# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Jardiance 10 mg film-coated tablets
Jardiance 25 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Jardiance 10 mg film-coated tablets
Each tablet contains 10 mg empagliflozin.

Excipient with known effect
Each tablet contains lactose monohydrate equivalent to 154.3 mg lactose anhydrous.

Jardiance 25 mg film-coated tablets
Each tablet contains 25 mg empagliflozin.

Excipient with known effect
Each tablet contains lactose monohydrate equivalent to 107.4 mg lactose anhydrous.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Jardiance 10 mg film-coated tablets
Round, pale yellow, biconvex, bevel-edged film-coated tablet debossed with “S10” on one side and the Boehringer Ingelheim logo on the other (tablet diameter: 9.1 mm).

Jardiance 25 mg film-coated tablets
Oval, pale yellow, biconvex film-coated tablet debossed with “S25” on one side and the Boehringer Ingelheim logo on the other (tablet length: 11.1 mm, tablet width: 5.6 mm).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Jardiance is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
- as monotherapy when metformin is considered inappropriate due to intolerance
- in addition to other medicinal products for the treatment of diabetes

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

## 4.2 Posology and method of administration

Posology

The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy with other medicinal products for the treatment of diabetes. In patients tolerating empagliflozin 10 mg once daily who have an eGFR ≥60 ml/min/1.73 $m^2$ and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg (see below and section 4.4).

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

*Special populations*
*Renal impairment*
Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. No dose adjustment is required for patients with an eGFR ≥60 ml/min/1.73 $m^2$ or CrCl ≥60 ml/min.

Empagliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73 $m^2$ or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 $m^2$ or CrCl below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 $m^2$ or CrCl persistently below 45 ml/min (see sections 4.4, 4.8, 5.1, and 5.2).

Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in these patients (see sections 4.4 and 5.2).

*Hepatic impairment*
No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population (see section 5.2).

*Elderly*
No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account (see sections 4.4 and 4.8). In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience (see section 4.4).

*Paediatric population*
The safety and efficacy of empagliflozin in children and adolescents has not yet been established. No data are available.

Method of administration

The tablets can be taken with or without food, swallowed whole with water. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

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

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

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

In patients where DKA is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with empagliflozin may be restarted once the patient's condition has stabilised.

Before initiating empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

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

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT-2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

The safety and efficacy of empagliflozin in patients with type 1 diabetes have not been established and empagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Renal impairment
Jardiance should not be initiated in patients with an eGFR below 60 ml/min/1.73 $m^2$ or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR is persistently below 60 ml/min/1.73 $m^2$ or CrCl <60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 $m^2$ or CrCl persistently below 45 ml/min. Empagliflozin should not be used in patients with ESRD or in patients on dialysis as it is not expected to be effective in these patients (see sections 4.2 and 5.2).

Monitoring of renal function
Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. Therefore assessment of renal function is recommended as follows:
- Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly (see sections 4.2, 5.1 and 5.2).

- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

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

Elevated haematocrit
Haematocrit increase was observed with empagliflozin treatment (see section 4.8).

Elderly
The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo (see section 4.8). Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE-inhibitors). Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended (see section 4.2).

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 (see section 5.1). 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 empagliflozin should be considered until the fluid loss is corrected.

Urinary tract infections
In a pool of placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg (see section 4.8). Complicated urinary tract infections (including serious urinary tract infections, 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.

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

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.

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

Lactose
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

*Diuretics*
Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

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

Pharmacokinetic interactions

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

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

The effect of UGT induction on empagliflozin has not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy.

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

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

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

Interaction studies suggest that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

*Effects of empagliflozin on other medicinal products*
Based on *in vitro* studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.
Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Co-administration of

digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in $C_{max}$ of digoxin. These changes were not considered to be clinically meaningful.

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

Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, diuretics and oral contraceptives.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of 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 (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Jardiance during pregnancy.

Breast-feeding

No data in humans are available on excretion of empagliflozin into milk. Available toxicological data in animals have shown excretion of empagliflozin in milk. A risk to the newborns/infants cannot be excluded. Jardiance should not be used during breast-feeding.

Fertility

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

## 4.7 Effects on ability to drive and use machines

Jardiance 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 is used in combination with a sulphonylurea and/or insulin.

## 4.8 Undesirable effects

Summary of the safety profile

A total of 15,582 patients with type 2 diabetes were included in clinical studies to evaluate the safety of empagliflozin, of which 10,004 patients received empagliflozin, either alone or in combination with metformin, a sulphonylurea, pioglitazone, DPP-4 inhibitors, or insulin.

In 6 placebo-controlled trials of 18 to 24 weeks duration, 3,534 patients were included of which 1,183 were treated with placebo and 2,351 with empagliflozin. The overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin (see description of selected adverse reactions).

Tabulated list of adverse reactions

Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received empagliflozin in placebo-controlled studies are presented in the table below (Table 1).

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), or very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported in placebo-controlled studies

| **System organ class** | **Very common** | **Common** | **Uncommon** | **Rare** |
|---|---|---|---|---|
| *Infections and infestations* | | Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[a]<br>Urinary tract infection[a] | | |
| *Metabolism and nutrition disorders* | Hypoglycaemia (when used with sulphonylurea or insulin)[a] | Thirst | | Diabetic ketoacidosis[*, b] |
| *Skin and subcutaneous disorders* | | Pruritus (generalised) | | |
| *Vascular disorders* | | | Volume depletion[a] | |
| *Renal and urinary disorders* | | Increased urination[a] | Dysuria | |
| *Investigations* | | Serum lipids increased[c] | Blood creatinine increased/Glomerular filtration rate decreased[a]<br>Haematocrit increased[d] | |

[a] see subsections below for additional information
[b] derived from postmarketing experience
[c] Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 4.9% and 5.7% versus 3.5%; HDL-cholesterol 3.3% and 3.6% versus 0.4%; LDL-cholesterol 9.5% and 10.0% versus 7.5%; triglycerides 9.2% and 9.9% versus 10.5%.
[d] Mean changes from baseline in haematocrit were 3.4% and 3.6% for empagliflozin 10 mg and 25 mg, respectively, compared to 0.1% 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.
[*] see section 4.4

Description of selected adverse reactions

*Hypoglycaemia*
The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as monotherapy, add-on to metformin, add-on to pioglitazone with or without metformin, as add-on to linagliptin and metformin, and as adjunct to standard care therapy and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to metformin and a sulfonylurea (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5%, placebo: 8.4%), add-on to basal insulin with or without metformin and with or without a sulphonylurea (empagliflozin 10 mg: 19.5%, empagliflozin 25 mg: 28.4%, placebo: 20.6% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25 mg: 36.1%, placebo 35.3% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8%, empagliflozin 25 mg: 41.3%, placebo: 37.2% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1%, empagliflozin 25 mg: 57.7%, placebo: 58% over the 52-week trial).

