Glyxambi®

1. NAME OF THE MEDICINAL PRODUCT

Glyxambi Film-Coated Tablets 10mg/5mg
Glyxambi Film-Coated Tablets 25mg/5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg or 25mg empagliflozin and 5mg linagliptin

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Glyxambi 10mg/5mg: Pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol, the other side is debossed with "10/5".

Glyxambi 25mg/5mg: Pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol, the other side is debossed with "25/5".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLYXAMBI tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate. (See Clinical Trials)

Limitations of Use
GLYXAMBI is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

GLYXAMBI has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using GLYXAMBI.

4.2 Posology and method of administration

Recommended Dosage
The recommended dose of GLYXAMBI is 10 mg empagliflozin/5 mg linagliptin once daily in the morning, taken with or without food. In patients tolerating GLYXAMBI, the dose may be increased to 25 mg empagliflozin/5 mg linagliptin once daily.

In patients with volume depletion, correcting this condition prior to initiation of GLYXAMBI is recommended.

No studies have been performed specifically examining the safety and efficacy of GLYXAMBI in patients previously treated with other oral antihyperglycemic agents and switched to GLYXAMBI. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Patients with Renal Impairment
Assessment of renal function is recommended prior to initiation of GLYXAMBI and periodically thereafter.

GLYXAMBI should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

GLYXAMBI should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2

Patients with hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment.
Empagliflozin exposure is increased in patients with severe hepatic impairment and therapeutic experience in such patients is limited. Therefore, GLYXAMBI is not recommended for use in this population.

Elderly Patients
No dosage adjustment is recommended based on age. Therapeutic experience in patients aged 75 years and older is limited. Initiation of GLYXAMBI therapy in this population is not recommended (see Special Warnings and Precautions).

Paediatric population
The safety and effectiveness of GLYXAMBI in children below 18 years of age have not been established. GLYXAMBI is not recommended for use in patients under 18 years of age.

Combination therapy
When GLYXAMBI 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 Interactions and Side effects)

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

4.3 Contraindications

Hypersensitivity to empagliflozin or linagliptin or any of the excipients.

4.4 Special warning and precautions for use

GLYXAMBI should not be used in patients with type 1 diabetes.

Diabetic ketoacidosis

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

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness.

Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. If ketoacidosis is suspected, GLYXAMBI should be discontinued, patient should be evaluated, and prompt treatment should be instituted.

Patients who may be at higher risk of ketoacidosis while taking GLYXAMBI include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration, and patients with a history of ketoacidosis. GLYXAMBI should be used with caution in these patients. When reducing the insulin dose (see Dosage and Administration) caution should be taken. In patients treated with GLYXAMBI consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI in clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if GLYXAMBI treatment has been interrupted.

Necrotizing fasciitis of the perineum (Fournier's gangrene)

Postmarketing cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.

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

Hypoglycaemia

In clinical trials of linagliptin or of empagliflozin as part of combination therapy with agents not known to cause hypoglycaemia (e.g. metformin, thiazolidinediones) rates of hypoglycaemia reported with linagliptin or empagliflozin were similar to rates in patients taking placebo (see Side Effects).

Caution is advised when GLYXAMBI is used in combination with a sulphonylurea or insulin. A dose reduction of the sulphonylurea or insulin may be considered.

Acute pancreatitis

Use of dipeptidyl peptidase-4 (DPP 4) inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis.

If pancreatitis is suspected, GLYXAMBI should be discontinued; if acute pancreatitis is confirmed, GLYXAMBI should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Use in patients with renal impairment

GLYXAMBI should not be initiated in patients with an eGFR less than 45 ml/min/1.73 m^2.

GLYXAMBI should be discontinued if eGFR is persistently less than 45 ml/min/1.73m^2

Monitoring of renal function

Due to its mechanism of action, the efficacy of empagliflozin is dependent on renal function. Therefore, an assessment of renal function is recommended prior to the initiation of treatment with GLYXAMBI and also periodically during treatment, i.e., at least yearly.

Use in patients at risk for volume depletion

Based on the mode of action of SGLT-2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced decrease 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 GLYXAMBI should be considered until the fluid loss is corrected.

Urinary tract infections

In the pooled placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg. Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. **Temporary interruption of GLYXAMBI should be considered in patients with complicated urinary tract infections.**

Bullous pemphigoid

Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported in 0.2% of patients on treatment with linagliptin and in no patient on placebo. **If bullous pemphigoid is suspected, GLYXAMBI should be discontinued.**

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.

Elderly patients

A higher risk of volume depletion adverse reactions were reported in patients aged 75 years and older, treated with empagliflozin, especially at 25 mg/day (see section 4.8). Therapeutic experience is limited with GLYXAMBI in patients > 75 years of age, and, no experience is available in patients aged 85 years and older. Initiation of therapy with GLYXAMBI in this population is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions between the two components of this fixed-dose combination have been observed in clinical studies.

No drug interaction studies have been performed with GLYXAMBI and other medicinal products, however, such studies have been conducted with the individual active substances.

No clinically meaningful pharmacokinetic interactions were observed when empagliflozin or linagliptin were co-administered with other commonly used medicinal products. Based on results of pharmacokinetic studies, no dose adjustment of GLYXAMBI is recommended when co-administered with commonly prescribed medicinal products (see section Pharmacological Properties), except those mentioned below.

Insulin and sulphonylureas

Insulin and sulphonylureas may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or sulphonylureas may be required to reduce the risk of hypoglycaemia when used in combination with GLYXAMBI (see section Dosage and Administration, Special Warnings and Precautions, Side Effects).

Diuretics

Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section Special Warnings and Precautions).

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

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

Lithium

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

UGT inhibitors and inducers

Empagliflozin is primarily metabolised via uridine 5'-diphosphoglucuronosyltransferases (UGT); however, a clinically relevant effect of UGT inhibitors on empagliflozin is not expected (see section Pharmacological Properties).

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

Inducers of P-gp or CYP3A4 isozymes

Co-administration of rifampicin decreased linagliptin exposure by 40%, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-glycoprotein (P-gp) or cytochrome P450 (CYP) isozyme CYP3A4 inducer, particularly if these are administed long-term (see section Pharmacological Properties). Co- administration with other potent inducers of P-gp and CYP3A4, such as carbamazepine, phenobarbital and phenytoin, has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of empagliflozin and linagliptin in pregnant women. Nonclinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure it is recommended to avoid the use of GLYXAMBI during pregnancy unless clearly needed.

Lactation

No data in humans are available on excretion of empagliflozin and linagliptin into milk.

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

Fertility

No studies on the effect on human fertility have been conducted for GLYXAMBI or with the individual

components.

