ジャディアンス錠 10mg

に関する資料

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日本ベーリンガーインゲルハイム株式会社

第 1 部 申請書等行政情報及び添付文書に関する情報

JAN あるいは販売名：	エンパグリフロジン
剤形・含量：	錠剤 ・ 10mg
文書名：	1.5 起原又は発見の経緯及び開発の経緯
文書作成日：	12 January 2023

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1. 起原又は発見の経緯

エンパグリフロジン（ジャディアンス®）は，ベーリンガーインゲルハイム社（以下，BI）が開発した経口投与可能な強力かつ選択性の高いナトリウム-グルコース共役輸送担体 2（SGLT-2）阻害薬である。エンパグリフロジンは，2 型糖尿病や慢性心不全治療薬として世界的に製造販売承認されており，広く臨床現場で使用されている。日本では，ジャディアンス®10 mg 錠及び 25 mg 錠が 2014 年 12 月に 2 型糖尿病の効能又は効果で承認され，ジャディアンス®10 mg 錠が 2021 年 11 月に慢性心不全の効能又は効果の追加承認を取得し，臨床現場で使用されている。

2. 開発の経緯

1245-0025 試験は，米国食品医薬品局（FDA）の「新規糖尿病治療薬の心血管系疾患発症リスク評価に関する新基準（2008 年 12 月）」に従って長期投与時の心血管系に対する安全性を検討するため，心血管リスクの高い 2 型糖尿病患者を対象としてエンパグリフロジン 10mg 及び 25mg を用いて実施されたイベント主導型，国際共同，二重盲検，並行群間，プラセボ対照試験であった。当該試験結果に基づき，心・腎関連イベントに対する有効性及び安全性が同等であった 2 用量のうち，より低曝露となる 10 mg を用いて慢性腎臓病への適応拡大に向けた開発を開始した。

本剤の慢性腎臓病に対する開発において実施した試験は臨床試験のみであり，これらの種類及び実施期間を（図 2: 1 開発の経緯図）に示す。

なお，医薬品医療機器総合機構（PMDA）との対面助言における PMDA からの助言，及びそれらの反映を含む開発の経緯の詳細は［CTD2.5_1.2 項］に記載した。

図 2: 1 開発の経緯図

資料の種類				[redacted]	CTD番号
臨床	第III相	比較対照試験（1245-0137）	慢性腎臓病患者を対象とした心腎アウトカムを評価する，エンパグリフロジン1日1回投与に関する国際多施設共同，無作為化，並行群間，二重盲検，プラセボ対照比較臨床試験（EMPA-KIDNEY試験）		5.3.5.1-01
		比較対照試験（1245-0025）	心血管系リスクを有する2型糖尿病患者を対象としたプラセボ対象二重盲検国際共同心血管系安全性試験（EMPA-REG OUTCOME試験）		5.3.5.1-02

2.1 品質に関する試験の概略

品質に関する新たな試験は実施していない。

2.2 非臨床試験成績の概略

非臨床試験として新たな試験は実施していない。既公表文献の結果を用いて，腎臓病におけるエンパグリフロジンの作用を，様々な刺激により病態が誘導される複数の薬理学的モデル，すな

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わち，ヒト近位尿細管細胞株を用いた *in vitro* モデル，糖尿病を有している腎臓病動物モデル及び正常血糖の腎臓病動物モデルを用いて検討した。

なお，その他の薬理，薬物動態，及び毒性試験成績は，2 型糖尿病に対する治療薬としての承認申請時に提出済みである。

2.3 臨床試験成績の概略

本申請の臨床データパッケージは，開発の経緯図（図 2: 1 開発の経緯図）に示した 1245-0137 試験及び 1245-0025 試験の 2 試験で構成される。これらの試験結果に基づき，このたび表 2.3: 1 申請内容の概略（下線部：変更箇所）に示す効能又は効果及び用法及び用量に係る製造販売承認事項一部変更申請に至った。

なお，臨床試験結果の詳細はコモンテクニカルドキュメント（CTD）第 2 部，及び本剤の有効性，安全性に基づく有用性に関しては，［CTD2.5_6 項］をそれぞれ参照のこと。

表 2.3: 1 申請内容の概略（下線部：変更箇所）

効能又は効果（案）	<ジャディアンス錠 10mg・25mg> 2 型糖尿病 <ジャディアンス錠 10mg> 慢性心不全 ただし、慢性心不全の標準的な治療を受けている患者に限る。 慢性腎臓病
用法及び用量（案）	<2 型糖尿病> 通常、成人にはエンパグリフロジンとして 10mg を 1 日 1 回朝食前又は朝食後に経口投与する。なお、効果不十分な場合には、経過を十分に観察しながら 25mg1 日 1 回に増量することができる。 <慢性心不全> 通常、成人にはエンパグリフロジンとして 10mg を 1 日 1 回朝食前又は朝食後に経口投与する。 <慢性腎臓病> 通常、成人にはエンパグリフロジンとして 10mg を 1 日 1 回経口投与する。

2.4 申請効能以外の開発状況

現在，国内外において，急性心筋梗塞患者における心不全による入院及び死亡のリスクの低減に対するエンパグリフロジンの効果を検討する国際共同第 III 相試験（1245-0202 試験，EMPACT-MI）を実施している。

第 1 部 申請書等行政情報及び添付文書に関する情報

JAN あるいは販売名：	エンパグリフロジン
剤形・含量：	錠剤 ・ 10mg
文書名：	1.6 外国における使用状況等に関する資料
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1. 外国における使用状況

エンパグリフロジン（ジャディアンス錠 10 mg 及び同錠 25 mg）は，成人 2 型糖尿病患者の血糖コントロールを改善する，食事及び運動療法の補助療法として 2014 年 4 月に初めて承認され，2023 年 12 月において（以下同様），オーストラリア（2014 年 4 月承認），欧州連合（以下 EU，2014 年 5 月承認），米国（2014 年 8 月承認）を含む 100 カ国以上で承認されている。更に，10～17 歳の 2 型糖尿病小児患者を対象とした DINAMO 試験において，エンパグリフロジンの 26 週間投与によって，HbA1c の低下に関してエンパグリフロジンのプラセボに対する統計学的優越性が示されたことから，米国（2023 年 6 月承認）及び EU（2023 年 12 月承認）を含む 30 カ国以上で，10 歳以上の小児においても 2 型糖尿病患者の血糖コントロールを改善する，食事及び運動療法の補助療法としてエンパグリフロジンは承認されている。

その他に，心血管アウトカム試験（EMPA-REG OUTCOME）に基づき，米国，カナダ，オーストラリアなどを含む 50 カ国で「確定された心血管疾患を合併する 2 型糖尿病患者の心血管死のリスク減少」の効能・効果で承認され，EU を含む 50 カ国以上では，効能・効果に修正が加えられたり，国によっては，臨床試験の項に心血管アウトカム試験の肯定的な結果が明記された。

また，エンパグリフロジン（ジャディアンス錠 10mg）の慢性心不全に関する適応は，左室駆出率が低下した慢性心不全治療薬として，EU（2021 年 6 月承認），米国（2021 年 8 月承認）を含む 100 カ国以上で，さらに，左室駆出率の保たれた患者に適応可能な慢性心不全治療薬として米国（2022 年 2 月承認），EU（2022 年 3 月承認）を含む 100 カ国以上で承認された。

なお，エンパグリフロジン（ジャディアンス錠 10mg）の慢性腎臓病に関する適応は，EU（2023 年 7 月承認），イギリス（2023 年 9 月承認）及び米国（2023 年 9 月承認）を含む 50 カ国以上で承認された。

2. 外国における添付文書

2.1 企業中核データシート

企業中核データシート（CCDS）を添付する［CTD1.6-02］。

2.2 EU 添付文書

欧州添付文書（2023 年 8 月版）及び邦訳の概略を添付する［CTD1.6-03］。

2.3 米国添付文書

米国添付文書（2023 年 9 月版）及び邦訳を添付する［CTD1.6-04］。

COMPANY CORE DATA SHEET	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	Jardiance
[redacted]	Empagliflozin
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

[redacted]

非開示情報のため，2～78頁削除

CCDS NO. [redacted] [redacted] **20**[redacted]

[redacted]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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.

Excipients 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.

Excipients 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

Type 2 diabetes mellitus

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 combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart failure

Jardiance is indicated in adults for the treatment of symptomatic chronic heart failure.

Chronic kidney disease

Jardiance is indicated in adults for the treatment of chronic kidney disease.

4.2 Posology and method of administration

Posology

Type 2 diabetes mellitus
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).

Heart failure
The recommended dose is 10 mg empagliflozin once daily.

Chronic kidney disease
The recommended dose is 10 mg empagliflozin once daily.

All indications
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).

If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day.

Special populations
Renal impairment
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m^2.

In patients with an eGFR <60 ml/min/1.73 m^2 the daily dose of empagliflozin is 10 mg.

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of empagliflozin is reduced in patients with an eGFR <45 ml/min/1.73 m^2 and likely absent in patients with an eGFR <30 ml/min/1.73 m^2. Therefore, if eGFR falls below 45 ml/min/1.73 m^2, additional glucose lowering treatment should be considered if needed (see sections 4.4, 4.8, 5.1 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).

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.

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

Ketoacidosis

Cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes mellitus 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 ketoacidosis is more likely to occur with higher doses of empagliflozin. Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.