*Major hypoglycaemia (events requiring assistance)*
No increase in major hypoglycaemia was observed with empagliflozin compared to placebo as monotherapy, add-on to metformin, add-on to metformin and a sulfonylurea, add-on to pioglitazone with or without metformin, add-on to linagliptin and metformin, as adjunct to standard care therapy and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to basal insulin with or without metformin and with or without a sulfonylurea (empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo: 0% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo 0% over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 1.6%, empagliflozin 25 mg: 0.5%, placebo: 1.6% during initial 18 weeks treatment when insulin could not be adjusted and over the 52-week trial).

*Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection*
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in patients treated with empagliflozin (empagliflozin 10 mg: 4.0%, empagliflozin 25 mg: 3.9%) compared to placebo (1.0%). These infections were reported more frequently in females treated with empagliflozin compared to placebo, and the difference in frequency was less pronounced in males. The genital tract infections were mild or moderate in intensity.

*Increased urination*
Increased urination (including the predefined terms pollakiuria, polyuria, and nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg: 3.5%, empagliflozin 25 mg: 3.3%) compared to placebo (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was similar for placebo and empagliflozin (<1%).

*Urinary tract infection*
The overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%) and higher in empagliflozin 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity (mild, moderate, severe) of urinary tract infection was similar in patients treated with empagliflozin and placebo. Urinary tract infection was reported more frequently in females treated with empagliflozin compared to placebo; there was no difference in males.

*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 similar in patients treated with empagliflozin (empagliflozin 10 mg: 0.6%, empagliflozin 25 mg: 0.4%) and placebo (0.3%). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3%) or empagliflozin 25 mg (4.3%) compared to placebo (2.1%).

*Blood creatinine increased/Glomerular filtration rate decreased*
The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).
Initial increases in creatinine and initial decreases in estimated glomerular filtration rates in patients treated with empagliflozin were generally transient during continuous treatment or reversible after drug discontinuation of treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Symptoms

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

Therapy

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Other blood glucose lowering drugs, excl. insulins, ATC code: A10BX12

Mechanism of action

Empagliflozin is a reversible, highly potent ($IC_{50}$ of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

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

In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24 hour dosing interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction. The glucosuria observed with empagliflozin is accompanied by diuresis which may contribute to sustained and moderate

reduction of blood pressure. The glucosuria, natriuresis and osmotic diuresis observed with empagliflozin may contribute to the improvement in cardiovascular outcomes.

Clinical efficacy and safety

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

Glycaemic efficacy and cardiovascular outcomes have been assessed in a total of 14,663 patients with type 2 diabetes who were treated in 12 double-blind, placebo- and active-controlled clinical studies, of which 9,295 received empagliflozin (empagliflozin 10 mg: 4,165 patients; empagliflozin 25 mg: 5,130 patients). Five studies had treatment durations of 24 weeks; extensions of those and other studies had patients exposed to empagliflozin for up to 102 weeks.

Treatment with empagliflozin as monotherapy and in combination with metformin, pioglitazone, a sulphonylurea, DPP-4 inhibitors, and insulin lead to clinically relevant improvements in HbA1c, fasting plasma glucose (FPG), body weight, and systolic and diastolic blood pressure. 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. Higher baseline HbA1c was associated with a greater reduction in HbA1c. In addition, empagliflozin as adjunct to standard care therapy reduced cardiovascular mortality in patients with type 2 diabetes and established cardiovascular disease.

*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. Treatment with empagliflozin resulted in a statistically significant ($p<0.0001$) reduction in HbA1c compared to placebo (Table 2) and a clinically meaningful decrease in FPG.
In a prespecified analysis of patients (N=201) with a baseline HbA1c ≥8.5%, treatment resulted in a reduction in HbA1c from baseline of -1.44% for empagliflozin 10 mg, -1.43% for empagliflozin 25 mg, -1.04% for sitagliptin, and an increase of 0.01% for placebo.
In the double-blind placebo-controlled extension of this study, reductions of HbA1c, body weight and blood pressure were sustained up to Week 76.

Table 2: Efficacy results of a 24 week placebo-controlled study of empagliflozin as monotherapy[a]

| | Placebo | Jardiance | | Sitagliptin |
|---|---|---|---|---|
| | | 10 mg | 25 mg | 100 mg |
| 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] (97.5% CI) | | -0.74* (-0.90, -0.57) | -0.85* (-1.01, -0.69) | -0.73 (-0.88, -0.59)[3] |
| N | 208 | 204 | 202 | 200 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]** | 12.0 | 35.3 | 43.6 | 37.5 |
| 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] (97.5% CI) | | -1.93* (-2.48, -1.38) | -2.15* (-2.70,-1.60) | 0.52 (-0.04, 1.00)[3] |
| N | 228 | 224 | 224 | 223 |
| **SBP (mmHg)[4]** | | | | |
| 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] (97.5% CI) | | -2.6* (-5.2, -0.0) | -3.4* (-6.0, -0.9) | 0.8 (-1.4, 3.1)[3] |

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[1] Mean adjusted for baseline value
[2] Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
[3] 95% CI
[4] LOCF, values after antihypertensive rescue censored
*p-value <0.0001

*Combination therapy*
*Empagliflozin as add-on to metformin, sulphonylurea, pioglitazone*
Empagliflozin as add-on to metformin, metformin and a sulphonylurea, or pioglitazone with or without metformin resulted in statistically significant ($p<0.0001$) reductions in HbA1c and body weight compared to placebo (Table 3). In addition it resulted in a clinically meaningful reduction in FPG, systolic and diastolic blood pressure compared to placebo.
In the double-blind placebo-controlled extension of these studies, reduction of HbA1c, body weight and blood pressure were sustained up to Week 76.