Nonclinical studies of empagliflozin alone and of linagliptin alone do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effect on ability to drive and use machines

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

4.8 Undesirable effects

A total of 2173 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of GLYXAMBI, of which 1005 patients were treated with GLYXAMBI. In clinical trials, patients were treated for up to 24 or 52 weeks.

The most frequent side effect was urinary tract infection (see description of selected side effects). The most serious adverse reactions were ketoacidosis (< 0.1%), pancreatitis (0.2%), hypersensitivity (0.6%), and hypoglycaemia (2.4%) (see section 4.4).

Overall, the safety profile of GLYXAMBI was comparable to the safety profiles of the individual components (empagliflozin and linagliptin).

The side effects shown in Table 1 listed by system organ class, are based on the safety profiles of empagliflozin and linagliptin monotherapy, and were also reported in clinical trials and post marketing surveillance with GLYXAMBI. No additional side effects were identified with GLYXAMBI as compared to the individual components.

Table 1 Side effects reported in patients taking empagliflozin or linagliptin as monotherapy

	Empagliflozin and Linagliptin
System Organ class	Side effect
Infections and infestations	**Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections**[1,2] **Urinary tract infection**[1,2] **(including pyelonephritis and urosepsis)**[5] **Necrotizing fasciitis of the perineum (Fournier´s gangrene)**[5] **Nasopharyngitis**[3]
Immune system disorders	**Hypersensitivity**[3] **Angioedema**[4,5] **Urticaria**[4,5]
Metabolism and nutrition disorders	**Hypoglycaemia (when used with sulphonylurea or insulin)**[2] **Ketoacidosis**[5]
Renal and urinary disorders	**Increased urination**[1,2] **Dysuria**[1]
Respiratory, thoracic & mediastinal disorders	**Cough**[3]
Skin and subcutaneous tissue disorders	**Rash**[4,5] **Pruritus**[1] Bullous pemphigoid[3,a]
Gastrointestinal disorders	**Constipation** **Pancreatitis**[3] **Mouth ulceration**[4]
Vascular disorders	**Volume depletion**[1,2]

General disorders and administration site conditions	**Thirst**[1]
Investigations	Increased amylase[2] Lipase increased[3,6] Haematocrit increased[1,7] Serum lipids increased[1,7] Glomerular filtration rate decreased[1,2] Blood creatinine increased[1,2] Amylase increased[3,b]

[1] derived from empagliflozin experiences
[2] see subsections below for additional information
[3] derived from linagliptin experiences
[4] derived from linagliptin postmarketing experience
[5]derived from empagliflozin postmarketing experience
[6] based on lipase elevations >3xULN observed in clinical trials
[7] see section clinical trials for additional information
[a] In the CARMELINA study (see section 5.1), bullous pemphigoid was reported in 0.2% patients treated with linagliptin and in no patients treated with placebo.
[b] In the CAROLINA study (see section Clinical Trials), amylase increase to > 3xULN was reported in 0.99% of patients treated with linagliptin and in 0.54% of patients treated with glimepiride.

Description of selected side effects

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

Hypoglycaemia

In pooled clinical trials of GLYXAMBI in patients with type 2 diabetes and inadequate glycaemic control on background metformin, the incidence of confirmed hypoglycaemic events was low (<1.5%; for confirmed clinical events per trial see Table 2).

One patient administered GLYXAMBI experienced a confirmed (investigator-defined), major hypoglycaemic event in the active- or placebo-controlled trials and none required assistance.

Table 2 Confirmed hypoglycaemic events – Glyxambi 10 mg/5 mg and Glyxambi 25 mg/5 mg

	Trial 1275.1 (Add-on to Metformin)				
	Glyxambi® 10 mg/5 mg	**Glyxambi® 25 mg/5 mg**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Linagliptin 5 mg**
Number of patients analysed, N (%)	136 (100.0)	137 (100.0)	141 (100.0)	141 (100.0)	132 (100.0)
Patients with endpoint, N (%)	3 (2.2)	5 (3.6)	2 (1.4)	5 (3.5)	3 (2.3)
	Trial 1275.1 (treatment naïve)				
	Glyxambi® 10 mg/5 mg	**Glyxambi® 25 mg/5 mg**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**	**Linagliptin 5 mg**
Number of patients analysed, N (%)	136 (100.0)	136 (100.0)	135 (100.0)	135 (100.0)	135 (100.0)
Patients with endpoint, N (%)	0 (0.0)	0 (0.0)	4 (3.0)	1 (0.7)	1 (0.7)

	Trial 1275.9 (Add-on to metformin + Linagliptin 5 mg)		
	Empagliflozin 10 mg	**Empagliflozin 25 mg**	**Placebo**
Number of patients analysed, N (%)	112 (100.0)	110 (100.0)	110 (100.0)
Patients with endpoint, N (%)	0 (0.0)	3 (2.7)	1 (0.9)

	Trial 1275.10 (Add-on to metformin + Empagliflozin)			
	Metformin + Empagliflozin 10mg		**Metformin + Empagliflozin 25 mg**	
	Linagliptin 5 mg	**Placebo**	**Linagliptin 5 mg**	**Placebo**
Number of patients analysed, N (%)	126 (100.0)	128 (100.0)	112 (100.0)	112 (100.0)
Patients with endpoint, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)

Hypoglycaemia for empagliflozin

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

Major hypoglycaemia with empagliflozin (events requiring assistance)

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

The frequency of patients with major hypoglycaemic events was increased in patients treated with empagliflozin compared to placebo when given as add-on to insulin +/- metformin and +/- sulfonylurea.

Hypoglycaemia with linagliptin

The most frequently reported adverse event in clinical trials with linagliptin was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea (22.9% vs 14.8% in placebo).

Hypoglycaemias in the placebo-controlled studies (10.9%; N=471) were mild (80%; N=384) or moderate (16.6%; N=78) or severe (1.9%; N=9) in intensity.

Urinary tract infection

In clinical trials with GLYXAMBI, the frequency of urinary tract infection adverse events (GLYXAMBI 25 mg/5 mg: 9.2%; GLYXAMBI 10 mg/5 mg: 8.8%) has been comparable to those reported from the empagliflozin clinical trials.

In empagliflozin trials, the overall frequency of urinary tract infection adverse events was similar in

patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%), and higher in patients treated with empagliflozin 10 mg (8.8%). The intensity of urinary tract infections was similar to placebo for mild, moderate, and severe intensity reports. Urinary tract infection events were reported more frequently for empagliflozin compared to placebo in female patients, but not in male patients.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

In clinical trials with GLYXAMBI, the frequency of genital infection adverse events (GLYXAMBI 25 mg/5 mg: 3.1%; GLYXAMBI 10 mg/5 mg: 3.5%) has been comparable to those reported from the empagliflozin clinical trials.

