muntah, dehidrasi, penurunan berat badan yang cepat atau ketoasidosis. Ketoasidosis adalah suatu kondisi dimana zat yang disebut “badan keton” menumpuk dalam darah sehingga dapat menyebabkan pre-koma diabetes. Gejala termasuk penurunan berat badan cepat, merasa sakit atau menjadi sakit, nyeri perut, nafas cepat dan berat, mengantuk, bau manis yang tidak biasa yang keluar dari napas anda.
- bila anda pernah mengalami pre-koma diabetikum.
- bila anda memiliki masalah dengan ginjal anda.
- bila anda memiliki infeksi berat seperti infeksi yang mempengaruhi paru-paru atau sistem bronkial atau ginjal anda. Infeksi berat dapat menyebabkan masalah ginjal yang akan menempatkan anda pada resiko asidosis laktat (lihat Peringatan dan Perhatian).
- bila anda kehilangan air dari tubuh anda (dehidrasi), contohnya karena diare berkepanjangan atau diare berat, atau bila anda mengalami muntah beberapa kali secara berturut-turut. Dehidrasi dapat menyebabkan masalah pada ginjal, yang dapat menempatkan anda pada resiko asidosis laktat (lihat Peringatan dan Perhatian)
- Jika anda diobati untuk gagal jantung akut atau baru saja mengalami serangan jantung, memiliki masalah yang berat dengan sirkulasi anda (seperti syok) atau mengalami kesulitan bernapas. Hal ini dapat menyebabkan kurangnya pasokan oksigen ke jaringan yang dapat menempatkan anda pada resiko untuk laktat asidosis (lihat Peringatan dan Perhatian)
- bila anda memiliki masalah dengan hati anda.
- bila anda minum alkohol berlebihan, baik setiap hari atau hanya saat tertentu saja (harap lihat bab “Jardiance Duo dengan alkohol”).
- Pembedahan / Operasi : Jika Anda perlu menjalani operasi besar, Anda harus berhenti menggunakan Jardiance Duo selama dan beberapa saat setelah prosedur. Dokter Anda akan memutuskan kapan Anda harus berhenti dan kapan memulai kembali perawatan Anda dengan Jardiance Duo.

### **Peringatan dan perhatian**

Bicaralah kepada dokter, apoteker atau perawat anda sebelum mengonsumsi dan selama pengobatan dengan Jardiance Duo:

- Bila Anda mengidap diabetes tipe 1. Tipe ini biasanya diidap sejak Anda masih kecil dan badan Anda tidak memproduksi insulin sama sekali.
- Bila Anda mengalami penurunan berat badan yang cepat, merasa mual atau muntah, nyeri perut, rasa haus yang berlebihan, nafas cepat dan berat, bingung, ngantuk atau kelelahan yang tidak biasa, nafas berbau manis, rasa manis atau rasa logam pada mulut, atau bau urin atau keringat yang berbeda, segera hubungi dokter atau rumah sakit terdekat segera. Gejala tersebut dapat merupakan gejala "*diabetic ketoacidosis*" yaitu masalah yang timbul pada diabetes karena adanya peningkatan kadar badan keton di dalam urin atau darah berdasarkan hasil pengujian laboratorium. Risiko terjadinya *diabetic ketoacidosis* dapat meningkat seiring dengan puasa yang berkepanjangan, terlalu banyak minum minuman keras, dehidrasi, penurunan dosis insulin yang mendadak, atau semakin tingginya kebutuhan insulin karena menjalani operasi besar atau mengalami penyakit berat.
- Bila Anda berusia 75 tahun atau lebih tua, peningkatan berkemih yang disebabkan oleh obat ini dapat mempengaruhi keseimbangan cairan pada tubuh Anda dan meningkatkan risiko dehidrasi. Gejala-gejalanya dapat dilihat pada bagian 4. Kemungkinan Efek Samping – Dehidrasi.
- Bila anda berusia 85 tahun atau lebih, maka anda sebaiknya tidak memulai mengonsumsi Jardiance Duo.
- Bila anda sedang sakit, mengalami diare atau demam, atau bila anda tidak dapat makan atau minum. Kondisi ini dapat menyebabkan dehidrasi. Dokter anda mungkin meminta anda untuk menghentikan konsumsi Jardiance Duo hingga anda sembuh untuk mencegah hilangnya cairan tubuh yang terlalu banyak.
- Bila anda mengalami infeksi serius pada ginjal atau saluran kemih yang disertai demam. Dokter anda mungkin meminta anda untuk menghentikan konsumsi Jardiance Duo hingga anda sembuh.
- Bila anda membutuhkan injeksi dengan obat kontras yang mengandung yodium, contohnya sebelum Xray atau scan. Anda harus memberitahukan kepada dokter anda dan menghentikan konsumsi obat ini sebelum, saat dilakukan Xray dan selama 2 hari atau lebih setelahnya bergantung pada kerja ginjal anda. Pengobatan dengan agen kontras mengandung yodium dapat mengurangi fungsi ginjal dan meningkatkan resiko efek samping karena komponen metformin. Pastikan anda minta saran kepada dokter anda kapan anda dapat memulai pengobatan anda kembali.
- Bila anda akan menjalani pembedahan dengan anestesia. Anda harus menghentikan mengonsumsi Jardiance Duo paling sedikit 48 jam sebelum rencana pembedahan dengan anestesi umum dan tidak boleh memulai mengonsumsinya hingga paling sedikit 48 jam setelahnya; ikuti instruksi dokter anda tentang menghentikan dan memulai kembali obat anda.
- Perawatan kaki  
Seperti pasien diabetes lainnya, sangat penting untuk melakukan pemeriksaan kaki secara berkala dan ikuti saran perawatan kaki lainnya yang disarankan oleh tenaga kesehatan Anda.