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

| **Add-on to metformin therapy** | | | |
|---|---|---|---|
| | **Placebo** | **Jardiance** | |
| | | **10 mg** | **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 | 217 | 213 |
| **Body Weight (kg)** | | | |
| Baseline (mean) | 79.73 | 81.59 | 82.21 |
| Change from baseline[1] | -0.45 | -2.08 | -2.46 |
| Difference from placebo[1] (97.5% CI) | | -1.63* (-2.17, -1.08) | -2.01* (-2.56, -1.46) |
| N | 207 | 217 | 213 |
| **SBP (mmHg)[2]** | | | |
| Baseline (mean) | 128.6 | 129.6 | 130.0 |
| Change from baseline[1] | -0.4 | -4.5 | -5.2 |
| Difference from placebo[1] (95% CI) | | -4.1* (-6.2, -2.1) | -4.8* (-6.9, -2.7) |
| **Add-on to metformin and a sulphonylurea therapy** | | | |
| | **Placebo** | **Jardiance** | |
| | | **10 mg** | **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 | 225 | 225 | 216 |
| **Body Weight (kg)** | | | |
| Baseline (mean) | 76.23 | 77.08 | 77.50 |
| Change from baseline[1] | -0.39 | -2.16 | -2.39 |
| Difference from placebo[1] (97.5% CI) | | -1.76* (-2.25, -1.28) | -1.99* (-2.48, -1.50) |
| N | 225 | 225 | 216 |
| **SBP (mmHg)[2]** | | | |
| Baseline (mean) | 128.8 | 128.7 | 129.3 |
| Change from baseline[1] | -1.4 | -4.1 | -3.5 |
| Difference from placebo[1] (95% CI) | | -2.7 (-4.6, -0.8) | -2.1 (-4.0, -0.2) |

| Add-on to pioglitazone +/- metformin therapy | | | |
|---|---|---|---|
| | **Placebo** | **Jardiance** | |
| | | **10 mg** | **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 placebo[1] (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%[2]** | 7.7 | 24 | 30 |
| 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 placebo[1] (97.5% CI) | | -1.95* (-2.64, -1.27) | -1.81* (-2.49, -1.13) |
| N | 165 | 165 | 168 |
| **SBP (mmHg)[3]** | | | |
| 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) |

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

[1] Mean adjusted for baseline value

[2] Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure

[3] LOCF, values after antihypertensive rescue censored

***** p-value <0.0001

*In combination with metformin in drug-naïve patients*

A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in drug-naïve patients. Treatment with empagliflozin in combination with metformin (5 mg and 500 mg; 5 mg and 1000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1000 mg given twice daily) provided statistically significant improvements in HbA1c (Table 4) and led to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin).

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

| | Empagliflozin 10 mg[b] | | | Empagliflozin 25 mg[b] | | | Metformin[c] | |
|---|---|---|---|---|---|---|---|---|
| | + Met 1000 mg[c] | + Met 2000 mg[c] | No Met | + Met 1000 mg[c] | + Met 2000 mg[c] | No Met | 1000 mg | 2000 mg |
| N | 169 | 171 | 172 | 170 | 170 | 167 | 171 | 170 |
| **HbA1c (%)** | | | | | | | | |
| Baseline (mean) | 8.68 | 8.65 | 8.62 | 8.84 | 8.66 | 8.86 | 8.69 | 8.55 |
| Change from baseline[1] | -1.98 | -2.07 | -1.35 | -1.93 | -2.08 | -1.36 | -1.18 | -1.75 |
| Comparison vs. empa (95% CI)[1] | -0.63* (-0.86, -0.40) | -0.72* (-0.96, -0.49) | | -0.57* (-0.81, -0.34) | -0.72* (-0.95, -0.48) | | | |
| Comparison vs. met (95% CI)[1] | -0.79* (-1.03, -0.56) | -0.33* (-0.56, -0.09) | | -0.75* (-0.98 -0.51) | -0.33* (-0.56, -0.10) | | | |

Met = metformin; empa = empagliflozin

[1] mean adjusted for baseline value

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

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

[c] Given in two equally divided doses per day

*$p \leq 0.0062$ for HbA1c

*Empagliflozin in patients inadequately controlled with metformin and linagliptin*

In patients inadequately controlled with metformin and linagliptin 5 mg, treatment with both empagliflozin 10 mg or 25 mg resulted in statistically significant ($p<0.0001$) reductions in HbA1c and body weight compared to placebo (Table 5). In addition it resulted in clinically meaningful reductions in FPG, systolic and diastolic blood pressure compared to placebo.

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

| **Add-on to metformin and linagliptin 5 mg** | | | |
|---|---|---|---|
| | **Placebo**[5] | **Empagliflozin**[6] | |
| | | **10 mg** | **25 mg** |
| N | 106 | 109 | 110 |
| **HbA1c (%)**[3] | | | |
| Baseline (mean) | 7.96 | 7.97 | 7.97 |
| Change from baseline[1] | 0.14 | -0.65 | -0.56 |
| Difference from placebo (95% CI) | | -0.79* (-1.02, -0.55) | -0.70* (-0.93, -0.46) |
| N | 100 | 100 | 107 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%**[2] | 17.0 | 37.0 | 32.7 |
| N | 106 | 109 | 110 |
| **Body Weight (kg)**[3] | | | |
| Baseline (mean) | 82.3 | 88.4 | 84.4 |
| Change from baseline[1] | -0.3 | -3.1 | -2.5 |
| Difference from placebo (95% CI) | | -2.8* (-3.5, -2.1) | -2.2* (-2.9, -1.5) |
| N | 106 | 109 | 110 |
| **SBP (mmHg)**[4] | | | |
| Baseline (mean) | 130.1 | 130.4 | 131.0 |
| Change from baseline[1] | -1.7 | -3.0 | -4.3 |
| Difference from placebo (95% CI) | | -1.3 (-4.2, 1.7) | -2.6 (-5.5, 0.4) |

[1] Mean adjusted for baseline value
[2] Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[3] MMRM model on FAS (OC) included baseline HbA1c, baseline eGFR (MDRD), geographical region, visit, treatment, and treatment by visit interaction. For weight, baseline weight was included.
[4] MMRM model included baseline SBP and baseline HbA1c as linear covariate(s), and baseline eGFR, geographical region, treatment, visit, and visit by treatment interaction as fixed effects.
[5] Patients randomized to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin
[6] Patients randomized to the empagliflozin 10 mg or 25 mg groups were receiving empagliflozin 10 mg or 25 mg and linagliptin 5 mg with background metformin
* p-value <0.0001

In a prespecified subgroup of patients with baseline HbA1c greater or equal than 8.5% the reduction from baseline in HbA1c was -1.3% with empagliflozin 10 mg or 25 mg at 24 weeks (p<0.0001) compared to placebo.

*Empagliflozin 24 months data, as add-on to metformin in comparison to glimepiride*
In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (up to 4 mg per day) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA1c (Table 6), and a clinically meaningful reduction in FPG, compared to glimepiride. Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure and a statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, p<0.0001).