In empagliflozin trials, vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg (4.0%) and empagliflozin 25 mg (3.9%) compared to placebo (1.0%), and were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination

In clinical trials with GLYXAMBI, the frequency of increased urination adverse events (GLYXAMBI 25 mg/5 mg: 1.7%; GLYXAMBI 10 mg/5 mg: 0.8%) has been comparable to those reported from the empagliflozin clinical trials.

As expected via its mechanism of action, in clinical trials with empagliflozin, increased urination (as assessed by PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin 10 mg (3.5%) and 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 comparable between placebo and empagliflozin (<1%).

Volume depletion

In clinical trials with GLYXAMBI, the frequency of patients with volume depletion adverse events (GLYXAMBI 25 mg/5 mg: 0.6%; GLYXAMBI 10 mg/5 mg: 0.5%) in Glyxambi treatment groups has been comparable to the frequencies in the those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, the overall frequency of patients with volume depletion adverse events was similar to placebo (placebo 0.3%, empagliflozin 10 mg 0.6%, and empagliflozin 25 mg 0.4%). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older. In patients ≥75 years of age the frequency of patients with volume depletion events was similar for empagliflozin 10 mg (2.3%) compared to placebo (2.1%), but it increased with empagliflozin 25 mg (4.3%).

Blood creatinine increased and glomerular filtration rate decreased

In clinical trials with GLYXAMBI®, the frequency of patients with increased blood creatinine (GLYXAMBI® 25 mg/5 mg: 0.4%; GLYXAMBI® 10 mg/5 mg: 0%) **and decreased glomerular filtration rate** (GLYXAMBI® 25 mg/5 mg: 0.4%; GLYXAMBI® 10 mg/5 mg: 0.6%) **has been comparable to those reported from the empagliflozin clinical trials.**

In clinical trials with empagliflozin, the overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was 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%).

In placebo-controlled, double-blind studies up to 76 weeks, initial transient increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0.02 mg/dL, empagliflozin 25 mg

0.01 mg/dL) **and initial transient decreases in estimated glomerular filtration rates** (mean change from baseline after 12 weeks: empagliflozin 10 mg -1.34 mL/min/1.73m2, empagliflozin 25 mg -1.37 mL/min/1.73m2) **have been observed**. **These changes were generally reversible during continuous treatment or after drug discontinuation.**

4.9 Overdose

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

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were well tolerated. There is no experience with doses above 600 mg in humans.

Therapy

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD19

Mode of Action

Combination empagliflozin/ linagliptin

The mechanism of action of empagliflozin, which is independent of the insulin pathway and β-cell function, is different from and complementary to the mechanisms of currently available medications to treat Type 2 diabetes mellitus (T2DM). Therefore the efficacy of empagliflozin was found to be additive to all drugs with other mechanisms of action, such as dipeptidyl peptidase-4 (DPP-4) inhibitors.

The combination of empagliflozin and linagliptin, after single oral dosing, showed a superior effect on glycemic control (OGTT) as compared to the respective monotherapies tested in diabetic ZDF rats. Chronic treatment of empagliflozin in combination with linagliptin significantly improved insulin sensitivity (tested by euglycemic- hyperinsulinemic clamp studies) in diabetic db/db mice. The improved insulin sensitivity was significantly superior with the combination in comparison to the monotherapies.

Empagliflozin

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC_{50} of 6278 nM), responsible for glucose absorption in the gut. In the kidney, the glucose filtered is almost completely reabsorbed by SGLT2 (up to 90%) and to a lesser extent by SGLT1 located in the S1 and S3 segments of the proximal tubule of the nephron respectively. Empagliflozin, by inhibiting the reabsorption of glucose by the kidney, leads to increased urinary glucose excretion that triggers the lowering of blood glucose after single oral dosing, as well as after chronic treatment. In addition, the glucosuric effect of empagliflozin, leading to calorie loss, translated into body weight reduction.

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

with T2DM and hyperglycemia, excess glucose is excreted in the urine.

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

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

Linagliptin

Linagliptin is an inhibitor of the enzyme DPP-4 an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose- dependent insulinotropic polypeptide). Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin binds selectively to DPP-4 and exhibits a >10000-fold selectivity versus DPP-8 or DPP-9 activity in vitro. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homoeostasis.

Clinical trials

A total of 2173 patients with T2DM and inadequate glycaemic control were treated in clinical studies to evaluate the safety and efficacy of GLYXAMBI; 1005 patients were treated with GLYXAMBI 10 or 25 mg, and linagliptin 5 mg**.** In clinical trials, patients were treated for up to 24 or 52 weeks.

GLYXAMBI added to metformin

In a factorial design study, patients inadequately controlled on metformin, 24-weeks treatment with GLYXAMBI 10 mg/5 mg and GLYXAMBI 25 mg/5 mg provided statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) compared to linagliptin 5 mg and also compared to empagliflozin 10 or 25 mg. Compared to linagliptin 5 mg GLYXAMBI provided statistically significant improvements in body weight.

A greater proportion of patients with a baseline HbA_{1c} ≥7.0% and treated with GLYXAMBI achieved a target HbA_{1c} of <7% compared to the individual components (Table 3). After 24 weeks' treatment with empagliflozin/linagliptin, both systolic and diastolic blood pressures were reduced, -5.6/-3.6 mmHg ($p<0.001$ versus linagliptin 5 mg for SBP and DBP) for GLYXAMBI 25mg/ 5 mg and -4.1/-2.6 mmHg ($p<0.05$ versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10mg/ 5 mg.

Clinically meaningful reductions in HbA_{1c} (Table 3) and both systolic and diastolic blood pressures were observed at week 52, -3.8/-1.6 mmHg ($p<0.05$ versus linagliptin 5 mg for SBP and DBP) for GLYXAMBI 25 mg/ 5 mg and -3.1/-1.6 mmHg ($p<0.05$ versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10 mg/ 5 mg.

After 24 weeks, rescue therapy was used in 1 (0.7%) patient treated with GLYXAMBI 25 mg/ 5 mg and in 3 (2.2%) patients treated with GLYXAMBI 10 mg / 5 mg, compared to 4 (3.1%) patients treated with linagliptin 5 mg and 6 (4.3%) patients treated with empagliflozin 25 mg and 1 (0.7%) patient treated with empagliflozin 10 mg.