**Untuk perhatian mengenai asidosis laktat beserta resikonya**

Karena komponen metformin, Jardiance Duo dapat menyebabkan komplikasi yang sangat jarang terjadi tapi sangat serius disebut asidosis laktat, terutama jika ginjal tidak bekerja dengan baik. Risiko asidosis laktat juga meningkat dengan diabetes yang tidak terkontrol, puasa perkepanjangan atau konsumsi alkohol, tubuh kekurangan cairan (dehidrasi) karena diare berat atau muntah, penyakit hati dan setiap kondisi medis di mana suatu wilayah dari tubuh kekurangan pasokan oksigen (seperti penyakit jantung akut yang berat).

Penting untuk Anda untuk mematuhi asupan obat Anda, petunjuk diet dan program olahraga teratur karena ini dapat mengurangi risiko asidosis laktat.

Timbulnya asidosis laktat dapat tidak kentara dan dapat terjadi gejala non-spesifik seperti muntah, sakit perut (nyeri perut) dengan kram otot, perasaan umum seperti merasa tidak enak badan dengan kelelahan yang berat, dan kesulitan bernapas.

Gejala lanjutan adalah berkurangnya suhu tubuh dan detak jantung.

**Jika Anda mengalami beberapa gejala ini, Anda harus mencari pertolongan medis segera, karena asidosis laktat dapat menyebabkan koma. Stop konsumsi Jardiance Duo dan hubungi dokter atau segera pergi ke rumah sakit terdekat.**

### **Fungsi ginjal**

Ginjal Anda akan diuji dengan tes darah sebelum Anda mulai mengonsumsi dan saat Anda mengonsumsi ini obat.

### **Glukosa urin**

Karena aksi kerja Jardiance Duo maka tes urin Anda akan positif untuk gula ketika Anda minum obat ini.

### **Anak dan remaja**

Jardiance Duo tidak direkomendasikan untuk anak dan remaja usia dibawah 18 tahun, karena obat ini belum diteliti pada populasi pasien ini.

### **Pemakaian obat-obatan lainnya dan Jardiance Duo**

Beritahukan kepada dokter atau apoteker anda bila anda sedang, baru saja mengonsumsi atau mungkin mengonsumsi obat lain.