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

| | **Empagliflozin 25 mg** | **Glimepiride[b]** |
|---|---|---|
| N | 765 | 780 |
| **HbA1c (%)** | | |
| Baseline (mean) | 7.92 | 7.92 |
| Change from baseline[1] | -0.66 | -0.55 |
| Difference from glimepiride[1] (97.5% CI) | -0.11* (-0.20, -0.01) | |
| N | 690 | 715 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]** | 33.6 | 30.9 |
| N | 765 | 780 |
| **Body Weight (kg)** | | |
| Baseline (mean) | 82.52 | 83.03 |
| Change from baseline[1] | -3.12 | 1.34 |
| Difference from glimepiride[1] (97.5% CI) | -4.46** (-4.87, -4.05) | |
| N | 765 | 780 |
| **SBP (mmHg)[2]** | | |
| Baseline (mean) | 133.4 | 133.5 |
| Change from baseline[1] | -3.1 | 2.5 |
| Difference from glimepiride[1] (97.5% CI) | -5.6** (-7.0,-4.2) | |

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[b] Up to 4 mg glimepiride
[1] Mean adjusted for baseline value
[2] LOCF, values after antihypertensive rescue censored
* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority
** p-value <0.0001

*Add-on to insulin therapy*
*Empagliflozin as add-on to multiple daily insulin*
The efficacy and safety of empagliflozin as add-on to multiple daily insulin with or without concomitant metformin therapy was evaluated in a double-blind, placebo-controlled trial of 52 weeks duration. During the initial 18 weeks and the last 12 weeks, the insulin dose was kept stable, but was adjusted to achieve pre-prandial glucose levels <100 mg/dl [5.5 mmol/l], and post-prandial glucose levels <140 mg/dl [7.8 mmol/l] between Weeks 19 and 40.
At Week 18, empagliflozin provided statistically significant improvement in HbA1c compared with placebo (Table 7).
At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared with placebo and a reduction in FPG and body weight.

Table 7: Efficacy results at 18 and 52 weeks in a placebo-controlled study of empagliflozin as add on to multiple daily doses of insulin with or without metformin

| | **Placebo** | **Jardiance** | |
|---|---|---|---|
| | | **10 mg** | **25 mg** |
| N | 188 | 186 | 189 |
| **HbA1c (%) at week 18** | | | |
| Baseline (mean) | 8.33 | 8.39 | 8.29 |
| Change from baseline[1] | -0.50 | -0.94 | -1.02 |
| Difference from placebo[1] (97.5% CI) | | -0.44* (-0.61, -0.27) | -0.52* (-0.69, -0.35) |
| N | 115 | 119 | 118 |
| **HbA1c (%) at week 52**[2] | | | |
| Baseline (mean) | 8.25 | 8.40 | 8.37 |
| Change from baseline[1] | -0.81 | -1.18 | -1.27 |
| Difference from placebo[1] (97.5% CI) | | -0.38*** (-0.62, -0.13) | -0.46* (-0.70, -0.22) |
| N | 113 | 118 | 118 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% at week 52** | 26.5 | 39.8 | 45.8 |
| N | 115 | 118 | 117 |
| **Insulin dose (IU/day) at week 52**[2] | | | |
| Baseline (mean) | 89.94 | 88.57 | 90.38 |
| Change from baseline[1] | 10.16 | 1.33 | -1.06 |
| Difference from placebo[1] (97.5% CI) | | -8.83# (-15.69, -1.97) | -11.22** (-18.09, -4.36) |
| N | 115 | 119 | 118 |
| **Body Weight (kg) at week 52**[2] | | | |
| Baseline (mean) | 96.34 | 96.47 | 95.37 |
| Change from baseline[1] | 0.44 | -1.95 | -2.04 |
| Difference from placebo[1] (97.5% CI) | | -2.39* (-3.54, -1.24) | -2.48* (-3.63, -1.33) |

[1] Mean adjusted for baseline value

[2] Week 19-40: treat-to-target regimen for insulin dose adjustment to achieve pre-defined glucose target levels (pre-prandial <100 mg/dl (5.5 mmol/l), post-prandial <140 mg/dl (7.8 mmol/l)

* p-value <0.0001

** p-value = 0.0003

*** p-value = 0.0005

# p-value = 0.0040

*Empagliflozin as add-on to basal insulin*

The efficacy and safety of empagliflozin as add-on to basal insulin with or without metformin and/or a sulphonylurea was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. During the initial 18 weeks the insulin dose was kept stable, but was adjusted to achieve a FPG <110 mg/dl in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA1c (Table 8).

At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared to placebo. Furthermore, empagliflozin resulted in a reduction in FPG, body weight, and blood pressure.

Table 8: Efficacy results at 18 and 78 weeks in a placebo-controlled study of empagliflozin as add-on to basal insulin with or without metformin or a sulphonylurea[a]

| | **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] (97.5% CI) | | -0.56* (-0.78, -0.33) | -0.70* (-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] (97.5% CI) | | -0.46* (-0.73, -0.19) | -0.62* (-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] (97.5% CI) | | -6.66** (-11.56, -1.77) | -5.92** (-11.00, -0.85) |

[a] Full analysis set (FAS) - Completers using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[1] mean adjusted for baseline value
* p-value <0.0001
** p-value <0.025

*Patients with renal impairment, 52 week placebo controlled data*
The efficacy and safety of empagliflozin as add-on to antidiabetic therapy was evaluated in patients with renal impairment in a double-blind, placebo-controlled study for 52 weeks. Treatment with empagliflozin led to a statistically significant reduction of HbA1c (Table 9) and clinically meaningful improvement in FPG compared to placebo at Week 24. The improvement in HbA1c, body weight, and blood pressure was sustained up to 52 weeks.

Table 9: Results at 24 week in a placebo-controlled study of empagliflozin in renally impaired type 2 diabetes patients[a]

| | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg | Placebo | Empagliflozin 25 mg |
|---|---|---|---|---|---|
| | eGFR ≥60 to <90 ml/min/1.73 m² | | | eGFR ≥30 to <60 ml/min/1.73 m² | |
| N | 95 | 98 | 97 | 187 | 187 |
| **HbA1c (%)** | | | | | |
| Baseline (mean) | 8.09 | 8.02 | 7.96 | 8.04 | 8.03 |
| Change from baseline[1] | 0.06 | -0.46 | -0.63 | 0.05 | -0.37 |
| Difference from placebo[1] (95% CI) | | -0.52* (-0.72, -0.32) | -0.68* (-0.88, -0.49) | | -0.42* (-0.56, -0.28) |
| N | 89 | 94 | 91 | 178 | 175 |
| **Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]** | 6.7 | 17.0 | 24.2 | 7.9 | 12.0 |
| N | 95 | 98 | 97 | 187 | 187 |
| **Body Weight (kg)[2]** | | | | | |
| Baseline (mean) | 86.00 | 92.05 | 88.06 | 82.49 | 83.22 |
| Change from baseline[1] | -0.33 | -1.76 | -2.33 | -0.08 | -0.98 |
| Difference from placebo[1] (95% CI) | | -1.43 (-2.09, -0.77) | -2.00 (-2.66, -1.34) | | -0.91 (-1.41, -0.41) |
| N | 95 | 98 | 97 | 187 | 187 |
| **SBP (mmHg)[2]** | | | | | |
| Baseline (mean) | 134.69 | 137.37 | 133.68 | 136.38 | 136.64 |
| Change from baseline[1] | 0.65 | -2.92 | -4.47 | 0.40 | -3.88 |
| Difference from placebo[1] (95% CI) | | -3.57 (-6.86, -0.29) | -5.12 (-8.41, -1.82) | | -4.28 (-6.88, -1.68) |

