GLYXAMBI®
Empagliflozin and Linagliptin

DESCRIPTION

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"

COMPOSITION

GLYXAMBI film-coated tablets contain 10 mg
D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S) (= empagliflozin)
and
1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl] 5 mg
-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]- (= linagliptin)

Excipient :
Tablet core: Mannitol, Pre-gelatinised starch, Maize starch, Copovidone, Crospovidone, Talc, Magnesium stearate,
Film coating: Hypromellose, Mannitol, Talc, Titanium dioxide, Macrogol 6000, Iron oxide yellow

INDICATIONS

GLYXAMBI (empagliflozin and linagliptin) is indicated for use in combination with metformin **(≥1500 mg/day)** as an adjunct to diet and exercise, to achieve glycemic control in adult patients with type 2 diabetes mellitus (T2DM):
- inadequately controlled on metformin **(≥1500 mg/day)** and empagliflozin, or
- inadequately controlled on metformin **(≥1500 mg/day)** and linagliptin.

DOSAGE AND ADMINISTRATION

The recommended dose is 1 film-coated tablet of GLYXAMBI 10 mg/5 mg (10 mg empagliflozin plus 5 mg linagliptin) once daily. The metformin dose should be continued.

Patients with renal impairment
Due to the mechanism of action, decreased renal function will result in reduced efficacy of empagliflozin

- In patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or creatinine clearance (CrCl) ≥60 mL/min, no dose adjustment is required.
- In patients with an eGFR <60 mL/min/1.73 m^2 or CrCl <60 mL/min, GLYXAMBI should not be used
- In patients with end-stage renal disease or in patients on dialysis, GLYXAMBI should not be used as empagliflozin is not expected to be effective in these patients

Patients with hepatic impairment
No dose adjustment is recommended for patients with hepatic impairment.

Elderly Patients
No dosage adjustment is recommended based on age. Therapeutic experience in patients aged 85 years and older is limited. Initiation of GLYXAMBI therapy in this population is not recommended

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.

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.

CONTRAINDICATIONS
Hypersensitivity to empagliflozin or linagliptin or any of the excipients.
Patients with eGFR less than 45 ml/min/1.73 m^2, severe renal impairment, end-stage renal disease and patients on dialysis

SPECIAL WARNINGS AND PRECAUTIONS
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.

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

Patients who may be at higher risk of ketoacidosis while taking 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)
Cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients treated

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.

Pancreatitis
Acute pancreatitis has been observed in patients taking linagliptin. If pancreatitis is suspected, GLYXAMBI should be discontinued.

Use in patients with renal impairment
GLYXAMBI should not be used in patients with an eGFR < 60 ml/min/1.73 m^2 or CrCl < 60 ml/min. Patients with eGFR less than 45 ml/min/1.73 m^2, severe renal impairment, end-stage renal disease and patients on dialysis are contraindicated.

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

- prior to GLYXAMBI initiation and periodically during treatment, i.e. at least yearly,
- prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

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. If bullous pemphigoid is suspected, GLYXAMBI should be discontinued.

Elderly patients
Patients aged 75 years and older may be at increased risk of volume depletion, therefore, GLYXAMBI should be prescribed with caution in these patients (see Side effects). Therapeutic experience in patients aged 85 years and older is limited. Initiation of therapy with GLYXAMBI in this population is not recommended.

Cardiac failure
Experience with empagliflozin in New York Heart Association (NYHA) class I-II is limited, and there is no experience in clinical studies with empagliflozin in NYHA class III-IV.

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

USE IN SPECIFIC POPULATIONS
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.

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

INTERACTIONS
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.

Inhibitors of P-gp or CYP3A4 isozymes
Co-administration of a single 5mg oral dose of linagliptinand multiple 200mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and Cmaxof linagliptin approximately twofold and threefold, respectively. The unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4 to 5-fold after co-administration with ritonavir. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will be not associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein / CYP3A4 inhibitors.

SIDE 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).

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[4,a]
Gastrointestinal disorders	Pancreatitis[3] Mouth ulceration[4] Constipation
Vascular disorders	Volume depletion[1,2]
General disorders and administration site conditions	Thirst[1]
Investigations	Glomerular filtration rate decreased[1,2] Blood creatinine increased[1,2] Lipase increased[3,6] Amylase increased[3,b] Haematocrit increased[1,7] Serum lipids increased[1,7]

[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 clinical trials), 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).