Penting untuk memberitahukan kepada dokter anda jika anda mengonsumsi:

- Obat yang dapat mengeluarkan air dari tubuh (diuretik), karena Jardiance Duo dapat meningkatkan resiko kehilangan terlalu banyak cairan. Dokter anda mungkin akan meminta anda menghentikan konsumsi Jardiance Duo. Tanda-tanda yang mungkin timbul akibat hilangnya terlalu banyak cairan dari tubuh anda terdapat dalam bab 4 “Efek samping yang mungkin terjadi”.
- Obat lain untuk menurunkan kadar gula dalam darah anda seperti obat sulfonilurea. Dokter anda mungkin akan menurunkan dosis obat-obat ini untuk mencegah kadar gula darah yang terlalu rendah (hipoglikemia).
- Obat-obatan yang dapat mempengaruhi jumlah metformin dalam darah, terutama apabila Anda memiliki gangguan fungsi ginjal (seperti verapamil, rifampicin, cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole, crizotinib, olaparib). Bronkodilator (beta-2 agonis) yang digunakan untuk mengobati asma.

- Kortikosteroid (diberikan per oral, melalui injeksi, atau dihirup), yang digunakan untuk mengobati inflamasi pada penyakit seperti asma dan artritis.
- Obat yang mengandung alkohol (lihat bagian Jardiance Duo dengan alcohol)
- Agen kontras mengandung yodium (obat-obatan yang digunakan selama-ray X, lihat bagian Peringatan dan Perhatian)
- Obat untuk nyeri dan inflamasi (NSAID dan inhibitor COX-2, seperti ibuprofen dan celecoxib)
- Obat untuk tekanan darah tinggi (inhibitor ACE atau antagonis reseptor angiotensin II)
- Bila anda mengonsumsi lithium, karena Jardiance Duo dapat menurunkan kadar lithium dalam darah anda.

### **Jardiance Duo dengan alkohol**

Terdapat peningkatan risiko asidosis laktat setelah mengonsumsi alkohol yang berlebihan (khususnya pada kasus puasa, malnutrisi, atau penyakit hati) Oleh karena itu, hindari konsumsi alkohol dan produk obat yang mengandung alkohol ketika anda mengonsumsi Jardiance Duo (Lihat “Efek samping yang mungkin terjadi”).

### **Kehamilan dan menyusui**

Bila anda hamil atau menyusui, berpikir anda mungkin hamil atau merencanakan untuk hamil, mintalah saran kepada dokter atau apoteker anda sebelum anda mengonsumsi obat ini.

Jangan mengonsumsi Jardiance Duo bila anda hamil. Belum diketahui apakah obat ini berbahaya untuk janin.

Metformin dapat masuk kedalam air susu ibu dalam jumlah kecil. Belum diketahui apakah empagliflozin dapat masuk kedalam air susu ibu. Jangan mengonsumsi Jardiance Duo bila anda sedang menyusui.

### **Mengemudi dan mengoperasikan mesin**

Jardiance Duo memiliki pengaruh kecil terhadap kemampuan mengemudi dan mengoperasikan mesin.

Mengonsumsi obat ini dikombinasi dengan obat lainnya seperti sulfonilurea dapat menyebabkan kadar gula darah turun menjadi terlalu rendah (hipoglikemia), yang dapat menyebabkan gejala seperti gemetar, berkeringat dan perubahan penglihatan, dan dapat mempengaruhi kemampuan Anda dalam mengemudi dan mengoperasikan mesin. Jangan mengemudi atau mengoperasikan alat atau mesin bila anda merasa pusing setelah mengonsumsi Jardiance Duo.

### **3. Bagaimana cara mengonsumsi Jardiance Duo**

Selalu mengonsumsi obat sesuai dengan instruksi dokter anda. Tanyakan kepada dokter atau apoteker bila anda tidak yakin.

**Berapa banyak dosis obat yang harus dikonsumsi?**

Dosis Jardiance Duo bervariasi tergantung pada kondisi Anda dan dosis obat diabetes yang Anda gunakan. Dokter Anda akan menyesuaikan dosis Anda seperlunya dan memberitahu Anda kekuatan obat yang harus Anda konsumsi.

Dosis yang dianjurkan adalah satu tablet dua kali sehari. Dokter biasanya akan memulai pengobatan Jardiance Duo dengan meresepkan kekuatan tablet yang berisi dosis yang sama metformin yang sudah Anda konsumsi (500 mg, 850 mg atau 1.000 mg dua kali sehari), dan dosis terendah empagliflozin (5 mg dua kali sehari). Jika Anda sudah mengonsumsi kedua obat secara terpisah, dokter akan memulai pengobatan dengan tablet Jardiance Duo yang akan berisi jumlah yang sama dari kedua obat tersebut.