Table 3 Efficacy Parameters in Clinical Study Comparing GLYXAMBI to Individual Components as Add-on Therapy in Patients Inadequately Controlled on Metformin

	GLYXAMBI® 25 mg / 5 mg	GLYXAMBI® 10 mg / 5 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Linagliptin 5 mg
Primary endpoint: HbA_{1c} (%) – 24 weeks					
Number of patients analysed	**134**	**135**	**140**	**137**	**128**
Baseline mean (SE)	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
Change from baseline at week 24[1]: - adjusted mean[2] (SE)	-1.19 (0.06)	-1.08 (0.06)	-0.62 (0.06)	-0.66 (0.06)	-0.70 (0.06)
Comparison vs. empagliflozin[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	vs. 25 mg -0.58 (0.09) -0.75, -0.41 <0.0001	vs. 10 mg -0.42 (0.09) -0.59, -0.25 <0.0001	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	-0.50 (0.09) -0.67, -0.32 <0.0001	-0.39 (0.09) -0.56, -0.21 <0.0001	--	--	--
HbA_{1c} (%) – 52 weeks[4]					
Number of patients analysed	**134**	**135**	**140**	**137**	**128**
Baseline mean (SE)	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
Change from baseline at week 52[1]: - adjusted mean[2] (SE)	-1.21 (0.07)	-1.05 (0.07)	-0.64 (0.07)	-0.69 (0.07)	-0.48 (0.07)
Comparison vs. empagliflozin[1]: - adjusted mean[2] (SE) - 95.0% CI	vs. 25 mg -0.57 (0.10) -0.77, -0.37	vs. 10 mg -0.36 (0.10) -0.56, -0.17	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI	-0.73 (0.10) -0.93, -0.53	-0.57 (0.10) -0.77, -0.37	--	--	--
Key secondary endpoint: FPG [mg/dL] - 24 weeks					
Number of patients analysed	**133**	**134**	**139**	**136**	**127**
Baseline mean (SE)	154.62 (2.89)	156.68 (2.98)	159.89 (3.21)	161.64 (2.98)	156.35 (2.72)
Change from baseline at week 24[1]: - adjusted mean[2] (SE)	-35.25 (2.53)	-32.18 (2.52)	-18.83 (2.47)	-20.84 (2.50)	-13.05 (2.59)
Comparison vs. empagliflozin[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	vs. 25 mg -16.43 (3.54) -23.37, -9.48 <0.0001	vs. 10 mg -11.34 (3.55) -18.31, -4.37 0.0015	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	-22.20 (3.62) -29.30, -15.10 <0.0001	-19.12 (3.61) -26.21, -12.03 <0.0001	--	--	--
Key secondary endpoint: Body Weight [kg] - 24 weeks					
Number of patients analysed	**134**	**135**	**140**	**137**	**128**
Baseline mean (SE)	85.47 (1.64)	86.57 (1.64)	87.68 (1.49)	86.14 (1.55)	85.01 (1.62)
Change from baseline at week 24[1]: - adjusted mean[2,3] (SE)	-2.99 (0.31)	-2.60 (0.30)	-3.18 (0.30)	-2.53 (0.30)	-0.69 (0.31)
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	-2.30 (0.44) -3.15, -1.44 <0.0001	-1.91 (0.44) -2.77, -1.05 <0.0001			
Key secondary endpoint: Patients with HbA_{1c} <7% - 24 weeks					
Number of patients, N (%)	**123 (100.0)**	**128 (100.0)**	**132 (100.0)**	**125 (100.0)**	**119 (100.0)**
Patients with HbA_{1c} <7% at week 24	76 (61.8)	74 (57.8)	43 (32.6)	35 (28.0)	43 (36.1)
Comparison[5] vs. empagliflozin: - odds ratio - 95.0% CI - p-value	vs. 25 mg 4.191 2.319, 7.573 <0.0001	vs. 10 mg 4.500 2.474, 8.184 <0.0001	--	--	--

Comparison[5] vs. linagliptin 5 mg: - odds ratio - 95.0% CI - p-value	 3.495 1.920, 6.363 <0.0001	 2.795 1.562, 5.001 0.0005	--	--	--

[1] Last observation (prior to glycaemic rescue) carried forward (LOCF)
[2] Mean adjusted for baseline value and stratification
[3] ANCOVA model includes baseline body weight, baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (LOCF). The comparisons vs. empagliflozin were exploratory and not part of the testing hierarchy (GLYXAMBI® 25 mg/ 5 mg vs. empagliflozin 25 mg: adjusted mean 0.19 (95% CI -0.65, 1.03) kg; GLYXAMBI® 10 mg/ 5 mg vs. empagliflozin 10 mg: -0.07 (-0.91, 0.77) kg)
[4] Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[5] Logistic regression includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (NCF), patients with HbA_{1c} of 7% and above at baseline

In a prespecified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5% the reduction from baseline in HbA_{1c} with GLYXAMBI 25 mg/ 5 mg was -1.8% at 24 weeks ($p<0.0001$ versus linagliptin 5 mg, $p<0.001$ versus empagliflozin 25 mg) and -1.8% at 52 weeks ($p<0.0001$ versus linagliptin 5 mg, $p<0.05$ versus empagliflozin 25 mg) and with GLYXAMBI 10 mg/ 5 mg -1.6% at 24 weeks ($p<0.01$ versus linagliptin 5 mg, n.s. versus empagliflozin 10 mg) and -1.5% at 52 weeks ($p<0.01$ versus linagliptin 5 mg, n.s. versus empagliflozin 10 mg).

GLYXAMBI in treatment-naïve patients

In a factorial design study, after 24-weeks treatment, GLYXAMBI 25 mg/ 5 mg in treatment-naïve patients provided statistically significant improvement in HbA_{1c} compared to linagliptin 5 mg, but there was no statistically significant difference between GLYXAMBI 25 mg/ 5 mg and empagliflozin 25 mg (Table 4). GLYXAMBI 10 mg/ 5 mg had a 0.4% decrease in HbA_{1c} as compared to empagliflozin 10 mg. Compared to linagliptin 5 mg both doses of GLYXAMBI provided statistically relevant improvements in body weight. After 24 weeks' treatment with GLYXAMBI, both systolic and diastolic blood pressures were reduced, -2.9/-1.1 mmHg (n.s. versus linagliptin 5 mg for SBP and DBP) for GLYXAMBI25 mg/ 5 mg and -3.6/-0.7 mmHg ($p<0.05$ versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10 mg/ 5 mg. Rescue therapy was used in 2 (1.5%) patients treated with GLYXAMBI 25 mg/ 5 mg and in 1 (0.7%) patient treated with GLYXAMBI 10 mg / 5 mg compared to 11 (8.3%) patients treated with linagliptin 5 mg, 1 (0.8%) patient treated with empagliflozin 25 mg and 4 (3.0%) patients treated with empagliflozin 10 mg

Table 4 Efficacy Parameters in Clinical Study Comparing GLYXAMBI to Individual Components as Add-on Therapy in Treatment-Naïve Patients

