Boehringer Ingelheim

GLYXAMBI®

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

3.1 Product description

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

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLYXAMBI is indicated to improve glycaemic control in adults with type 2 diabetes mellitus:

- instead of empagliflozin, when diet, exercise and treatment with empagliflozin ± metformin do not provide adequate glycaemic control
- instead of linagliptin, when diet, exercise and treatment with linagliptin ± metformin do not provide adequate glycaemic control

GLYXAMBI can be used to replace the free combination of empagliflozin and linagliptin in adult patients with type 2 diabetes mellitus who are already being treated with this combination.

4.2 Posology and method of administration

Posology

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

In patients who tolerate this starting dose and require additional glycaemic control, the dose can be increased to 1 film-coated tablet of GLYXAMBI 25 mg/5 mg (25 mg empagliflozin plus 5 mg linagliptin) once daily.

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 4.4, 4.5 and 4.8).

Patients switching from empagliflozin (either 10 mg or 25 mg daily dose) and linagliptin (5 mg daily dose) to GLYXAMBI should receive the same daily dose of empagliflozin and linagliptin in the fixed dose combination as in separate tablets. The metformin dose should be continued.

Special populations

Renal impairment

GLYXAMBI is not recommended for use in patients with eGFR <30 ml/min/1.73 m^2. (see Special warning and precautions for use).

No dose adjustment is required for patients with eGFR ≥30 ml/min/1.73 m^2.

Hepatic impairment

No dose adjustment is required in patients with mild to moderate hepatic impairment.

Empagliflozin exposure is increased in patients with severe hepatic impairment and therapeutic experience in such patients is limited (see section 5.2). Therefore, GLYXAMBI is not recommended for use in this population.

Elderly

No dosage adjustment based on age is required. However, renal function and risk of volume depletion should be taken into account in patients 75 years and older (see sections 4.4 and 4.8).

Paediatric population

The safety and efficacy of GLYXAMBI in paediatric patients below 18 years of age have not been established. GLYXAMBI is not recommended for use in patients under 18 years of age. Available data on the single components are described in sections Clinical Trials, and Pharmacokinetics.

Method of administration

GLYXAMBI tablets are for oral use and can be taken with or without a meal at any time of the day at regular intervals. The tablets should be swallowed whole with water. If a dose is missed, and it is 12 hours or more until the next dose, the dose should be taken as soon as the patient remembers. The next dose should be taken at the usual time. If a dose is missed, and it is less than 12 hours until the next dose, the dose should be skipped and the next dose should be taken at the usual time. A double dose should not be taken to compensate for a forgotten dose.

4.3 Contraindications

Hypersensitivity to the active substances, to any other Sodium-Glucose-Co-Transporter-2 (SGLT2) inhibitor, to any other Dipeptidyl-Peptidase-4 (DPP-4) inhibitor, or to any of the excipients listed in section 6.1.

4.4 Special warning and precautions for use

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

Diabetic ketoacidosis

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

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

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

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

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

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 section 5.2 Pharmacokinetics).

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

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

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

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).

Use with medicinal products known to cause hypoglycaemia

Empagliflozin and linagliptin as single agents showed an incidence of hypoglycaemia comparable to placebo when used alone or in combination with other antidiabetics not known to cause hypoglycaemia (e.g. metformin, thiazolidinediones). When used in combination with antidiabetics known to cause hypoglycaemia (e.g. sulphonylureas and/or insulin), the incidence of hypoglycaemia of both agents was increased (see section 4.8).

There are no data about the hypoglycaemic risk of GLYXAMBI when used with insulin and/or sulphonylurea. However, caution is advised when GLYXAMBI is used in combination with antidiabetics. A dose reduction of the sulphonylurea or insulin may be considered (see section 4.2 and 4.5).

Acute pancreatitis

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

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

Monitoring of renal function

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function (see sections 4.2, 5.1 and 5.2). 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 with renal impairment

GLYXAMBI is not recommended for use in patients with eGFR <30 ml/min/1.73 m^2.

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 blood pressure (see section 5.1). Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy (e.g. thiazide and loop diuretics, see also section 4.5) 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 GLYXAMBI clinical trials, the incidence of urinary tract infections was overall similar between the patients treated with GLYXAMBI and the patients treated with empagliflozin or linagliptin. The frequencies were comparable to the incidence of urinary tract infections in empagliflozin clinical trials (see section 4.8).

In a pool of placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo and higher in patients treated with empagliflozin 10 mg (see section 4.8). Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Pyelonephritis and urosepsis were not reported from the clinical trials in patients treated with GLYXAMBI. However, temporary interruption of GLYXAMBI should be considered in patients with complicated urinary tract infections.

Lower limb amputations

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

Hepatic injury

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

Urine laboratory assessments

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

Elevated haematocrit

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

Elderly Patients

A higher risk of volume depletion adverse reactions were reported in patients aged 75 years and older, treated with empagliflozin, especially at 25 mg/day (see section 4.8). Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

Bullous pemphigoid

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with GLYXAMBI and other medicinal products;

however, such studies have been conducted with the individual active substances. Based on results of pharmacokinetic studies, no dose adjustment of GLYXAMBI is recommended when co-administered with commonly prescribed medicinal products, except those mentioned below.

Pharmacodynamic interactions

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 and 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).

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.

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.

Pharmacokinetic interactions

Effects of other medicinal products on empagliflozin

Empagliflozin is mainly excreted unchanged. A minor fraction is metabolised via uridine 5'-diphosphoglucuronosyltransferases (UGT); therefore, a clinically relevant effect of UGT inhibitors on empagliflozin is not expected (see section 5.2). The effect of UGT induction on empagliflozin has not been studied. Co-administration with known inducers of UGT enzymes should be avoided because of a risk of decreased efficacy of empagliflozin.

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

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

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

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

Effects of empagliflozin on other medicinal products

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

Effects of other medicinal products on linagliptin

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 administered long-term (see section 5.2). Co-administration with other potent inducers of P-gp and CYP3A4, such as carbamazepine, phenobarbital and phenytoin, has not been studied.

Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, increased the AUC and C_{max} of 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.

Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of linagliptin were not influenced by co-administration with metformin and glibenclamide.

Effects of linagliptin on other medicinal products

Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme 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.

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-gp and organic cationic transporter (OCT).

4.6 Fertility, pregnancy and lactation

The effects of GLYXAMBI on pregnancy, breast-feeding and fertility are not known. Effects related to the individual active substances are described below.

Pregnancy

There are no data from the use of empagliflozin and linagliptin in pregnant women.
Animal studies show that empagliflozin and linagliptin cross the placenta during late gestation, but do not indicate direct or indirect harmful effects with respect to early embryonic development with either empagliflozin or linagliptin (see section 5.3). Animal studies with empagliflozin have shown adverse effects on postnatal development (see section 5.3). As a precautionary measure it is preferable to

avoid the use of GLYXAMBI during pregnancy.

Breast-feeding

No data in humans are available on excretion of empagliflozin and linagliptin into milk. Available non-clinical data in animals have shown excretion of empagliflozin and linagliptin in milk. A risk to newborns or infants cannot be excluded. GLYXAMBI should not be used during breast-feeding.

Fertility

No studies on the effect on human fertility have been conducted with GLYXAMBI or with the individual active substances. Non-clinical studies with empagliflozin and linagliptin as single agents do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effect on ability to drive and use machines

GLYXAMBI has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when GLYXAMBI is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin and analogues, sulphonylureas).

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reaction was urinary tract infection (7.5 % with GLYXAMBI 10 mg empagliflozin / 5 mg linagliptin and 8.5 % with GLYXAMBI 25 mg empagliflozin / 5 mg linagliptin) (see Description of selected adverse reactions). The most serious adverse reactions were ketoacidosis (< 0.1%), pancreatitis (0.2%), hypersensitivity (0.6%), and hypoglycaemia (2.4%) (see section 4.4).

Overall, the safety profile of GLYXAMBI was in line with the safety profiles of the individual active substances (empagliflozin and linagliptin). No additional adverse reactions were identified with GLYXAMBI.

Tabulated list of adverse reactions

The adverse reactions shown in the table below (see Table 1) are listed by system organ class and are based on the safety profiles of empagliflozin and linagliptin monotherapy. The information about adverse reactions not reported in GLYXAMBI clinical trials is based on the experience from empagliflozin and linagliptin. Adverse reactions marked with an asterisk (*) are further discussed in section “Description of selected adverse reactions” below.

Frequency categories 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), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Urinary tract infection[1,*] (including pyelonephritis and urosepsis)[4]
	Common	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections[1,*]
	Common	Nasopharyngitis[2]
	Not known	Necrotizing fasciitis of the perineum (Fournier´s gangrene)[4]
Immune system disorders	Uncommon	Hypersensitivity[2]
	Uncommon	Angioedema[3,4], urticaria[3,4]
Metabolism and nutrition disorders	Common	Hypoglycaemia (when used with sulphonylurea or insulin)[*]
	Common	Thirst
	Rare	Diabetic ketoacidosis[4,#]
Respiratory, thoracic and mediastinal disorders	Common	Cough[2]
Gastrointestinal disorders	Common	Constipation
	Uncommon	Pancreatitis[2]
	Rare	Mouth ulceration[3]
Skin and subcutaneous tissue disorders	Common	Pruritus[1]
	Common	Rash[3,4]
	Not known	Bullous pemphigoid[2,a]
Vascular disorders	Uncommon	Volume depletion[1,*]
Renal and urinary disorders	Common	Increased urination[1,*]
	Uncommon	Dysuria[1]
Investigations	Common	Lipase increased[2]
	Common	Amylase increased[2, b]
	Uncommon	Haematocrit increased[1,5]
	Uncommon	Serum lipids increased[1,6]
	Uncommon	Blood creatinine increased/Glomerular filtration rate decreased[1,*]

[1] derived from empagliflozin experiences
[2] derived from linagliptin experiences
[3] derived from linagliptin postmarketing experience
[4] derived from empagliflozin postmarketing experience
[5] Mean changes from baseline in haematocrit were 3.3% and 4.2% for GLYXAMBI 10 mg/5 mg and 25 mg/5 mg, respectively, compared to 0.2% for placebo. In a clinical trial with empagliflozin, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.
[6] Mean percent increases from baseline for GLYXAMBI 10 mg/5 mg and 25 mg/5 mg versus placebo, respectively, were total cholesterol 3.2% and 4.6% versus 0.5%; HDL-cholesterol 8.5% and 6.2% versus 0.4%; LDL-cholesterol 5.8% and 11.0% versus 3.3%; triglycerides -0.5% and 3.3% versus 6.4 %.
[a] In the CARMELINA study (see section 5.1), bullous pemphigoid was reported in 0.2% patients treated with linagliptin and in no patients treated with placebo.
[b] In the CAROLINA study (see section Clinical Trials), amylase increase to > 3xULN was reported in 0.99% of patients treated with linagliptin and in 0.54% of patient treated with glimepiride.
[#] see section 4.4
[*] see subsection below for additional information

Description of selected adverse reactions

Hypoglycaemia

In pooled clinical trials of GLYXAMBI in patients with type 2 diabetes and inadequate glycaemic control on background metformin, the frequency of the reported hypoglycaemic events was 2.4 %. The incidence of confirmed hypoglycaemic events was low (< 1.5 %). There was no notable difference of the incidence in patients treated with different dose strengths of GLYXAMBI compared to the treatment with empagliflozin or linagliptin.

One patient administered GLYXAMBI experienced a confirmed (investigator-defined), major hypoglycaemic event (defined as an event requiring assistance) in the active- or placebo-controlled trials (overall frequency 0.1 %).

Based on the experience with empagliflozin and linagliptin, an increase of the risk of hypoglycaemia is expected with the concomitant treatment of insulin and /or sulphonylurea (see section 4.4 and information below)

Hypoglycaemia with 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 (empagliflozin 10 mg: 16.1 %, empagliflozin 25 mg: 11.5 %, placebo: 8.4 %), add-on to basal insulin +/- metformin and +/-sulphonylurea (empagliflozin 10 mg: 19.5 %, empagliflozin 25 mg: 28.4 %, placebo: 20.6 % during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25 mg: 36.1 %, placebo 35.3 % over the 78 week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8 %, empagliflozin 25 mg: 41.3 %, placebo: 37.2 % during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1 %, empagliflozin 25 mg: 57.7 %, placebo: 58 % over the 52-week trial).

Major hypoglycaemia 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 basal insulin +/- metformin and +/- sulphonylurea (empagliflozin 10 mg: 0 %, empagliflozin 25 mg: 1.3 %, placebo: 0 % during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 0 %, empagliflozin 25 mg: 1.3 %, placebo 0 % over the 78-week trial), and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 1.6 %, empagliflozin 25 mg: 0.5 %, placebo: 1.6 % during initial 18 weeks treatment when insulin could not be adjusted and over the 52-week trial).

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), moderate (16.6 %; N=78) or severe (1.9 %; N=9) in intensity.

Urinary tract infection

In clinical trials with GLYXAMBI, there was no notable difference of the frequency of urinary tract infections in patients treated with GLYXAMBI (GLYXAMBI 25 mg/5 mg: 8.5 %; GLYXAMBI 10 mg/5 mg: 7.5 %) compared to the patients treated with empagliflozin and linagliptin. The frequencies have been comparable to those reported from the empagliflozin clinical trials (see also section 4.4).

In empagliflozin trials, the overall frequency of urinary tract infection 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 %). 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 was reported more frequently in female patients treated with empagliflozin compared to placebo, but not in male patients.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

In clinical trials with GLYXAMBI, genital infections in patients treated with GLYXAMBI (GLYXAMBI 25 mg/5 mg: 3.0 %; GLYXAMBI 10 mg/5 mg: 2.5 %) were reported more frequently than for linagliptin but less frequently than for empagliflozin. Overall, the frequencies for GLYXAMBI have 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 infections 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, increased urination in patients treated with GLYXAMBI (GLYXAMBI 25 mg/5 mg: 2.6 %; GLYXAMBI 10 mg/5 mg: 1.4 %) was reported more frequently than for linagliptin and with similar frequency than for empagliflozin. Overall, the frequencies for GLYXAMBI have been comparable to those reported from the empagliflozin clinical trials.

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

Volume depletion

In clinical trials with GLYXAMBI, there was no notable difference in the frequency of volume depletion in patients treated with GLYXAMBI (GLYXAMBI 25 mg/5 mg: 0.4 %; GLYXAMBI 10 mg/5 mg: 0.8 %) compared to the patients treated with empagliflozin and linagliptin. The frequencies have been comparable to those reported from the empagliflozin clinical trials.

In clinical trials with empagliflozin, the overall frequency of volume depletion [including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope] was similar in patients treated with empagliflozin (empagliflozin 10 mg: 0.6 %, empagliflozin 25 mg: 0.4 %) and

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

Blood creatinine increased/Glomerular filtration rate decreased

In clinical trials with GLYXAMBI, the frequency of patients with increased blood creatinine (GLYXAMBI 25 mg/5 mg: 0.4%; GLYXAMBI 10 mg/5 mg: 0%) and decreased glomerular filtration rate (GLYXAMBI 25 mg/5 mg: 0.4%; GLYXAMBI 10 mg/5 mg: 0.6%) has been comparable to those reported from the empagliflozin clinical trials.
The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate were similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).

Elderly
In clinical trials, nineteen patients 75 years or older were treated with GLYXAMBI. No patient was older than 85 years. The safety profile of GLYXAMBI did not differ in the elderly. Based on empagliflozin experiences, elderly patients may be at increased risk of volume depletion (see sections 4.2, 4.4 and 5.2).

4.9 Overdose

In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent.

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were generally 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. Linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of oral blood glucose lowering drugs, ATC code: A10BD19

Mechanism of action

GLYXAMBI combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: empagliflozin, a sodium-glucose co-transporter (SGLT2) inhibitor, and linagliptin, DPP-4 inhibitor.

Empagliflozin

Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of SGLT2. Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5,000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut.

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

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

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

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

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 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 glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in the glucose homeostasis. Linagliptin binds selectively to DPP-4 and exhibits a > 10,000-fold selectivity versus DPP-8 or DPP-9 activity *in vitro*.

Clinical efficacy and safety

A total of 2,173 patients with type 2 diabetes mellitus and inadequate glycaemic control were treated in clinical studies to evaluate the safety and efficacy of GLYXAMBI; 1,005 patients were treated with GLYXAMBI 10 mg empagliflozin/5 mg linagliptin or 25 mg empagliflozin/5 mg linagliptin**.** 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 were treated for 24-weeks with GLYXAMBI 10 mg/5 mg, GLYXAMBI 25 mg/5 mg, empagliflozin 10 mg, empagliflozin 25 mg or linagliptin 5 mg. The treatment with GLYXAMBI resulted in statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) compared to linagliptin 5 mg and also compared to empagliflozin 10 mg or 25 mg. GLYXAMBI also provided statistically significant improvements in body weight compared to linagliptin 5 mg.

Table 2 Efficacy parameters in clinical study comparing GLYXAMBI to individual active substances 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	--	--	--

[1] Last observation (prior to glycaemic rescue) carried forward (LOCF)
[2] Mean adjusted for baseline value and stratification

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

Overall, the effects on HbA_{1c} reduction observed at 24 weeks were sustained at week 52.

Empagliflozin in patients inadequately controlled on metformin and linagliptin

In patients inadequately controlled on maximally tolerated doses of metformin, open label linagliptin 5 mg was added for 16 weeks. In patients inadequately controlled after this 16 week period, patients received double-blind treatment with either empagliflozin 10 mg, empagliflozin 25 mg or placebo for 24-weeks. After this double-blind period, treatment with both empagliflozin 10 mg and empagliflozin 25 mg provided statistically significant improvements in HbA_{1c}, FPG and body weight compared to placebo; all patients continued treatment with metformin and linagliptin 5 mg during the study. A statistically significant greater number of patients with a baseline $HbA_{1c} \geq 7.0$ % treated with both doses of empagliflozin achieved a target HbA_{1c} of <7 % compared to placebo (see Table 3). After 24-weeks treatment with empagliflozin, 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 and -1.3/-0.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 10 mg.

After 24 weeks, rescue therapy was used in 4 (3.6 %) patients treated with empagliflozin 25 mg and in 2 (1.8 %) patients treated with empagliflozin 10 mg, compared to 13 (12.0 %) patients treated with

placebo (all patients on background metformin + linagliptin 5 mg).

Table 3 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	
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 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] Mixed-effects models for repeated measurements (MMRM) 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 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 and linagliptin 5 mg) and with empagliflozin 10 mg/ linagliptin 5 mg -1.3 % at 24 weeks (p<0.0001 versus placebo and linagliptin 5 mg).

Linagliptin 5 mg in patients inadequately controlled on metformin and empagliflozin 10 mg or empagliflozin 25 mg

In patients inadequately controlled on maximally tolerated doses of metformin, open label empagliflozin 10 mg or empagliflozin 25 mg was added for 16 weeks. In patients inadequately controlled after this 16 week period, patients received double-blind treatment with either linagliptin 5 mg or placebo for 24-weeks. After this double-blind period, treatment in both populations (metformin + empagliflozin 10 mg and metformin + empagliflozin 25 mg) linagliptin 5 mg provided statistically significant improvements in HbA_{1c} compared to placebo; all patients continued treatment with metformin and empagliflozin during the study. A statistically significant greater number of patients with a baseline HbA_{1c} ≥7.0 % and treated with linagliptin achieved a target HbA_{1c} of <7 % compared to placebo (see Table 4).

Table 4 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

	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	
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 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

Cardiovascular safety

Empagliflozin cardiovascular outcome (EMPA-REG OUTCOME) study

The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with type 2 diabetes and established cardiovascular disease. A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA_{1c} was 8.1 %, and 71.5 % were male. At baseline, 74 % of patients were being treated with metformin, 48 % with insulin, and 43 % with a sulphonylurea. About half of the patients (52.2 %) had an eGFR of 60-90 ml/min/1.73 m^2, 17.8 % of 45-60 ml/min/1.73 m^2 and 7.7 % of 30-45 ml/min/1.73 m^2.

At week 12, an adjusted mean (SE) improvement in HbA_{1c} when compared to baseline of 0.11 % (0.02) in the placebo group, 0.65 % (0.02) and 0.71 % (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA_{1c} of 0.08 % (0.02) in the placebo group, 0.50 % (0.02) and 0.55 % (0.02) in the empagliflozin 10 and 25 mg groups.

Empagliflozin was superior in reducing the primary combined endpoint of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg and confirmed by an improved overall survival (see Table 5).

Table 5 Treatment effect for the primary composite endpoint, its components and mortality[a]

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

CV = cardiovascular, MI = myocardial infarction

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

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

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

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

Heart failure requiring hospitalization

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

Nephropathy

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

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

Linagliptin cardiovascular and renal safety (CARMELINA) study

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

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

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

Linagliptin cardiovascular safety (CAROLINA) study

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.

Paediatric population

GLYXAMBI is not recommended for use in children below 18 years of age as the safety and effectiveness have not been established.

The clinical efficacy and safety of empagliflozin 10 mg with possible dose-increase to 25 mg or linagliptin 5 mg once daily has been studied in children and adolescents from 10 to 17 years with T2DM in a double-blind, randomised, placebo-controlled, parallel group study (DINAMO) over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks. The mean HbA1c was 8.03% at baseline. The primary endpoint of the study was the change in HbA1c from baseline to the end of 26 weeks, regardless of glycaemic rescue or treatment discontinuation.

Overall, the safety profile of empagliflozin and linagliptin was similar to that observed in the adult population treated with empagliflozin or linagliptin.

Empagliflozin:
Empagliflozin was superior to placebo in reducing HbA1c. The treatment difference of adjusted mean change in HbA1c between empagliflozin and placebo was -0.84% (95% CI -1.50, -0.19; p=0.0116). The adjusted mean change in HbA1c from baseline in patients treated with empagliflozin (N=52) was -0.17% and 0.68 % in patients treated with placebo (N=53).

Linagliptin:
Treatment with linagliptin did not provide significant improvement in HbA1c. The treatment difference of adjusted mean change in HbA1c between linagliptin and placebo was -0.34% (95% CI -0.99, 0.30; p=0.2935). The adjusted mean change in HbA1c from baseline was 0.33% in patients treated with linagliptin and 0.68% in patients treated with placebo.

5.2 Pharmacokinetic properties

Pharmacokinetics of the Fixed Dose Combination:

The rate and extent of absorption of empagliflozin and linagliptin in GLYXAMBI are equivalent to the bioavailability of empagliflozin and linagliptin when administered as individual tablets. The pharmacokinetics of empagliflozin and linagliptin as single agents have been extensively characterized in healthy subjects and patients with type 2 diabetes. Pharmacokinetics were generally similar in healthy subjects and in patients with type 2 diabetes.
GLYXAMBI showed a similar food effect as the individual active substances. GLYXAMBI can therefore be taken with or without food.