**Cara mengonsumsi obat ini**

- Telan seluruh tablet dengan air
- Telanlah tablet bersama dengan makanan untuk mengurangi kemungkinan nyeri lambung.
- Konsumsi tablet dua kali sehari secara oral.

Dokter Anda mungkin meresepkan JARDIANCE bersama dengan obat antidiabetik oral lainnya. Ingatlah untuk meminum semua obat sesuai dengan instruksi yang diberikan oleh dokter Anda agar dapat dicapai hasil terbaik bagi kesehatan Anda.

Diet dan olah raga dapat membantu tubuh anda untuk menggunakan gula darah Anda sendiri secara lebih baik. Penting untuk tetap melaksanakan program diet dan olah raga yang telah direkomendasikan oleh dokter anda ketika anda mengonsumsi Jardiance Duo.

**Bila anda mengonsumsi Jardiance Duo lebih banyak dari seharusnya**

Bila anda mengonsumsi Jardiance Duo lebih banyak dari seharusnya, anda mungkin akan mengalami asidosis laktat. Gejala asidosis laktat yang bersifat non-spesifik seperti merasa atau menjadi sangat sakit, muntah, nyeri perut, kram otot, perasaan tidak enak badan dengan kelelahan yang parah atau kesulitan bernapas. Gejala lanjutan adalah berkurangnya suhu tubuh dan detak jantung. Bila hal ini terjadi pada anda maka anda perlu perawatan di rumah sakit segera karena asidosis laktat dapat menyebabkan koma. Hentikan mengonsumsi obat ini dan hubungi dokter atau rumah sakit terdekat segera (lihat bab 4). Bawalah serta paket/ kemasan obat anda.

**Bila anda terlupa mengonsumsi Jardiance Duo**

Bila anda terlupa satu dosis, konsumsi obat ini segera begitu anda ingat. Bila anda tidak ingat hingga tiba jadwal konsumsi dosis berikutnya, lewatkan dosis yang terlupa dan kembali ke jadwal biasa. Jangan mengonsumsi obat ini dengan dosis ganda.

**Bila anda berhenti mengonsumsi Jardiance Duo**

Jangan berhenti mengonsumsi Jardiance Duo tanpa berkonsultasi terlebih dahulu dengan dokter anda. Kadar gula darah anda dapat meningkat ketika anda menghentikan konsumsi Jardiance Duo.

Bila anda memiliki pertanyaan lebih lanjut mengenai cara menggunakan obat ini, bertanyalah kepada dokter, apoteker atau perawat anda.

#### **4. Efek samping yang mungkin terjadi**

Seperti semua obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Hentikan mengonsumsi Jardiance Duo dan kunjungilah dokter anda segera mungkin bila anda memperhatikan terdapatnya efek samping serius atau potensial efek samping serius sebagai berikut:

**Asidosis laktat.** Metformin, salah satu bahan aktif dalam obat ini dapat menyebabkan efek samping yang sangat jarang (dapat memengaruhi hingga 1 dari 10.000 orang) tetapi serius yang disebut 'asidosis laktat'. Ini adalah penumpukan asam laktat dalam darah yang dapat menyebabkan kematian. Asidosis laktat adalah kegawatan medis dan harus dirawat inap di rumah sakit. Kejadian ini memengaruhi pasien yang memiliki ginjal yang tidak bekerja sempurna.

Tanda-tanda 'asidosis laktat' adalah:

- merasa atau menjadi sangat sakit
- muntah, nyeri perut
- kram otot
- kelelahan yang parah
- kesulitan bernapas

Bila hal ini terjadi pada anda, anda memerlukan perawatan rumah sakit segera karena asidosis laktat dapat menyebabkan koma. Hentikan mengonsumsi obat ini segera dan hubungi dokter atau segera kunjungi rumah sakit terdekat. Bawalah serta paket obat anda.

**Hubungi dokter atau rumah sakit terdekat langsung jika Anda mengalami salah satu dari efek samping berikut :**

**Diabetic ketoacidosis, jarang terjadi (mungkin mempengaruhi sampai 1 dalam 1.000 orang)**

Ini adalah tanda-tanda ketoasidosis diabetik (lihat juga bagian Peringatan dan Perhatian):

- Peningkatan kadar "badan keton" dalam urin atau darah
- Penurunan berat badan yang cepat
- Perasaan sakit atau sakit
- Sakit perut
- Rasa haus yang berlebihan
- Nafas cepat dan berat
- Merasa bingung
- Mengantuk atau kelelahan yang tidak biasa
- Rasa manis pada nafas Anda, rasa manis atau rasa besi pada mulut Anda, atau bau yang berbeda pada urin atau keringat.