	GLYXAMBI® 25 mg / 5 mg	**GLYXAMBI® 10 mg / 5 mg**	**Empagliflozin 25 mg**	**Empagliflozin 10 mg**	**Linagliptin 5 mg**
Primary endpoint: HbA_{1c} (%) - 24 weeks					
Number of patients analysed	**134**	**135**	**133**	**132**	**133**
Baseline mean (SE)	7.99 (0.08)	8.04 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)
Change from baseline at week 24[1]: - adjusted mean[2] (SE)	 -1.08 (0.07)	 -1.24 (0.07)	 -0.95 (0.07)	 -0.83 (0.07)	 -0.67 (0.07)
Comparison vs. empagliflozin[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	vs. 25 mg -0.14 (0.10) -0.33, 0.06 0.1785	vs. 10 mg -0.41 (0.10) -0.61, -0.21 not assessed	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	 -0.41 (0.10) -0.61, -0.22 <0.0001	 -0.57 (0.10) -0.76, -0.37 not assessed	--	--	--
HbA_{1c} (%) – 52 weeks[4]					
Number of patients analysed	**134**	**135**	**133**	**132**	**133**
Baseline mean (SE)	7.99 (0.08)	8.04 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)

	GLYXAMBI® 25 mg / 5 mg	GLYXAMBI® 10 mg / 5 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Linagliptin 5 mg
Change from baseline at week 52[1]: - adjusted mean (SE)	-1.17 (0.08)	-1.22 (0.08)	-1.01 (0.08)	-0.85 (0.08)	-0.51 (0.08)
Comparison vs. empagliflozin[1]: - adjusted mean (SE) - 95.0% CI	vs. 25 mg -0.16 (0.12) -0.39, 0.07	vs. 10 mg -0.37 (0.12) -0.60, -0.14	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean (SE) - 95.0% CI	-0.66 (0.12) -0.90, -0.43	-0.71 (0.12) -0.94, -0.48	--	--	--
Key secondary endpoint: FPG [mg/dL] - 24 weeks					
Number of patients analysed	**134**	**135**	**133**	**132**	**133**
Baseline mean (SE)	156.10 (3.09)	157.18 (3.05)	152.83 (3.38)	160.27 (3.59)	156.03 (3.22)
Change from baseline at week 24[1]: - adjusted mean[2] (SE)	-29.55 (2.67)	-28.21 (2.66)	-24.24 (2.68)	-22.39 (2.69)	-5.92 (2.68)
Comparison vs. empagliflozin[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	vs. 25 mg -5.31 (3.78) -12.74, 2.11 not assessed	vs. 10 mg -5.82 (3.78) -13.25, 1.61 not assessed	--	--	--
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	-23.63 (3.78) -31.06, -16.21 not assessed	-22.29 (3.77) -29.71, -14.88 not assessed	--	--	--
Key secondary endpoint: Body Weight [kg] – 24 weeks					
Number of patients analysed	**134**	**135**	**133**	**132**	**133**
Baseline mean (SE)	87.92 (1.57)	87.30 (1.59)	86.73 (1.71)	87.82 (2.08)	89.51 (1.74)
Change from baseline at week 24[1]: - adjusted mean[3] (SE)	-2.00 (0.36)	-2.74 (0.36)	-2.13 (0.36)	-2.27 (0.37)	-0.78 (0.36)
Comparison vs. linagliptin 5 mg[1]: - adjusted mean[2] (SE) - 95.0% CI - p-value	-1.22 (0.51) -2.23, -0.21 not assessed	-1.96 (0.51) -2.97, -0.95 not assessed	--	--	--
Key secondary endpoint: Patients with HbA_{1c} <7% - 24 weeks					
Number of patients (%)	**121 (100.0)**	**122 (100.0)**	**118 (100.0)**	**121 (100.0)**	**127 (100.0)**
With HbA_{1c} <7% at week 24	67 (55.4)	76 (62.3)	49 (41.5)	47 (38.8)	41 (32.3)
Comparison[5] vs. empagliflozin: - odds ratio - 95.0% CI - p-value	vs. 25 mg 1.893 1.095, 3.274 not assessed	vs. 10 mg 2.961 1.697, 5.169 not assessed	--	--	--
Comparison[5] vs. linagliptin 5 mg: - odds ratio - 95.0% CI - p-value	3.065 1.768, 5.314 not assessed	4.303 2.462, 7.522 not assessed	--	--	--

1 Last observation (prior to glycaemic rescue) carried forward (LOCF)

2 Mean adjusted for baseline value and stratification

3 ANCOVA model includes baseline body weight, baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (LOCF). The comparisons vs. empagliflozin were exploratory and not part of the testing hierarchy (GLYXAMBI®25 mg/ 5 mg vs. empagliflozin 25 mg: adjusted mean 0.19 (95% CI -0.65, 1.03) kg; GLYXAMBI®10 mg/ 5 mg vs. empagliflozin 10 mg: -0.07 (-0.91, 0.77) kg)

4 Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints. Specification 'not assessed' means that the previous hierarchical test in the confirmatory sequence failed so no subsequent testing was performed.

5 Logistic regression includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (NCF), patients with HbA_{1c} of 7% and above at baseline

In a prespecified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5%, the reduction

from baseline in HbA_{1c} with GLYXAMBI 25 mg/ 5 mg was -1.9% at 24 weeks (p<0.0001 versus linagliptin 5 mg, n.s. versus empagliflozin 25 mg) and -2.0% at 52 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 25 mg) and with GLYXAMBI 10 mg/ 5 mg -1.9% at 24 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 10 mg) and -2.0% at 52 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 10 mg).

Empagliflozin in patients inadequately controlled on metformin and linagliptin

In patients inadequately controlled on metformin and linagliptin 5 mg, 24-weeks treatment with both empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 25 mg/linagliptin 5 mg provided statistically significant improvements in HbA_{1c}, FPG and body weight compared to placebo/linagliptin 5 mg. A statistically significant difference in the number of patients with a baseline HbA_{1c} ≥7.0% and treated with both doses of empagliflozin/linagliptin achieved a target HbA_{1c} of <7% compared to placebo/linagliptin 5 mg (Table 5). After 24 weeks' treatment with empagliflozin/linagliptin, both systolic and diastolic blood pressures were reduced, -2.6/-1.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 25 mg/linagliptin 5 mg and -1.3/-0.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 10 mg/linagliptin 5 mg.

After 24 weeks, rescue therapy was used in 4 (3.6%) patients treated with empagliflozin 25 mg/linagliptin 5 mg and in 2 (1.8%) patients treated with empagliflozin10 mg/linagliptin 5 mg, compared to 13 (12.0%) patients treated with placebo/linagliptin 5 mg.