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

[1] Mean adjusted for baseline value

[2] Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure

* p<0.0001

*Cardiovascular outcome*

The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with type 2 diabetes and established cardiovascular disease. A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA1c was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a sulfonylurea. About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 $m^2$, 17.8% of 45-60 ml/min/1.73 $m^2$ and 7.7% of 30-45 ml/min/1.73 $m^2$.

At week 12, an adjusted mean (SE) improvement in HbA1c when compared to baseline of 0.11% (0.02) in the placebo group, 0.65% (0.02) and 0.71% (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA1c of 0.08% (0.02) in the placebo group, 0.50% (0.02) and 0.55% (0.02) in the empagliflozin 10 and 25 mg groups.

Empagliflozin was superior in reducing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg (Figure 1) and confirmed by an improved overall survival (Table 10).

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

Table 10: Treatment effect for the primary composite endpoint, its components and mortality[a]

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

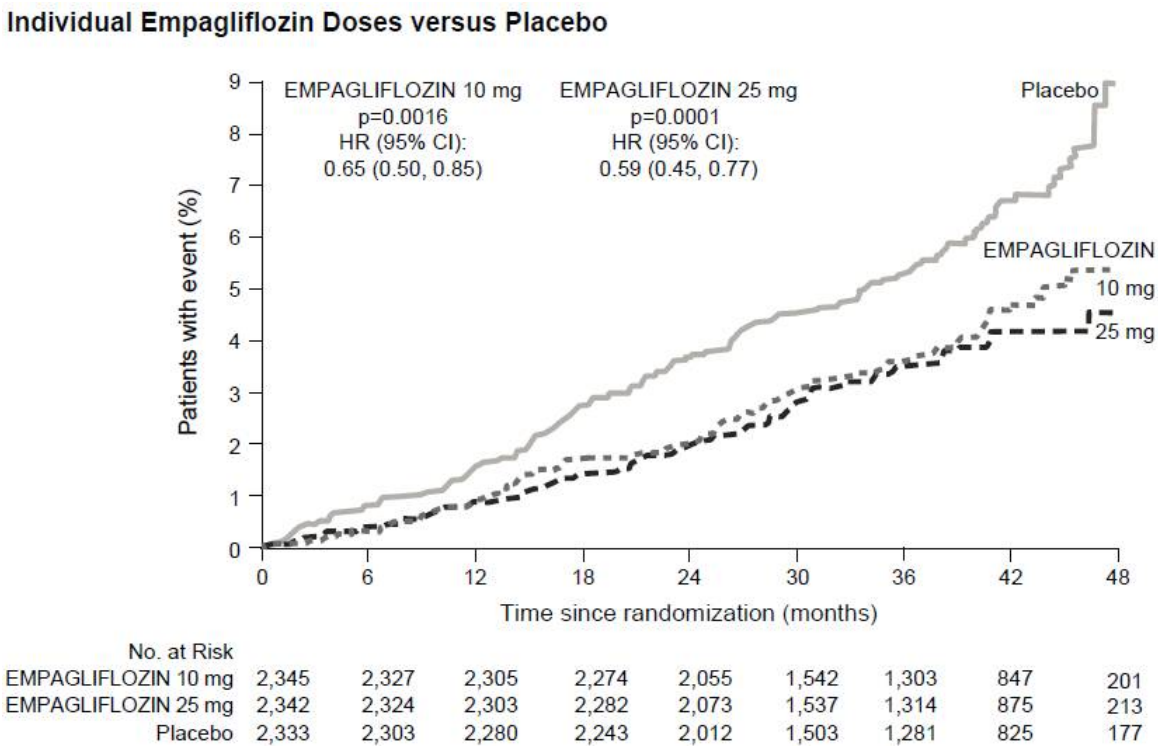
CV = cardiovascular, MI = myocardial infarction

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

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

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

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




Fasting plasma glucose

In four placebo-controlled studies, treatment with empagliflozin as monotherapy or add-on therapy to metformin, pioglitazone, or metformin plus a sulfonylurea resulted in mean changes from baseline in FPG of -20.5 mg/dl [-1.14 mmol/l] for empagliflozin 10 mg and -23.2 mg/dl [-1.29 mmol/l] for empagliflozin 25 mg compared to placebo (7.4 mg/dl [0.41 mmol/l]). This effect was observed after 24 weeks and maintained for 76 weeks.

2-hour post-prandial glucose

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

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=184, mean baseline HbA1c 11.15%) resulted in a clinically meaningful reduction in HbA1c from baseline of 3.27% at week 24; no placebo or empagliflozin 10 mg arms were included in these studies.

Body weight

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

Blood pressure

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic and up to 2 antihypertensive therapies. Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, and 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (Table 11). Treatment with empagliflozin provided reductions in seated SBP and DBP.

Table 11: Efficacy results at 12 week in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure[a]

| | **Placebo** | **Jardiance** | |
|---|---|---|---|
| | | **10 mg** | **25 mg** |
| N | 271 | 276 | 276 |
| **HbA1c (%) at week 12[1]** | | | |
| Baseline (mean) | 7.90 | 7.87 | 7.92 |
| Change from baseline[2] | 0.03 | -0.59 | -0.62 |
| Difference from placebo[2] (95% CI) | | -0.62* (-0.72, -0.52) | -0.65* (-0.75, -0.55) |
| **24 hour SBP at week 12[3]** | | | |
| Baseline (mean) | 131.72 | 131.34 | 131.18 |
| Change from baseline[4] | 0.48 | -2.95 | -3.68 |
| Difference from placebo[4] (95% CI) | | -3.44* (-4.78, -2.09) | -4.16* (-5.50, -2.83) |
| **24 hour DBP at week 12[3]** | | | |
| Baseline (mean) | 75.16 | 75.13 | 74.64 |
| Change from baseline[5] | 0.32 | -1.04 | -1.40 |
| Difference from placebo[5] (95% CI) | | -1.36** (-2.15, -0.56) | -1.72* (-2.51, -0.93) |

[a] Full analysis set (FAS)
[1] LOCF, values after taking antidiabetic rescue therapy censored
[2] Mean adjusted for baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products
[3] LOCF, values after taking antidiabetic rescue therapy or changing antihypertensive rescue therapy censored
[4] Mean adjusted for baseline SBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products
[5] Mean adjusted for baseline DBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products
* p-value <0.0001
** p-value <0.001

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

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Jardiance in one or more subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

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

Biotransformation

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

Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [$^{14}$C]-empagliflozin solution to healthy volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Special populations

*Renal impairment*
In patients with mild, moderate or severe renal impairment (eGFR <30 - <90 ml/min/1.73 m$^2$) and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as

compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure.