Hal ini dapat terjadi pada berapa pun kadar gula darah Anda. Dokter Anda dapat memutuskan untuk menghentikan pemberian obat Jardiance Duo secara sementara atau permanen.

**Hubungi dokter anda segera mungkin bila anda memerhatikan efek samping berikut ini:**

**Gula darah rendah (hipoglikemia), sering terjadi (dapat memengaruhi  $\geq 1$  dari 10 orang)**

Bila anda mengonsumsi Jardiance Duo bersama dengan obat lainnya yang dapat menurunkan gula darah, seperti sulfonilurea maka risiko anda mengalami kadar gula darah rendah meningkat. Tanda kadar gula darah rendah adalah:

- gemetar, berkeringat, merasa sangat cemas atau bingung, denyut jantung cepat
- sangat lapar, sakit kepala

Dokter anda akan memberitahukan kepada anda bagaimana tata laksana kadar gula darah yang rendah dan apa yang harus dilakukan bila anda mengalami tanda-tanda diatas. Bila anda memiliki gejala gula darah rendah, makanlah tablet glukosa, makanan ringan yang mengandung tinggi gula atau minuman jus buah. Ukurlah gula darah anda bila memungkinkan dan beristirahatlah.

**Infeksi saluran kemih, sering terjadi (dapat memengaruhi hingga 1 dari 10 orang)**

Tanda-tanda infeksi saluran kemih adalah:

- rasa terbakar/perih ketika berkemih
- urin tampak keruh
- nyeri pada panggul, atau nyeri punggung tengah (ketika ginjal terinfeksi)

Dorongan untuk berkemih atau berkemih lebih sering mungkin disebabkan cara kerja Jardiance Duo, tetapi hal tersebut dapat juga merupakan tanda-tanda infeksi saluran kemih. Bila anda memerhatikan terjadi peningkatan gejala-gejala tersebut, anda harus menghubungi dokter anda.

**Dehidrasi, tidak sering terjadi (dapat memengaruhi hingga 1 hingga 100 orang)**

Tanda-tanda dehidrasi tidak spesifik, tetapi mungkin termasuk :

- haus yang tidak biasa
- kepala terasa ringan atau pusing bila berdiri
- pingsan atau penurunan kesadaran

**Efek samping lainnya ketika mengonsumsi Jardiance Duo:**

Sangat sering terjadi

- mual, muntah
- diare atau sakit perut
- hilang nafsu makan

Sering terjadi

- infeksi jamur pada genital

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- berkemih lebih sering dari biasa atau perlu berkemih lebih sering
- gatal
- perubahan rasa
- ruam atau kulit kemerahan
- merasa haus
- perubahan kadar kolesterol darah
- konstipasi
- penurunan atau rendahnya kadar vitamin B12 dalam darah

Tidak sering terjadi

- rasa tegang atau nyeri ketika mengosongkan kandung kemih
- tes darah dapat menunjukkan perubahan yang berhubungan dengan fungsi ginjal (kreatinin atau urea)
- urtikaria (biduran)
- tes darah dapat menunjukkan peningkatan jumlah sel darah merah dalam darah (hematokrit)

Sangat jarang terjadi

- abnormalitas tes fungsi hati, inflamasi hati (hepatitis)
- kemerahan pada kulit (eritema), gatal atau ruam gatal (bentol)

#### **Pelaporan efek samping**

Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk efek samping yang mungkin terjadi yang belum tercantum di leaflet ini. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut: Telepon: +62 21 21684084 atau Email: [IDSafety@zuelligpharma.com](mailto:IDSafety@zuelligpharma.com)

#### **5. Bagaimana cara menyimpan Jardiance Duo**

Simpanlah obat ini jauh dari pandangan dan jangkauan anak-anak.

Jangan menggunakan obat ini setelah tanggal kadaluarsa yang tertulis pada blister dan karton setelah 'EXP'.

Tanggal kadaluarsa merujuk pada hari terakhir pada bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan mengonsumsi obat ini bila kemasan rusak atau menunjukkan tanda-tanda kerusakan.

Jangan membuang obat apapun melalui pembuangan limbah air atau limbah rumah tangga. Bertanyalah kepada apoteker Anda bagaimana cara membuang obat-obatan yang tidak Anda gunakan lagi. Tindakan ini akan membantu melindungi lingkungan.

## **6. Isi kemasan dan informasi lainnya**

### **Apakah yang terkandung dalam Jardiance Duo**

Bahan aktif dalam obat ini adalah empagliflozin dan metformin.

Setiap tablet salut selaput Jardiance Duo 5 mg/500 mg mengandung empagliflozin 5mg dan metformin hidroklorida 500 mg.

Setiap tablet salut selaput Jardiance Duo 12,5 mg/500 mg mengandung empagliflozin 5mg dan metformin hidroklorida 500 mg.

Setiap tablet salut selaput Jardiance Duo 12,5 mg/850 mg mengandung empagliflozin 12,5 mg dan metformin hidroklorida 850mg.

Setiap tablet salut selaput Jardiance Duo 12,5 mg/1000 mg mengandung empagliflozin 12,5 mg dan metformin hidroklorida 1000mg.

Bahan lainnya adalah:

- Tablet utama: tepung jagung, copovidone, silika anhidrosa koloidal, magnesium stearat.
- Salut selaput: hipromelose, makrogol 400, titanium dioksida, talk, iron oxide yellow untuk tablet Jardiance Duo 5 mg/500 mg, iron oxide black untuk tablet Jardiance Duo 12,5 mg/500 mg, tablet Jardiance Duo 12,5 mg/850 mg dan tablet Jardiance Duo 12,5 mg/1000 mg, iron oxide red untuk tablet Jardiance Duo 12,5 mg/500 mg, tablet Jardiance Duo 12,5 mg/850 mg dan tablet Jardiance Duo 12,5 mg/1000 mg,

### **Seperti apakah tampilan dan isi kemasan Jardiance Duo**

Tablet salut selaput Jardiance Duo 5 mg/500 mg berwarna kuning jingga, berbentuk oval, bikonveks. Tiap tablet memiliki cetakan "S5" dan logo Boehringer Ingelheim pada satu sisi dan "500" pada sisi lainnya.

Tablet salut selaput Jardiance Duo 12,5 mg/500 mg berwarna ungu coklat pucat, berbentuk oval, bikonveks. Tiap tablet memiliki cetakan "S12" dan logo Boehringer Ingelheim pada satu sisi dan "500" pada sisi lainnya.

Tablet salut selaput Jardiance Duo 12,5 mg/850 mg berwarna putih merah muda, berbentuk oval, bikonveks. Tiap tablet memiliki cetakan "S12" dan logo Boehringer Ingelheim pada satu sisi dan "850" pada sisi lainnya.

Tablet salut selaput Jardiance Duo 12,5 mg/1000 mg berwarna ungu kecoklatan, berbentuk oval, bikonveks. Tiap tablet memiliki cetakan "S12" dan logo Boehringer Ingelheim pada satu sisi dan "1000" pada sisi lainnya.

Ukuran paket adalah 30x1, tablet salut selaput.

### **Harus dengan resep dokter**

#### **Kondisi penyimpanan :**

Simpan di bawah suhu 30°C

Simpan di tempat yang aman, jauhkan dari jangkauan anak-anak

ID: EREG10015512500140  
ERE10015512500141  
ERE10015512500142  
ERE10015512500143

**Diproduksi Oleh :**

Boehringer Ingelheim Hellas Single Member S.A.  
Koropi, Yunani

**Untuk :**

Boehringer Ingelheim International GmbH  
Ingelheim am Rhein, Jerman

**Diregistrasi oleh :**

PT Tunggal Idaman Abdi  
Jakarta, Indonesia

**Nomor Registrasi**

|                            |                   |
|----------------------------|-------------------|
| Jardiance Duo 5/500 mg     | : DKI2356100217A1 |
| Jardiance Duo 12,5/500 mg  | : DKI2356100217B1 |
| Jardiance Duo 12,5/850 mg  | : DKI2356100217C1 |
| Jardiance Duo 12,5/1000 mg | : DKI2356100217D1 |

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