The risk of 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 ketoacidosis is suspected or diagnosed, treatment with empagliflozin should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

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

Patients who may be at higher risk of ketoacidosis 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 ketoacidosis while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

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

Renal impairment

Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m^2.

In patients with an eGFR <60 ml/min/1.73 m^2 the daily dose of empagliflozin is 10 mg (see section 4.2).

The glucose lowering efficacy of empagliflozin is dependent on renal function, and is reduced in patients with an eGFR <45 ml/min/1.73 m^2 and is likely absent in patients with an eGFR <30 ml/min/1.73 m^2 (see section 4.2, 5.1 and 5.2).

Monitoring of renal function
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, 4.8, 5.1 and 5.2).
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying 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.

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).

Complicated urinary tract infections

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

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients with diabetes mellitus taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier´s gangrene is suspected, Jardiance should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Lower limb amputations

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

Hepatic injury

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

Elevated haematocrit

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

Chronic kidney disease

Patients with albuminuria may benefit more from treatment with empagliflozin.

Infiltrative disease or Takotsubo cardiomyopathy

Patients with infiltrative disease or with Takotsubo cardiomyopathy have not been specifically studied. Therefore, efficacy in these patients has not been established.

Urine laboratory assessments

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

Interference with 1,5-anhydroglucitol (1,5-AG) assay

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

Lactose

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

Sodium

Each tablet contains less than 1 mmol sodium (23 mg), that is to say essentially ‘sodium free’.

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 (e.g. induction by rifampicin or phenytoin) on empagliflozin has not been studied. Co-treatment with known inducers of UGT enzymes is not recommended due to a potential risk of decreased efficacy. If an inducer of these UGT enzymes must be co-administered, monitoring of glycaemic control to assess response to Jardiance is appropriate.

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

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

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

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

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

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

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

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

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

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

Type 2 diabetes mellitus
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).

Heart failure
The EMPEROR studies included patients with heart failure and either reduced ejection fraction (N=3 726) or preserved ejection fraction (N=5 985) treated with empagliflozin 10 mg or placebo. Approximately half of the patients had type 2 diabetes mellitus. The most frequent adverse reaction of the pooled EMPEROR-Reduced and EMPEROR-Preserved studies was volume depletion (empagliflozin 10 mg: 11.4%. placebo: 9.7%).

Chronic kidney disease
The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6 609) treated with 10 mg empagliflozin or placebo. About 44% of the patients had type 2 diabetes mellitus. The most frequent adverse events in the EMPA-KIDNEY study were gout (empagliflozin 7.0% vs placebo

8.0%), and acute kidney injury (empagliflozin 2.8% vs placebo 3.5%) which were more frequently reported in patients on placebo.

The overall safety profile of empagliflozin was generally consistent across the studied indications.

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: Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very Rare**
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[a] Urinary tract infection (including pyelonephritis and urosepsis)[a]		Necrotising fasciitis of the perineum (Fournier´s gangrene)*	
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[a]	Thirst	Ketoacidosis*		
Gastrointestinal disorders		Constipation			
Skin and subcutaneous tissue disorders		Pruritus (generalised) Rash	Urticaria Angioedema		
Vascular disorders	Volume depletion[a]				
Renal and urinary disorders		Increased urination[a]	Dysuria		Tubulo-interstitial nephritis
Investigations		Serum lipids increased[a]	Blood creatinine increased/ Glomerular filtration rate decreased[a] Haematocrit increased[a]		

[a] see subsections below for additional information
* 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 sulphonylurea (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).

In the EMPEROR heart failure studies, similar frequency of hypoglycaemia was noted when used add-on to sulphonylurea or insulin (empagliflozin 10 mg: 6.5%, placebo: 6.7%).

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 sulphonylurea, 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 sulphonylurea (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: 0.5%, empagliflozin 25 mg: 0.5%, placebo: 0.5% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 1.6%, empagliflozin 25 mg: 0.5%, placebo: 1.6% over the 52-week trial).

In the EMPEROR heart failure studies, major hypoglycaemia was observed at similar frequencies in patients with diabetes mellitus when treated with empagliflozin and placebo as add-on to sulphonylurea or insulin (empagliflozin 10 mg: 2.2%, placebo: 1.9%).

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.

In the EMPEROR heart failure studies, the frequency of these infections was more pronounced in patients with diabetes mellitus (empagliflozin 10 mg: 2.3%; placebo: 0.8%) than in patients without diabetes mellitus (empagliflozin 10 mg: 1.7%; placebo: 0.7%) when treated with empagliflozin compared to placebo.

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%).

In the EMPEROR heart failure studies, increased urination was observed at similar frequencies in patients treated with empagliflozin and placebo (empagliflozin 10 mg: 0.9%, placebo 0.5%).

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.
Consistently, in the EMPA-REG OUTCOME study, patients treated with empagliflozin experienced an initial fall in eGFR (mean: 3 ml/min/1.73 m^2). Thereafter, eGFR was maintained during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting acute haemodynamic changes may play a role in these renal function changes. This phenomenon is also observed in the EMPEROR heart failure studies and the EMPA-KIDNEY study.

Serum lipids increased
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%.

Haematocrit increased
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.

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 in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin 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, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK03

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 5 000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

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

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

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to: increasing

tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating of sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodeling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.

Clinical efficacy and safety

Type 2 diabetes mellitus
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 pre-specified 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 1 000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1 000 mg given twice daily) provided statistically significant improvements in 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 1 000 mg[c]	+ Met 2 000 mg[c]	No Met	+ Met 1 000 mg[c]	+ Met 2 000 mg[c]	No Met	1 000 mg	2 000 mg
N	161	167	169	165	169	163	167	162
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 randomised to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin
[6] Patients randomised 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 pre-specified 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 predefined 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 7 020 patients were treated (empagliflozin 10 mg: 2 345, empagliflozin 25 mg: 2 342, placebo: 2 333) and followed for a median of 3.1 years. The mean age was 63 years, the mean 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 sulphonylurea. 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 preventing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg (Figure 1) and confirmed by an improved overall survival (Table 10). The effect of empagliflozin on the primary combined endpoint of CV death, non-fatal MI, or non-fatal stroke was largely independent of glycaemic control or renal function (eGFR) and generally consistent across eGFR categories down to an eGFR of 30 ml/min/1.73 m^2 in the EMPA-REG OUTCOME study.

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

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

	Placebo	**Empagliflozin[b]**
N	2 333	4 687
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)

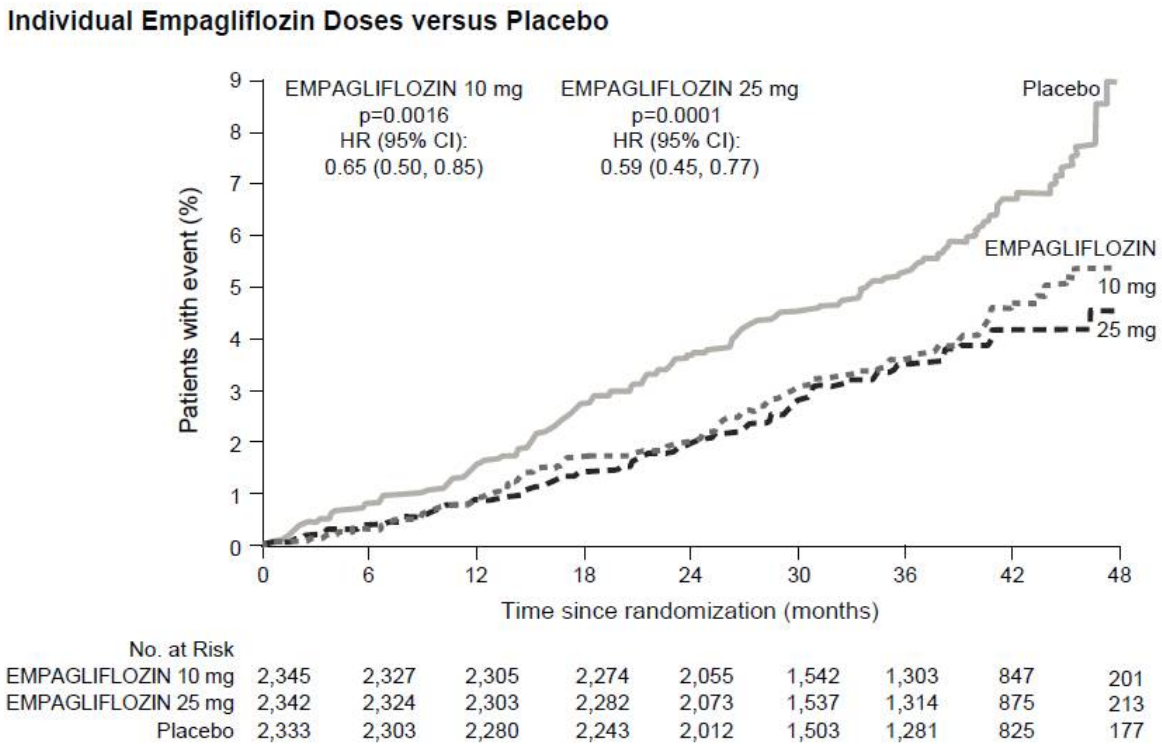
CV = cardiovascular, MI = myocardial infarction

[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



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

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

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

Fasting plasma glucose
In four placebo-controlled studies, treatment with empagliflozin as monotherapy or add-on therapy to metformin, pioglitazone, or metformin plus a sulphonylurea 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.