*Hepatic impairment*
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and $C_{max}$ by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

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

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

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

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

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

## 5.3 Preclinical safety data

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

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

Empagliflozin is not genotoxic.

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

maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

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

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Lactose monohydrate
Microcrystalline cellulose
Hydroxypropylcellulose
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

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

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

PVC/aluminium perforated unit dose blisters.
Pack sizes of 7 x 1, 10 x 1, 14 x 1, 28 x 1, 30 x 1, 60 x 1, 70 x 1, 90 x 1, and 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

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

## 7. MARKETING AUTHORISATION HOLDER

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

## 8. MARKETING AUTHORISATION NUMBER(S)

Jardiance 10 mg film-coated tablets
EU/1/14/930/010
EU/1/14/930/011
EU/1/14/930/012
EU/1/14/930/013
EU/1/14/930/014
EU/1/14/930/015
EU/1/14/930/016
EU/1/14/930/017
EU/1/14/930/018

Jardiance 25 mg film-coated tablets
EU/1/14/930/001
EU/1/14/930/002
EU/1/14/930/003
EU/1/14/930/004
EU/1/14/930/005
EU/1/14/930/006
EU/1/14/930/007
EU/1/14/930/008
EU/1/14/930/009

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 May 2014

## 10. DATE OF REVISION OF THE TEXT

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

# ANNEX II

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

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

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

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

Boehringer Ingelheim Ellas A.E.
5th km Paiania – Markopoulo
Koropi Attiki, 19400
Greece

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

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Jardiance 10 mg film-coated tablets
Empagliflozin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of empagliflozin.

## 3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 film-coated tablets
10 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
60 x 1 film-coated tablets
70 x 1 film-coated tablets
90 x 1 film-coated tablets
100 x 1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/930/010 7 tablets
EU/1/14/930/011 10 tablets
EU/1/14/930/012 14 tablets
EU/1/14/930/013 28 tablets
EU/1/14/930/014 30 tablets
EU/1/14/930/015 60 tablets
EU/1/14/930/016 70 tablets
EU/1/14/930/017 90 tablets
EU/1/14/930/018 100 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Jardiance 10 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blisters (perforated)**

## 1. NAME OF THE MEDICINAL PRODUCT

Jardiance 10 mg tablets
Empagliflozin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Jardiance 25 mg film-coated tablets
Empagliflozin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg of empagliflozin.

## 3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

7 x 1 film-coated tablets
10 x 1 film-coated tablets
14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
60 x 1 film-coated tablets
70 x 1 film-coated tablets
90 x 1 film-coated tablets
100 x 1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/930/001 7 tablets
EU/1/14/930/002 10 tablets
EU/1/14/930/003 14 tablets
EU/1/14/930/004 28 tablets
EU/1/14/930/005 30 tablets
EU/1/14/930/006 60 tablets
EU/1/14/930/007 70 tablets
EU/1/14/930/008 90 tablets
EU/1/14/930/009 100 tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Jardiance 25 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blisters (perforated)**

## 1. NAME OF THE MEDICINAL PRODUCT

Jardiance 25 mg tablets
Empagliflozin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Jardiance 10 mg film-coated tablets**
**Jardiance 25 mg film-coated tablets**
empagliflozin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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

**What is in this leaflet**



## 1. What Jardiance is and what it is used for

Jardiance contains the active substance empagliflozin which works by blocking a protein in the kidneys called sodium-glucose co-transporter 2 (SGLT2). SGLT2 prevents glucose from being excreted in urine by absorbing glucose into the bloodstream as blood is being filtered in the kidneys. By blocking this protein, the medicine causes glucose (blood sugar), sodium (salt) and water to be removed via the urine. Blood glucose levels, which are too high because of your type 2 diabetes, are thereby reduced.

- Jardiance is used to treat type 2 diabetes in adult patients (aged 18 years and older) that cannot be controlled by diet and exercise alone.
- Jardiance can be used without other medicines in patients who cannot take metformin (another diabetes medicine).
- Jardiance can also be used with other medicines for the treatment of diabetes. These may be medicines taken by mouth or given by injection such as insulin.

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

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

## 2. What you need to know before you take Jardiance

**Do not take Jardiance:**
- if you are allergic to empagliflozin or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before taking this medicine, and during treatment:
- about what you can do to prevent dehydration
- if you have "type 1 diabetes". This type usually starts when you are young and your body does not produce any insulin.
- if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, contact a doctor or the nearest hospital straight away. These symptoms could be a sign of "diabetic ketoacidosis" – a problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests. The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness.
- if you have serious kidney problems – your doctor may ask you to take a different medicine.
- if you are 75 years old or older, as increased passing of urine due to the medicine may affect fluid balance in your body and increase your risk of dehydration. Possible signs are listed in section 4, 'Possible side effects' under 'dehydration'.
- if you are 85 years old or older as you should not start taking Jardiance.
- if you are being sick, have diarrhoea or fever, or if you are not able to eat or drink. These conditions can cause dehydration. Your doctor may ask you to stop taking Jardiance until you recover to prevent loss of too much body fluid.
- if you have a serious infection of the kidney or the urinary tract with fever. Your doctor may ask you to stop taking Jardiance until you have recovered.

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

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

**Children and adolescents**
Jardiance is not recommended for children and adolescents under 18 years, because it has not been studied in these patients.

**Other medicines and Jardiance**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
It is important to tell your doctor:
- if you are taking a medicine used to remove water from the body (diuretic). Your doctor may ask you to stop taking Jardiance. Possible signs of losing too much fluid from your body are listed in section 4 'Possible side effects'.
- if you are taking other medicines that lower the amount of sugar in your blood such as insulin or a "sulphonylurea" medicine. Your doctor may want to lower the dose of these other medicines, to prevent your blood sugar levels from getting too low (hypoglycaemia).

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use Jardiance if you are

pregnant. It is unknown if Jardiance is harmful to the unborn child. Do not use Jardiance if you are breast-feeding. It is not known if Jardiance passes into human breast milk.

