Trajenta®

(linagliptin) 5mg tablets

TRAJENTA® is the only DPP-4 inhibitor with 2 cardiovascular outcome trials (CVOTs).

13,000 type 2 diabetes (T2D) adult patients

were included in CARMELINA® and CAROLINA®[1-6*]

CARMELINA®[1-3] T2D patients with established CV and/or kidney disease n=6,979 TRAJENTA vs. placebo

CAROLINA®[4-6] Relatively early T2D patients at increased CV risk n=6,033 TRAJENTA® vs. glimepiride

Recently, the long-term cardiovascular (CV) and kidney safety profile of TRAJENTA® has been comprehensively assessed via prespecified CARMELINA® and CAROLINA® subgroup analyses in

>2,000 patients aged 75 and older[3,6]

< 65 Years (6,026 Patients)

65 to 74 Years (4,929 Patients)

≥ 75 Years (2,057 Patients)

CARMELINA®[1-3]

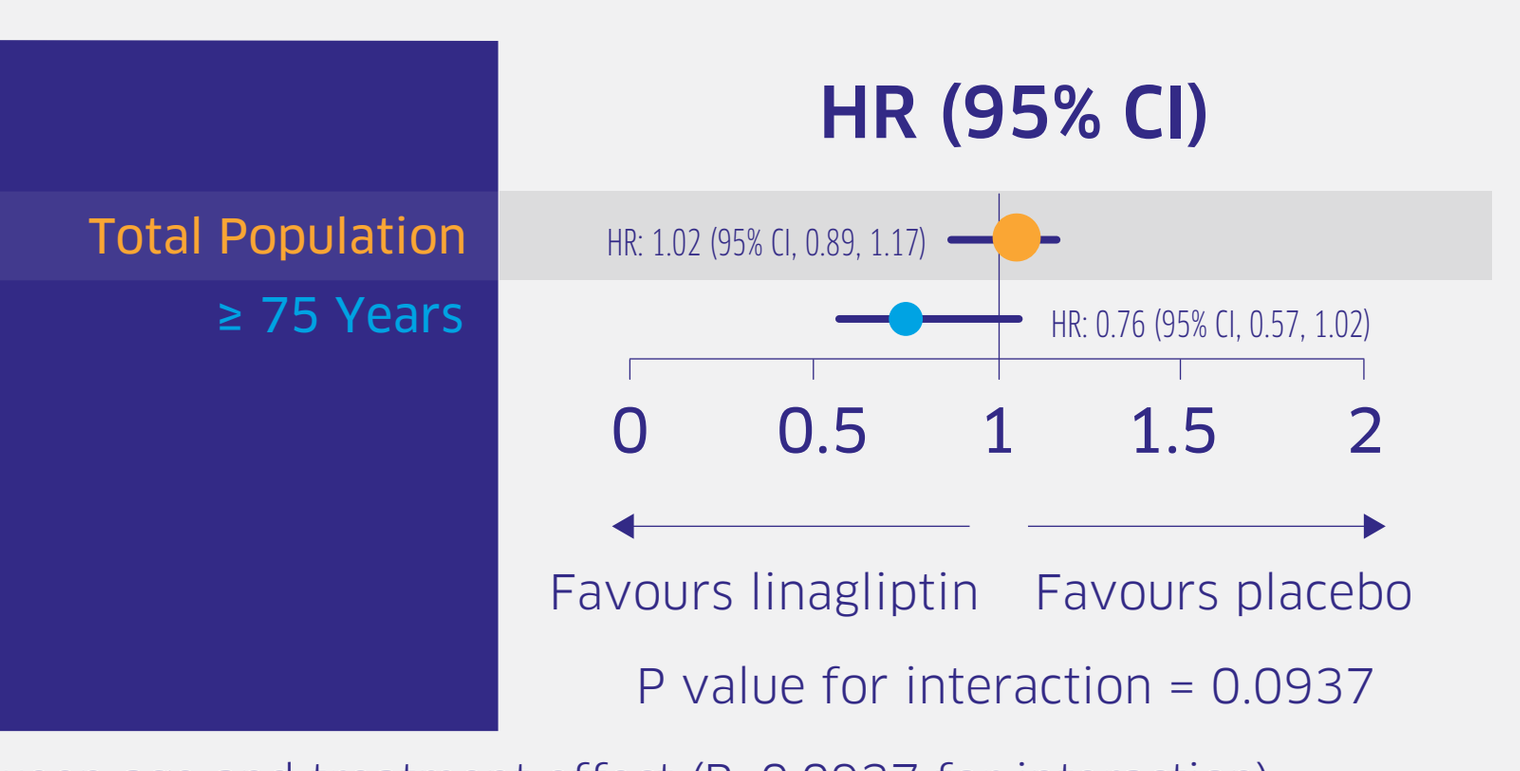
In CARMELINA®, TRAJENTA®

did not increase the risk

of CV or kidney events, compared to placebo, in adult patients including those aged 75 years or older[3†]