Urinary tract infection
In clinical trials with GLYXAMBI, the frequency of urinary tract infection adverse events (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 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.

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

Increased urination
In clinical trials with GLYXAMBI, the frequency of increased urination adverse events (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 10 mg/5 mg: 0.5%) has been comparable to 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 10 mg/5 mg: 0%) and decreased glomerular filtration rate (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/1.73m^2, empagliflozin 25 mg -1.37 mL/min/1.73m^2) have been observed. These changes were generally reversible during continuous treatment or after drug discontinuation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via following contact:
Telephone: **+62 21 21684084** Or Email: **IDsafety@zuelligpharma.com**

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.

PHARMACOLOGICAL 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 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 was reduced, -4.1/-2.6 mmHg ($p<0.05$ versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10 mg/5 mg.

Clinically meaningful reductions in HbA_{1c} (Table 3) and both systolic and diastolic blood pressures were observed at week 52, -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 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 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).

Empagliflozin in patients inadequately controlled on metformin and linagliptin

In patients inadequately controlled on metformin and linagliptin 5 mg, 24-weeks treatment with empagliflozin 10 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 4). After 24 weeks' treatment with empagliflozin/linagliptin, both systolic and diastolic blood pressures were reduced, -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 2 (1.8%) patients treated with empagliflozin 10 mg/linagliptin 5 mg, compared to 13 (12.0%) patients treated with placebo/linagliptin 5 mg.

Table 4 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 10 mg/linagliptin 5 mg -1.3% at 24 weeks (p<0.0001 versus placebo+linagliptin 5 mg).

Linagliptin 5 mg in patients inadequately controlled on empagliflozin 10 mg 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 5). 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).

Table 5 Efficacy Parameters in Clinical Studies Comparing GLYXAMBI 10 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

5	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% for GLYXAMBI 10mg/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 versus placebo, respectively, were total cholesterol 3.2% versus 0.5%; HDL-cholesterol 8.5% versus 0.4%; LDL-cholesterol 5.8% versus 3.3%; triglycerides -0.5% versus 6.4 %.

Cardiovascular safety
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.

In the CARMELINA 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)=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)], when added to standard of care in adult patients with T2DM with increased CV risk evidenced by a history of established macrovascular or renal disease. 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.

There have been no clinical studies establishing conclusive evidence of GLYXAMBI's effect on cardiovascular morbidity and mortality.

PHARMACOKINETICS
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%.

Metabolism

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

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39.1% and 35.8%, respectively. 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.

Metabolism
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
In patients with an eGFR less than 60 ml/min/1.73 m^2 or CrCl less than 60 ml/min, GLYXAMBI should not be used.

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 renal impairment. However, due to the mechanism of action, the efficacy of Jardiance is dependent on renal function, and therefore GLYXAMBI is contraindicated for use in patients with eGFR less than 45 ml/min/1.73 m^2, severe renal impairment, end-stage renal disease and patients on dialysis.

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.

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.

Availability :
Film coated tablet 10 mg/5 mg
Box, 3 blisters @ 10 film coated tablet Reg. No: DKI2424200717A1

Only on doctor's prescription
Harus dengan resep dokter

Storage conditions :
Store below 30°C
Store in a safe place, out of the reach of children

Manufactured by :
Rottendorf Pharma GmbH
Ennigerloh, Germany

For :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by :
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Version: 20-1225

Produk Informasi untuk Pasien

Glyxambi®
(Empagliflozin/Linagliptin)
Tablet salut selaput 10 mg/5 mg

Obat ini merupakan obat dalam pengawasan khusus. Hal ini untuk membantu didapatkannya informasi baru keamanan obat secara cepat. Anda dapat membantu dengan melaporkan efek samping apapun yang terjadi. Lihat akhir bab ini tentang bagaimana cara melaporkan efek samping.

Bacalah seluruh lembar informasi ini dengan seksama sebelum mulai mengonsumsi obat ini karena lembar ini berisi informasi yang bermanfaat untuk anda.
- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali.
- Bila Anda memiliki pertanyaan lebih lanjut, bertanyalah kepada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda saja. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka, walau tanda-tanda penyakit mereka sama dengan Anda.
- Bila Anda mengalami efek samping apapun, bicarakan kepada dokter, apoteker atau perawat Anda, termasuk efek samping yang belum tertulis dalam leaflet ini.