Table 5 Efficacy Parameters in the Clinical Study Comparing Empagliflozin to placebo as Add-on Therapy in Patients Inadequately Controlled on Metformin and Linagliptin 5 mg

	Metformin + Linagliptin 5 mg		
	Empagliflozin 10 mg[1]	**Empagliflozin 25 mg[1]**	**Placebo[2]**
HbA1c (%) - 24 weeks[3]			
N	109	110	106
Baseline (mean)	7.97	7.97	7.96
Change from baseline (adjusted mean)	-0.65	-0.56	0.14
Comparison vs. placebo (adjusted mean) (95% CI)[2]	-0.79 (-1.02, -0.55) p<0.0001	-0.70 (-0.93, -0.46) p<0.0001	
FPG (mg/dL) – 24 weeks[3]			
N	109	109	106
Baseline (mean)	167.9	170.1	162.9
Change from baseline (adjusted mean)	-26.3	-31.6	6.1
Comparison vs. placebo (adjusted mean) (95% CI)	-32.4 (-41.7, -23.0) p<0.0001	-37.7 (-47.0, -28.3) p<0.0001	
Body Weight-24 weeks[3]			
N	109	110	106
Baseline (mean) in kg	88.4	84.4	82.3
Change from baseline (adjusted mean)	-3.1	-2.5	-0.3
Comparison vs. placebo (adjusted mean) (95% CI)[1]	-2.8 (-3.5, -2.1) p<0.0001	-2.2 (-2.9, -1.5) p<0.0001	
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% - 24 weeks[4]			
N	100	107	100
Patients (%) achieving A1C <7%	37.0	32.7	17.0
Comparison vs. placebo (odds ratio) (95% CI)[5]	4.0 (1.9, 8.7)	2.9 (1.4, 6.1)	

[1]Patients randomized to the empagliflozin 10 mg or 25 mg groups were receiving GLYXAMBI® 10 mg/5 mg or 25 mg/5 mg with background metformin

[2]Patients randomized to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin

[3]MMRM model on FAS (OC) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, visit treatment,and treatment by visit interaction. For FPG, baseline FPG is also included. For weight, baseline weight is also included.

[4]not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
[5]Logistic regression on FAS (NCF) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA_{1c} of 7% and above at baseline

In a prespecified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5% the reduction from baseline in HbA_{1c} with empagliflozin 25 mg/linagliptin 5 mg was -1.3% at 24 weeks (p<0.0001 versus placebo+linagliptin 5 mg) and with empagliflozin 10 mg/linagliptin 5 mg -1.3% at 24 weeks (p<0.0001 versus placebo+linagliptin 5 mg).

Linagliptin 5mg in patients inadequately controlled on empagliflozin10mg and metformin

In patients inadequately controlled on empagliflozin 10 mg and metformin, 24-weeks treatment with empagliflozin 10 mg/linagliptin 5 mg provided statistically significant improvements in HbA_{1c} and FPG compared to placebo/empagliflozin 10 mg. Compared to placebo/empagliflozin 10 mg, empagliflozin 10 mg/linagliptin 5 mg provided similar results on body weight. A statistically significantly greater proportion of patients with a baseline HbA_{1c} ≥7.0% and treated with the empagliflozin 10 mg/linagliptin 5 mg achieved a target HbA_{1c} of <7% compared to placebo/empagliflozin 10 mg (Table 6). After 24 weeks' treatment with empagliflozin 10 mg/linagliptin 5 mg, both systolic and diastolic blood pressures were similar to placebo/empagliflozin 10 mg (n.s. for SBP and DBP).

After 24 weeks, rescue therapy was used in 2 (1.6%) patients treated with empagliflozin 10 mg/linagliptin 5 mg and in 5 (4.0%) patients treated with placebo/empagliflozin 10 mg.

In a prespecified subgroup of patients (n=66) with baseline HbA_{1c} greater or equal than 8.5%, the reduction from baseline in HbA_{1c} empagliflozin 10 mg/linagliptin 5 mg (n=31) was -0.97% at 24 weeks (p=0.0875 versus placebo/empagliflozin 10 mg).

Linagliptin 5mg inpatients inadequately controlled on empagliflozin 25mg and metformin

In patients inadequately controlled on empagliflozin 25 mg and metformin, 24-weeks treatment with empagliflozin 25 mg/linagliptin 5 mg provided statistically significant improvements in HbA_{1c} and FPG compared to placebo/empagliflozin 25 mg. Compared to placebo/empagliflozin 25 mg, empagliflozin 25 mg/linagliptin 5 mg provided similar results on body weight. A statistically significantly greater proportion of patients with a baseline HbA_{1c} ≥7.0% and treated with the empagliflozin 25 mg/linagliptin 5 mg achieved a target HbA_{1c} of <7% compared to placebo/empagliflozin 25 mg (Table 6). After 24 weeks' treatment with empagliflozin 25 mg/linagliptin 5 mg, both systolic and diastolic blood pressures were similar to placebo/empagliflozin 25 mg (n.s. for SBP and DBP).

After 24 weeks, rescue therapy was used in 0 (0.0%) patients treated with empagliflozin 25 mg/linagliptin 5 mg and in 3 (2.7%) patients treated with placebo/empagliflozin 25 mg.

In a prespecified subgroup of patients (n=42) with baseline HbA_{1c} greater or equal than 8.5%, the reduction from baseline in HbA_{1c} with empagliflozin 25 mg/linagliptin 5 mg (n=20) was -1.16% at 24 weeks (p=0.0046 versus placebo+empagliflozin 25 mg).

Table 6 Efficacy Parameters in Clinical Studies Comparing GLYXAMBI10 mg/5 mg to Empagliflozin 10 mg as well as GLYXAMBI 25 mg/5 mg to Empagliflozin 25 mg as Add-on Therapy in Patients Inadequately Controlled on Empagliflozin 10 mg/25 mg and Metformin