Heart failure

Empagliflozin in patients with heart failure and reduced ejection fraction
A randomised, double-blind, placebo-controlled study (EMPEROR-Reduced) was conducted in 3 730 patients with chronic heart failure (New York Heart Association [NYHA] II-IV) and reduced ejection fraction (LVEF ≤40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care heart failure therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent) and eGFR (CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Heart Failure therapy at baseline included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (88.3%), beta blockers (94.7%), mineralocorticoid receptor antagonists (71.3%) and diuretics (95.0%).

A total of 1 863 patients were randomised to empagliflozin 10 mg (placebo: 1 867) and followed for a median of 15.7 months. The study population consisted of 76.1% men and 23.9% women with a mean age of 66.8 years (range: 25-94 years), 26.8% were 75 years of age or older. 70.5% of the study population were White, 18.0% Asian and 6.9% Black/African American. At randomisation, 75.1% of patients were NYHA class II, 24.4% were class III and 0.5% were class IV. The mean LVEF was 27.5%. At baseline, the mean eGFR was 62.0 ml/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. About half of the patients (51.7%) had an eGFR of ≥60 ml/min/1.73 m^2, 24.1% of 45 to <60 ml/min/1.73 m^2, 18.6% of 30 to <45 ml/min/1.73 m^2 and 5.3% 20 to <30 ml/min/1.73 m^2.

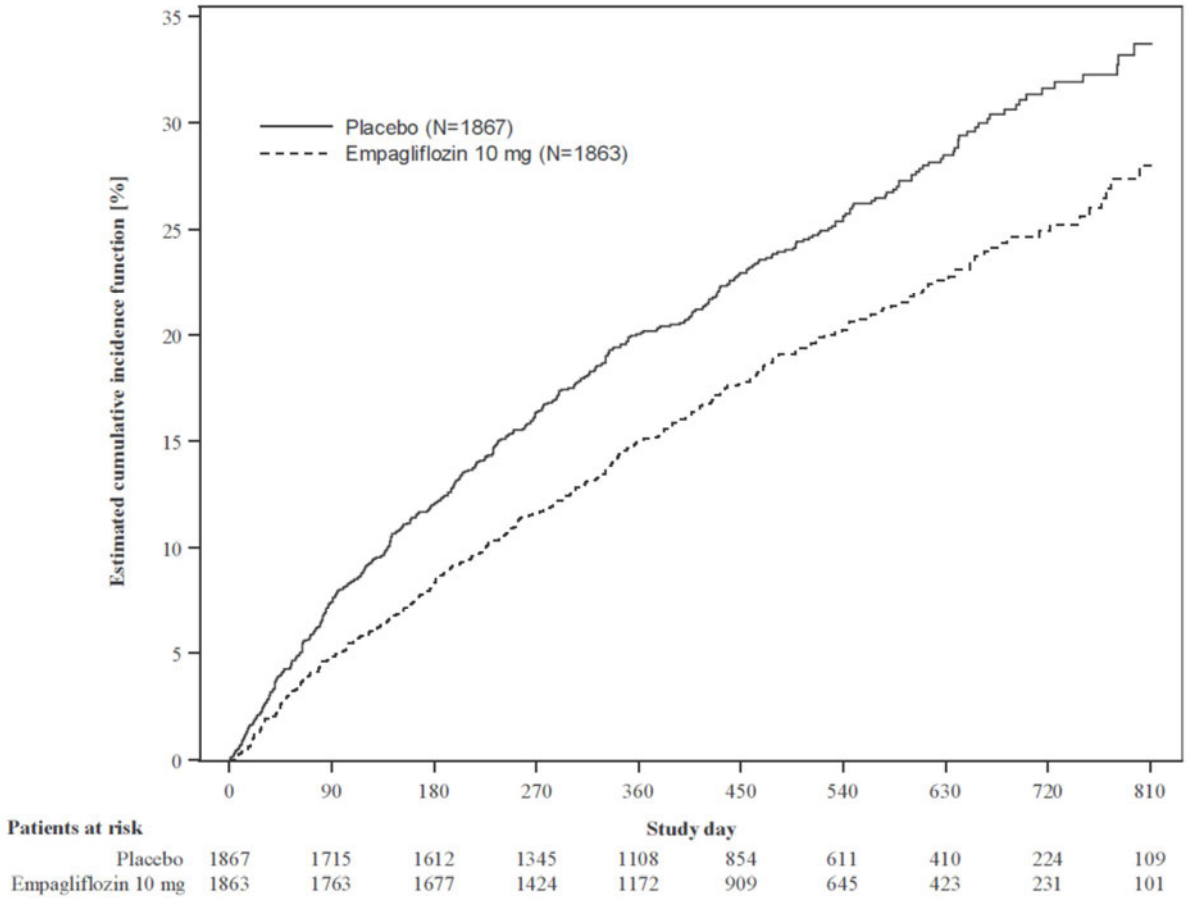
Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline (Table 12; Figure 2).

Table 12: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

	Placebo	**Empagliflozin 10 mg**
N	1 867	1 863
Time to first event of CV death or HHF, N (%)	462 (24.7)	361 (19.4)
Hazard ratio vs. placebo (95% CI)*		0.75 (0.65, 0.86)
p−value for superiority		<0.0001
CV Death, N (%)	202 (10.8)	187 (10.0)
Hazard ratio vs. placebo (95% CI)		0.92 (0.75, 1.12)
HHF (first occurrence), N (%)	342 (18.3)	246 (13.2)
Hazard ratio vs. placebo (95% CI)		0.69 (0.59, 0.81)
HHF (first and recurrent), N of events	553	388
Hazard ratio vs. placebo (95% CI)*		0.70 (0.58, 0.85)
p−value		0.0003
eGFR (CKD-EPI)cr slope, Rate of decline (ml/min/1.73m^2/year)**	-2.28	-0.55
Treatment difference vs. placebo (95% CI)		1.73 (1.10, 2.37)
p-value		< 0.0001

CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation
* CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomised set.
**eGFR slope was analysed based on the treated set. Intercept is -0.95 ml/min/1.73 m^2 for placebo and -3.02 ml/min/1.73 m^2 for empagliflozin. The intercept represents the acute effect on eGFR while the slope represents the long-term effect.

Figure 2 Time to first event of adjudicated CV death or HHF



The results of the primary composite endpoint were generally consistent with a hazard ratio (HR) below 1 across the pre-specified subgroups, including patients with heart failure, with or without type 2 diabetes mellitus and with or without renal impairment (down to an eGFR of 20 ml/min/1.73 m^2).

Empagliflozin in patients with heart failure and preserved ejection fraction

A randomised, double-blind, placebo-controlled study (EMPEROR-Preserved) was conducted in 5 988 patients with chronic heart failure (NYHA II-IV) and preserved ejection fraction (LVEF >40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent), and eGFR (CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Baseline therapy included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (80.7%), beta blockers (86.3%), mineralocorticoid receptor antagonists (37.5%) and diuretics (86.2%).

A total of 2 997 patients were randomised to empagliflozin 10 mg (placebo: 2 991) and followed for a median of 26.2 months. The study population consisted of 55.3% men and 44.7% women with a mean age of 71.9 years (range: 22-100 years), 43.0% were 75 years of age or older. 75.9% of the study population were White, 13.8% Asian and 4.3% Black/African American. At randomisation, 81.5% of patients were NYHA class II, 18.1% were class III and 0.3% were class IV. The EMPEROR-Preserved study population included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 60.6 ml/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. About half of the patients (50.1%) had an eGFR of ≥60 ml/min/1.73 m^2, 26.1% of 45 to <60 ml/min/1.73 m^2, 18.6% of 30 to <45 ml/min/1.73 m^2 and 4.9% 20 to <30 ml/min/1.73 m^2.

Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline (Table 13; Figure 3).