Apa isi selebaran ini

1. Apakah Glyxambi dan digunakan untuk apakah obat ini

Glyxambi adalah obat anti-diabetes yang mengandung dua zat aktif yang disebut empagliflozin dan linagliptin:
- Empagliflozin bekerja menghambat protein dalam ginjal yang disebut *sodium-glucose co-transporter 2* (SGLT2). SGLT2 mencegah glukosa diekskresikan melalui urin dengan menyerap glukosa kembali ke dalam aliran darah pada saat darah sedang disaring oleh ginjal. Dengan penghambatan protein ini, Glyxambi menyebabkan pengeluaran glukosa (gula darah) melalui urin sehingga kadar gula darah yang tinggi, karena diabetes tipe 2 yang Anda alami, menjadi turun.
- Linagliptin bekerja dengan cara yang berbeda, yaitu dengan mengaktifkan pankreas untuk menghasilkan lebih banyak insulin untuk menurunkan kadar glukosa darah. Hal ini dilakukan dengan cara menghalangi protein yang disebut DPP-4.

Glyxambi ditambahkan ke metformin untuk mengobati diabetes tipe 2 pada pasien dewasa yang diabetesnya tidak dapat dikendalikan saat diobati dengan metformin (≥1500 mg/hari) dalam kombinasi dengan empagliflozin, atau bila diobati dengan metformin (≥1500 mg/hari) dalam kombinasi dengan linagliptin.
Penting agar Anda melanjutkan rencana diet dan olahraga Anda seperti yang direkomendasikan oleh dokter, apoteker atau perawat Anda.

Apa itu diabetes tipe 2?
Diabetes tipe 2 adalah suatu penyakit yang berasal dari gen dan gaya hidup Anda. Bila Anda memiliki diabetes tipe 2, berarti pankreas Anda tidak menghasilkan insulin dalam jumlah yang cukup untuk

mengontrol kadar glukosa dalam darah Anda, dan tubuh Anda tidak dapat menggunakan insulinnya sendiri secara efektif. Kadar gula darah yang tinggi dalam darah dapat menyebabkan masalah kesehatan seperti penyakit jantung, penyakit ginjal, kebutaan, dan sirkulasi darah yang buruk pada anggota tubuh

2. Apa yang perlu Anda ketahui sebelum mengonsumsi Glyxambi

Jangan mengonsumsi Glyxambi:

- jika Anda alergi terhadap empagliflozin, linagliptin, penghambat SGLT2 lainnya (misalnya dapagliflozin, canagliflozin), penghambat DPP-4 lainnya (misalnya sitagliptin, vildagliptin), atau bahan lain dari obat ini (tercantum dalam bagian 6).
- Jika Anda memiliki gangguan ginjal berat atau menjalani cuci darah (dialisis).

Peringatan dan perhatian

Bicarakan dengan dokter, apoteker, atau perawat Anda sebelum minum obat ini dan selama pengobatan:

- Jika Anda menderita diabetes tipe 1 (tubuh Anda tidak menghasilkan insulin). Glyxambi seharusnya tidak digunakan untuk mengobati diabetes tipe 1.
- Bila Anda mengalami penurunan berat badan yang cepat, merasa mual atau muntah, nyeri perut, rasa haus yang berlebihan, nafas cepat dan berat, bingung, mengantuk atau kelelahan yang tidak biasa, nafas berbau manis, rasa manis atau rasa logam pada mulut, atau bau urin atau keringat yang berbeda, segera hubungi dokter atau rumah sakit terdekat segera. Gejala tersebut disebut gejala "*diabetic ketoacidosis*" yaitu masalah yang timbul pada diabetes karena adanya peningkatan kadar badan keton di dalam urin atau darah berdasarkan hasil pengujian laboratorium. Risiko terjadinya *diabetic ketoacidosis* dapat meningkat seiring dengan puasa yang berkepanjangan, terlalu banyak minum minuman keras, dehidrasi, penurunan dosis insulin yang mendadak, atau semakin tingginya kebutuhan insulin karena menjalani operasi besar atau mengalami penyakit berat.
- Jika Anda mengonsumsi obat anti-diabetes lain yang dikenal sebagai sulfoniurea (misalnya glimepiride, glipizide) dan atau insulin. Dokter Anda mungkin ingin mengurangi dosis obat-obatan ini saat Anda mengonsumsinya bersama Glyxambi, untuk menghindari gula darah terlalu rendah (hipoglikemia).
- Jika Anda memiliki atau pernah menderita penyakit pankreas.
- Jika Anda mengidap masalah ginjal serius – dokter Anda mungkin akan meresepkan Anda obat yang lain.
- Jika Anda berusia 75 tahun atau lebih, seiring meningkatnya jumlah air kencing karena obat tersebut dapat mempengaruhi keseimbangan cairan dalam tubuh Anda dan meningkatkan risiko dehidrasi. Kemungkinan tanda-tanda dehidrasi, lihat bagian 4.
- Jika Anda berusia 75 tahun atau lebih, maka tidak disarankan untuk memulai pengobatan ini pada usia di atas 75 tahun.

Hubungi dokter Anda jika Anda mengalami hal-hal berikut selama pengobatan dengan Glyxambi:

- Jika Anda mengalami gejala pankreatitis akut, seperti sakit perut yang persisten dan berat. Kemungkinan tanda-tanda tercantum di bagian 4, 'Kemungkinan efek samping'. Dokter Anda mungkin perlu mengubah pengobatan.
- Jika Anda sakit, menderita diare atau demam, atau jika Anda tidak dapat makan atau minum. Kondisi ini dapat menyebabkan dehidrasi. Dokter Anda mungkin meminta Anda untuk berhenti minum Glyxambi sampai Anda sembuh, untuk mencegah hilangnya terlalu banyak cairan tubuh.
- Jika Anda memiliki infeksi serius pada ginjal atau saluran kemih dengan demam. Dokter Anda mungkin meminta Anda untuk harus berhenti mengonsumsi Glyxambi sampai Anda sembuh.

Fungsi ginjal

Sebelum memulai pengobatan Glyxambi dan secara teratur selama pengobatan, dokter Anda akan memeriksa seberapa baik fungsi ginjal Anda.

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

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

Obat-obatan lainnya dan Glyxambi
Beritahu dokter atau apoteker Anda jika Anda mengonsumsi, baru saja mengonsumsi atau mungkin mengonsumsi obat lain. Anda harus memberi tahu dokter Anda jika Anda mengonsumsi obat berikut ini:
- Obat anti-diabetes lainnya, seperti sulfonilurea. Dokter Anda mungkin menurunkan dosis obat lainnya ini, untuk mencegah kadar gula darah Anda tidak bertambah rendah.
- Obat yang digunakan untuk mengeluarkan air dari tubuh Anda (diuretik). Dokter Anda mungkin meminta Anda untuk berhenti mengonsumsi Glyxambi
- Obat yang mungkin berpengaruh pada perubahan empagliflozin atau linagliptin pada tubuh Anda seperti rifampisin (antibiotik yang digunakan untuk mengobati tuberkulosis) atau obat tertentu yang digunakan untuk mengobati kejang (seperti karbamazepin, fenobarbital atau fenitoin). Pengaruh Glyxambi dapat berkurang.

Kehamilan, menyusui dan kesuburan
Jika Anda hamil, mungkin Anda hamil atau berencana untuk melahirkan, mintalah saran dari dokter Anda sebelum mengonsumsi obat ini.
Tidak diketahui apakah Glyxambi berbahaya bagi anak yang belum lahir. Sebagai tindakan pencegahan sebaiknya Anda menghindari konsumsi obat ini selama kehamilan.
Tidak diketahui apakah zat aktif masuk ke dalam ASI pada manusia. Jangan konsumsi obat ini jika sedang menyusui.
Tidak diketahui apakah Glyxambi memiliki efek pada kesuburan pada manusia.

Mengemudi dan mengoperasikan mesin
Glyxambi sedikit mempengaruhi kemampuan mengemudi dan mengoperasikan mesin.

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

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

Berapa banyak dosis obat yang harus dikonsumsi?
- Dosis awal yang biasa adalah 10 mg empagliflozin ditambah 5 mg linagliptin sekali sehari. Untuk dosis ini Glyxambi tersedia sebagai tablet salut selaput 10 mg/5 mg.

Cara mengonsumsi obat ini
- Telan seluruh tablet dengan air.

- Anda dapat mengonsumsi Glyxambi dengan atau tanpa makanan.
- Anda dapat mengonsumsi tablet kapan saja. Namun, cobalah untuk mengonsumsi pada waktu yang sama setiap hari.
  Hal ini akan membantu Anda mengingat untuk mengonsumsi.

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

Diet dan olah raga dapat membantu tubuh anda agar menggunakan gula darah Anda sendiri secara lebih baik. Penting bagi Anda untuk tetap menjaga program diet dan olah raga sesuai yang direkomendasikan oleh dokter ketika Anda minum Glyxambi.

Gangguan ginjal:
Bicaralah dengan dokter Anda jika Anda memiliki masalah ginjal. Dokter Anda mungkin membatasi dosis Anda atau memutuskan untuk menggunakan pengobatan lainnya.

Kerusakan hati:
Bicaralah dengan dokter Anda jika Anda menderita gangguan hati berat. Glyxambi tidak dianjurkan dan dokter Anda mungkin memutuskan untuk menggunakan pengobatan alternatif.

Lansia :
Terdapat sedikit pengalaman pada pasien berusia 75 tahun atau lebih. Pengobatan dengan Glyxambi sebaiknya tidak dimulai pada pasien di atas usia 75 tahun.

Jika Anda mengonsumsi Glyxambi lebih banyak dari yang seharusnya
Jika Anda mengonsumsi obat ini lebih banyak daripada seharusnya, segera bicarakan dengan dokter atau pergi ke rumah sakit. Bawa kemasan obat itu bersama Anda.

Jika Anda lupa mengonsumsi Glyxambi
Apa yang harus dilakukan jika lupa mengonsumsi tablet tergantung berapa lama sampai dosis berikutnya:
- Jika 12 jam atau lebih sampai dosis berikutnya, konsumsi Glyxambi segera setelah Anda ingat. Kemudian konsumsi dosis berikutnya pada waktu yang biasa.
- Jika kurang dari 12 jam sampai dosis berikutnya, lewati dosis yang tidak terjawab. Kemudian konsumsi dosis berikutnya pada waktu yang biasa
- Jangan konsumsi dosis ganda obat ini untuk menggantikan dosis yang terlupakan.

Jika Anda berhenti mengonsumsi Glyxambi
Jangan berhenti mengonsumsi obat ini tanpa terlebih dahulu berkonsultasi dengan dokter Anda. Kadar gula darah Anda dapat meningkat saat Anda berhenti mengonsumsi Glyxambi.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat Anda.

4. Kemungkinan efek samping
Seperti semua obat, obat ini dapat menimbulkan efek samping, walaupun tidak semua orang mengalaminya.
Hubungi dokter atau rumah sakit terdekat jika Anda memiliki efek samping berikut ini:

Ketoasidosis diabetik, jarang terjadi (terdapat hingga 1 dari 1.000 orang)

Berikut ini adalah tanda-tanda ketoasidosis diabetes (lihat juga bagian 2, 'Peringatan dan perhatian'):
- peningkatan kadar "badan keton" dalam urin atau darah Anda
- penurunan berat badan yang cepat
- merasa sakit atau sedang sakit
- sakit perut
- haus yang berlebihan
- napas cepat dan dalam
- kebingungan
- mengantuk atau kelelahan yang tidak biasa
- bau manis nafas Anda, rasa manis atau logam di mulut Anda atau bau yang berbeda dengan urin atau keringat Anda.

Hal ini dapat terjadi yang terlepas dari kadar glukosa darah. Dokter Anda mungkin memutuskan untuk sementara atau secara permanen menghentikan pengobatan Anda dengan obat ini.

Hubungi dokter Anda segera jika Anda mengalami efek samping berikut ini:
Reaksi alergi, jarang terjadi (terdapat hingga 1 dari 100 orang)
Obat ini dapat menyebabkan reaksi alergi, yang mungkin serius, termasuk gatal-gatal (urtikaria) dan pembengkakan wajah, bibir, lidah, dan tenggorokan yang dapat menyebabkan kesulitan bernafas atau menelan (angioedema).

Peradangan pankreas (pankreatitis), jarang terjadi
Obat ini dapat menyebabkan pankreatitis, yang ditunjukkan dengan adanya rasa nyeri pada perut yang menjalar ke punggung, dan bisa disertai dengan perasaan sakit atau nyeri yang hebat yang dapat menjalar ke punggung Anda, sering disertai dengan perasaan sakit atau nyeri. Dokter Anda perlu mengganti pengobatan Anda.

Gula darah rendah (hipoglikemia), biasa terjadi (terdapat hingga 1 dari 10 orang)
Jika Anda mengonsumsi Glyxambi dengan obat lain yang dapat menyebabkan gula darah rendah, seperti sulfonilurea atau insulin, Anda berisiko untuk mendapatkan gula darah terlalu rendah (hipoglikemia). Tanda gula darah terlalu rendah dapat meliputi:
- gemetar, berkeringat, merasa sangat cemas atau bingung, detak jantung cepat
- lapar berlebihan, sakit kepala

Dokter Anda akan memberi tahu Anda bagaimana cara mengobati kadar gula darah rendah dan apa yang harus dilakukan jika Anda mendapatkan tanda-tanda di atas. Jika Anda memiliki gejala gula darah rendah, makanlah tablet glukosa, snack tinggi gula atau minum jus buah. Ukur gula darah Anda jika memungkinkan dan istirahat.

Infeksi saluran kemih, biasa terjadi
Tanda-tanda infeksi saluran kemih adalah:
- sensasi terbakar saat buang air kecil
- urin yang tampak keruh
- nyeri pada panggul, atau nyeri pertengahan punggung (saat ginjal terinfeksi)

Keinginan untuk buang air kecil atau buang air kecil yang lebih sering dapat disebabkan oleh obat ini, tapi karena juga dapat menjadi tanda infeksi saluran kemih, jika Anda mengetahui adanya peningkatan gejala tersebut, Anda harus menghubungi dokter Anda.

<u>Hilangnya cairan tubuh (dehidrasi), jarang terjadi</u>
Tanda-tanda dehidrasi tidak spesifik, namun dapat meliputi:
- haus yang tidak biasa
- kepala seperti berputar atau pusing saat berdiri

- pingsan atau kehilangan kesadaran

Efek samping lainnya saat mengonsumsi Glyxambi:

Biasa terjadi
- infeksi jamur pada alat kelamin, seperti sariawan
- hidung atau tenggorokan yang meradang (nasofaringitis)
- batuk
- berkemih lebih banyak dari biasanya atau keinginan berkemih lebih sering
- gatal
- ruam kulit
- peningkatan enzim darah amilase
- peningkatan enzim lipase pancreas
- konstipasi

Tidak biasa terjadi
- tegang atau sakit saat mengosongkan kandung kemih
- tes darah laboratorium mungkin menunjukkan perubahan kadar lemak dalam darah, peningkatan jumlah sel darah merah (peningkatan hematokrit), dan perubahan yang berkaitan dengan fungsi ginjal (penurunan laju filtrasi dan peningkatan kreatinin darah)

Jarang terjadi
- sariawan di mulut

Frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang ada)
- kulit melepuh (pemfigoid bulosa)

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

5. Bagaimana cara menyimpan Glyxambi

Jauhkan obat ini dari pandangan dan jangkauan anak.

Jangan konsumsi obat ini setelah tanggal kadaluwarsa yang tercantum pada blister dan kemasan setelah EXP. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

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

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

6. Isi kemasan dan informasi lainnya

Apa kandungan Glyxambi
- Zat aktif adalah empagliflozin dan linagliptin. Setiap tablet salut selaput mengandung empagliflozin 10 mg dan linagliptin 5 mg.

Bahan lainnya adalah:
Inti tablet: manitol, pati pra-gelatinis, pati jagung, copovidone, crospovidone, talk dan magnesium stearat.
Lapisan salut: hypromellose, manitol, talk, titanium dioksida, makrogol 6000 dan besi oksida kuning.

Apa bentuk Glyxambi dan isi kemasan

- Tablet salut selaput Glyxambi 10 mg/5 mg (tablet) berwarna kuning pucat, bentuk segitiga, permukaan rata, dan bertepi miring. Terdapat angka "10/5" di satu sisi dan logo Boehringer Ingelheim di sisi lain. Panjang setiap sisi tablet berukuran 8 mm.

Glyxambi tersedia dalam blister dosis unit PVC/PVDC/aluminium.
Kemasan tablet salut selaput berukuran 30x1

Harus dengan resep dokter

Kondisi penyimpanan :
Simpan di bawah suhu 30°C
Simpan di tempat yang aman, jauhkan dari jangkauan anak-anak

Diproduksi oleh :
Rottendorf Pharma GmbH
Ennigerloh, Jerman

Untuk :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Jerman

Diimpor oleh :
PT Tunggal Idaman Abdi
Jakarta, Indonesia

Nomor Registrasi : DKI2424200717A1
Glyxambi 10 mg/5 mg

Version: 20-1225