	Metformin + Empagliflozin 10mg		Metformin + Empagliflozin 25 mg	
	Linagliptin 5 mg	**Placebo**	**Linagliptin 5 mg**	**Placebo**
HbA1c (%) – 24 weeks[1]				
N	122	125	109	108
Baseline (mean)	8.04	8.03	7.82	7.88
Change from baseline (adjusted mean)	-0.53	-0.21	-0.58	-0.10
Comparison vs. placebo (adjusted mean) (95% CI)	-0.32 (-0.52, -0.13) p=0.0013		-0.47 (-0.66, -0.28) p<0.0001	
FPG (mg/dL) – 24 weeks[1]				
N	120	123	107	107
Baseline (mean)	157.9	155.6	152.3	155.0
Change from baseline (adjusted mean)	-8.0	3.7	-12.3	-4.4
Comparison vs. placebo (adjusted mean) (95% CI)	-11.7 (-20.6, -2.8) p=0.0103		-7.9 (-15.6, -0.2) p=0.0452	
Body Weight – 24 weeks[1]				
N	120	124	109	107
Baseline (mean) in kg	88.47	85.58	85.86	89.93
Change from baseline (adjusted mean)	-0.20	-0.79	-0.17	-0.26
Comparison vs. placebo (adjusted mean) (95% CI)	0.60 (-0.10, 1.30) p=0.0945		0.09 (-0.63, 0.82) p=0.8008	
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% – 24 weeks[2]				
N	116	119	100	107
Patients (%) achieving A1C <7%	25.9	10.9	36.0	15.0
Comparison vs. placebo (odds ratio) (95% CI)[3]	3.965 (1.771, 8.876) p=0.0008		4.429 (2.097, 9.353) p<0.0001	

Patients randomized to the Linagliptin 5 mg group were receiving either fixed dose combination tablets GLYXAMBI® 10 mg/5 mg plus metformin or fixed dose combination tablets GLYXAMBI® 25 mg/5 mg plus metformin; patients randomized to the placebo group were receiving Placebo plus Empagliflozin 10 mg plus metformin or Placebo plus Empagliflozin 25 mg plus metformin

1 MMRM model on FAS (OC) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, visit, treatment, and treatment by visit interaction. For FPG, baseline FPG is also included.

2 not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

3 Logistic regression on FAS (NCF) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA_{1c} of 7% and above at baseline

Laboratory parameters

Hematocrit increased

In a placebo controlled trial, mean changes from baseline in haematocrit were 3.3% and 4.2% for GLYXAMBI® 10mg/5mg and 25mg/5mg, respectively, compared to 0.2% for placebo. In the EMPA-REG OUTCOME trial, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

Serum lipids increased

In a placebo controlled trial, mean percent increases from baseline for GLYXAMBI® 10mg/5mg and 25mg/5mg versus placebo, respectively, were total cholesterol 3.2% and 4.6% versus 0.5%; HDL-cholesterol 8.5% and 6.2% versus 0.4%; LDL-cholesterol 5.8% and 11.0% versus 3.3%; triglycerides -0.5% and 3.3% versus 6.4 %.

Cardiovascular safety

Empagliflozin cardiovascular outcome (EMPA-REG OUTCOME) study

In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) by 14% when added to standard of care in adults with T2DM and established CV disease. This result was driven by a 38% reduction in CV death, with no significant difference in the risk of non-fatal myocardial infarction or non-fatal stroke.

Linagliptin cardiovascular and renal safety (CARMELINA) study

The double-blind, placebo-controlled CARMELINA study evaluated the cardiovascular and renal safety of linagliptin versus placebo as adjunct to standard care therapy in patients with type 2 diabetes

and with increased CV risk evidenced by a history of established macrovascular or renal disease. A total of 6979 patients were treated (linagliptin 5 mg: 3494, placebo: 3485) and followed for a median of 2.2 years. The study population included 1211 (17.4 %) patients ≥ 75 years of age, the mean HbA_{1c} was 8.0 %, 63 % were male. Approximately 19 % of the population had an eGFR of 45-60 mL/min/1.73 m^2, 28 % of 30-45 mL/min/1.73 m^2 and 15 % of <30 mL/min/1.73 m^2.

Linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) [HR=1.02; (95 % CI 0.89, 1.17); p=0.0002 for non-inferiority], or the risk of combined endpoint of renal death, ESRD, 40% or more sustained decrease in eGFR [HR=1.04; (95 % CI 0.89, 1.22)]. In analyses for albuminuria progression (change from normoalbuminuria to micro-or macroalbuminuria, or from microalbuminuria to macroalbuminuria) the estimated hazard ratio was 0.86 (95 % CI 0.78, 0.95) for linagliptin versus placebo. In addition, linagliptin did not increase the risk of hospitalization for heart failure [HR=0.90; (95 % CI 0.74, 1.08)]. No increased risk of CV death or all-cause mortality was observed.

Safety data from this study was in line with previous known safety profile of linagliptin.

In the CAROLINA study, linagliptin did not increase the risk of the combined endpoint of CV death, non-fatal myocardial infarction or non-fatal stroke (MACE-3) [Hazard Ratio (HR)=0.98; (95% CI 0.84, 1.14); p<0.0001 for non-inferiority], when added to standard of care in adult patients with T2DM with increased CV risk compared to glimepiride. For the entire treatment period the rate of patients with moderate or severe hypoglycaemia was 6.5% on linagliptin versus 30.9% on glimepiride, severe hypoglycaemia (requiring assistance) occurred in 0.3% of patients on linagliptin versus 2.2% on glimepiride.

5.2 Pharmacokinetic properties

Pharmacokinetics of the Fixed Dose Combination

The rate and extent of absorption of empagliflozin and linagliptin in empagliflozin/linagliptin are equivalent to the bioavailability of empagliflozin and linagliptin when administered as individual tablets.

The pharmacokinetics of empagliflozin and linagliptin have been extensively characterized in healthy volunteers and patients with T2DM. No clinically relevant differences in pharmacokinetics were seen between healthy volunteers and T2DM patients.

Pharmacokinetics of the single components

Empagliflozin:

Absorption
After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 1.5 h post-dose. Plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Systemic exposure increased in a dose-proportional manner for single- dose and steady-state suggesting linear pharmacokinetics with respect to time.

A high-fat, high calorie meal prior to intake of 25 mg empagliflozin resulted in slightly lower exposure compared to fasted condition. The effect was not considered clinically relevant and empagliflozin may be administered with or without food.

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

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

Elimination
The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. Consistent with half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin:

Absorption
After oral administration, linagliptin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 1.5 hours post-dose.

After once-daily dosing, steady-state plasma concentrations are reached by the third dose. Plasma AUC increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for AUC were small (12.6% and 28.5%, respectively). Plasma AUC increased in a less than dose-proportional manner.

The absolute bioavailability of linagliptin is approximately 30%. As coadministration of a high-fat, high calorie meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food.

Distribution
As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75-89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 20-30% were unbound in plasma.

Biotransformation
Metabolism plays a subordinate role in the elimination of linagliptin. Following a [^{14}C]linagliptin oral 10 mg dose, only 5% of the radioactivity was excreted in urine. The main metabolite with a relative exposure of 13.3% of linagliptin at steady state was pharmacologically inactive and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Elimination
Plasma concentrations declined in an at least biphasic manner with a long terminal half- life (more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of the drug. The effective half-life for accumulation, as determined from oral administration of multiple doses of
5 mg linagliptin, is approximately 12 hours.