Table 13: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

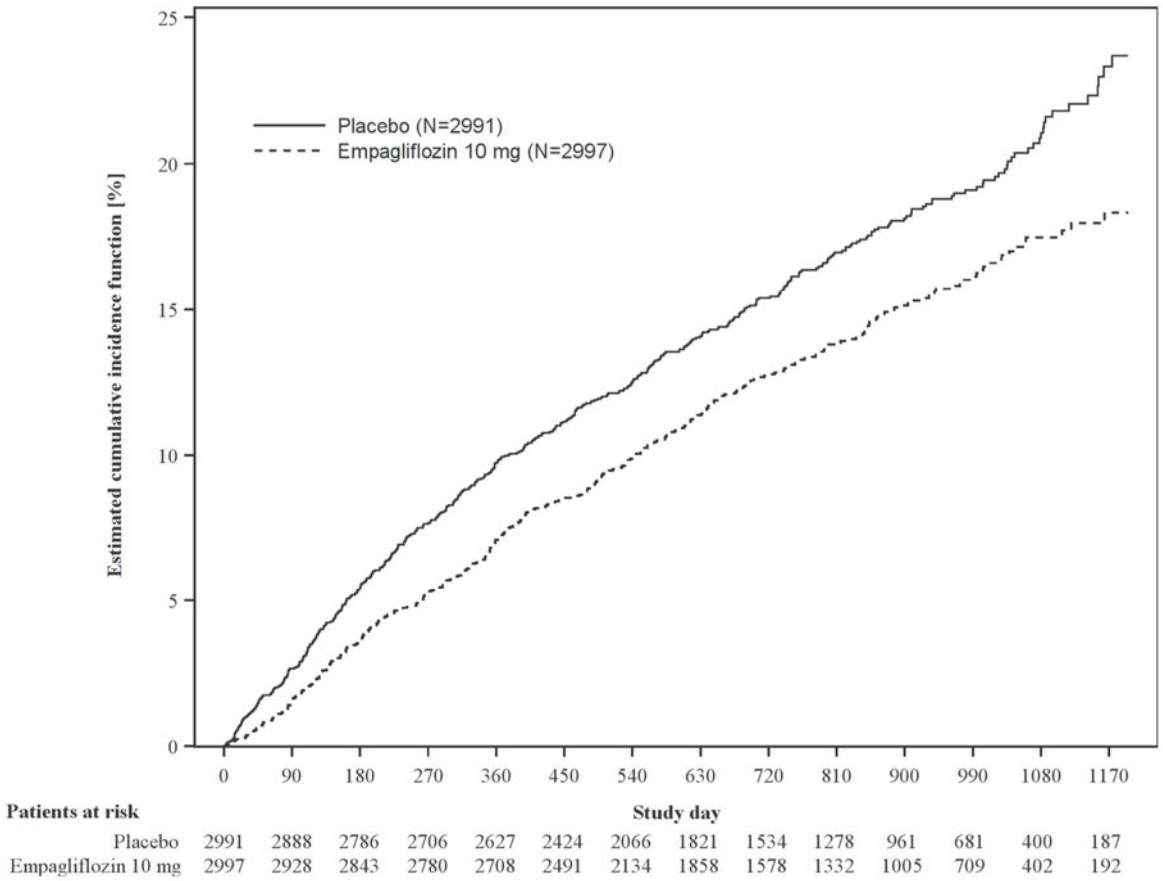
	Placebo	**Empagliflozin 10 mg**
N	2 991	2 997
Time to first event of CV death or HHF, N (%)	511 (17.1)	415 (13.8)
Hazard ratio vs. placebo (95% CI)*		0.79 (0.69, 0.90)
p−value for superiority		0.0003
CV Death, N (%)	244 (8.2)	219 (7.3)
Hazard ratio vs. placebo (95% CI)		0.91 (0.76, 1.09)
HHF (first occurrence), N (%)	352 (11.8)	259 (8.6)
Hazard ratio vs. placebo (95% CI)		0.71 (0.60, 0.83)
HHF (first and recurrent), N of events	541	407
Hazard ratio vs. placebo (95% CI)*		0.73 (0.61, 0.88)
p−value		0.0009
eGFR (CKD-EPI)cr slope, Rate of decline (ml/min/1.73m^2/year)**	-2.62	-1.25
Treatment difference vs. placebo (95% CI)		1.36 (1.06, 1.66)
p-value		< 0.0001

CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation

* CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomised set.

**eGFR slope was analysed based on the treated set. Intercept is -0.18 ml/min/1.73 m^2 for placebo and -3.02 ml/min/1.73 m^2 for empagliflozin. The intercept represents the acute effect on eGFR while the slope represents the long-term effect.

Figure 3 Time to first event of adjudicated CV death or HHF



The results of the primary composite endpoint were consistent across each of the pre-specified subgroups categorized by e.g., LVEF, diabetes status or renal function (down to an eGFR of 20 ml/min/1.73 m^2).

Chronic kidney disease

A randomised, double-blind, placebo-controlled study of empagliflozin 10 mg once daily (EMPA-KIDNEY) was conducted in 6 609 patients with chronic kidney disease (eGFR ≥20 - <45 ml/min/1.73 m^2; or eGFR ≥45 - <90 ml/min/1.73 m^2 with urinary albumin to creatinine ratio (UACR) ≥200 mg/g) to assess cardio-renal outcomes as adjunct to standard of care therapy. The primary endpoint was the time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 ml/min/1.73 m^2, end-stage kidney disease, or renal death) or CV death. First occurrence of hospitalisation for heart failure or CV death, all-cause hospitalisation (first and recurrent), and all-cause mortality were included in the confirmatory testing. Baseline therapy included an appropriate use of a RAS-inhibitor (85.2% ACE inhibitor or angiotensin receptor blocker).

A total of 3 304 patients were randomised to empagliflozin 10 mg (placebo: 3 305) and followed for a median of 24.3 months. The study population consisted of 66.8% men and 33.2% women with a mean age of 63.3 years (range: 18-94 years), 23.0% were 75 years of age or older. 58.4% of the study population were White, 36.2% Asian and 4.0% Black/African American.

At baseline, the mean eGFR was 37.3 ml/min/1.73 m^2, 21.2% patients had an eGFR of ≥45 ml/min/1.73 m^2, 44.3% of 30 to <45 ml/min/1.73 m^2 and 34.5% <30 ml/min/1.73 m^2 including 254 patients with an eGFR <20 ml/min /1.73 m^2. The median UACR was 329 mg/g, 20.1% patients had an UACR <30 mg/g, 28.2% had an UACR 30 to ≤300 mg/g and 51.7% had an UACR >300 mg/g; 41.1% of patients had an UACR <200 mg/g. Primary causes of CKD were diabetic

nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%).

Empagliflozin was superior in reducing the risk of the primary composite endpoint of kidney disease progression or CV death compared with placebo (see Table 14). Additionally, empagliflozin significantly reduced the risk of all-cause hospitalisation (first and recurrent).

Table 14: Treatment effect for the primary composite and key secondary endpoints included in the pre-specified confirmatory testing and its components

	Placebo	**Empagliflozin 10 mg**
N	3 305	3 304
Time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 ml/min/1.73 m^2, end-stage kidney disease* (ESKD), or renal death) or CV death, N (%)	558 (16.9)	432 (13.1)
Hazard ratio vs. placebo (99.83% CI)		0.72 (0.59, 0.89)
p−value for superiority		<0.0001
Sustained ≥40% eGFR decline from randomisation, N (%)	474 (14.3)	359 (10.9)
Hazard ratio vs. placebo (95% CI)		0.70 (0.61, 0.81)
p-value		<0.0001
ESKD* or sustained eGFR <10 ml/min/1.73 m^2, N (%)	221 (6.7)	157 (4.8)
Hazard ratio vs. placebo (95% CI)		0.69 (0.56, 0.84)
p-value		0.0003
Renal death, N (%)**	4 (0.1)	4 (0.1)
Hazard ratio vs. placebo (95% CI)		
p-value		
CV Death, N (%)	69 (2.1)	59 (1.8)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.19)
p-value		0.3366
ESKD or CV Death, N (%)[#]	217 (6.6)	163 (4.9)
Hazard ratio vs. placebo (95% CI)		0.73 (0.59, 0.89)
p-value		0.0023
Occurrence of all-cause hospitalisation (first and recurrent), N of events	1 895	1 611
Hazard ratio vs. placebo (99.03% CI)		0.86 (0.75, 0.98)
p-value		0.0025

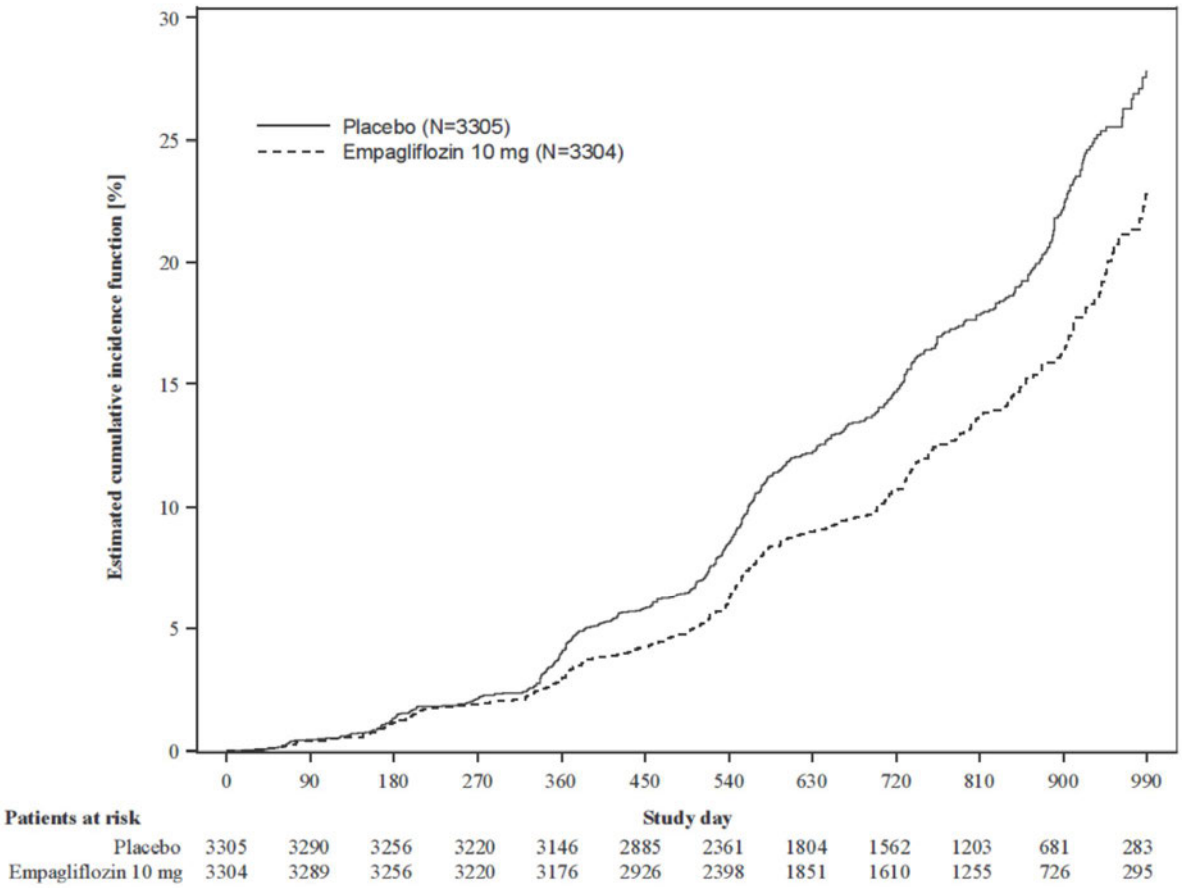
CV = cardiovascular, HHF = hospitalisation for heart failure, eGFR = Estimated glomerular filtration rate

* End-stage kidney disease (ESKD) is defined as the initiation of maintenance dialysis or receipt of a kidney transplant.