Primary Endpoint (3P-MACE)[‡]

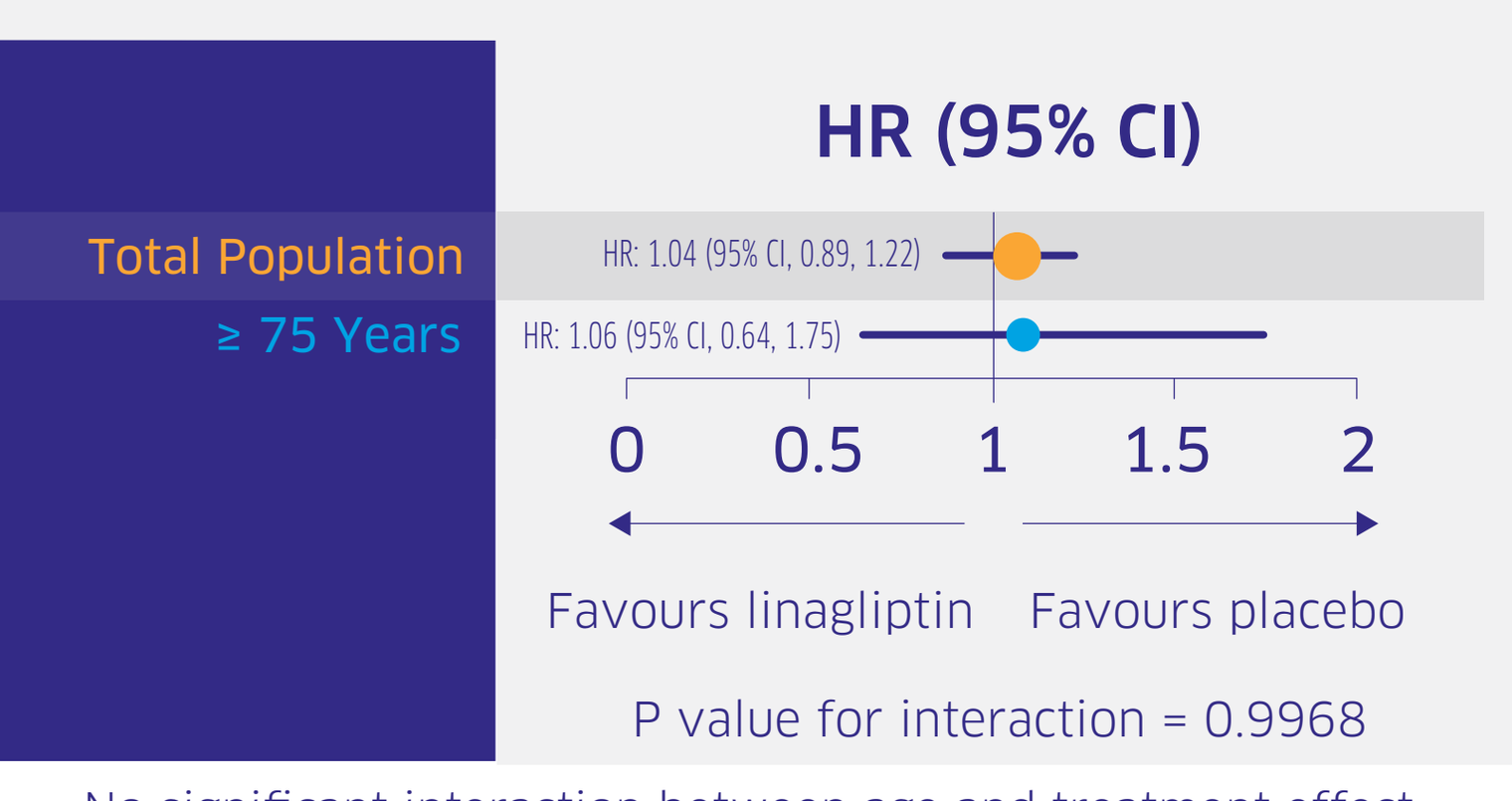
The primary endpoint occurred in 434/3,494 (12.4%) and 420/3,485 (12.1%) patients in the linagliptin and placebo groups, respectively



No significant interaction between age and treatment effect (P=0.0937 for interaction). Total population: P = 0.74 for superiority, p<0.001 for non inferiority

Key Secondary Endpoint (Kidney Outcome)[#]

The composite kidney outcome occurred in 327/3,494 (9.4%) and 306/3,485 (8.8%) patients in the linagliptin and placebo groups, respectively



No significant interaction between age and treatment effect (P=0.9968 for interaction). Total population: P = 0.62

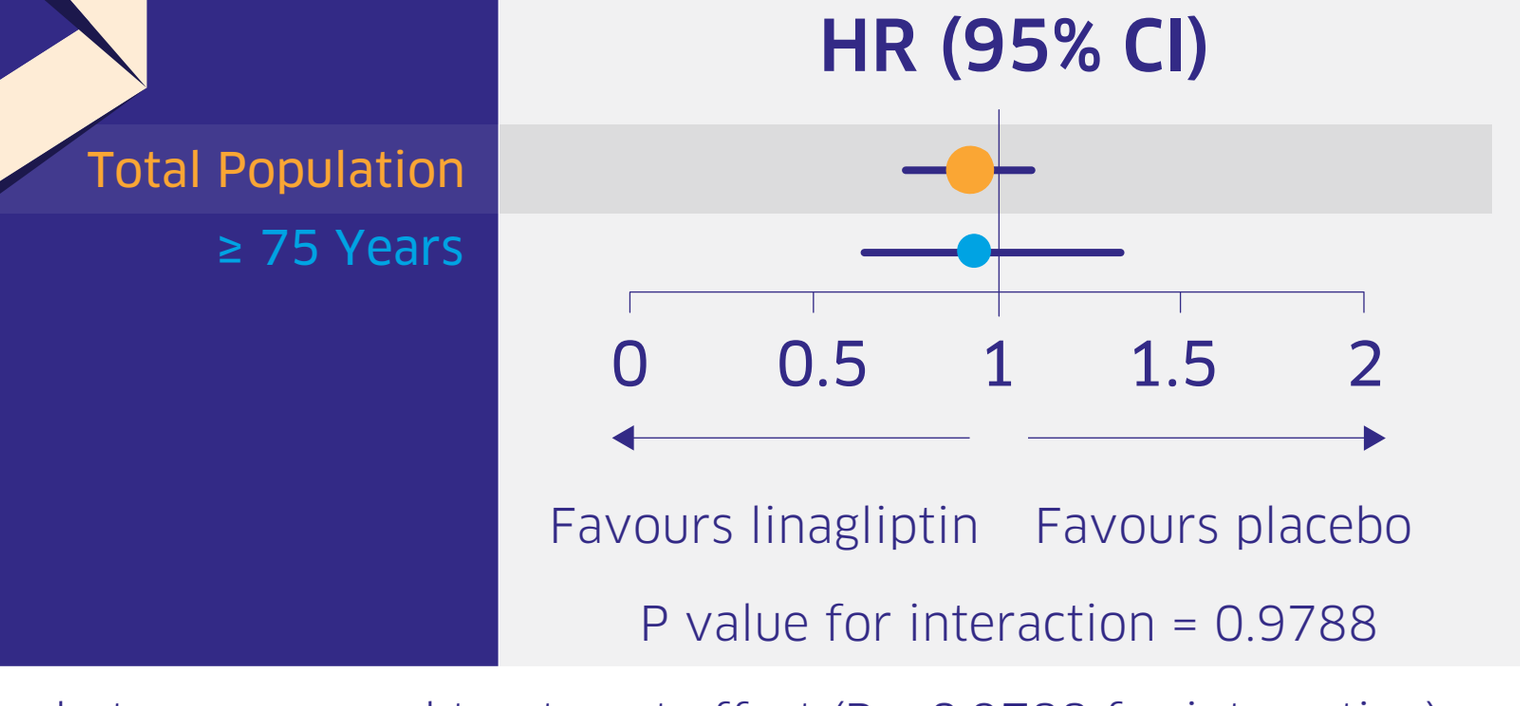
Furthermore, in adult patients including those aged 75 years or older in CARMELINA®, TRAJENTA® was

not associated with an increased risk

of hospitalisation for heart failure (HHF)[§] versus placebo

HR: 0.90 (95% CI, 0.74, 1.08); p = 0.26 for superiority for total population HR: 0.92 (95% CI, 0.63, 1.35) for patients ≥75 years

Exploratory Endpoint (HHF)[§]



No significant interaction between age and treatment effect (P = 0.9788 for interaction). Total population: P = 0.26

In 2020

CAROLINA®[4-6]

In CAROLINA®, TRAJENTA®

did not increase

the risk of CV events, compared to glimepiride, in adult patients including those aged 75 years or older[6†]

HR: 0.98 (95% CI, 0.84, 1.14); p = 0.76 for superiority, p <0.001 for non-inferiority for total population. HR: 0.99 (95% CI, 0.74, 1.31) for patients ≥75 years

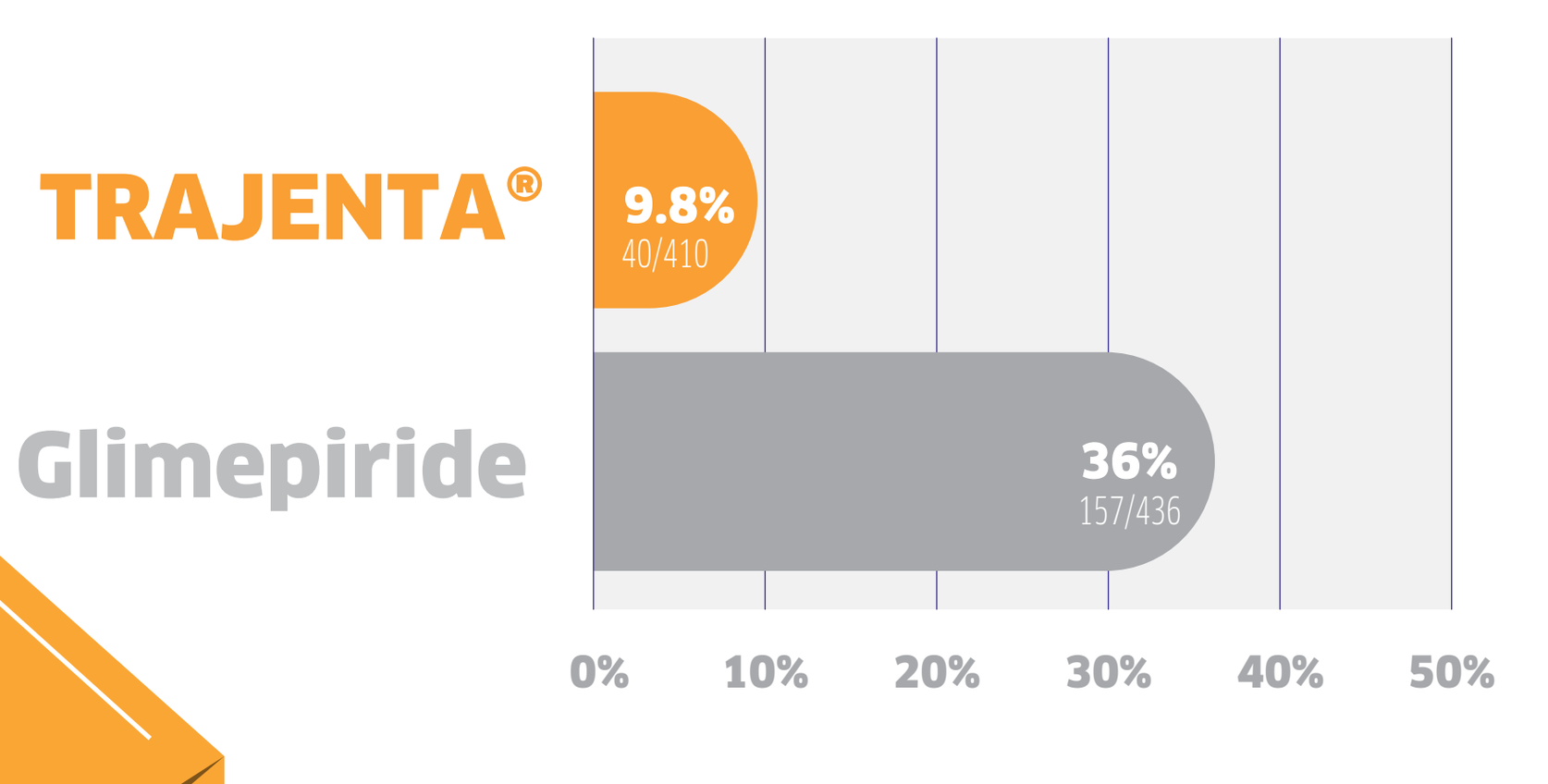
There was a

lower risk of hypoglycaemia

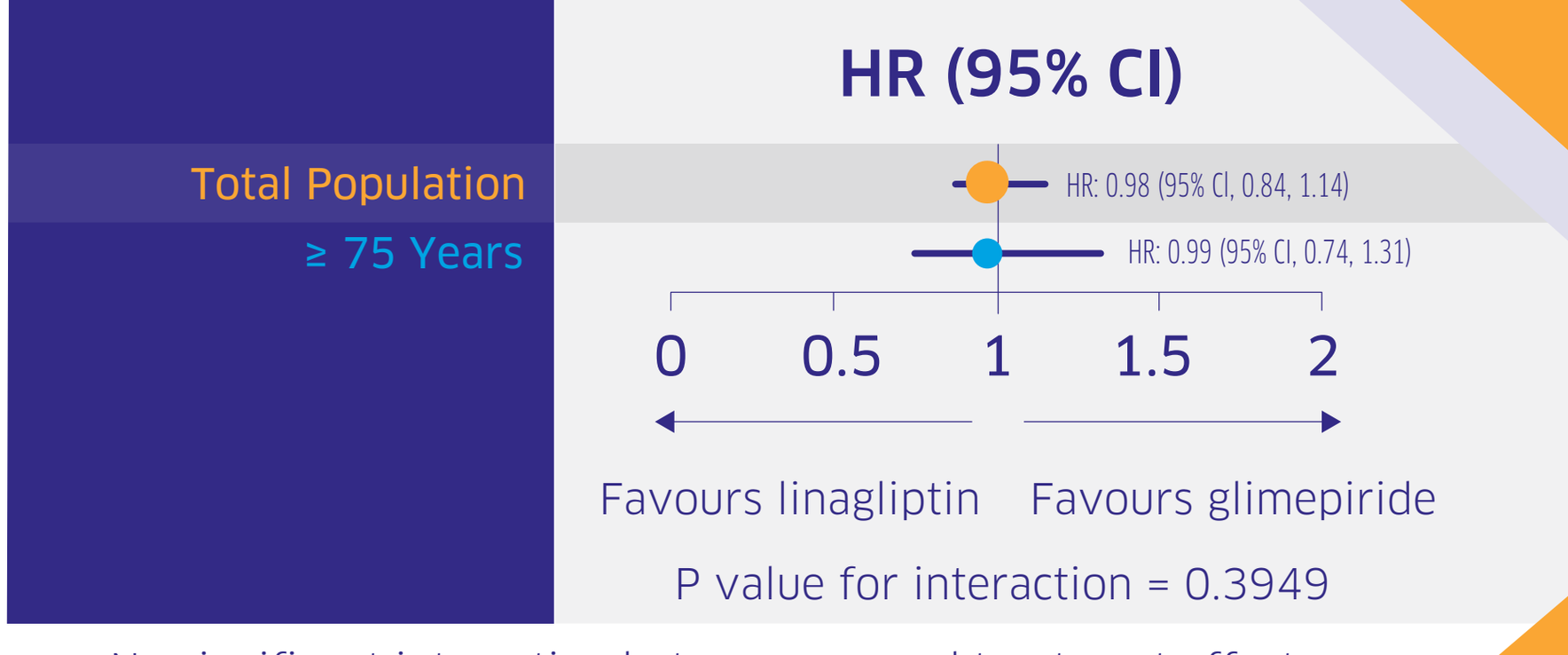
with TRAJENTA®, compared to glimepiride[5,6##]