Pharmacokinetics of the single components:

Empagliflozin

Absorption

After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1.5 hours post dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma area under the concentration-time curve (AUC) and C_{max} were 1,870 nmol.h/L and 259 nmol/L with empagliflozin 10 mg and 4,740 nmol.h/L and 687 nmol/L with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose proportional manner. The single dose and steady state pharmacokinetic parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time.
Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16 % and C_{max} by approximately 37 % compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

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

Biotransformation

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-, 3-, and 6-O-glucuronide). Systemic exposure of

each metabolite was less than 10 % of total drug-related material. *In vitro* studies suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8 and UGT1A9.

Elimination

Based on the population pharmacokinetic analysis, the apparent terminal elimination half life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 L/hour. The inter subject and residual variabilities for empagliflozin oral clearance were 39.1 % and 35.8 %, respectively. With once daily dosing, steady state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with the half life, up to 22 % accumulation, with respect to plasma AUC, was observed at steady state.

Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, approximately 96 % of the drug-related radioactivity was eliminated in faeces (41 %) or urine (54 %). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Linagliptin

Absorption

After oral administration of a 5 mg dose to healthy volunteers or patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

After once daily dosing of 5 mg linagliptin, steady-state plasma concentrations are reached by the third dose. Plasma 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). Due to the concentration dependent binding of linagliptin to DPP-4, the pharmacokinetics of linagliptin based on total exposure is not linear; indeed total plasma AUC of linagliptin increased in a less than dose-proportional manner while unbound AUC increases in a roughly dose-proportional manner.

The absolute bioavailability of linagliptin is approximately 30 %. Co-administration of a high-fat meal with linagliptin prolonged the time to reach C_{max} by 2 hours and lowered C_{max} by 15 % but no influence on AUC_{0-72h} was observed. No clinically relevant effect of C_{max} and T_{max} changes is expected; therefore linagliptin may be administered with or without food.

The steady state plasma $AUC_{\tau,ss}$ and $C_{max,ss}$ concentrations of linagliptin were 153 nmol*hr/L and 12.9 nmol/L for linagliptin 5 mg once daily for 7 days.

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 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 high concentrations, where DPP-4 is fully saturated, 70-80 % of linagliptin was bound to other plasma proteins than DPP-4, hence 20-30 % were unbound in plasma.

Biotransformation

Following a [^{14}C] linagliptin oral 10 mg dose, approximately 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 which was found to be pharmacologically inactive and thus to not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Elimination

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 medicinal product. The effective half-life for accumulation of linagliptin, 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

Empagliflozin

In patients with mild, moderate or severe renal impairment (eGFR <30 to <90 mL/min/1.73 m^2) and patients with kidney failure or end stage renal disease (ESRD), AUC of empagliflozin increased by approximately 18 %, 20 %, 66 %, and 48 %, respectively compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20 % higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure (see section 4.2).

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 insufficiency compared to subjects with normal renal function. The study included patients with renal insufficiency 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 ESRD on haemodialysis. In addition patients with T2DM and severe renal impairment (<30 mL/min) were compared to T2DM patients with normal renal function. 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 T2DM patients with severe RI was increased by about 1.4-fold compared to T2DM patients with 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 (see section 4.2).

Hepatic impairment

Empagliflozin
In patients with mild, moderate and severe hepatic insufficiency (Child-Pugh classification), mean AUC and C_{max} of empagliflozin increased (AUC by 23 %, 47 %, 75 % and C_{max} by 4 %, 23 %,48 %) compared to subjects with normal hepatic function (see section 4.2).

Linagliptin
In non-diabetic 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 subjects following administration of multiple 5 mg doses of linagliptin.

Body mass index

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

Gender

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

Race

No clinically relevant difference in pharmacokinetics of empagliflozin and linagliptin were seen in population pharmacokinetic analysis and dedicated phase I studies.

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 80 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Paediatric patients

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

A paediatric Phase 3 trial examined the pharmacokinetics and pharmacodynamics (HbA1c change from baseline) of empagliflozin 10 mg with a possible dose-increase to 25 mg in children and adolescents 10 to 17 years of age with type 2 diabetes mellitus. The observed exposure-response relationship was overall comparable in adults and children and adolescents. Oral administration of empagliflozin resulted in exposure within the range observed in adult patients. The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 26.6 nmol/L and 308 nmol/L with empagliflozin 10 mg once daily and 67.0 nmol/L and 525 nmol/L with empagliflozin 25 mg once daily.

Linagliptin
A paediatric Phase 2 study examined the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA_{1c} (-0.63% vs -0.48%, n.s.). Due to the limited nature of the data set the results should be interpreted cautiously.

A paediatric Phase 3 trial examined the pharmacokinetics and pharmacodynamics (HbA1c change from baseline) of 5 mg linagliptin in children and adolescents 10 to 17 years of age with type 2

diabetes mellitus. The observed exposure-response relationship was overall comparable in paediatric and adult patients. Oral administration of linagliptin resulted in exposure within the range observed in adult patients. The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 4.30 nmol/L and 12.6 nmol/L, respectively.

Drug interactions

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

In vitro assessment of empagliflozin

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

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7.

Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not Organic Anion Transporter 1 (OAT1) and Organic Cation Transporter 2 (OCT2). Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

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

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

In vitro assessment of linagliptin

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.

5.3 Preclinical safety data

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and linagliptin.
Focal areas of hepatocellular necrosis were found in the combination groups at ≥15: 30 mg/kg linagliptin: empagliflozin (3.8 times the clinical exposure for linagliptin and 7.8 times the clinical exposure for empagliflozin) as well as in the group treated with empagliflozin alone but not in the control group. The clinical relevance of this finding remains uncertain.
At exposures sufficiently in excess of exposure in humans after therapeutic doses, the combination of empagliflozin and linagliptin was not teratogenic and did not show maternal toxicity. Adverse effects on renal development were not observed after administration of empagliflozin alone, linagliptin alone or after administration of the combined products.

Empagliflozin

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

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

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

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

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

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

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

Linagliptin

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

In long-term toxicity studies in rodents and Cynomolgus monkeys, signs of toxicity were observed at exposures greater than 300-times the clinical dose of linagliptin.

Liver, kidneys and gastrointestinal tract are the principal target organs of toxicity in mice and rats. At exposures greater than 1,500-times the clinical exposure, side effects on reproductive organs, thyroid and the lymphoid organs were seen in rats. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dog-specific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450-times the clinical exposure. At more than 100-times clinical exposure, irritation of the stomach was the major finding in monkeys.

Oral 2-year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (>200-times human exposure) is not considered relevant for humans. Based on these studies there is no concern for carcinogenicity in humans.

Linagliptin had no adverse effects on fertility or early embryonic development at exposures greater than 900-times the clinical exposure. Linagliptin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, linagliptin caused a slight retardation of skeletal ossification in the rat and increased embryofoetal loss in the rabbit.

In the pre- and postnatal toxicity study with linagliptin in rats, reduced weight gain in offspring was observed at maternal exposures approximately 1,500-times the maximal clinical exposure to linagliptin. No such effect was seen at systemic exposure 49-times the maximal clinical exposure to linagliptin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please refer to the packaging for information on shelf-life.

6.4 Special precaution for storage

Store below 30°C.

6.5 Nature and contents of container

Blister card of Aluminium-PVC/PVDC in cartons containing 30 film-coated tablets.

7. MANUFACTURER

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Ostenfelder Str. 51 – 61
59320 Ennigerloh
Germany

For
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

8. DATE OF REVISION

22 June 2026