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

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

**Jardiance contains lactose**
Jardiance contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Jardiance

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

**How much to take**
- The starting dose of Jardiance is one 10 mg tablet once a day. Your doctor will decide whether to increase your dose to 25 mg once a day.
- Your doctor may limit your dose to 10 mg once a day if you have a kidney problem.
- Your doctor will prescribe the strength that is right for you. Do not change your dose unless your doctor has told you to.

**Taking this medicine**
- Swallow the tablet whole with water
- You can take the tablet with or without food
- You can take the tablet at any time of the day. However, try to take it at the same time each day. This will help you to remember to take it.

Your doctor may prescribe Jardiance together with another diabetes medicine. Remember to take all medicines as directed by your doctor to achieve the best results for your health.

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

**If you take more Jardiance than you should**
If you take more Jardiance than you should, talk to a doctor immediately or go to a hospital immediately. Take the medicine pack with you.

**If you forget to take Jardiance**
What to do if you forget to take a tablet depends on how long it is until your next dose.
- If it is 12 hours or more until your next dose, take Jardiance as soon as you remember. Then take your next dose at the usual time.
- If it is less than 12 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose of Jardiance to make up for a forgotten dose.

**If you stop taking Jardiance**
Do not stop taking Jardiance without first consulting your doctor. Your blood sugar levels may increase when you stop taking Jardiance.

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

## 4. Possible side effects

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

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

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

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

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

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

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

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

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

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

**Other side effects while taking Jardiance:**
Common
- genital yeast infection (thrush)

- passing more urine than usual or needing to pass urine more often
- itching
- thirst
- blood tests may show changes in blood fat (cholesterol) levels in your blood

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

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

## 5. How to store Jardiance

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

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

This medicine does not require any special storage conditions.

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

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

## 6. Contents of the pack and other information

**What Jardiance contains**
- The active substance is empagliflozin.
  - Each tablet contains 10 mg or 25 mg empagliflozin.

- The other ingredients are:
  - tablet core: lactose monohydrate (see end of section 2 under 'Jardiance contains lactose'), cellulose microcrystalline, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate
  - film-coating: hypromellose, titanium dioxide (E171), talc, macrogol (400), iron oxide yellow (E172)

**What Jardiance looks like and contents of the pack**
Jardiance 10 mg film-coated tablets are round, pale yellow, biconvex and bevel-edged. They have "S10" on one side and the Boehringer Ingelheim logo on the other side. The tablets are 9.1 mm in diameter.
Jardiance 25 mg film-coated tablets are oval, pale yellow and biconvex. They have "S25" on one side and the Boehringer Ingelheim logo on the other side. The tablet is 11.1 mm long and has a width of 5.6 mm.

Jardiance tablets are available in PVC/aluminium perforated unit dose blisters. The pack sizes are 7 x 1, 10 x 1, 14 x 1, 28 x 1, 30 x 1, 60 x 1, 70 x 1, 90 x 1, and 100 x 1 film-coated tablets.

Not all pack sizes may be marketed in your country.

**Marketing Authorisation Holder**

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

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

Boehringer Ingelheim Ellas A.E.
5th km Paiania – Markopoulo
Koropi Attiki, 19400
Greece

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
SCS Boehringer Ingelheim Comm.V
Tél/Tel: +32 2 773 33 11

**Lietuva**
Boehringer Ingelheim RCV GmbH & Co KG
Lietuvos filialas
Tel: +370 37 473922

**България**
Бьорингер Ингелхайм РЦВ ГмбХ и Ко. КГ - клон България
Тел: +359 2 958 79 98

**Luxembourg/Luxemburg**
SCS Boehringer Ingelheim Comm.V
Tél/Tel: +32 2 773 33 11

**Česká republika**
Boehringer Ingelheim spol. s r.o.
Tel: +420 234 655 111

**Magyarország**
Boehringer Ingelheim RCV GmbH & Co KG
Magyarországi Fióktelepe
Tel: +36 1 299 89 00

**Danmark**
Boehringer Ingelheim Danmark A/S
Tlf: +45 39 15 88 88

**Malta**
Boehringer Ingelheim Ltd.
Tel: +44 1344 424 600

**Deutschland**
Boehringer Ingelheim Pharma GmbH & Co. KG
Tel: +49 (0) 800 77 90 900

Lilly Deutschland GmbH
Tel. +49 (0) 6172 273 2222

**Nederland**
Boehringer Ingelheim b.v.
Tel: +31 (0) 800 22 55 889

**Eesti**
Boehringer Ingelheim RCV GmbH & Co KG
Eesti filiaal
Tel: +372 612 8000

**Norge**
Boehringer Ingelheim Norway KS
Tlf: +47 66 76 13 00

**Ελλάδα**
Boehringer Ingelheim Ellas A.E.
Τηλ: +30 2 10 89 06 300

**Österreich**
Boehringer Ingelheim RCV GmbH & Co KG
Tel: +43 1 80 105-0

**España**
Boehringer Ingelheim España, S.A.
Tel: +34 93 404 51 00

Lilly S.A.
Tel: +34 91 663 50 00

**Polska**
Boehringer Ingelheim Sp. z o.o.
Tel: +48 22 699 0 699

**France**
Boehringer Ingelheim France S.A.S.
Tél: +33 3 26 50 45 33

Lilly France SAS
Tél: +33 1 55 49 34 34

**Portugal**
Boehringer Ingelheim, Unipessoal, Lda.
Tel: +351 21 313 53 00

Lilly Portugal Produtos Farmacêuticos, Lda
Tel: +351 21 412 66 00

**Hrvatska**
Boehringer Ingelheim Zagreb d.o.o.
Tel: +385 1 2444 600

**Ireland**
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Eli Lilly and Company (Ireland) Limited
Tel: +353 1 661 4377

**Ísland**
Vistor hf.
Sími: +354 535 7000

**Italia**
Boehringer Ingelheim Italia S.p.A.
Tel: +39 02 5355 1

Eli Lilly Italia S.p.A.
Tel: +39 05 5425 71

**Κύπρος**
Boehringer Ingelheim Ellas A.E.
Τηλ: +30 2 10 89 06 300

**Latvija**
Boehringer Ingelheim RCV GmbH & Co KG
Latvijas filiāle
Tel: +371 67 240 011

**România**
Boehringer Ingelheim RCV GmbH & Co KG
Viena - Sucursala Bucureşti
Tel: +40 21 302 28 00

**Slovenija**
Boehringer Ingelheim RCV GmbH & Co KG
Podružnica Ljubljana
Tel: +386 1 586 40 00

**Slovenská republika**
Boehringer Ingelheim RCV GmbH & Co KG
organizačná zložka
Tel: +421 2 5810 1211

**Suomi/Finland**
Boehringer Ingelheim Finland Ky
Puh/Tel: +358 10 3102 800

**Sverige**
Boehringer Ingelheim AB
Tel: +46 8 721 21 00

**United Kingdom**
Boehringer Ingelheim Ltd.
Tel: +44 1344 424 600

Eli Lilly and Company Limited
Tel: +44 1256 315 000

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

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

# Annex IV

# Scientific conclusions

**Scientific conclusions**

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used together with diet and exercise in patients with type 2 diabetes, either alone or in combination with other diabetes medicines.