Following administration of an oral [^{14}C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Specific Populations

Renal Impairment

Based on pharmacokinetics, no dosage adjustment is recommended for GLYXAMBI in patients with renal impairment.

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

Linagliptin:
A study was conducted to compare pharmacokinetics in patients with mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min) RI and patients with ESRD on hemodialysis. In addition patients with T2DM and severe RI (<30 mL/min) were compared to T2DM patients with normal renal function.

Under steady-state conditions, linagliptin exposure in patients with mild RI was comparable to healthy subjects. In patients with moderate RI, a moderate increase in exposure of about 1.7-fold was observed compared with control. Exposure in patients with T2DM and severe RI was increased by about 1.4-fold compared to patients with T2DM and normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe RI. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis. In addition, mild renal insufficiency had no effect on linagliptin pharmacokinetics in patients with T2DM as assessed by population pharmacokinetic analyses.

Hepatic Impairment

Based on pharmacokinetics of the two individual components, no dosage adjustment of GLYXAMBI is recommended in patients with hepatic impairment.

Body Mass Index (BMI)

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

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

Race

No dosage adjustment is necessary for GLYXAMBI based on population pharmacokinetic analysis and on dedicated phase I studies.

Geriatric

Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin or linagliptin based on population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric

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

Drug Interactions

In vitro assessment of drug interactions*:*

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

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

For linagliptin:
Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes. Linagliptin is a P-glycoprotein substrate, and inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on these results and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-gp substrates.

Linagliptin was a substrate for OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2, suggesting a possible OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and reabsorption of linagliptin in vivo. OATP2, OATP8, OCTN1, OCT1 and OATP2 activities were slightly to weakly inhibited by linagliptin.

In vivo assessment of drug interactions

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

Empagliflozin:
Empagliflozin had no clinically relevant effect on the pharmacokinetics of linagliptin, metformin, glimepiride, pioglitazone, sitagliptin, warfarin, digoxin, verapamil, ramipril, simvastatin, torasemide, hydrochlorothiazide and oral contraceptives when coadministered in healthy volunteers. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59%), rifampicin (35%), or probenecid (53%). These changes were not considered to be clinically meaningful.

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

Linagliptin:
Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin, empagliflozin, or oral contraceptives providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Changes in overall exposure (AUC) of linagliptin were seen following co-administration with ritonavir (approx. 2-fold increase) and rifampicin (40% decrease). These changes were not considered to be clinically meaningful.

5.3 Preclinical safety data

TOXICOLOGY

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and linagliptin. Signs of toxicity were observed at exposures greater than 13 times the clinical AUC exposure. These studies indicated that no additive toxicity was is caused by the combination of empagliflozin and linagliptin.

Carcinogenicity

No carcinogenicity studies with the combination of empagliflozin and linagliptin have been performed.

Empagliflozin did not increase the incidence of tumors in female rats at doses up to the highest dose of 700 mg/kg/day, which is approximately 72 times the clinical AUC exposure of 25 mg. In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node, were observed at 700 mg/kg/day, but not at 300 mg/kg/day, which is approximately 26 times the clinical exposure of 25 mg. These tumors are common in rats and are unlikely to be relevant to humans. Empagliflozin did not increase the incidence of tumors in female mice at doses up to 1000 mg/kg/day, which is approximately 62 times the clinical exposure of 25 mg. Renal tumors were not observed in male mice at 300 mg/kg/day, which is approximately 11 times the clinical exposure of 25 mg. There was an increase in renal adenomas and carcinomas in male mice given empagliflozin at 700 mg/kg/day, which is approximately 45 times the clinical exposure of 25 mg. The mode of action for these tumors 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 tumors are considered not relevant to humans.

A two-year carcinogenicity study was conducted in male and female rats given oral doses of linagliptin of 6, 18, and 60 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 60 mg/kg/day. This dose results in exposures approximately 418 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 5 mg/day based on AUC comparisons. A two-year carcinogenicity study was conducted in male and female mice given oral doses of 8, 25 and 80 mg/kg/day. There was no evidence of a carcinogenic potential up to 80 mg/kg/day, approximately 242 times human exposure at the MRHD.

Genotoxicity

No genotoxicity studies with the combination of empagliflozin and linagliptin have been performed.

Empagliflozin and linagliptin are not genotoxic.

Reproduction Toxicity

The combined products administered during the period of organogenesis were not teratogenic in rats up to and including a combined dose of 700 mg/kg/day empagliflozin and 140 mg/kg/day linagliptin, which is 253- and 353-times the clinical AUC exposure. No maternal toxicity was seen in a combination of 300 mg/kg/day empagliflozin and 60 mg/kg/day linagliptin which is 99- and 227-times the clinical AUC exposure. Adverse effects on renal development were not observed after administration of empagliflozin

alone, linagliptin alone or after administration of the combined products.

Nonclinical studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic at doses up to 300 mg/kg in the rat or rabbit, which corresponds to approximately 48- and 122-times or 128- and 325-times the clinical dose of empagliflozin based on AUC exposure associated with the 25 mg and 10 mg doses, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155- and 393-times the clinical dose associated with the 25 mg and 10 mg doses, respectively. Maternally toxic doses in the rabbit also caused increased embryofetal loss at doses approximately 139- and 353-times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

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

In rat fertility studies of linagliptin with oral gavage doses of 10, 30 and 240 mg/kg/day, males were treated for 4 weeks prior to mating and during mating; females were treated 2 weeks prior to mating through gestation day 6. No adverse effect on early embryonic development, mating, fertility, and bearing live young were observed up to the highest dose of 240 mg/kg/day (approximately 943 times human exposure at the MRHD of
5 mg/day based on AUC comparisons).

In the studies on embryo-fetal development in rats and rabbits, linagliptin was shown to be not teratogenic at dosages up to and including 240 mg/kg/day (943x MRHD) in the rat and 150 mg/kg/day (1943x MRHD) in the rabbit.

A NOAEL of 30 mg/kg/day (49x MRHD) and 25 mg/kg (78x MRHD) was derived for embryo-fetal toxicity in the rat and the rabbit, respectively.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Mannitol, Pregelatinized starch, Maize starch, Copovidone, Crospovidone, Talc, Magnesium stearate

Film coating: Hypromellose, Mannitol, Talc, Titanium dioxide, Macrogol 6000, Iron oxide (yellow) for 10mg/5mg Tablets and Iron oxide (pink) for 25mg/5mg Tablets.

6.2 Storage condition

Store at or below 30°C.

6.3 Nature and contents of container

Blister card of Aluminium-PVC/PVDC in cartons containing 10 or 30 film-coated tablets.
Not all pack sizes may be marketed.

7. MANUFACTURER

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or

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