** There were too few events of renal death to compute a reliable hazard ratio.

[#] Predefined as one of the two stopping criteria in the pre-planned interim analysis.

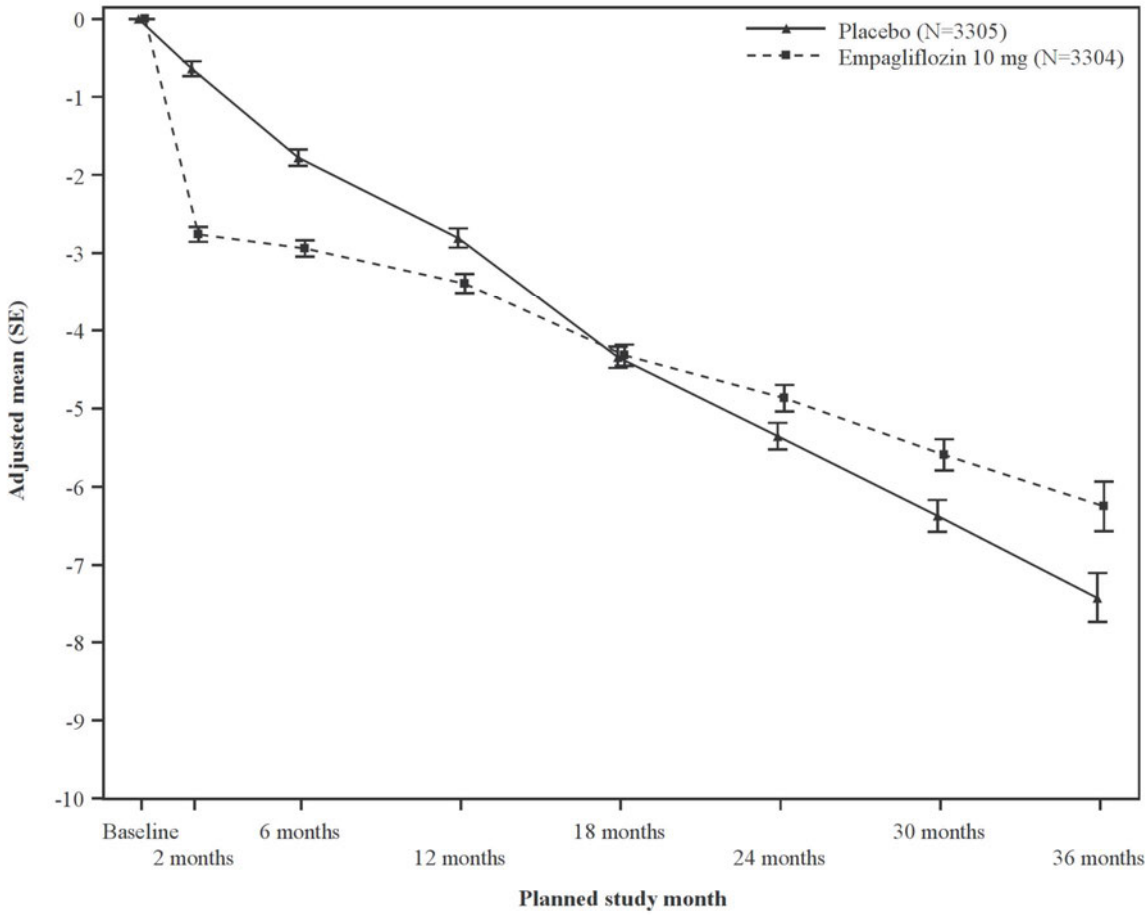
Figure 4 Time to first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function



The results of the primary composite endpoint were generally consistent across the pre-specified subgroups, including eGFR categories, underlying cause of renal disease, diabetes status, or background use of RAS inhibitors. Treatment benefits were more clearly evident in patients with higher levels of albuminuria.

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (Figure 5). Empagliflozin slowed the annual rate of eGFR decline compared to placebo by 1.37 ml/min/1.73 m^2/year (95% CI 1.16, 1.59), based on a pre-specified analysis of all eGFR measurements taken from the 2-month visit to the final follow-up visit. Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation as demonstrated in several of the empagliflozin studies, supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 5 Change in eGFR over time*



*eGFR (CKD-EPI) (ml/min/1.73 m^2) MMRM results over time - randomised set.

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).

The European Medicines Agency has waived the obligation to submit the results of studies with Jardiance in all subsets of the paediatric population in heart failure (see section 4.2 for information on paediatric use).

The European Medicines Agency has waived the obligation to submit the results of studies with Jardiance in all subsets of the paediatric population in chronic kidney disease (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 1 870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4 740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and

steady-state pharmacokinetic parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with type 2 diabetes.

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

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

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

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

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

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
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
Date of latest renewal: 14 February 2019

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.

付録 I

製品概要

1. 医薬品名

Jardiance 10 mg フィルムコート錠
Jardiance 25 mg フィルムコート錠

2. 定性的及び定量的組成

Jardiance 10 mg フィルムコート錠

1 錠中にエンパグリフロジンとして 10 mg を含有する。

既知の作用を有する添加物
添加剤として 1 錠中に 154.3 mg のラクトース一水和物を含有する。

Jardiance 25 mg フィルムコート錠

1 錠中にエンパグリフロジンとして 25 mg を含有する。

既知の作用を有する添加物
添加剤として 1 錠中に無水乳頭 107.4 mg としてラクトース一水和物を含有する。

全添加剤の一覧については，6.1 項を参照のこと。

3. 剤形

フィルムコート錠（錠剤）

Jardiance 10 mg フィルムコート錠

円形，うすい黄色，はす縁の両凸のフィルムコート錠で，片面に「S10」，反対面に Boehringer Ingelheim のロゴが刻印されている（錠剤径：9.1 mm）。

Jardiance 25 mg フィルムコート錠

楕円形，うすい黄色，両凸のフィルムコート錠で，片面に「S25」，反対面に Boehringer Ingelheim のロゴが刻印されている（錠剤長：11.1 mm，錠剤幅：5.6 mm）。

4. 臨床的特性

4.1 効能又は効果

2 型糖尿病

Jardiance はコントロール不十分な成人の 2 型糖尿病の治療において食事療法及び運動療法の補助療法として適応される。
- 忍容性がないため，メトホルミンの使用が不適切と考えられる場合の単独療法
- 他の糖尿病治療薬剤との併用療法

併用療法，血糖コントロール／心血管イベント／腎イベントに対する効果，及び試験対象とした患者集団に関しては 4.4，4.5 及び 5.1 項参照のこと。

心不全

Jardiance は成人における症候性慢性心不全の治療として適応される。

慢性腎臓病

Jardiance は成人における慢性腎臓病の治療として適応される。

4.2　用量及び用法

用量

2 型糖尿病
推奨される開始用量は，単独療法及び他の糖尿病治療薬との併用療法について，エンパグリフロジンとして 1 日 1 回 10 mg である。10 mg のエンパグリフロジンの 1 日 1 回投与に忍容性があり，eGFR が 1 回の測定で 60 mL/分/1.73 m^2 以上であり，より厳格な血糖コントロールが必要な患者では，用量を 1 日 1 回 25 mg に増量することができる。1 日最高投与量は 25 mg である（下記及び 4.4 項参照）。

心不全
推奨される用量はエンパグリフロジンとして 1 日 1 回 10 mg である。

慢性腎臓病
推奨される用量はエンパグリフロジンとして 1 日 1 回 10 mg である。

全ての適応症
本剤をスルホニル尿素薬又はインスリンと併用する場合，低血糖症のリスクを低減するためにスルホニル尿素薬又はインスリンの減量を検討してもよい（4.5 及び 4.8 項参照）。

服用を忘れた場合は，患者が気付いたときに直ちに服用することが望ましい。同日に倍量を服用しないこと。

特別な集団
腎機能障害患者
使用経験が限られているため，eGFR が 20 mL/分/1.73 m^2 未満の患者にエンパグリフロジンによる治療を開始することは推奨されない。

eGFR が 60 mL/分/1.73 m^2 未満の患者に対するエンパグリフロジンの 1 日量は 10 mg である。

2 型糖尿病患者では，エンパグリフロジンの血糖低下作用は eGFR が 45 mL/分/1.73 m^2 未満の患者では減弱し，eGFR が 30 mL/分/1.73 m^2 未満の患者では認められない可能性が高い。したがって，eGFR が 45 mL/分/1.73 m^2 未満に低下した場合は，必要に応じて追加の血糖降下治療を検討するべきである（4.4，4.8，5.1 及び 5.2 項参照）。