In March 2016 the EMA was informed by the Marketing authorization holder (MAH) of canagliflozin about an approximately 2-fold increase of lower limb amputations in canagliflozin-treated subjects compared to placebo in the MAH sponsored ongoing cardiovascular (CV) event study CANVAS. In addition, an analysis of the ongoing renal study CANVAS-R with a similar population as CANVAS showed a numerical imbalance with regards to amputation events.

Further to the information received by the EMA, the Independent Data Monitoring Committee (IDMC) for the CANVAS and CANVAS-R studies, which has access to all un-blinded CV outcome and safety data, recommended that the study should continue, that action to minimize this potential risk should be taken and that participants should be informed adequately about this risk.

The European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004 on 15 April 2016; the PRAC was requested to assess the impact on the benefit-risk balance of canagliflozin containing medicinal products, to assess whether this is a class issue and to issue a recommendation by 31 March 2017 on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked and whether provisional measures are necessary to ensure the safe and effective use of these medicinal products.

A Direct Healthcare Professional Communication (DHPC) was circulated on 2 May 2016 to inform healthcare professionals that a two-fold higher incidence of lower limb amputation (primarily of the toe) had been seen in a clinical trial with canagliflozin; in addition, the need to counsel patients about the importance of routine preventative foot care was highlighted. The communication also asked healthcare professionals to consider treatment discontinuation in patients who develop amputation preceding events.

Furthermore, the PRAC considered that a class effect could not be excluded, as all SGLT2 inhibitors share the same mechanism of action, as the potential mechanism leading to an increased amputation risk is not known, and as an underlying cause specific to canagliflozin containing medicines only cannot be identified at the moment. Consequently, the EC requested on 6 July 2016 to extend the current procedure to include all of the authorised products of the class of SGLT2 inhibitors.

**Overall summary of the scientific evaluation by the PRAC**

Having considered all available data, the PRAC was of the view that the growing data on amputation in the CANVAS and CANVAS-R trial confirm an increased amputation risk for canagliflozin; it is unlikely that the difference in amputation risk seen with canagliflozin compared to placebo is a finding by chance. The PRAC also considered that data on amputation events from clinical trials and post-marketing surveillance for dapagliflozin and empagliflozin-containing medicines are either not available to the same extent as for canagliflozin-containing medicines or here were some limitations in the data collection.

The PRAC was also of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class. All members of the class share the same mode of action and there is no confirmed underlying mechanism that is canagliflozin-specific. The mechanism of action that would allow understanding which patients are at risk is therefore still unclear.

PRAC noted that an increased amputation risk has only become apparent with canagliflozin so far, but one large cardiovascular outcome study (DECLARE) is still on-going for dapagliflozin and amputation events were not been systematically captured within the completed large cardiovascular outcome study conducted with empagliflozin (EMPA-REG). Hence, it is currently not possible to establish whether the increased amputation risk is a class effect or not.

Therefore, having considered all the data submitted, in view of the above, the PRAC concluded that the benefit-risk balance of the bove listed products remains positive, but considered that changes to the product information of all authorised SGLT2 inhibitors adding information on the risk of lower limb amputations, as well as additional pharmacovigilance activities to be reflected in the RMP, are

warranted. The CANVAS and CANVAS-R studies and the CREDENCE and DECLARE Studies are planned to be completed in 2017 and 2020, respectively. Final analysis of these studies, after un-blinding, will provide further information on the benefit/risk of SGLT2 inhibitors particularly of the risk of lower limb amputations.

**Grounds for PRAC recommendation**

Whereas

The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for the products listed in Annex A;

The PRAC reviewed the totality of the data submitted by the marketing authorisation holders in relation to the risk of lower limb amputation in patients treated with Sodium-glucose co-transporter 2 (SGLT2) inhibitors for type 2 diabetes mellitus;

The PRAC considered that the available data on amputation in the CANVAS and CANVAS-R trials confirm that treatment with canagliflozin may contribute to an increased risk of amputation of the lower limb, mainly of the toe;

The PRAC was also of the opinion that a mechanism of action, allowing to understand which patients are at risk, is still unclear;

The PRAC was of the view that it is currently not possible to identify an underlying cause for the observed imbalances in amputation risk that would be specifically attributable to canagliflozin-containing medicines and not to the other products of the class;

The PRAC noted that data on amputation events from clinical trials and post-marketing surveillance for dapagliflozin and empagliflozin-containing medicines are either not available to the same extent as for canagliflozin-containing medicines or there were some limitations in the data collection of these events;

The PRAC therefore considered that the risk may constitute a possible class effect;

Because no specific risk factors could be identified apart from general amputation risk factors potentially contributing to the events, the PRAC recommended that patients should be advised on routine preventative foot care and maintaining adequate hydration as a general advice to prevent amputation;

The PRAC was therefore of the view that the risk of lower limb amputation should be included in the product information for all products listed in Annex A, with a warning highlighting to healthcare professional and patients the importance of routine preventative foot care. The warning for canagliflozin also includes information that, in patients developing amputation preceding events, consideration may be given to discontinue treatment. For canagliflozin, lower limb amputations (mainly of the toe) have been also included, as an adverse drug reaction, in the product information;

The PRAC also considered that additional information on amputation events should be collected through appropriate case report forms (CRFs) for clinical trials, follow-up questionnaires for post-marketing cases, use of common MedDRA preferred term (PT) lists for amputation preceding events, and appropriate meta-analyses of large studies including cardiovascular outcome studies. All RMPs should be updated accordingly via an appropriate variation to be submitted no later than one month of the European Commission decision;

The PRAC, as a consequence, concluded that the benefit-risk balance of the SGLT2 inhibitor containing products identified in Annex A remains favourable, subject to the agreed amendments to the product information and additional pharmacovigilance activities to be reflected in the RMP.

The PRAC therefore recommended that the variation to the terms of the marketing authorisation for the above listed products referred to in Annex A, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation, was warranted.

**CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

**Overall conclusion**

The CHMP, as a consequence, considers that the benefit-risk balance of Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy remain favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy.