APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

Glyxambi® 10/5 mg

Glyxambi® 25/5 mg

film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

GLYXAMBI 10/5 mg contains 10 mg empagliflozin and 5 mg linagliptin.
GLYXAMBI 25/5 mg contains 25 mg empagliflozin and 5 mg linagliptin.
Sugar free. Contains mannitol.
For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

GLYXAMBI 10/5 mg film-coated tablets are 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 25/5 mg film-coated tablets are 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 glycaemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate (see Sections 4.2 and 5.1 Clinical trials).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The recommended starting dose is GLYXAMBI 10/5 mg (empagliflozin 10 mg/linagliptin 5 mg) once daily. In patients tolerating GLYXAMBI 10/5 mg once daily and requiring additional glycaemic control, the dose can be increased to GLYXAMBI 25/5 mg (empagliflozin 25 mg/linagliptin 5 mg) once daily. In patients already on empagliflozin, the dose of GLYXAMBI should provide the dose of empagliflozin similar to the dose already being taken by the patient. GLYXAMBI can be taken with or without food and at any time of day.

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 4.5 and 4.8).

For patients taking metformin, the metformin dose should be continued.

Special Populations

Patients with renal impairment

Assess renal function prior to initiation of empagliflozin and periodically thereafter.
Glycaemic control is reduced in patients with eGFR <30 mL/min/1,73 m^2.
GLYXAMBI is contraindicated in patients with eGFR <30 mL/min/1,73 m^2.
Therapeutic experience with GLYXAMBI is limited in patients with eGFR <60 mL/min.
No dose adjustment is required for patients with eGFR ≥30 mL/min/1,73 m^2 (see Sections 4.3 and 4.4).

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 75 years and older is limited. Initiation of GLYXAMBI therapy in this population is not recommended (see Section 4.4). Patients aged 75 years and older should be prescribed with caution (see Section 4.4).

Paediatric population

GLYXAMBI should not be given to children under 18 years of age.
The safety and effectiveness of GLYXAMBI in children below 18 years of age have not been established.

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.

Method of administration

For oral use.

4.3 CONTRAINDICATIONS

Hypersensitivity to empagliflozin or linagliptin or any of the excipients listed in section 6.1.

Patients with severe renal impairment (eGFR <30 mL/min/1,73m^2), end-stage renal disease and patients on dialysis. The efficacy of empagliflozin is dependent on renal function (see Section 4.4).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

GLYXAMBI should not be used in patients with type 1 diabetes (see Section 4.1).

Diabetic ketoacidosis

GLYXAMBI should not be used for the treatment of diabetic ketoacidosis.
Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalisation, have been reported in post-marketing surveillance in patients treated with SGLT2 inhibitors, including empagliflozin. Fatal cases of ketoacidosis have been reported in

patients taking empagliflozin.

Patients treated with GLYXAMBI who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with GLYXAMBI may be present even if blood glucose levels are less than 13,8 mmol/L.
Signs and symptoms of ketoacidosis may include excessive thirst, nausea, vomiting, abdominal pain, generalised malaise, and shortness of breath. If ketoacidosis is suspected, GLYXAMBI should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement.
Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.
Before initiating GLYXAMBI, consider factors in the patient history that may predispose to ketoacidosis.
Factors that predispose patients to ketoacidosis include a low carbohydrate diet, dehydration, acute illness, surgery, a previous ketoacidosis, insulin deficiency from any cause (including insulin pump failure, history of pancreatitis, or pancreatic surgery), malnourishment/reduced caloric intake or increased insulin requirements due to infections, and alcohol abuse. GLYXAMBI should be used with caution in these patients. When reducing the insulin dose in patients requiring insulin, caution should be taken (see Section 4.2). Consider monitoring for ketoacidosis and temporarily discontinuing GLYXAMBI in clinical situations known to predispose to ketoacidosis. In these situations, consider monitoring of ketones, even if GLYXAMBI treatment has been interrupted.
Treatment should be interrupted in patients who are hospitalised for acute serious medical illnesses.

Surgery
Treatment with GLYXAMBI should be ceased prior to major surgery. An increase in other glucose lowering medicines may be required during this time.

Patients scheduled for non-urgent surgery who have not ceased empagliflozin should be assessed and consideration should be given to postponing the procedure.

Treatment with GLYXAMBI may be restarted once the patient's condition has stabilised and oral intake is normal.

Hypoglycaemia
In clinical trials of linagliptin or of empagliflozin as part of combination therapy with medicines 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 Section 4.8).

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when GLYXAMBI is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin may be considered.

Pancreatitis

Acute pancreatitis has been observed in patients taking linagliptin (see Section 4.8). If pancreatitis is suspected, GLYXAMBI should be discontinued.

Use in patients at risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in BP. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in BP could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, BP measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with GLYXAMBI should be considered until the fluid loss is corrected.

Urosepsis and pyelonephritis

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including empagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see Section 4.8).

Discontinuation of empagliflozin may be considered in cases of recurrent urinary tract infections.

Genital infections including life threatening necrotising fasciitis

SGLT2 inhibitors such as GLYXAMBI have been associated with an increased risk of genital infection in both males and females caused by bacteria and/or fungi. Genital fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis.

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotising infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalisation, 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 necrotising fasciitis. If suspected, GLYXAMBI should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in a long-term clinical study with another SGLT2 inhibitor. The medicine in that study is not empagliflozin. However, it is unknown whether this constitutes a class effect. In a pooled safety analysis of 12 620 patients with T2DM the frequency of patients with lower limb amputations was similar between empagliflozin and placebo. In the largest placebo controlled trial in 7 020 patients (EMPA-REG OUTCOME trial), in which 88 % of all the cases of amputations were reported, lower limb amputations occurred in 1,8 % of patients treated with

empagliflozin 10 mg, in 2,0 % of patients treated with empagliflozin 25 mg, and in 1,8 % of patients in the placebo arm. It is important to regularly examine the feet and counsel all diabetic patients on routine preventative foot care.

Bullous pemphigoid
Bullous pemphigoid has been observed in patients taking linagliptin. If bullous pemphigoid is suspected, GLYXAMBI should be discontinued.

Rhabdomyolysis
Rhabdomyolysis has been reported during use of DPP-4 inhibitor containing products such as GLYXAMBI. However, causality could not be assessed due to confounding factors such as concomitant use of medicines (statins, colchicine, etc.) or co-morbid conditions (renal failure, hypovolaemia, etc.), known to cause or predispose to development of rhabdomyolysis. Close monitoring of patients using DPP-4 inhibitor containing products in presence of predisposing risk factors is recommended.

Arthralgia
There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with linagliptin.

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

Use in renal impairment
Empagliflozin increases serum creatinine and decreases eGFR (see Section 4.8). Renal function abnormalities can occur after initiating empagliflozin. Patients with hypovolaemia may be more susceptible to these changes.

There have been post-marketing reports of acute kidney injury, some requiring hospitalisation and dialysis, in patients receiving SGLT2 inhibitors, including empagliflozin; some reports involved patients younger than 65 years of age.

GLYXAMBI is contraindicated for use in patients with eGFR <30 mL/min/1,73 m^2 (see Sections 4.2 and 4.3).
Therapeutic experience with GLYXAMBI is limited in patients with eGFR <60 mL/min.

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

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

Patients treated with empagliflozin can experience an initial fall in eGFR. More intensive monitoring of renal function is recommended, particularly following treatment initiation, if empagliflozin is used in patients with an eGFR <60 mL/min/1,73 m^2, especially if the eGFR is

<45 mL/min/1,73 m^2.
GLYXAMBI should be discontinued when the eGFR is below 30 mL/min/1,73 m^2 or CrCl <30 mL/min (see Section 4.3).

Use in the elderly
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 Section 4.8). Therapeutic experience in patients aged 75 years and older is limited. Initiation of therapy with GLYXAMBI in this population is not recommended.

Paediatric use
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.

Effect on laboratory tests
Urine will test positive for glucose while patients are taking GLYXAMBI due to the nature of the mechanism of action of SGLT2 inhibitors (see Section 5.1).

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION
No interactions between the two components of this fixed-dose combination have been observed in clinical studies.

No medicine 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 5.1), 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 Sections 4.2, 4.4, 4.8).

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

Lithium
Empagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after empagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing

doctor in order to monitor serum concentration of lithium.

UGT inhibitors and inducers
Empagliflozin is primarily metabolised via UGT (see Section 5.2); however, a clinically relevant effect of UGT inhibitors on empagliflozin is not expected.

Rifampicin
A study was conducted to assess the effect of rifampicin, a potent inductor of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Multiple co-administration of linagliptin with rifampicin, resulted in a 39,6 % and 43,8 % decreased linagliptin steady-state AUC and C_{max} and about 30 % decreased DPP-4 inhibition at trough. Thus linagliptin in combination with strong P-glycoprotein inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

Ritonavir
A study was conducted to assess the effect of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, on the pharmacokinetics of linagliptin. Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir increased the AUC and C_{max} of linagliptin approximately two-fold and three-fold, respectively. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will not be 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 or CYP3A4 inhibitors and dose adjustment is not required.

4.6 FERTILITY, PREGNANCY AND LACTATION
Pregnancy
There is a limited amount of data from the use of empagliflozin and linagliptin in pregnant women. It is recommended to avoid the use of GLYXAMBI during pregnancy unless clearly needed.

In a study in pregnant rats, oral co-administration of 700 mg/kg empagliflozin and 140 mg/kg linagliptin during the period of organogenesis was associated with decreased foetal weight and an increased incidence of minor foetal skeletal abnormalities, occurring in conjunction with maternotoxicity. No adverse effects on embryofetal development were observed with administration of 300 mg/kg empagliflozin and 60 mg/kg linagliptin in combination, yielding approximately 100 and 230 times the exposure to empagliflozin and linagliptin in patients at the maximum recommended human dose.

Empagliflozin
Empagliflozin administered during the period of organogenesis was not teratogenic at doses up to 300 mg/kg in the rat or rabbit, which corresponds to approximately 48- and 122-times or 128- and 325-times the clinical dose of empagliflozin based on AUC exposure associated with the 25 mg and 10 mg doses, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155- and 393-times the clinical dose associated with the 25 mg and 10 mg doses, respectively. Maternally toxic doses in the rabbit also caused increased embryofetal loss at doses approximately 139- and 353-times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

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

Specialised studies in rats with other members of the pharmacological class have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Similar effects have been seen for empagliflozin at approximately 11 times the clinical AUC exposure associated with the 25 mg dose. These findings were absent after a 13 week drug-free recovery period.

Linagliptin
Linagliptin was shown to cross the placenta in rats and rabbits.

In animal embryofetal development studies, linagliptin was shown to be not teratogenic in rats at oral doses up to 240 mg/kg/day (approximately 1 000 times the exposure in patients at the MRHD, based on plasma AUC) and up to 150 mg/kg/day in the rabbit (approximately 2 000 times human exposure). However, post-implantation loss was increased in both species at these upper dose levels (together with maternotoxicity), and there was an increase in runts and a slight increase in the incidence of foetal visceral variations in the rabbit. No adverse effects on embryofetal development were observed at up to 30 mg/kg/day in the rat (50 times human exposure) and up to 25 mg/kg/day in the rabbit (78 times human exposure).

Breastfeeding
Mothers should not breastfeed their infants when taking GLYXAMBI. 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 and its metabolites in milk.

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

Animal studies conducted with empagliflozin alone and linagliptin alone do not indicate adverse effects on fertility in patients.

Empagliflozin
Studies in rats at doses of empagliflozin up to 700 mg/kg/day, do not indicate direct or indirect harmful effects with respect to fertility. In female rats this dose was 90- and 155-fold the systemic AUC exposure anticipated with a human dose of 10 and 25 mg.

Linagliptin
No adverse effects on fertility were observed in male and female rats given linagliptin orally up to the highest dose of 240 mg/kg/day (yielding approximately 1 000 times the plasma AUC obtained in patients at the maximum recommended human dose [MRHD] of 5 mg/day) prior to and throughout mating.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. If patients experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 UNDESIRABLE EFFECTS

Adverse events in clinical trials

A total of 2 173 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of GLYXAMBI, of which 1 005 patients were treated with GLYXAMBI. In clinical trials, patients were treated for up to 24 or 52 weeks.

The most frequent adverse reaction was urinary tract infection (see 'Description of selected adverse reactions').

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

The adverse reactions 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 adverse reactions were identified with GLYXAMBI as compared to the individual components.

Tabulated list of adverse reactions

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

Table 1 Adverse reactions and assigned frequencies, derived from clinical trials or post-marketing experience

GLYXAMBI Adverse reactions			
System Organ Class	**MedDRA term (Preferred Terms)**	**GLYXAMBI 10/5 mg (empagliflozin/ linagliptin)**	**GLYXAMBI 25/5 mg (empagliflozin/ linagliptin)**
Infections and infestations	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[1,4]	Common	Common
	Urinary tract infection[1,4]	Common	Common
	Urosepsis[6]	Not known	Not known
	Pyelonephritis[6]	Not known	Not known
	Necrotising fasciitis of the perineum (Fournier's gangrene)[6]	Not known	Not known

GLYXAMBI Adverse reactions			
System Organ Class	**MedDRA term (Preferred Terms)**	**GLYXAMBI 10/5 mg (empagliflozin/ linagliptin)**	**GLYXAMBI 25/5 mg (empagliflozin/ linagliptin)**
	Nasopharyngitis[2]	Common	Common
Immune system disorders	Hypersensitivity[2]	Uncommon	Uncommon
	Angio-oedema[3,6]	Not known	Uncommon
	Urticaria[3,6]	Uncommon	Not known
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[4]	Common	Common
	Ketoacidosis[6]	Uncommon	Not known
Renal and urinary disorders	Increased urination[1,4]	Common	Common
	Dysuria[1]	Uncommon	Uncommon
Reproductive system and breast disorders	Phimosis[6]	Not known	Not known
Respiratory, thoracic and mediastinal disorders	Cough[2]	Common	Common
Skin and subcutaneous tissue disorders	Rash[3,6]	Common	Uncommon
	Pruritus[1]	Uncommon	Common
	Bullous pemphigoid[3,a]	Not known	Not known
	Severe cutaneous adverse reactions (SCARs) [3,b]	Not known	Not known
Gastrointestinal disorders	Pancreatitis[2]	Uncommon	Not known
	Mouth ulceration[3]	Rare	Not known
	Constipation	Common	Common
Musculoskeletal and connective tissue disorders	Arthralgia[3]	Common	Common
	Rhabdomyolysis[3]	Not known	Not known
General disorders and administration site conditions	Thirst[1]	Not known	Uncommon

GLYXAMBI Adverse reactions			
System Organ Class	**MedDRA term (Preferred Terms)**	**GLYXAMBI 10/5 mg (empagliflozin/ linagliptin)**	**GLYXAMBI 25/5 mg (empagliflozin/ linagliptin)**
Investigations	Blood creatinine increased[1,4]	Not known	Uncommon
	Glomerular filtration rate decreased[1,4]	Uncommon	Uncommon
	Lipase increased[2,5]	Common	Common
	Haematocrit increased[1,4]	Not known	Not known
	Serum lipids increased[1,4]	Common	Common
	Amylase increased[2,c]	Common	Uncommon
Vascular disorders	Volume depletion[1,4]	Uncommon	Uncommon

[1] derived from empagliflozin experiences
[2] derived from linagliptin experiences
[3] derived from linagliptin post-marketing experience
[4] refer to subsections below for additional information
[5] based on lipase elevations >3 x ULN observed in clinical trials
[6] derived from empagliflozin post-marketing experiences
[a] In the CARMELINA study (see section 5.1 Clinical Trials), bullous pemphigoid was reported in 0,2 % patients treated with linagliptin and in no patients treated with placebo
[b] such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), erythema multiforme and erythroderma (generalised exfoliative dermatitis)
[c] In the CAROLINA study (see section 5.1, 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 adverse reactions

The frequencies below are calculated for adverse reactions 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 10/5 mg and GLYXAMBI 25/5 mg

	Trial 1275.1 (Add-on to Metformin)				
	GLYXAMBI 10/5 mg	**GLYXAMBI 25/5 mg**	**Empa-gliflozin 10 mg**	**Empa-gliflozin 25 mg**	**Linagliptin 5 mg**
Number of patients	136 (100,0)	137 (100,0)	141 (100,0)	141 (100,0)	132 (100,0)

analysed, N (%)					
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 10/5 mg	**GLYXAMBI 25/5 mg**	**Empa-gliflozin 10 mg**	**Empa-gliflozin 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 10 mg		**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 sulphonylurea, and as add-on to insulin +/- metformin and +/- sulphonylurea.

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 +/- sulphonylurea, 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 +/- sulphonylurea.

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 25/5 mg: 9,2 %; GLYXAMBI 10/5 mg: 8,8 %) has been comparable to those reported from the empagliflozin clinical trials.

In empagliflozin trials, the overall frequency of urinary tract infection was similar in patients treated with empagliflozin 25 mg (7,0 %) and placebo (7,2 %), and higher in patients treated with empagliflozin 10 mg (8,8 %). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity 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 25/5 mg: 3,1 %; GLYXAMBI 10/5 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 %). These adverse events were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

Increased urination
In clinical trials with GLYXAMBI, the frequency of increased urination adverse events (GLYXAMBI 25/5 mg: 1,7 %; GLYXAMBI 10/5 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 preferred term 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 25/5 mg: 0,6 %; GLYXAMBI 10/5 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 (including the predefined terms BP (ambulatory) decreased, SBP decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension and syncope) was similar to placebo (0,6 % for empagliflozin 10 mg, 0,4 % for empagliflozin 25 mg and 0,3 % for placebo). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients aged 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
Use of empagliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes play a role in the renal function abnormalities observed with empagliflozin.

Renal-related adverse reactions (e.g. acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with empagliflozin.

In clinical trials with GLYXAMBI, the frequency of patients with increased blood creatinine (GLYXAMBI 25/5 mg: 0,4 %; GLYXAMBI 10/5 mg: 0 %) and decreased glomerular filtration rate (GLYXAMBI 25/5 mg: 0,4 %; GLYXAMBI 10/5 mg: 0,6 %) has been comparable to those reported from the empagliflozin clinical trials.

Laboratory parameters
Haematocrit increased
In clinical trials with GLYXAMBI, mean changes from baseline in haematocrit were 2,9 % and 3,2 % for GLYXAMBI 10/5 mg and 25/5 mg.

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 clinical trials with GLYXAMBI, mean percent increases from baseline for GLYXAMBI 10/5 mg and 25/5 mg respectively, were total cholesterol 3,0 % and 3,4 %; HDL cholesterol 6,8 % and 5,8 %; LDL cholesterol 5,4 % and 5,4 %; triglycerides 2,7 % and 4,2 %.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

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.

Treatment
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. The removal of empagliflozin by haemodialysis has not been studied.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacological Classification: A 21.2 Oral hypoglycaemics

Mechanism of action
Combination empagliflozin/linagliptin
Empagliflozin and linagliptin act by separate and complementary mechanisms to treat type 2 diabetes mellitus (T2DM). The combination of empagliflozin and linagliptin, after single oral dosing, showed a superior effect on glycaemic control (oral glucose tolerance test) as compared to the respective monotherapies tested in diabetic ZDF rats.

Empagliflozin
Empagliflozin is a reversible competitive inhibitor of SGLT2 with an IC_{50} of 1,3 nM. It has a 5 000-fold selectivity over human SGLT1 (IC_{50} of 6 278 nM), responsible for glucose absorption in the gut.
SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for re-absorption of glucose from the glomerular filtrate back into the circulation. In patients with T2DM and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

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 glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

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

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

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

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

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). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. 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 binding to DPP-4 is reversible but long lasting and thus leads to a sustained increase and a prolongation of active incretin levels. *In vitro*, linagliptin inhibits DPP-4 with nanomolar potency and exhibits a >10 000 fold selectivity versus DPP-8 or DPP-9 activity.

Clinical trials

A total of 2 173 patients with T2DM and inadequate glycaemic control were treated in clinical studies to evaluate the safety and efficacy of GLYXAMBI; 1 005 patients were treated with empagliflozin 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 (mean daily dose 1 889,0 (± 470,9) mg at baseline), 24 weeks treatment with GLYXAMBI 10/5 mg and GLYXAMBI 25/5 mg provided statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) compared to linagliptin 5 mg alone and also compared to empagliflozin 10 or 25 mg alone. Compared to linagliptin 5 mg GLYXAMBI provided statistically significant improvements in body weight. A greater proportion of patients with a baseline $HbA_{1c} \geq 7,0$ % and treated with GLYXAMBI achieved a target HbA_{1c} of <7 % compared to the individual components (Table 3).

After 24 weeks treatment with GLYXAMBI, both systolic (SBP) and diastolic blood pressures (DBP) were reduced, -5,6/-3,6 mmHg (p<0,001 versus linagliptin 5 mg for SBP and DBP) for GLYXAMBI 25/5 mg and -4,1/-2,6 mmHg (p<0,05 versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10/5 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 25/5 mg and -3,1/-1,6 mmHg (p<0,05 versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10/5 mg.

After 24 weeks, rescue therapy was used in 1 (0,7 %) patient treated with GLYXAMBI 25/5 mg

and in 3 (2,2 %) patients treated with GLYXAMBI 10/5 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 25/5 mg	GLYXAMBI 10/5 mg	Empa-gliflozin 25 mg	Empa-gliflozin 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]:	vs. 25 mg	vs. 10 mg	--	--	--
- adjusted mean[2] (SE)	-0,58 (0,09)	-0,42 (0,09)			
- 95,0 % CI	-0,75; -0,41	-0,59; -0,25			
- p-value	<0,0001	<0,0001			
Comparison vs. linagliptin 5 mg[1]:			--	--	--
- adjusted mean[2] (SE)	-0,50 (0,09)	-0,39 (0,09)			
- 95,0 % CI	-0,67; -0,32	-0,56; -0,21			
- p-value	<0,0001	<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)

	GLYXAMBI 25/5 mg	GLYXAMBI 10/5 mg	Empa-gliflozin 25 mg	Empa-gliflozin 10 mg	Linagliptin 5 mg
Comparison vs. empagliflozin[1]:	vs. 25 mg	vs. 10 mg	--	--	--
- adjusted mean[2] (SE)	-0,57 (0,10)	-0,36 (0,10)			
- 95,0 % CI	-0,77; -0,37	-0,56; -0,17			
Comparison vs. linagliptin 5 mg[1]:			--	--	--
- adjusted mean[2] (SE)	-0,73 (0,10)	-0,57 (0,10)			
- 95,0 % CI	-0,93; -0,53	-0,77; -0,37			
Key secondary endpoint: FPG [mmol/L] - 24 weeks					
Number of patients analysed	**133**	**134**	**139**	**136**	**127**
Baseline mean (SE)	8,59 (0,16)	8,70 (0,17)	8,88 (0,18)	8,98 (0,17)	8,69 (0,15)
Change from baseline at week 24[1]:					
- adjusted mean[2] (SE)	-1,96 (0,14)	-1,79 (0,14)	-1,05 (0,14)	-1,16 (0,14)	-0,73 (0,14)
Comparison vs. empagliflozin[1]:	vs. 25 mg	vs. 10 mg	--	--	--
- adjusted mean[2] (SE)	-0,91 (0,20)	-0,63 (0,20)			
- 95,0 % CI	-1,30; -1,30	-1,02; -0,24			
- p-value	<0,0001	0,0015			
Comparison vs. linagliptin 5 mg[1]:			--	--	--
- adjusted mean[2] (SE)	-1,23 (0,20)	-1,06 (0,20)			
- 95,0 % CI	-1,63; -0,84	-1,46; -0,67			
- p-value	<0,0001	<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]:					

	GLYXAMBI 25/5 mg	GLYXAMBI 10/5 mg	Empa-gliflozin 25 mg	Empa-gliflozin 10 mg	Linagliptin 5 mg
- 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)	-2,30 (0,44)	-1,91 (0,44)			
- 95,0 % CI	-3,15; -1,44	-2,77; -1,05			
- p-value	<0,0001	<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:	vs. 25 mg	vs. 10 mg	--	--	--
- odds ratio	4,191	4,500			
- 95,0 % CI	2,319; 7,573	2,474; 8,184			
- p-value	<0,0001	<0,0001			
Comparison[5] vs. linagliptin 5 mg:			--	--	--
- odds ratio	3,495	2,795			
- 95,0 % CI	1,920; 6,363	1,562; 5,001			
- p-value	<0,0001	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 25/5 mg vs. empagliflozin 25 mg: adjusted mean 0,19 (95 % CI -0,65; 1,03) kg; GLYXAMBI 10/5 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 pre-specified subgroup of patients with baseline HbA_{1c} greater or equal than 8,5 % the reduction from baseline in HbA_{1c} with GLYXAMBI 25/5 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 10/5 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 25/5 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 25/5 mg and empagliflozin 25 mg (Table 4). GLYXAMBI 10/5 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 GLYXAMBI 25/5 mg and -3,6/-0,7 mmHg (p<0,05 versus linagliptin 5 mg for SBP, n.s. for DBP) for GLYXAMBI 10/5 mg. Rescue therapy was used in 2 (1,5 %) patients treated with GLYXAMBI 25/5 mg and in 1 (0,7 %) patient treated with GLYXAMBI 10/5 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 25/5 mg	**GLYXAMBI 10/5 mg**	**Empa-gliflozin 25 mg**	**Empa-gliflozin 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]:	vs. 25 mg	vs. 10 mg	--	--	--
- adjusted mean[2] (SE)	-0,14 (0,10)	-0,41 (0,10)			
- 95,0 % CI	-0,33; 0,06	-0,61; -0,21			
- p-value	0,1785	not assessed			
Comparison vs. linagliptin 5 mg[1]:			--	--	--
- adjusted mean[2] (SE)	-0,41 (0,10)	-0,57 (0,10)			
- 95,0 % CI	-0,61; -0,22	-0,76; -0,37			
- p-value	<0,0001	not assessed			
HbA_{1c} (%) – 52 weeks[4]					

	GLYXAMBI 25/5 mg	GLYXAMBI 10/5 mg	Empa-gliflozin 25 mg	Empa-gliflozin 10 mg	Linagliptin 5 mg
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 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]:	vs. 25 mg	vs. 10 mg	--	--	--
- adjusted mean (SE)	-0,16 (0,12)	-0,37 (0,12)			
- 95,0 % CI	-0,39; 0,07	-0,60; -0,14			
Comparison vs. linagliptin 5 mg[1]:			--	--	--
- adjusted mean (SE)	-0,66 (0,12)	-0,71 (0,12)			
- 95,0 % CI	-0,90; -0,43	-0,94; -0,48			
Key secondary endpoint: FPG [mmol/L] - 24 weeks					
Number of patients analysed	**134**	**135**	**133**	**132**	**133**
Baseline mean (SE)	8,67 (0,17)	8,73 (0,17)	8,49 (0,19)	8,90 (0,20)	8,67 (0,18)
Change from baseline at week 24[1]:					
- adjusted mean[2] (SE)	-1,64 (0,15)	-1,57 (0,15)	-1,35 (0,15)	-1,24 (0,15)	-0,33 (0,15)
Comparison vs. empagliflozin[1]:	vs. 25 mg	vs. 10 mg	--	--	--
- adjusted mean[2] (SE)	-0,30 (0,21)	-0,32 (0,21)			
- 95,0 % CI	-0,71; 0,12	-0,74; 0,09			
- p-value	not assessed	not assessed			
Comparison vs. linagliptin 5 mg[1]:			--	--	--
- adjusted mean[2] (SE)	-1,31 (0,21)	-1,24 (0,21)			

	GLYXAMBI 25/5 mg	GLYXAMBI 10/5 mg	Empa-gliflozin 25 mg	Empa-gliflozin 10 mg	Linagliptin 5 mg
- 95,0 % CI	-1,73; -0,90	-1,65; -0,83			
- p-value	not assessed	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)	-1,22 (0,51)	-1,96 (0,51)			
- 95,0 % CI	-2,23; -0,21	-2,97; -0,95			
- p-value	not assessed	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:	vs. 25 mg	vs. 10 mg	--	--	--
- odds ratio	1,893	2,961			
- 95,0 % CI	1,095; 3,274	1,697; 5,169			
- p-value	not assessed	not assessed			
Comparison[5] vs. linagliptin 5 mg:			--	--	--
- odds ratio	3,065	4,303			
- 95,0 % CI	1,768; 5,314	2,462; 7,522			
- p-value	not assessed	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 25/5 mg vs. empagliflozin 25 mg: adjusted mean 0,19 (95 % CI -0,65; 1,03) kg; GLYXAMBI 10/5 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 pre-specified subgroup of patients with baseline HbA_{1c} greater or equal than 8,5 %, the reduction from baseline in HbA_{1c} with GLYXAMBI 25/5 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 10/5 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 (mean daily dose 1 975,7 (± 457,7) mg at baseline), 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} \geq$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 empagliflozin 10 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]
HbA_{1c} (%) - 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 (mmol/L) – 24 weeks[3]			
N	109	109	106
Baseline (mean)	9,3	9,45	9,1
Change from baseline (adjusted mean)	-1,5	-1,8	0,3

	Metformin + Linagliptin 5 mg		
	Empagliflozin 10 mg[1]	Empagliflozin 25 mg[1]	Placebo[2]
Comparison vs. placebo (adjusted mean) (95 % CI)	-1,8 (-2,3; -1,3) p<0,0001	-2,1 (-2,6; -1,6) 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 HbA_{1c} <7 % with baseline HbA_{1c} ≥7 % - 24 weeks[4]			
N	100	107	100
Patients (%) achieving HbA_{1c} <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 randomised to the empagliflozin 10 mg or 25 mg groups were receiving GLYXAMBI 10/5 mg or 25/5 mg with background metformin

[2] Patients randomised 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 visit by treatment 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 pre-specified 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 5 mg in patients inadequately controlled on empagliflozin 10 mg and metformin

In patients inadequately controlled on empagliflozin 10 mg and metformin (mean daily dose 2 101,8 (± 478,6) mg at baseline), 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 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 pre-specified 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 5 mg in patients inadequately controlled on empagliflozin 25 mg and metformin
In patients inadequately controlled on empagliflozin 25 mg and metformin (mean daily dose 2 003,9 (± 438,8) mg at baseline), 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} \geq$7,0 % and treated with 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 pre-specified 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 GLYXAMBI 10/5 mg to Empagliflozin 10 mg as well as GLYXAMBI 25/5 mg to Empagliflozin 25 mg as Add-on Therapy in Patients Inadequately Controlled on Empagliflozin 10 mg/25 mg and Metformin

	Metformin + Empagliflozin 10 mg		**Metformin + Empagliflozin 25 mg**	
	Linagliptin 5 mg	**Placebo**	**Linagliptin 5 mg**	**Placebo**
HbA_{1c} (%) – 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 (mmol/L) – 24 weeks[1]				
N	120	123	107	107
Baseline (mean)	8,8	8,6	8,5	8,6
Change from baseline (adjusted mean)	-0,4	0,2	-0,7	-0,2

	Metformin + Empagliflozin 10 mg		Metformin + Empagliflozin 25 mg	
	Linagliptin 5 mg	**Placebo**	**Linagliptin 5 mg**	**Placebo**
Comparison vs. placebo (adjusted mean) (95 % CI)	-0,7 (-1,1;-0,2) p=0,0103		-0,4 (-0,9; 0,0) 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 HbA_{1c} <7 % with baseline HbA_{1c} ≥7 % – 24 weeks[2]				
N	116	119	100	107
Patients (%) achieving HbA_{1c} <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 randomised to the linagliptin 5 mg group were receiving either fixed dose combination tablets GLYXAMBI 10/5 mg plus metformin or fixed dose combination tablets GLYXAMBI 25/5 mg plus metformin; patients randomised 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 visit by treatment 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

Cardiovascular safety

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

Linagliptin cardiovascular safety study (CAROLINA)
CAROLINA was a randomised study in 6 033 patients with early type 2 diabetes and increased CV risk or established complications who were treated with linagliptin 5 mg (3 023) or glimepiride 1–4 mg (3 010) added to standard of care (including background therapy with metformin in 83 % of patients) targeting regional standards for HbA_{1c} and CV risk factors. The mean age for study population was 64 years and included 2 030 (34 %) patients $\geq$ 70 years of age. The study population included 2 089 (35 %) patients with cardiovascular disease and 1 130 (19 %) patients with renal impairment with an eGFR <60mL/min/1,73m^2 at baseline. The mean HbA_{1c} at baseline was 7,15 %.
The study was designed to demonstrate non-inferiority for the primary cardiovascular endpoint which was a composite of the first occurrence of cardiovascular death or a non-fatal myocardial infarction (MI) or a non-fatal stroke (3P-MACE).
After a median follow up of 6,25 years, linagliptin did not increase the risk of major adverse cardiovascular events (Table 7) as compared to glimepiride. Results were consistent for patients treated with or without metformin.

Table 7 Major adverse cardiovascular events (MACE) and mortality by treatment group in the CAROLINA study

	Linagliptin 5 mg		Glimepiride (1-4 mg)		Hazard Ratio
	Number of Subjects (%)	Incidence Rate per 1 000 PY*	Number of Subjects (%)	Incidence Rate per 1 000 PY*	(95 % CI)
Number of patients	3023		3010		
Primary CV composite (Cardiovascular death, non-fatal MI, non-fatal stroke)	356 (11,8)	20,7	362 (12,0)	21,2	0,98 (0.84, 1.14)**

* PY=patient years
** Test on non-inferiority to demonstrate that the upper bound of the 95 % CI for the hazard ratio is less than 1,3

For the entire treatment period (median time on treatment 5,9 years) the rate of patients with moderate or severe hypoglycaemia was 6,5% on linagliptin versus 30,9 % on glimepiride, severe hypoglycaemia 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.

5.2 PHARMACOKINETIC PROPERTIES
The rate and extent of absorption of empagliflozin and linagliptin in GLYXAMBI

(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 characterised in healthy volunteers and patients with T2DM. No clinically relevant differences in pharmacokinetics were seen between healthy volunteers and T2DM patients.

The following statements reflect the pharmacokinetic properties of the individual active substances of GLYXAMBI.

Absorption

Empagliflozin

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations (C_{max}) with a median C_{max}, (t_{max}) of 1,5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase.

The steady-state mean plasma area under the curve (AUC) was 4 740 nmol·h/L and C_{max} was 687 nmol/L with 25 mg empagliflozin once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.

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

Linagliptin

The pharmacokinetics of linagliptin have been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteer patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median t_{max}) occurring 1,5 hours post-dose.

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin 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 of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of 5 mg linagliptin are reached by the third dose. Plasma area under the curve (AUC) of linagliptin 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 linagliptin AUC were small (12,6 % and 28,5 %, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

The absolute bioavailability of linagliptin is approximately 30 %. Because co-administration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food.
In vitro studies indicated that linagliptin is a substrate of P-glycoprotein and of CYP3A4. Ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, led to a two-fold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-glycoprotein and CYP3A, resulted in an approximate 40 % decreased linagliptin steady-state AUC, presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein.

Distribution

Empagliflozin

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 %.

Linagliptin

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 1 110 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 the peak plasma concentration in humans at 5 mg/day, approximately 10 % of linagliptin is unbound.

Metabolism

Empagliflozin

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.

Linagliptin

Following a [^{14}C]-linagliptin oral 10 mg dose, only 5 % of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13,3 % of linagliptin at steady-state was detected and was found to be pharmacologically inactive and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Excretion

Empagliflozin

The apparent terminal elimination half-life of empagliflozin was estimated to be 12,4 h and apparent oral clearance was 10,6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39,1 % and 35,8 %, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22 % accumulation, with

respect to plasma AUC, was observed at steady-state. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95,6 % of the drug related radioactivity was eliminated in faeces (41,2 %) or urine (54,4 %). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Linagliptin
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.

Pharmacokinetics in special patient groups

Pharmacokinetics in children
Studies characterising the pharmacokinetics of empagliflozin or linagliptin in paediatric patients have not been performed.

Pharmacokinetics in the elderly
Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin or linagliptin based on population pharmacokinetic analysis. Elderly subjects (65 to 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

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 and patients with kidney failure/end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18 %, 20 %, 66 %, and 48 %, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20 % higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. In line with the Phase I study, the population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal impairment.

Linagliptin
A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with end stage renal disease (ESRD) on haemodialysis. In addition, patients with type 2 diabetes mellitus and severe renal impairment (< 30 mL/min) were compared to patients with type 2 diabetes mellitus and normal renal function.

Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula: CrCl = [140 – age (years)] x weight (kg) {x 0,85 for female patients} / [72 x serum creatinine (mg/dL)]. Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1,7-fold was observed compared with control. Exposure in patients with type 2 diabetes mellitus and severe renal impairment was increased by about 1,4-fold compared to patients with type 2 diabetes mellitus 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 renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal impairment. In addition, mild renal impairment had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes mellitus as assessed by population pharmacokinetic analyses.

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

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

Linagliptin
In patients with mild, moderate and severe hepatic insufficiency (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin.

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

Race
No dosage adjustment is necessary based on race.

Empagliflozin
Based on the population pharmacokinetic analysis, AUC was estimated to be 13,5 % higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2.

Linagliptin
Race had no obvious effect on the plasma concentrations of linagliptin based on a composite

analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African American, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy volunteers and African American type 2 diabetes patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Empagliflozin

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

Linagliptin

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay in the rat.

Carcinogenicity

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

Empagliflozin

Two-year oral carcinogenicity studies were conducted in mice and rats. There was an increase in renal adenomas and carcinomas in male mice given empagliflozin at 1 000 mg/kg/day. No renal tumours were seen at 300 mg/kg/day (11- and 28-times the exposure at the clinical dose of 25 mg and 10 mg, respectively). These tumours are likely associated with a metabolic pathway not present in humans, and are considered to be irrelevant to patients given 10 or 25 mg empagliflozin. No drug-related tumours were seen in female mice or female rats at doses up to 1 000 and 700 mg/kg/day, respectively, resulting in exposures at least 60 times that expected at the clinical dose of 10 or 25 mg empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node, were observed at 700 mg/kg/day, but not at 300 mg/kg/day (approximately 26- and 65-times the exposure at the clinical dose of 25 mg and 10 mg, respectively). These tumours are common in rats and are unlikely to be relevant to humans.

Linagliptin

No evidence of carcinogenicity was observed with linagliptin in 2-year studies in mice and rats given oral doses up to 80 mg/kg/day and 60 mg/kg/day, respectively.

These doses correspond to approximately 300- and 400-times the human exposure (plasma AUC) at the MRHD of 5 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film-coated tablet of GLYXAMBI 10/5 mg contains the following inactive ingredients:

mannitol (107 mg/tablet), pregelatinised maize starch, maize starch, copovidone, crospovidone, purified talc, magnesium stearate, hypromellose, titanium dioxide, macrogol, iron oxide yellow.

Each film-coated tablet of GLYXAMBI 25/5 mg contains the following inactive ingredients: mannitol (92 mg/tablet), pregelatinised maize starch, maize starch, copovidone, crospovidone, purified talc, magnesium stearate, hypromellose, titanium dioxide, macrogol, iron oxide red.

6.2 INCOMPATIBILITIES
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE
The manufacturing and expiry dates can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store at or below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER
GLYXAMBI 10/5 mg and 25/5 mg are available in transparent PVC/PVDC/Aluminium blister packs containing 30 film-coated tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

GLYXAMBI 10/5 mg: 55/21.2/0030
GLYXAMBI 25/5 mg: 55/21.2/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 18 October 2022

10 DATE OF REVISION OF THE TEXT

01 November 2025