肝機能障害患者
肝機能障害患者には用量調節を必要としない。重度の肝機能障害患者でエンパグリフロジンの曝露量が増加する。重度の肝機能障害患者の治療経験は少ないため，この集団での使用は推奨されない（5.2 項参照）。

老年者
年齢による用量調節は推奨されない。75 歳以上の患者では，体液量減少のリスク増加を考慮すること（4.4 項及び 4.8 項参照）。

小児患者
小児及び青年に投与した場合のエンパグリフロジンの安全性及び有効性は確立されていない。使用経験がない。

用法

本剤は食事の有無にかかわらず投与でき，かまずに水で服用する。

4.3　禁忌

本剤の有効成分又は 6.1 項に列記した添加物のいずれかに過敏症のある患者。

4.4　特別な警告及び使用上の注意

ケトアシドーシス

生命を脅かす症例及び死亡症例を含むケトアシドーシスがエンパグリフロジンなどの SGLT2 阻害薬を投与された糖尿病患者に報告されている。多数の症例での臨床症状は非定型であり，血糖値は 14 mmol/L（250 mg/dL）未満と中等度の増加に過ぎなかった。高用量のエンパグリフロジンによりケトアシドーシス出現の可能性が高くなるか否かは不明である。糖尿病のない患者ではケトアシドーシスが起こる可能性は低いものの，このような患者にもケトアシドーシスの症例が報告されている。

悪心，嘔吐，食欲不振，腹痛，過度の口渇，呼吸困難，錯乱，異常な疲労，又は眠気などの非特異的な症状が発現した場合には，ケトアシドーシスのリスクを考慮する必要がある。血糖値にかかわらず，これらの症状が出現した場合には，すぐにケトアシドーシスを評価すべきである。

ケトアシドーシス疑い又はケトアシドーシスと診断された場合には，エンパグリフロジンの投与をすぐに中止すべきである。

大手術や急性で重篤な疾患のために入院した患者においては，投与を中断すべきである。これらの患者に対しては，ケトンのモニタリングが推奨される。尿中よりも血中ケトン値測定が望ましい。ケトン値が正常であり，患者の状態が安定している場合は，エンパグリフロジン投与を再開してもよい。

エンパグリフロジンを開始する前に，ケトアシドーシスの素因となり得る病歴の要因を考慮すること。

ケトアシドーシスのリスクが増加するおそれがある患者には，β 細胞の予備能が低い患者（例えば，低 C-ペプチドや成人潜在性自己免疫性糖尿病［LADA］を有する 2 型糖尿病患者や膵炎の既往を有する患者），摂食制限や重度の脱水に至る病態を有する患者，インスリンを減量した患者，及び急性疾患，外科手術，又はアルコール乱用のためインスリン必要量が増加した患者が含まれる。これらの患者には SGLT2 阻害薬を慎重に使用すべきである。

SGLT2 阻害薬の投与中にケトアシドーシスの既往を有する患者には，その他の明らかな増悪因子が特定され，それが解決されない限り，SGLT2 阻害薬の投与再開は推奨されない。

Jardiance は 1 型糖尿病患者に投与しないこと。1 型糖尿病患者の臨床試験プログラムから得られたデータから，プラセボと比較してインスリンの補助療法としてエンパグリフロジン 10 mg 及び 25 mg を投与された患者にケトアシドーシスの発現が増加し一般的にみられたことが判明した。

腎機能障害患者

使用経験が限られているため，eGFR が 20 mL/分/1.73 m^2 未満の患者にエンパグリフロジンによる治療を開始することは推奨されない。

eGFR が 60 mL/分/1.73 m^2 未満の患者に対するエンパグリフロジンの 1 日量は 10 mg である（4.2 項参照）。

エンパグリフロジンの血糖低下作用は腎機能に依存しており，eGFR が 45 mL/分/1.73 m^2 未満の患者では減弱し，eGFR が 30 mL/分/1.73 m^2 未満の患者では認められない可能性が高い（4.2，5.1 及び 5.2 項参照）。

腎機能モニタリング
以下のとおり腎機能を評価することを推奨する。
- 本剤の投与開始前，及び投与中は 1 年に 1 回以上定期的に評価（4.2，4.8，5.1 及び 5.2 項参照）
- 腎機能に対して悪影響を及ぼすおそれがある併用薬の投与を開始する前に評価

体液量減少のリスク

SGLT2 阻害薬の作用機序に基づき，糖尿を伴う浸透圧利尿は軽微な血圧低下につながる可能性がある（5.1 項参照）。したがって，心血管疾患を有することが知られている患者，低血圧の既往歴があり血圧降下薬による治療を受けている患者，又は 75 歳以上の患者など，エンパグリフロジン誘発性血圧低下によりリスクが提起される可能性がある患者では注意を払うべきである。

エンパグリフロジンの投与を受ける患者では，体液喪失の原因となる可能性がある状態（例えば，胃腸疾患）の場合，体液量及び電解質の注意深いモニタリング（例えば，身体的診察，血圧測定，ヘマトクリット値などの臨床検査）が推奨される。体液喪失が治癒するまでエンパグリフロジンの投与の一時中止を考慮すべきである。

老年者

尿中グルコース排泄に対するエンパグリフロジンの作用は，水分補給状態に影響する可能性のある浸透圧利尿と関連性がある。これらは 75 歳以上の患者が対象となる可能性があり，体液量減少のリスク増加のおそれがある。エンパグリフロジンを投与したこれらの患者では、プラセボと比較して、体液量減少に関連した副作用を発症している患者が多い（4.8 項参照）。したがって，体液量減少に至る可能性のある医薬品（例えば，利尿薬や ACE 阻害薬）を併用投与している場合，水分摂取量に特別な注意を払うべきである。

複雑性尿路感染

エンパグリフロジンを投与した患者において，腎盂腎炎や尿路性敗血症などの複雑性尿路感染の症例が報告されている（4.8 項参照）。合併症を伴う尿路感染患者に対して，エンパグリフロジンの一時中止を考慮すべきである。

会陰壊死性筋膜炎（フルニエー壊疽）

SGLT2 阻害薬を服用した糖尿病患者（男女）において，会陰壊死性筋膜炎（フルニエー壊疽としても知られる）の症例が報告されている。本疾患はまれだが重篤であり，緊急の外科的介入及び抗生物質投与を要する，生命を脅かす可能性のある事象である。

性器や会陰部の疼痛，圧痛，紅斑，又は腫脹の症状が発熱や倦怠感に伴って合併した場合，患者に対して治療を求めるよう助言すべきである。尿路・性器感染又は会陰膿瘍のいずれかが壊死性筋膜炎に先行する可能性があることに留意すること。フルニエー壊疽が疑われる場合，Jardiance を中止してすぐに治療を開始すべきである（抗生物質や外科的デブリードマンなど）。

下肢切断

他の SGLT2 阻害薬を用いた長期臨床試験において，下肢切断（主に足指）症例の増加がみられる。これがクラス効果によるものかは不明である。全ての糖尿病患者と同様に，日常の予防的フットケアについて患者に助言することが重要である。

肝障害

臨床試験においてエンパグリフロジンに関する肝障害の症例が報告されている。エンパグリフロジンと肝障害との因果関係は確立されていない。

ヘマトクリット増加

エンパグリフロジン投与によりヘマトクリット増加がみられた（4.8 項参照）。

慢性腎臓病

アルブミン尿を呈する患者はエンパグリフロジンによる治療でより大きなベネフィットが得られる可能性がある。

浸潤性疾患又はたこつぼ型心筋症

特に浸潤性疾患又はたこつぼ型心筋症の患者を対象とした研究は実施されていない。したがって，これらの患者に対する有効性は確立されていない。

尿検査

作用機序により，Jardiance を服薬している患者では尿のブドウ糖検査で陽性の結果が得られる。

1,5-アンヒドログルシトール（1,5-AG）検査への影響

SGLT2 阻害薬を服用している患者の 1,5-AG の測定値には信頼性がないため，1,5-AG アッセイによって血糖コントロールをモニタリングすることは推奨されない。他の方法で血糖コントロールをモニタリングすることが推奨される。

ラクトース（乳糖）

本錠剤中にラクトースを含有する。まれな遺伝的障害であるガラクトース不耐症，全ラクターゼ欠乏症，又はグルコース・ガラクトース吸収不良症を有する患者に対し，本剤を投与しないこと。

ナトリウム

1 錠中に 1 mmol 未満（23 mg）のナトリウムを含有する，すなわち基本的にナトリウムを含有しない。

4.5　薬剤相互作用及びその他の相互作用

薬力学的相互作用

利尿薬
エンパグリフロジンはチアジド系利尿薬やループ利尿薬の利尿作用を増大させる可能性があり，また脱水や低血圧のリスクを増大させる可能性がある（4.4 項参照）。

インスリン及びインスリン分泌促進薬
インスリン及びスルホニル尿素薬などのインスリン分泌促進薬は，低血糖症のリスクを増大させる可能性がある。したがって，エンパグリフロジンと併用する場合，低血糖症のリスクを減らすために低用量のインスリン又はインスリン分泌促進薬を投与する必要があると思われる（4.2 項及び 4.8 項参照）。

