# JARDIANCE®

## (empagliflozin)

### NAME OF THE MEDICINE

Active Ingredient: empagliflozin

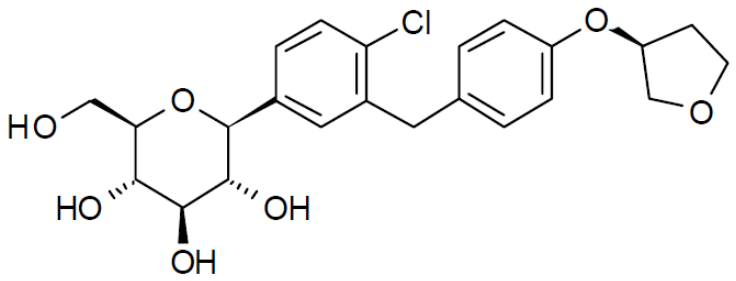
Chemical name: (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol

Molecular formula: $C_{23}H_{27}ClO_7$

CAS number: 864070-44-0

Molecular weight: 450.91

Structural formula:




### DESCRIPTION

Empagliflozin is a white to yellowish powder. It is very slightly soluble in water, slightly soluble in acetonitrile and ethanol, sparingly soluble in methanol and practically insoluble in toluene. Empagliflozin is not hygroscopic and no polymorphism has been observed. It is neither a hydrate nor a solvate. Partition coefficient: log P = log D (pH 7.4): 1.7.

JARDIANCE are film-coated tablets for oral administration containing either 10 mg or 25 mg of empagliflozin.

Each JARDIANCE tablet also contains: lactose, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, talc, macrogol 400, iron oxide yellow.

### PHARMACOLOGY

Pharmacotherapeutic group: SGLT2 Inhibitor, ATC code: A10BX12.

#### Pharmacodynamics

Empagliflozin is a reversible 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.

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

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

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

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

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

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

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

**Pharmacokinetics**

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations ($C_{max}$) with a median time to reach $C_{max}$ ($t_{max}$) of 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 area under the curve (AUC) was 4740 nmol.h/L and $C_{max}$ was 687 nmol/L with 25 mg empagliflozin once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.

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

Distribution

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

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide).

Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

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 half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [$^{14}$C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Pharmacokinetics in special patient groups

*Pharmacokinetics in children*

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

*Pharmacokinetics in the elderly*

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

*Pharmacokinetics in patients with renal insufficiency*

In patients with mild (eGFR: 60 - < 90 mL/min/1.73m$^2$), moderate (eGFR: 30 - < 60 mL/min/1.73 m$^2$), severe (eGFR: <30 mL/min/1.73 m$^2$) renal impairment and patients with kidney failure/end stage renal disease (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.

*Pharmacokinetics in patients with hepatic insufficiency*

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

*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$^2$ compared to non-Asian patients with a BMI of 25 kg/m$^2$.

## CLINICAL TRIALS

A total of 11250 patients with T2DM were evaluated in 10 double-blind, placebo- and active-controlled clinical studies, of which 3021 patients received empagliflozin 10 mg and 3994 received empagliflozin 25 mg. Four studies had a treatment duration of 24 weeks; in extensions of those studies, and other trials, patients were exposed to JARDIANCE for up to 102 weeks.

Treatment with empagliflozin as monotherapy and in combination with metformin, pioglitazone, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, and insulin lead to clinically relevant improvements in glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, systolic BP (SBP) and diastolic BP (DBP). Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA1c goal of less than 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. There was a clinically meaningful improvement in HbA1c in all subgroups of gender, race, geographic region, time since diagnosis of T2DM, BMI, insulin resistance based on HOMA-IR, and beta cell function based on HOMA-β. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Clinically meaningful HbA1c reduction was seen in patients with eGFR > 45 mL/min/1.73m² (see DOSAGE AND ADMINISTRATION, Patients with Renal Insufficiency). In patients aged 75 years and older, reduced efficacy of JARDIANCE was observed.

### Empagliflozin as monotherapy

The efficacy and safety of empagliflozin as monotherapy was evaluated in a double-blind, placebo- and active-controlled study of 24 weeks duration in treatment-naïve patients. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and blood pressure (systolic, SBP and diastolic, DBP) after 24 weeks of treatment.

Treatment with JARDIANCE resulted in statistically significant reductions in HbA1c, body weight and SBP compared to placebo (Table 1) and a clinically meaningful decrease in FPG. A numerical decrease in DBP was seen but did not reach statistical significance (-1.0 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg, -0.5 mmHg for placebo, and +0.7 mmHg for sitagliptin).

In a prespecified analysis of patients (n=201) with a baseline HbA1c ≥ 8.5% to ≤ 10% empagliflozin resulted in a reduction in HbA1c from baseline of -1.44% for empagliflozin 10 mg, -1.43% for empagliflozin 25 mg, +0.01% for placebo, and -1.04% for sitagliptin.

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.66% for empagliflozin 10 mg, -0.82% for empagliflozin 25 mg, +0.09% for placebo, and -0.57% for sitagliptin), body weight (change from baseline of -1.92 kg for empagliflozin 10 mg, -2.48 kg for empagliflozin 25 mg, -0.29 kg for placebo, and +0.29 kg for sitagliptin) and BP (SBP: change from baseline of -4.1 mmHg for empagliflozin 10 mg, -3.9

mmHg for empagliflozin 25 mg, +0.7 mmHg for placebo, and -1.4 mmHg for sitagliptin, DBP: change from baseline of -1.3 mmHg for empagliflozin 10 mg, -1.8 mmHg for empagliflozin 25 mg, +0.1 mmHg for placebo, and -0.4 mmHg for sitagliptin) were sustained up to 52 weeks of treatment.

Treatment with JARDIANCE daily significantly improved markers of beta cell function, including HOMA-β and proinsulin to insulin ratio.

**Table 1 Results of a 24 week (LOCF) placebo-controlled study of JARDIANCE as monotherapy (Full Analysis Set)**

| JARDIANCE as monotherapy | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg | Sitagliptin 100mg |
|---|---|---|---|---|
| N | 228 | 224 | 224 | 223 |
| **HbA1c (%)** | | | | |
| Baseline (mean) | 7.91 | 7.87 | 7.86 | 7.85 |
| Change from baseline[1] | 0.08 | -0.66 | -0.78 | -0.66 |
| Difference from placebo[1] | | -0.74* | -0.85* | -0.73 |
| (97.5% CI) | | (-0.90, -0.57) | (-1.01, -0.69) | (-0.88, -0.59)[3] |
| N | 208 | 204 | 202 | 200 |
| **Patients (%) achieving HbA1c < 7% with baseline HbA1c ≥ 7%[4]** | 12.0 | 35.3 | 43.6 | 37.5 |
| N | 226 | 223 | 233 | 223 |
| **Fasting plasma glucose (mmol/L)** | | | | |
| Baseline (mean) | 8.59 | 8.48 | 8.47 | 8.17 |
| Change from baseline[1] | 0.65 | -1.08 | -1.36 | -0.38 |
| Difference from placebo[1] | | -1.73* | -2.01* | -1.04* |
| (95% CI) | | (-2.03, -1.43) | (-2.31, -1.71) | (-1.34, -0.73) |
| N | 228 | 224 | 224 | 223 |
| **Body weight (kg)** | | | | |
| Baseline (mean) | 78.23 | 78.35 | 77.80 | 79.31 |
| Change from baseline[1] | -0.33 | -2.26 | -2.48 | 0.18 |
| Difference from placebo[1] | | -1.93* | -2.15* | 0.52 |
| (97.5% CI) | | (-2.48, -1.38) | (-2.70,-1.60) | (-0.04, 1.00)[3] |
| N | 228 | 224 | 224 | 223 |
| **Patients(%) achieving weight loss of >5%[4]** | 4.4 | 22.8 | 29.0 | 6.3 |
| N | 228 | 224 | 224 | 223 |
| **Systolic blood pressure (mmHg)[2]** | | | | |
| Baseline (mean) | 130.4 | 133.0 | 129.9 | 132.5 |
| Change from baseline[1] | -0.3 | -2.9 | -3.7 | 0.5 |
| Difference from placebo[1] | | -2.6# | -3.4# | 0.8 |
| (97.5% CI) | | (-5.2, 0.0) | (-6.0, -0.9) | (-1.4, 3.1)[3] |

1 mean adjusted for baseline value
2 Last observation carried forward (LOCF), values after antihypertensive rescue censored
3 95% CI
4 not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
*p value <0.0001; # p value < 0.05

### 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 with T2DM not controlled on metformin. The

primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment.

Treatment with JARDIANCE resulted in statistically significant improvements in HbA1c and body weight, and clinically meaningful reductions in FPG and BP compared to placebo (Table 2).

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.68% for empagliflozin 10 mg, -0.76% for empagliflozin 25 mg and -0.06% for placebo), body weight (change from baseline of -2.07 kg for empagliflozin 10 mg, -2.67 kg for empagliflozin 25 mg and -0.49 kg for placebo) and BP (SBP: change from baseline of -3.7 mmHg for empagliflozin 10 mg, -4.3 mmHg for empagliflozin 25 mg and -0.5 mmHg for placebo, DBP: change from baseline of -2.1 mmHg for empagliflozin 10 mg, -1.8 mmHg for empagliflozin 25 mg and -0.3 mmHg for placebo) were sustained up to 52 weeks of treatment.

**Table 2 Results of a 24 week (LOCF) placebo-controlled study of JARDIANCE as add-on to metformin (Full Analysis Set)**

| **JARDIANCE as add-on to metformin therapy** | **Placebo** | **Empagliflozin 10 mg** | **Empagliflozin 25 mg** |
|---|---|---|---|
| N | 207 | 217 | 213 |
| **HbA1c (%)** | | | |
| Baseline (mean) | 7.90 | 7.94 | 7.86 |
| Change from baseline[1] | -0.13 | -0.70 | -0.77 |
| Difference from placebo[1] (97.5% CI) | | -0.57* (-0.72, -0.42) | -0.64* (-0.79, -0.48) |
| N | 184 | 199 | 191 |
| **Patients (%) achieving HbA1c < 7% with baseline HbA1c ≥ 7%[2]** | 12.5 | 37.7 | 38.7 |
| N | 207 | 216 | 213 |
| **Fasting plasma glucose (mmol/L)** | | | |
| Baseline (mean) | 8.66 | 8.58 | 8.29 |
| Change from baseline[1] | 0.35 | -1.11 | -1.24 |
| Difference from placebo[1] (95% CI) | | -1.47* (-1.74, -1.20) | -1.59* (-1.86, -1.32) |
| N | 207 | 217 | 213 |
| **Body weight (kg)** | | | |
| Baseline (mean) | 79.73 | 81.59 | 82.21 |
| Change from baseline[1] | -0.45 | -2.08 | -2.46 |
| Difference from placebo[1] (97.5% CI) | | -1.63* (-2.17, -1.08) | -2.01* (-2.56, -1.46) |
| N | 207 | 217 | 213 |
| **Patients (%) achieving weight loss of >5%** | 4.8 | 21.2 | 23.0 |
| N | 207 | 217 | 213 |
| **Systolic blood pressure (mmHg)[2]** | | | |
| Baseline (mean) | 128.6 | 129.6 | 130.0 |
| Change from baseline[1] | -0.4 | -4.5 | -5.2 |
| Difference from placebo[1] (95% CI) | | -4.1* (-6.2, -2.1) | -4.8* (-6.9, -2.7) |