Incidence of ≥1 episode of hypoglycaemic event was lower with linagliptin (n = 320 (10.6%)) vs. glimepiride (n = 1,132 (37.7%)) across all predefined hypoglycaemia-severity categories HR: 0.23 (95% CI, 0.21, 0.26)

Percent of patients aged 75 and older experiencing ≥1 hypoglycaemic event[##]



Primary Endpoint (3P-MACE)[††]



No significant interaction between age and treatment effect (P = 0.3949 for interaction). Total population: P = 0.76 for superiority, P<0.001 for non inferiority

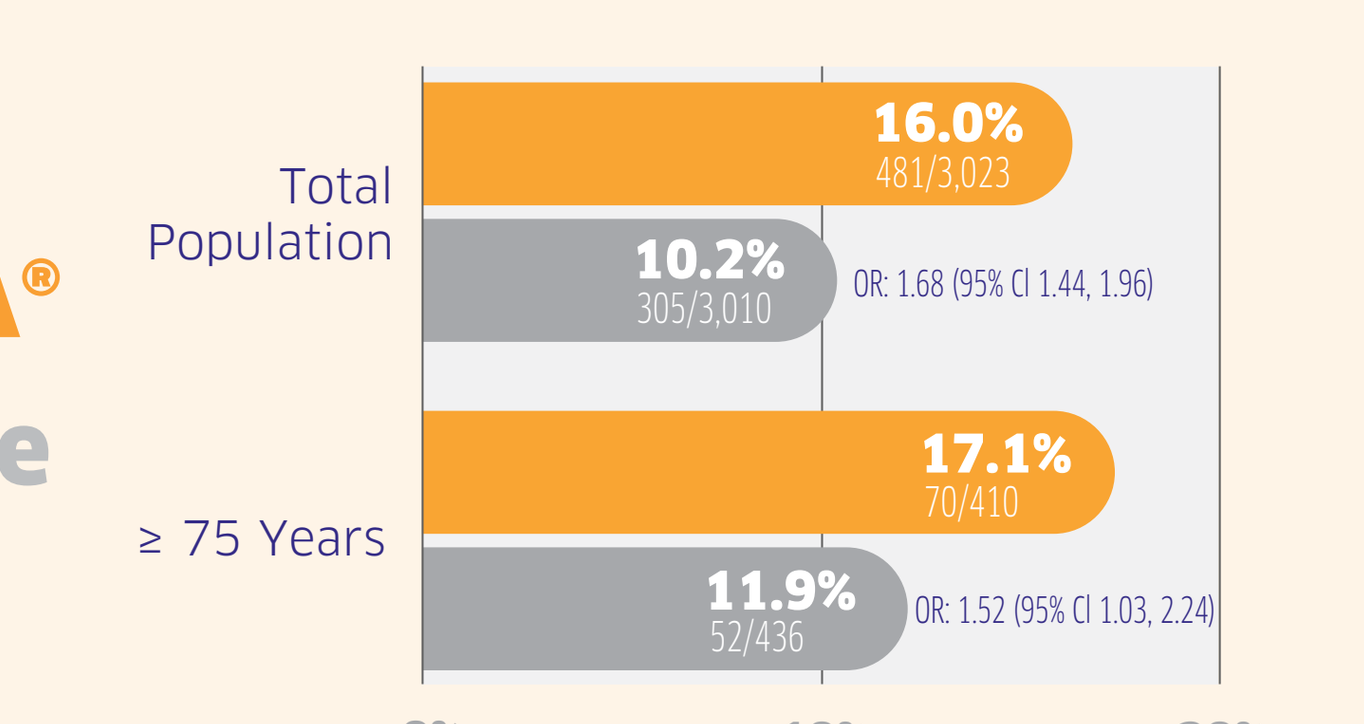
Percent of patients meeting the Composite Endpoint[‡‡]

(P value for interaction = 0.8446)