薬物動態学的相互作用

他の医薬品がエンパグリフロジンに及ぼす影響
In vitro データにより，ヒトにおけるエンパグリフロジンの一次代謝経路がウリジン 5'-二リン酸グルクロン酸転移酵素の UGT1A3，UGT1A8，UGT1A9 及び UGT2B7 によるグルクロン酸抱合であることが示唆される。エンパグリフロジンは，ヒト取り込み輸送体 OAT3，OATP1B1 及び OATP1B3 の基質だが，OAT1 及び OCT2 の基質ではない。エンパグリフロジンは，P-糖蛋白（P-gp）及び乳癌耐性蛋白（BCRP）の基質である。

エンパグリフロジンとプロベネシド（各種 UGT 酵素と OAT3 の阻害薬）との併用投与により，エンパグリフロジンの最高血漿濃度（C_{max}）は 26%増加し，濃度-時間曲線下面積（AUC）も 53%増加したが，これらの変化は臨床的に意味があるとはみなされなかった。

UGT 誘導（リファンピシン又はフェニトインによる誘導など）がエンパグリフロジンに及ぼす作用については検討されていない。効果が減弱するリスクがあるため，既知の UGT 酵素の誘導物質との併用投与は推奨されない。これらの UGT 酵素の誘導物質を併用投与しなければならない場合，Jardiance に対する反応を評価するために血糖コントロールをモニタリングすることが適切である。

In vitro での OAT3 及び OATP1B1/1B3 の輸送体阻害剤ゲムフィブロジルとの相互作用試験では，併用投与後，エンパグリフロジンの C_{max} が 15%増加し，AUC が 59%増加したことが示された。これらの変化は臨床的に意味があるとはみなされなかった。

リファンピシンとの併用投与による OATP1B1/1B3 輸送体の阻害の結果，エンパグリフロジンの C_{max} が 75%増加し，AUC が 35%増加したが，これらの変化は臨床的に意味があるとはみなされなかった。

P-gp 阻害薬ベラパミルの併用投与の有無にかかわらず，エンパグリフロジンの曝露量は同等であり，P-gp の阻害がエンパグリフロジンに対し臨床的に意味のある影響を及ぼさないことを示唆している。

薬物相互作用試験によると，エンパグリフロジンの薬物動態に対し，メトホルミン，グリメピリド，ピオグリタゾン，シタグリプチン，リナグリプチン，ワルファリン，ベラパミル，ラミプリル，シンバスタチン，トラセミド，及びヒドロクロロチアジドの併用投与は影響しないことが示唆される。

エンパグリフロジンが他の医薬品に及ぼす影響
エンパグリフロジンは，リチウム腎排泄を増加させ，血中リチウム濃度が低下する可能性がある。エンパグリフロジンの投与開始後及び用量変更後は，リチウムの血清中濃度をより頻繁にモニタリングすべきである。リチウムの血清中濃度をモニタリングするため，リチウム処方医に紹介すること。

In vitro 試験に基づくと，エンパグリフロジンは CYP450 アイソフォームを阻害，不活性化，又は誘導しない。エンパグリフロジンは，UGT1A1，UGT1A3，UGT1A8，UGT1A9，又は UGT2B7 を阻害しない。したがって，エンパグリフロジンと併用投与されるこれらの酵素の基質に主要 CYP450 アイソフォーム及び UGT アイソフォームが関与する薬物相互作用は，生じる可能性が低いと考えられる。

エンパグリフロジンは治療用量では P-gp を阻害しない。In vitro 試験に基づくと，エンパグリフロジンは P-gp の基質である薬剤との相互作用を引き起こす可能性は低いと考えられる。P-gp 基質であるジゴキシンとエンパグリフロジンとの併用投与の結果，ジゴキシンの AUC は 6%増加し，C_{max} は 14%増加したが，これらの変化は臨床的に意味があるとはみなされなかった。

エンパグリフロジンは，*in vitro* で臨床的に適切な血漿濃度では OAT3，OATP1B1，及び OATP1B3 などのヒト取り込み輸送体を阻害しない。すなわち，これらの取り込み輸送体の基質との薬物相互作用の可能性は低いと考えられる。

健康被験者を対象として実施した薬物相互作用試験によると，エンパグリフロジンはメトホルミン，グリメピリド，ピオグリタゾン，シタグリプチン，リナグリプチン，シンバスタチン，ワルファリン，ラミプリル，ジゴキシン，利尿薬，及び経口避妊薬の薬物動態に対し臨床的に意味のある影響を及ぼさないことが示唆されている。

4.6　生殖系，妊娠及び授乳

妊婦

妊婦に対しエンパグリフロジンを投与したデータはない。動物試験では妊娠後期におけるエンパグリフロジンの胎盤通過の程度が極めて少なく，早期胚発生に対する直接的又は間接的な悪影響は示されていない。しかし，動物試験では出生後の発達に対する有害作用がみられている（5.3 項参照）。予防措置として，妊娠中は Jardiance の使用を避けることが望ましい。

授乳婦

ヒトにおけるエンパグリフロジンの乳汁中への分泌に関するデータは得られていない。動物における毒性学的データではエンパグリフロジンの乳汁中への分泌が示されている。新生児／幼児に対するリスクは除外できない。授乳中は Jardiance を使用しないこと。

生殖系

Jardiance のヒト生殖系に及ぼす作用に関する試験は実施されていない。動物試験では，生殖系に関する直接的又は間接的な悪影響は示されていない（5.3 項参照）。

4.7　運転及び機械操作能に対する影響

Jardiance は運転及び機械を操作する能力に対して軽度な影響を及ぼす。患者に対し，特に本剤をスルホニル尿素薬及び／又はインスリンと併用した場合は，運転及び機械の使用中に低血糖症を起こさないように注意を促すこと。

4.8　副作用

安全性プロファイルの要約

2 型糖尿病
合計 15582 例の 2 型糖尿病患者を対象とした臨床試験においてエンパグリフロジンの安全性を評価した。このうち 10004 例にエンパグリフロジンを単剤か，メトホルミン，スルホニル尿素薬，ピオグリタゾン，DPP-4 阻害剤，又はインスリンとの併用のいずれかで投与した。

6 件のプラセボ対照臨床試験の 18～24 週間にわたる継続期間中に 3534 例を組み入れ，このうち 1183 例にはプラセボを，2351 例にはエンパグリフロジンを投与した。エンパグリフロジンを投与した患者における有害事象の発現率は，全体としてプラセボ投与患者の場合と類似していた。スルホニル尿素薬やインスリンと併用した場合に最も多く報告された副作用は低血糖症であった（特定の副作用の詳細を参照）。

心不全
EMPEROR 試験では，エンパグリフロジン 10 mg 又はプラセボの投与を受けた駆出率が低下した心不全患者 3726 例及び駆出率が維持された心不全患者 5985 例が含まれた。約半数の患者には 2 型糖尿病があった。EMPEROR-Reduced 試験と EMPEROR-Preserved 試験を合わせて最も多く認められた副作用は体液量減少であった（エンパグリフロジン 10 mg 群：11.4%，プラセボ群：9.7%）。

慢性腎臓病
EMPA-KIDNEY 試験では，エンパグリフロジン 10 mg 又はプラセボの投与を受けた慢性腎臓病患者 6609 例が含まれた。約 44%の患者には 2 型糖尿病があった。EMPA-KIDNEY 試験において最も多く認められた有害事象は，痛風（エンパグリフロジン群：7.0%，プラセボ群：8.0%）及び急性腎障害（エンパグリフロジン群：2.8%，プラセボ群：3.5%）（これはプラセボ群の患者でより多く報告

された）であった。

エンパグリフロジンの全般的な安全性プロファイルは，これまでに検討された適応症のものと概ね一致していた。

副作用一覧表

プラセボ対照臨床試験においてエンパグリフロジンを投与した患者において報告された，器官別大分類及び MedDRA 基本語により分類された副作用を下表（表 1）に表す。

副作用は発現頻度により列記する。頻度の定義は，極めて一般的（≧ 1/10），一般的（≧ 1/100 ～ < 1/10），一般的でない（≧ 1/1,000 ～ < 1/100），まれ（≧ 1/10,000 ～ < 1/1,000），又は極めてまれ（< 1/10,000），及び不明（入手可能なデータからは推定不能）とする。

表 1： プラセボ対照臨床試験及び市販後の使用経験において報告された副作用（MedDRA）

器官別大分類	極めて一般的	一般的	一般的でない	まれ	極めてまれ
感染症および寄生虫症		腟モニリア症，外陰腟炎，亀頭炎及びその他の性器感染[a]，尿路感染（腎盂腎炎及び尿路性敗血症を含む）[a]		会陰壊死性筋膜炎（フルニエ壊疽）*	
代謝および栄養障害	低血糖症（スルホニル尿素薬やインスリンと併用した場合）[a]	口渇	ケトアシドーシス*		
胃腸障害		便秘			
皮膚および皮下組織障害		そう痒症（全身性）発疹	蕁麻疹血管浮腫		
血管障害	体液量減少[a]				
腎および尿路障害		排尿増加[a]	排尿困難		尿細管間質性腎炎
臨床検査		血清脂質増加[a]	血中クレアチニン増加／糸球体濾過率減少[a] ヘマトクリット増加[a]		