1 mean adjusted for baseline value
2 not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
*p-value <0.0001

**Empagliflozin as add on to a combination of metformin and sulfonylurea therapy**

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients not sufficiently treated with a combination of metformin and a sulfonylurea. The primary endpoint was the change from baseline in HbA1c

after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment.

Treatment with JARDIANCE resulted in statistically significant improvements in HbA1c and body weight and clinically meaningful reductions in FPG and BP compared to placebo (Table 3).

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.75% for empagliflozin 10 mg, -0.70% for empagliflozin 25 mg and -0.04% for placebo), body weight (change from baseline of -2.23 kg for empagliflozin 10 mg, -2.31 kg for empagliflozin and -0.23 kg for placebo) and BP (SBP: change from baseline of -2.9 mmHg for empagliflozin 10 mg, -2.8 mmHg for empagliflozin 25 mg and 0.0 mmHg for placebo, DBP: change from baseline of -1.6 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg and -0.8 mmHg for placebo) were sustained up to 52 weeks of treatment.

**Table 3 Results of a 24 week (LOCF) placebo-controlled study of JARDIANCE as add-on to metformin and a sulfonylurea (Full Analysis Set)**

| **JARDIANCE as add-on to metformin and a sulfonylurea therapy** | **Placebo** | **Empagliflozin 10 mg** | **Empagliflozin 25 mg** |
|---|---|---|---|
| N | 225 | 225 | 216 |
| **HbA1c (%)** | | | |
| Baseline (mean) | 8.15 | 8.07 | 8.10 |
| Change from baseline[1] | -0.17 | -0.82 | -0.77 |
| Difference from placebo[1] (97.5% CI) | | -0.64* (-0.79, -0.49) | -0.59* (-0.74, -0.44) |
| N | 216 | 209 | 202 |
| **Patients (%) achieving HbA1c < 7% with baseline HbA1c ≥ 7%[2]** | 9.3 | 26.3 | 32.2 |
| N | 224 | 225 | 215 |
| **Fasting plasma glucose (mmol/L)** | | | |
| Baseline (mean) | 8.42 | 8.38 | 8.68 |
| Change from baseline[1] | 0.31 | -1.29 | -1.29 |
| Difference from placebo[1] (95% CI) | | -1.60* (-1.90, -1.30) | -1.60* (-1.90, -1.29) |
| N | 225 | 225 | 216 |
| **Body weight (kg)** | | | |
| Baseline (mean) | 76.23 | 77.08 | 77.50 |
| Change from baseline[1] | -0.39 | -2.16 | -2.39 |
| Difference from placebo[1] (97.5% CI) | | -1.76* (-2.25, -1.28) | -1.99* (-2.48, -1.50) |
| N | 225 | 225 | 216 |
| **Patients (%) achieving weight loss of >5%** | 5.8 | 27.6 | 23.6 |
| N | 225 | 225 | 216 |
| **Systolic blood pressure (mmHg)[2]** | | | |
| Baseline (mean) | 128.8 | 128.7 | 129.3 |
| Change from baseline[1] | -1.4 | -4.1 | -3.5 |
| Difference from placebo[1] (95% CI) | | -2.7# (-4.6, -0.8) | -2.1# (-4.0, -0.2) |

1 mean adjusted for baseline value
2 not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
*p-value <0.0001
# p value <0.05

2 hour post-prandial glucose

Treatment with empagliflozin as add-on to metformin or metformin plus sulfonylurea resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin: -2.55 mmol/L for empagliflozin 10 mg, 2.47 mmol/L for

empagliflozin 25 mg - and +0.33 mmol/L for placebo; add-on to metformin plus sulfonylurea: -1.98 mmol/L for empagliflozin 10 mg, -2.03 mmol/L for empagliflozin 25 mg and -0.13 mmol/L for placebo).

**Empagliflozin as add on to a combination of pioglitazone therapy (+/- metformin)**

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo-controlled study of 24 weeks duration in patients with T2DM not controlled on a combination of metformin and pioglitazone or pioglitazone alone. The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The key secondary endpoints were the change from baseline in FPG and body weight after 24 weeks of treatment.

Empagliflozin in combination with pioglitazone (mean dose ≥ 30 mg) with or without metformin resulted in statistically significant reductions in HbA1c, FPG, and body weight and clinically meaningful reductions in BP compared to placebo (Table 4).

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (change from baseline of -0.60% for empagliflozin 10 mg, -0.69% for empagliflozin 25 mg and -0.06% for placebo), body weight (change from baseline of -1.53 kg for empagliflozin 10 mg, -1.30 kg for empagliflozin 25 mg and +0.53 kg for placebo) and BP (SBP: change from baseline of -2.1 mmHg for empagliflozin 10 mg, -2.8 mmHg for empagliflozin 25 mg and +1.2 mmHg for placebo, DBP: change from baseline of -1.4 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg and +0.7 mmHg for placebo) were sustained up to 52 weeks of treatment.

**Table 4 Results of a 24 week (LOCF) placebo-controlled study of JARDIANCE as add-on to pioglitazone with or without metformin (Full Analysis Set)**

| Pioglitazone +/- metformin add-on therapy | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
|---|---|---|---|
| N | 165 | 165 | 168 |
| **HbA1c (%)** | | | |
| Baseline (mean) | 8.16 | 8.07 | 8.06 |
| Change from baseline[1] | -0.11 | -0.59 | -0.72 |
| Difference from placebo1 (97.5% CI) | | -0.48* (-0.69, -0.27) | -0.61* (-0.82, -0.40) |
| N | 155 | 151 | 160 |
| Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[3] | 7.7 | 24 | 38 |
| N | 165 | 163 | 168 |
| **Fasting plasma glucose (mmol/L)** | | | |
| Baseline (mean) | 8.43 | 8.44 | 8.43 |
| Change from baseline[1] | 0.37 | -0.94 | -1.23 |
| Difference from placebo1 (97.5% CI) | | -1.30* (-1.72, -0.91) | -1.58* (-2.04, -1.12) |
| N | 165 | 165 | 168 |
| **Body Weight (kg)** | | | |
| Baseline (mean) | 78.1 | 77.97 | 78.93 |
| Change from baseline[1] | 0.34 | -1.62 | -1.47 |
| Difference from placebo1 (97.5% CI) | | -1.95* (-2.64, -1.27) | -1.81* (-2.49, -1.13) |
| N | 165 | 165 | 168 |
| Patients(%) achieving weight loss of >5%[3] | 5.5 | 18.8 | 13.7 |
| N | 165 | 165 | 168 |
| **Systolic blood pressure (mmHg)[2]** | | | |
| Baseline (mean) | 125.7 | 126.5 | 126 |
| Change from baseline[1] | 0.7 | -3.1 | -4.0 |
| Difference from placebo[1] (95% CI) | | -3.9 (-6.23, -1.50) | -4.7 (-7.08, -2.37) |

1 mean adjusted for baseline value
2 Last observation carried forward (LOCF), values after antihypertensive rescue censored

3 not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
*p-value <0.0001

**Empagliflozin 52 week 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 T2DM and inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in non-inferior reduction in HbA1c, and a clinically meaningful reduction in FPG, compared to glimepiride (Table 5). Empagliflozin daily resulted in a statistically significant reduction in body weight, SBP and DBP (change from baseline in DBP of –1.9 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 (1.6% for empagliflozin, 20.4% for glimepiride, p<0.0001).

**Table 5 Results at 52 week (LOCF) in an active controlled study comparing JARDIANCE to glimepiride as add on to metformin (Full Analysis Set)**

| **Metformin add-on therapy in comparison to glimepiride** | **Empagliflozin 25 mg** | **Glimepiride** |
|---|---|---|
| N | 765 | 780 |
| **HbA1c (%)** | | |
| Baseline (mean) | 7.92 | 7.92 |
| Change from baseline[1] | -0.73 | -0.66 |
| Difference from glimepiride1(97.5% CI) | -0.07*(-0.16, 0.02) | |
| N | 690 | 715 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]** | 38.7 | 39.0 |
| N | 764 | 779 |
| **Fasting plasma glucose (mmol/L)** | | |
| Baseline (mean) | 8.32 | 8.31 |
| Change from baseline[1] | -1.08 | -0.48 |
| Difference from glimepiride[1] (95% CI) | -0.59 (-0.76, -0.43) | |
| N | 765 | 780 |
| **Body Weight (kg)** | | |
| Baseline (mean) | 82.52 | 83.03 |
| Change from baseline[1] | -3.21 | 1.60 |
| Difference from glimepiride[1] (97.5% CI) | -4.81** (-5.16, -4.46) | |
| N | 765 | 780 |
| Patients(%) achieving weight loss of >5%[2] | 32.8 | 2.7 |
| N | 765 | 780 |
| **Systolic blood pressure (mmHg)[2]** | | |
| Baseline (mean) | 133.4 | 133.5 |
| Change from baseline[1] | -3.6 | 2.2 |
| Difference from glimepiride[1] (97.5% CI) | -5.8** (-7.3, -4.4) | |

1 mean adjusted for baseline value
2 not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
* p<0.0001 for non-inferiority; ** p<0.0001 for superiority

**Empagliflozin as add on to basal insulin therapy**

The efficacy and safety of empagliflozin as add on to basal insulin with or without concomitant metformin and/or sulfonylurea therapy was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. The primary endpoint was the change from baseline in HbA1c after 18 weeks of treatment. The key secondary endpoints were the change from baseline in dose of basal insulin dose after 78 weeks of treatment and change from baseline in HbA1c after 78 weeks of treatment.

During the initial 18 weeks the insulin dose was kept stable, but was adjusted to achieve a FPG < 6.10 mmol/L in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA1c compared to placebo. A greater proportion of patients with a baseline HbA1c ≥ 7.0% achieved a target HbA1c of <7% compared to placebo. At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared to placebo (Table 6).

At week 78, empagliflozin resulted in a reduction in FPG (-0.58 mmol/L for empagliflozin 10 mg, -0.97 mmol/L for empagliflozin 25 mg and -0.30 mmol/L for placebo), body weight (-2.47 kg for empagliflozin 10 mg, -1.96 kg for empagliflozin 25 mg and +1.16 kg for placebo, p< 0.0001), BP (SBP: -4.1 mmHg for empagliflozin 10 mg, -2.4 mmHg for empagliflozin 25 mg and +0.1 mmHg for placebo, DBP: -2.9 mmHg for empagliflozin 10 mg, -1.5 mmHg for empagliflozin 25 mg and -0.3 mmHg for placebo).

**Table 6 Results at 18 and 78 weeks (LOCF) in a placebo-controlled study of JARDIANCE as add on to basal insulin with or without metformin or sulfonylurea (Full Analysis Set - Completers)[a]**

| **Basal insulin +/- metformin or sulfonylurea add-on therapy** | **Placebo** | **Empagliflozin 10 mg** | **Empagliflozin 25 mg** |
|---|---|---|---|
| N | 125 | 132 | 117 |
| **HbA1c (%) at week 18** | | | |
| Baseline (mean) | 8.10 | 8.26 | 8.34 |
| Change from baseline[1] | -0.01 | -0.57 | -0.71 |
| Difference from placebo[1] | | -0.56* | -0.70* |
| (97.5% CI) | | (-0.78,-0.33) | (-0.93, -0.47) |
| N | 112 | 127 | 110 |
| **HbA1c (%) at week 78** | | | |
| Baseline (mean) | 8.09 | 8.27 | 8.29 |
| Change from baseline[1] | -0.02 | -0.48 | -0.64 |
| Difference from placebo[1] | | -0.46* | -0.62* |
| (97.5% CI) | | (-0.73, -0.19) | (-0.90, -0.34) |
| N | 112 | 127 | 110 |
| **Basal insulin dose (IU/day) at week 78** | | | |
| Baseline (mean) | 47.84 | 45.13 | 48.43 |
| Change from baseline[1] | 5.45 | -1.21 | -0.47 |
| Difference from placebo[1] | | -6.66** | -5.92** |
| (97.5% CI) | | (-11.56, -1.77) | (-11.00, -0.85) |

[a] completer analysis
[1] mean adjusted for baseline value
*p-value ≤0.0001; **p-value <0.025

**Empagliflozin as add on to DPP-4 inhibitor therapy**

The efficacy and safety of empagliflozin as add on to DPP-4 inhibitors plus metformin, with or without one additional oral anti-diabetic drug was evaluated in 160 patients with T2DM and high cardiovascular risk. Treatment with empagliflozin for 28 weeks reduced Hb1Ac compared to placebo (change from baseline -0.52% for empagliflozin and -0.02% for placebo).

**Patients with renal impairment, 52 weeks placebo controlled data**

The efficacy and safety of empagliflozin as add on to anti-diabetic therapy was evaluated in patients with mild and moderate renal impairment in a double-blind, placebo-controlled study for 52 weeks.

Treatment with JARDIANCE led to statistically significant reduction of HbA1c and clinically meaningful improvement in FPG, body weight and BP compared to placebo at Week 24 (Table 7). The improvement in HbA1c, FPG, body weight, and BP was sustained up to 52 weeks.

**Table 7 Results at 24 weeks (LOCF) in a placebo-controlled study of JARDIANCE in renally impaired type 2 diabetes patients (Full Analysis Set)**

| | eGFR ≥ 60 to <90mL/min/1.73m² | | | eGFR ≥45 to <60mL/min/1.73m² | |
|---|---|---|---|---|---|
| | Placebo | Empagliflozin | | Placebo | Empagliflozin |
| | | 10 mg | 25 mg | | 25 mg |
| N | 95 | 98 | 97 | 89 | 91 |
| **HbA1c (%)** | | | | | |
| Baseline (mean) | 8.09 | 8.02 | 7.96 | 8.08 | 8.12 |
| Change from baseline[1] | 0.06 | -0.46 | -0.63 | -0.08 | -0.54 |
| Difference from placebo[1] (95% CI) | | -0.52* (-0.72, -0.32) | -0.68* (-0.88, -0.49) | | -0.46* (-0.66, -0.27) |
| N | 89 | 94 | 91 | 84 | 86 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%**[2] | 6.7 | 17.0 | 24.2 | 10.7 | 15.1 |
| N | 95 | 98 | 97 | 89 | 90 |
| **Fasting plasma glucose (mmol/L)** | | | | | |
| Baseline (mean) | 8.04 | 8.10 | 8.24 | 8.55 | 8.02 |
| Change from baseline[1] | 0.31 | -0.77 | -1.00 | 0.37 | -0.82 |
| Difference from placebo[1] (95% CI) | | -1.09 (-1.62, -0.55) | -1.32 (-1.86, -0.78) | | -1.19 (-1.77, -0.60) |
| N | 95 | 98 | 97 | 89 | 91 |
| **Body Weight (kg)**[2] | | | | | |
| Baseline (mean) | 86.00 | 92.05 | 88.06 | 83.20 | 84.90 |
| Change from baseline[1] | -0.33 | -1.76 | -2.33 | -0.25 | -0.98 |
| Difference from placebo[1] (95% CI) | | -1.43 (-2.09, -0.77) | -2.00 (-2.66, -1.34) | | -0.74(-1.50,0.03) |
| N | 95 | 98 | 97 | 89 | 91 |
| **Systolic blood pressure (mmHg)**[2] | | | | | |
| Baseline (mean) | 134.69 | 137.37 | 133.68 | 137.29 | 135.04 |
| Change from baseline[1] | 0.65 | -2.92 | -4.47 | 0.37 | -5.69 |
| Difference from placebo[1] (95% CI) | | -3.57 (-6.86, -0.29) | -5.12 (-8.41, -1.82) | | -6.07(-9.79, -2.34) |

1 mean adjusted for baseline value
2 not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
* p<0.0001

**Patients with high baseline HbA1c >10%**

In a pre-specified pooled analysis of three phase 3 studies, treatment with open-label empagliflozin 25 mg in patients with severe hyperglycaemia (N=257, mean baseline HbA1c 11.26%) resulted in a clinically meaningful reduction in HbA1c from baseline (-3.27%).

**Body weight**

In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin 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).

**Waist circumference**

At 24 weeks, treatment with empagliflozin as monotherapy or as add-on to metformin, pioglitazone, or metformin plus sulfonylurea resulted in sustained reduction of waist circumference over the duration of studies in a range of -1.7 cm to -0.9 cm for empagliflozin and -0.5 cm to +0.2 cm 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 T2DM and high BP on different oral anti-diabetic drugs and up to 2 antihypertensive agents (Table 8). Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c and reduction in 24 hour mean SBP and DBP as determined by ambulatory BP monitoring. Treatment with empagliflozin also 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 8 Results at 12 weeks (LOCF) in a placebo-controlled study of JARDIANCE in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)**

| | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
|---|---|---|---|
| N | 271 | 276 | 276 |
| **HbA1c (%)** | | | |
| Baseline (mean) | 7.90 | 7.87 | 7.92 |
| Change from baseline[1] | 0.03 | -0.59 | -0.62 |
| Difference from placebo[1] | | -0.62* | -0.65* |
| (95% CI) | | (-0.72, -0.52) | (-0.75, -0.55) |
| **24 hour systolic blood pressure (mmHg)** | | | |
| Baseline (mean) | 131.72 | 131.34 | 131.18 |
| Change from baseline[1] | 0.48 | -2.95 | -3.68 |
| Difference from placebo[1] | | -3.44* | -4.16* |
| (97.5% CI) | | (-4.78, -2.09) | (-5.50, -2.83) |
| **24 hour diastolic blood pressure (mmHg)** | | | |
| Baseline (mean) | 75.16 | 75.13 | 74.64 |
| Change from baseline[1] | 0.32 | -1.04 | -1.40 |
| Difference from placebo[1] | | -1.36** | -1.72* |
| (97.5% CI) | | (-2.15, -0.56) | (-2.51, -0.93) |

a completer analysis
[1] mean adjusted for baseline value
*p-value <0.0001
** p-value < 0.0008

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin resulted in a reduction in SBP (-3.9 mmHg for empagliflozin 10 mg and -4.3 mmHg for empagliflozin 25 mg) compared with placebo (-0.5 mmHg), and in DBP (-1.8 mmHg for empagliflozin 10 mg and -2.0 mmHg for empagliflozin 25 mg) compared with placebo (-0.5 mmHg), at week 24, that were maintained up to week 52.

## INDICATIONS

JARDIANCE is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see CLINICAL TRIALS).

## CONTRAINDICATIONS

Hypersensitivity to empagliflozin or any of the excipients in JARDIANCE.

Patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30mL/min/1.73 $m^2$ or CrCl < 30mL/min) or eGFR persistently < 45 mL/min/1.73 $m^2$ or CrCl persistently < 45mL/mL (CKD Stage 3B). The efficacy of JARDIANCE is dependent on renal function (see PRECAUTIONS).

## PRECAUTIONS

### General

JARDIANCE should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of the product is contraindicated. This product contains 113 mg of lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

### Use in patients with renal impairment

JARDIANCE is contraindicated for use in patients with eGFR < 45 mL/min/1.73 $m^2$ (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION – Patients with renal insufficiency).

### Monitoring of renal function

Due to the mechanism of action, the efficacy of empagliflozin is dependent on renal function. Therefore assessment of renal function is recommended:

- prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.

Empagliflozin should be discontinued when the eGFR is persistently below 45 mL/min/1.73 $m^2$ or CrCl < 45 mL/min (see CONTRAINDICATIONS).

**Urinary tract infections**

The overall frequency of urinary tract infection reported as adverse event was higher than placebo in patients treated with empagliflozin 10 mg and similar to placebo in patients treated with empagliflozin 25 mg (see ADVERSE EFFECTS). Complicated urinary tract infection (e.g. pyelonephritis or urosepsis) occurred at a similar frequency in patients treated with empagliflozin compared to placebo. However, temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

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

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in BP. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in BP 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, BP measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

**Combination with glucagon like peptide (GLP-1) analogues**

Empagliflozin has not been studied in combination with glucagon like peptide 1 (GLP-1) analogues.

**Effects on fertility**

No studies on the effect on human fertility have been conducted for JARDIANCE. Studies in rats at doses up to 700 mg/kg/day, do not indicate direct or indirect harmful effects with respect to fertility. In female rats this dose was 90- and 155-fold the systemic AUC exposure anticipated with a human dose of 10 and 25 mg.

**Use in pregnancy (Category D)**

There are limited data from the use of JARDIANCE in pregnant women. It is recommended to avoid the use of JARDIANCE during pregnancy unless clearly needed.

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.

Empagliflozin administered to female rats from gestation day 6 to lactation day 20 resulted in reduced weight gain in offspring at >30 mg/kg/day (maternal exposures approximately 4- and 11- times those seen with a clinical dose of 25 mg and 10 mg, respectively). No adverse

effects on postnatal development were noted at 10 mg/kg/day (maternal exposures approximately equivalent to those seen with a clinical dose of 25 mg).

Specialised studies in rats with other members of the pharmacological class have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Similar effects have not been excluded for empagliflozin. JARDIANCE should be used in pregnancy only if the expected benefit to the patients justifies the potential risk to the fetus.

**Use in lactation**

No data in humans are available on excretion of empagliflozin into milk. Available nonclinical data in animals have shown excretion of empagliflozin in milk. Reduced body weight was observed in rats exposed to empagliflozin *in utero* and through the consumption of maternal milk (see Use in pregnancy). Adverse effects on renal development have been observed in juvenile rats treated with other members of this pharmacological class. A risk to human newborns/infants cannot be excluded. It is recommended to discontinue breast feeding during treatment with JARDIANCE.

**Paediatric use**

Safety and effectiveness of JARDIANCE in children under 18 years of age have not been established.

**Use in the elderly**

Patients age 75 years and older may be at increased risk of volume depletion, therefore, JARDIANCE should be prescribed with caution in these patients (see ADVERSE EFFECTS).

Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended.

**Genotoxicity**

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

**Carcinogenicity**

Two-year oral carcinogenicity studies were conducted in mice and rats. There was an increase in renal adenomas and carcinomas in male mice given empagliflozin at 1000 mg/kg/day. No renal tumours were seen at 300 mg/kg/day (11- and 28-times the exposure at the clinical dose of 25mg and 10 mg, respectively). These tumours are likely associated with a metabolic pathway not present in humans, and are considered to be irrelevant to patients given 10 or 25 mg empagliflozin. No drug-related tumours were seen in female mice or female rates at doses up to 1000 and 700 mg/kg/day, respectively, resulting in exposures at least 60 times that expected at the clinical dose of 10 or 25 mg empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node, were observed at 700 mg/kg/day, but not at 300 mg/kg/day (approximately 26- and 65-times the exposure at the clinical does of 25 mg and 10 mg, respectively). These tumours are common in rats and are unlikely to be relevant to humans.

**Effect on laboratory tests**

Urine will test positive for glucose while patients are taking JARDIANCE due to the nature of the mechanism of action of the SGLT2 inhibitors (see PHARMACODYNAMICS).

### Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

## INTERACTIONS WITH OTHER MEDICINES

### Diuretics

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

### *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 UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit UGT1A1. 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 isoforms or UGT1A1 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, 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 interactions were observed when empagliflozin was co-administered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of JARDIANCE is recommended when co-administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, and hydrochlorothiazide in healthy volunteers. 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 metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, and oral contraceptives when co-administered in healthy volunteers.

## ADVERSE EFFECTS

A total of 13,076 patients with T2DM were treated in clinical studies to evaluate the safety of empagliflozin, of which 8400 patients were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a PPAR$\gamma$ agonist, DPP4 inhibitors, or insulin. In clinical trials, 2876 patients received treatment with JARDIANCE (empagliflozin) 10 mg and 3738 patients have received treatment with JARDIANCE (empagliflozin) 25 mg for at least 24 weeks, and 601 and 881 patients, respectively, for at least 76 weeks.

In these trials, the frequency of adverse effects leading to discontinuation was similar by treatment groups for placebo (5.3%), JARDIANCE 10 mg (4.8%) and JARDIANCE 25 mg (4.9%).

Placebo controlled double-blinded trials of 18 to 24 weeks of exposure included 2971 patients, of which 995 were treated with placebo, 999 were treated with JARDIANCE 10 mg and 977 were treated with JARDIANCE 25 mg (Table 9).

The most frequent adverse drug reaction was hypoglycaemia, which depended on the type of background therapy used in the respective studies (Table 9).

**Table 9 Side effects with at least 2% frequency (regardless of investigator reported causality assessment) reported in patients who received JARDIANCE in placebo controlled double-blind studies of 18 up to 24 weeks, classified by MedDRA System organ class and MedDRA Preferred terms**

| | Placebo n=995 % | Empagliflozin 10 mg n=999 % | Empagliflozin 25 mg n=977 % |
|---|---|---|---|
| **System Organ Class** Adverse reaction | | | |
| **Infection and infestations** | | | |
| Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections* | 0.8 | 3.0 | 3.3 |
| Urinary tract infections* | 7.5 | 9.3 | 7.6 |
| **Metabolism and nutrition disorders** | | | |
| Hypoglycaemia (when used with sulfonylurea or insulin) | | | |
| Combination with metformin and sulfonylurea[a] | 8.4 | 16.1 | 11.5 |
| Combination with insulin[b] | 22.4 | 22.5 | 29.7 |
| **Renal and urinary disorders** | | | |
| Increased urination | 1.0 | 3.4 | 3.2 |

* based on prespecified list of preferred terms;
[a] Frequency from add on to metformin and sulfonylurea study;
[b] Frequency from add on to basal insulin study after 18 weeks of treatment

**Hypoglycaemia**

The frequency of hypoglycaemia depended on the background therapy in the respective studies.

Minor hypoglycaemia (blood glucose 3.0-3.9 mmol/L)

The frequency of patients with minor hypoglycaemia was similar for JARDIANCE and placebo as monotherapy, as add-on to metformin, and as add-on to pioglitazone +/- metformin.

The frequency of patients with minor hypoglycaemia was increased in patients treated with JARDIANCE compared to placebo when given as add-on to metformin plus sulfonylurea (JARDIANCE 10 mg 10.3%, JARDIANCE 25 mg 7.4%, placebo 5.3%), and as add-on to insulin +/- metformin and +/-sulfonylurea (during initial 18 weeks treatment when insulin could not be adjusted, frequency was 5.9% with JARDIANCE 10 mg, 7.7% with JARDIANCE 25 mg and 5.3% with placebo; over the 78 week trial, frequency was 14.2% with JARDIANCE 10 mg, 12.3% with JARDIANCE 25 mg and 12.4% with placebo).

Major hypoglycaemia (blood glucose < 3.0 mmol/L)

The frequency of patients with major hypoglycaemic events was low (<1%) and similar for JARDIANCE and placebo as monotherapy, as add-on to metformin, and as add on to pioglitazone +/- metformin.

The frequency of patients with major hypoglycaemic events was increased in patients treated with JARDIANCE compared to placebo when given as add-on to metformin plus sulfonylurea (5.8% with JARDIANCE 10 mg, 4.1% with JARDIANCE 25 mg and 3.1% with placebo), or as add-on to insulin +/- metformin and +/-sulfonylurea (during initial 18 weeks treatment when insulin could not be adjusted, frequency was 13.6% with JARDIANCE 10 mg, 20.0% with JARDIANCE 25 mg and 15.3% with placebo; over the 78 week trial, frequency was 21.9% with JARDIANCE 10 mg, 23.2% with JARDIANCE 25 mg and 22.9% with placebo).

**Urinary tract infection**

The overall frequency of urinary tract infection was similar in patients treated with JARDIANCE 25 mg and placebo (7.6%) and higher in patients treated with JARDIANCE 10 mg (9.3%). Similar to placebo, urinary tract infection was reported more frequently for JARDIANCE in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo for mild, moderate, and severe intensity reports. Urinary tract infection events were reported more frequently for empagliflozin compared to placebo in female patients, but not in male patients.

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

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for JARDIANCE 10 mg (4.1%) and JARDIANCE 25 mg (3.7%) compared to placebo (0.9%). These adverse events were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

**Increased urination**

As expected via its mechanism of action, increased urination (as assessed by preferred term search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with JARDIANCE 10 mg (3.4%) and JARDIANCE 25 mg (3.2%) compared to placebo (1.0%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and JARDIANCE (<1%).

**Volume depletion**

The overall frequency of volume depletion (including the predefined terms BP (ambulatory) decreased, SBP decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension and syncope) was similar to placebo (0.5% for JARDIANCE 10 mg, 0.3% for JARDIANCE 25 mg and 0.3% for placebo). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older. In patients ≥ 75 years of age the frequency of volume depletion events was similar for JARDIANCE 10 mg (2.3%) compared to placebo (2.1%), but it increased with JARDIANCE 25 mg (4.4%).

### Cardiovascular safety

In a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from 12 phase II and III clinical studies involving 10036 patients with T2DM, empagliflozin did not increase cardiovascular risk.

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.

## DOSAGE AND ADMINISTRATION

The recommended starting dose of JARDIANCE is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. JARDIANCE can be taken with or without food.

### Patients with renal insufficiency

JARDIANCE is not recommended for use in patients with persistent eGFR < 45 mL/min/1.73 $m^2$ (see PRECAUTIONS). No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 $m^2$.

### Patients with hepatic insufficiency

No dose adjustment is recommended for patients with hepatic impairment.

### Elderly Patients

No dosage adjustment is recommended based on age. Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended (see PRECAUTIONS). Patients age 75 years and older should be prescribed with caution (see PRECAUTIONS).

### Paediatric population

Safety and effectiveness of JARDIANCE in children under 18 years of age have not been established.

### Combination therapy

When JARDIANCE is used in combination with a sulfonylurea or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see ADVERSE EFFECTS).

## OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Symptoms: 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. There is no experience with doses above 800 mg in humans.

Treatment: In the event of an overdose, supportive treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied.

## PRESENTATION AND STORAGE CONDITIONS

JARDIANCE 10 mg film-coated tablets are pale yellow, round, biconvex and bevel-edged tablets. One side is debossed with the code 'S10', the other side is debossed with the Boehringer Ingelheim company symbol.

JARDIANCE 25 mg film-coated tablets are pale yellow, oval, biconvex tablets. One side is debossed with the code 'S25', the other side is debossed with the Boehringer Ingelheim company symbol.

JARDIANCE 10 mg is available in PVC / Aluminium blister packs containing 10 (sample) and 30 tablets.

JARDIANCE 25 mg is available in PVC / Aluminium blister packs containing 10 (sample) and 30 tablets.

Store below 30°C.

## NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

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## POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 30 April 2014