[a]その他の情報については下記の細別を参照すること。
*4.4 項参照。

特定の副作用の詳細

低血糖
低血糖症の頻度はそれぞれの試験で用いた基礎治療薬によって左右され，個々の構成要素として，エンパグリフロジンとメトホルミンを投与された患者と比較して，単剤療法としてのエンパグリフロジンとプラセボ，メトホルミンへの追加療法，メトホルミンの有無にかかわらずピオグリタゾンへの追加療法，リナグリプチンとメトホルミンへの追加療法，並びに糖尿病治療薬による治療を受けていない患者における標準療法の補助及びエンパグリフロジンとメトホルミンへの併用療法と類似していた。メトホルミンとスルホニル尿素薬への追加療法（エンパグリフロジン 10 mg 群 16.1%，エンパグリフロジン 25 mg 群 11.5%，プラセボ群 8.4%），メトホルミンの有無及びスルホニル尿素薬の有無にかかわらず基礎インスリンへの追加療法（インスリン投与量調節不可能だった場合の初回 18 週治療で：エンパグリフロジン 10 mg 群 19.5%，エンパグリフロジン 25 mg 群 28.4%，プラセボ群 20.6%，78 週試験全体で：エンパグリフロジン 10 mg 及び 25 mg 群 36.1%，プラセボ群 35.3%），及びメトホルミンの有無にかかわらず MDI インスリンへの追加療法（インスリン投与量調節不可能だった場合の初回 18 週治療で：エンパグリフロジン 10 mg 群 39.8%，エンパグリフロジン 25 mg 群 41.3%，プラセボ群 37.2%，52 週試験全体で：エンパグリフロジン 10 mg 群 51.1%，エンパグリフロジン 25 mg 群 57.7%，プラセボ群 58%）として投与したところ，発現頻度の増加が認められた。

EMPEROR 心不全試験では，スルホニル尿素薬又はインスリンへの追加療法として投与された場合，低血糖は同様の頻度で認められた（エンパグリフロジン 10 mg 群：6.5%，プラセボ群：6.7%）。

重度低血糖症（介助を必要とする低血糖症）
重度低血糖症は，個々の構成要素としてエンパグリフロジンとメトホルミンを投与された患者と比較して，単独療法，メトホルミンへの追加療法，メトホルミンとスルホニル尿素薬への追加療法，及びメトホルミンの有無にかかわらずピオグリタゾンへの追加療法，リナグリプチンとメトホルミンへの追加療法，標準治療の補助，及び糖尿病治療薬による治療を受けていない患者におけるエンパグリフロジンとメトホルミンとの併用療法の場合，プラセボ群と比べて増加していなかった。メトホルミンの有無及びスルホニル尿素薬の有無にかかわらず基礎インスリンへの追加療法（インスリン投与量調節不可能だった場合の初回 18 週の治療で：エンパグリフロジン 10 mg 群 0%，エンパグリフロジン 25 mg 群 1.3%，プラセボ群 0%，78 週試験全体で：エンパグリフロジン 10 mg 群：0%，エンパグリフロジン 25 mg 群 1.3%，プラセボ群 0%），またメトホルミンの有無にかかわらず MDI インスリンへの追加療法として投与したところ，発現頻度の増加が認められた（インスリン投与量調節不可能だった場合の初回 18 週治療で：エンパグリフロジン 10 mg 群 0.5%，エンパグリフロジン 25 mg 群 0.5%，プラセボ群 0.5%；52 週試験全体で：エンパグリフロジン 10 mg 群 1.6%，エンパグリフロジン 25 mg 群 0.5%，プラセボ群 1.6%）。

EMPEROR 心不全試験では，スルホニル尿素薬又はインスリンへの追加治療としてエンパグリフロジンとプラセボを投与したところ，重度の低血糖症は糖尿病患者と同様の頻度で認められた（エンパグリフロジン 10 mg 投与群：2.2%，プラセボ投与群：1.9%）。

膣モニリア症，外陰膣炎，亀頭炎，及びその他の性器感染
膣モニリア症，外陰膣炎，亀頭炎及びその他の性器感染の報告頻度がプラセボ群患者（1.0%）と比較してエンパグリフロジン群患者の方が高かった（エンパグリフロジン 10 mg 群：4.0%，エンパグリフロジン 25 mg 群：3.9%）。これらの感染症の報告頻度はプラセボ群患者と比較してエンパグリフロジン群の女性患者の方が高く，男性患者では頻度の差が比較的小さかった。性器感染の程度は軽度ないし中等度であった。

EMPEROR 心不全試験では，エンパグリフロジンとプラセボによる投与を比較した場合，これらの感染症の頻度は糖尿病患者（エンパグリフロジン 10 mg 群：2.3%，プラセボ群：0.8%）の方が非糖尿病患者（エンパグリフロジン 10 mg 群：1.7%，プラセボ群：0.7%）よりも顕著であった。

排尿増加
排尿増加（事前定義された用語である頻尿，多尿，夜間頻尿を含む）が，プラセボ群（1.4%）と比較しエンパグリフロジン群において高頻度で認められた（エンパグリフロジン 10 mg 群：3.5%，エ

ンパグリフロジン 25 mg 群：3.3%）。排尿増加の程度は大部分が軽度ないし中等度であった。夜間頻尿の報告頻度は，プラセボ群とエンパグリフロジン群で類似していた（＜1%）。

EMPEROR 心不全試験では，排尿増加の頻度はエンパグリフロジン群とプラセボ群で類似していた（エンパグリフロジン 10 mg 群：0.9%，プラセボ群：0.5%）。

尿路感染
有害事象として報告された尿路感染の全般的な発現頻度は，エンパグリフロジン 25 mg 群（7.0%）とプラセボ群（7.2%）で類似しており，エンパグリフロジン 10 mg 群の方が高かった（8.8%）。プラセボと同様，慢性又は再発性尿路感染の既往歴があるエンパグリフロジン群の方が尿路感染の報告頻度が高かった。尿路感染の重症度（軽度，中等度，重度）は，エンパグリフロジン治療群とプラセボ群患者で類似していた。女性では，プラセボ群と比較しエンパグリフロジン治療群の方が尿路感染の報告が多かったが，男性では差異は認められなかった。

体液量減少
体液量減少（事前に定義された用語である血圧低下［外来］，収縮期血圧低下，脱水，低血圧，血液量減少症，起立性低血圧，失神などを含む）の全般的な発症頻度は，エンパグリフロジン群（エンパグリフロジン 10 mg：0.6%，エンパグリフロジン 25 mg：0.4%）とプラセボ群（0.3%）で類似していた。体液量減少の発現頻度は，75 歳以上の患者では，プラセボ群（2.1%）と比較しエンパグリフロジン 10 mg 群（2.3%）又はエンパグリフロジン 25 mg（4.3%）で増加した。

血中クレアチニン増加／糸球体濾過率減少
血中クレアチニン増加及び糸球体濾過率減少を有する患者の全体的な頻度は，エンパグリフロジンとプラセボで類似していた（血中クレアチニン増加：エンパグリフロジン 10 mg 群 0.6%，エンパグリフロジン 25 mg 群 0.1%，プラセボ群 0.5%，糸球体濾過率減少：エンパグリフロジン 10 mg 群 0.1%，エンパグリフロジン 25 mg 群 0%，プラセボ群 0.3%）。
エンパグリフロジン投与患者におけるクレアチニンの初回増加及び糸球体濾過率の初回減少は，通常，継続投与中に一過性，又は投与中止後に可逆的であった。
EMPA-REG OUTCOME 試験では，エンパグリフロジン投与患者に一貫して eGFR の初回低下が発現した（平均：3 mL/分/1.73 m^2）。その後，継続投与中に eGFR は維持された。投与中止後に平均 eGFR はベースライン値に回復したが，血行動態の急激な変化は，これらの腎機能の変化に役割を果たした可能性を示唆した。この現象は EMPEROR 心不全試験及び EMPA-KIDNEY 試験でも観察されている。

血清脂質増加
エンパグリフロジン 10 mg 群，エンパグリフロジン 25 mg 群，プラセボ群におけるベースラインからの平均増加率はそれぞれ，総コレステロールでは 4.9%，5.7%，3.5%，HDL コレステロールでは 3.3%，3.6%，0.4%，LDL コレステロールでは 9.5%，10.0%，7.5%，トリグリセリドでは 9.2%，9.9%，10.5%であった。

ヘマトクリット増加
ヘマトクリットのベースラインからの平均変化量は，プラセボ群の 0.1%に対してエンパグリフロジン 10 mg 群では 3.4%，エンパグリフロジン 25 mg 群では 3.6%であった。EMPA-REG OUTCOME 試験では，ヘマトクリット値は治療の中止から 30 日間の追跡調査期間後にベースライン値に回復した。

副作用の疑いがある事象の報告

承認後の医薬品の副作用の疑いがある事象の報告は重要である。この報告によってその医薬品のベネフィット／リスクバランスのモニタリングを継続できる。副作用の疑いがある事象があれば，付録 V に記載されている国家報告制度を通じて報告することを医療専門家に要請する。

4.9　過量投与

症状

比較対照臨床試験で，800 mg までのエンパグリフロジンを健康な志願者に単回投与した場合に，また 2 型糖尿病患者に 1 日 100 mg までのエンパグリフロジンを反復投与した場合に，毒性は全く認められなかった。エンパグリフロジンにより、尿中グルコース排泄が増加したため、尿量が増加した。尿量の増加が認められたが用量依存性はみられず，臨床的に重要ではない。ヒトにおいて 800 mg を超える用量での投与経験はない。

治療

過量投与した場合，治療は患者の臨床状態に応じて適切に開始するべきである。血液透析によるエンパグリフロジンの除去は検討されていない。