Importantly,

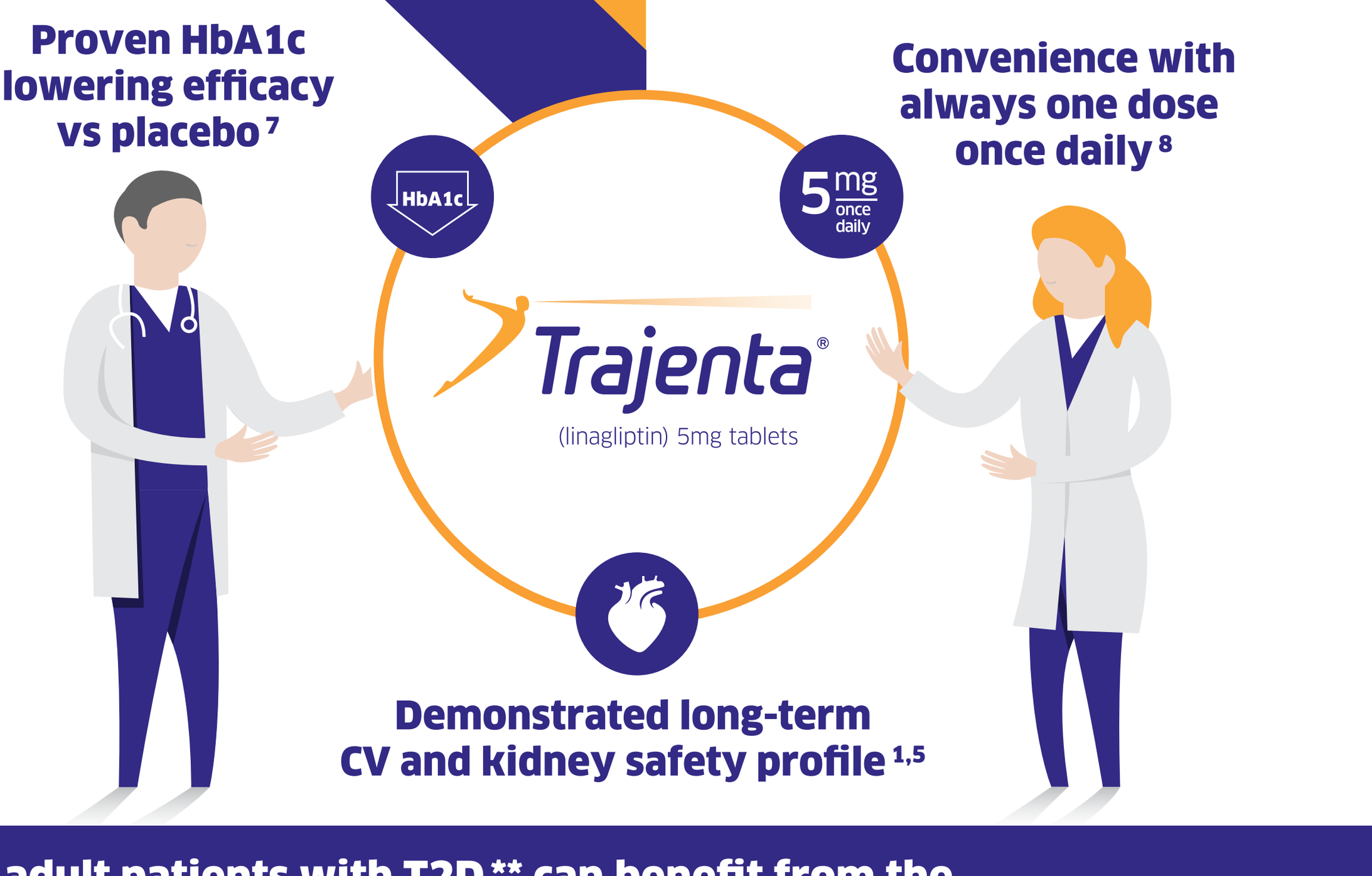
more patients

taking TRAJENTA® achieved target HbA1c without hypoglycaemia, weight gain and rescue medication vs glimepiride[‡‡]



Composite Endpoint[‡‡]
The proportion of participants with HbA1c ≤7.0% at the final visit without glycaemic rescue medication, without any episodes of moderate or severe hypoglycaemia and without >2% weight gain between the end of titration and final visit

TRAJENTA® is the only globally-available DPP-4i that combines proven efficacy, a demonstrated CV and kidney safety profile, and the unique convenience of always one dose, once daily



A broad range adult patients with T2D can benefit from the**

Simplicity of TRAJENTA®

Footnotes

* CARMELINA included 6,979 patients with albuminuria & previous macrovascular disease, and/or impaired kidney function with or without CV comorbidities. CAROLINA® included 6,033 patients with one or more of the following: a) previous vascular disease, b) evidence of vascular- related end-organ damage, c) age: ≥ 70 years and d) ≥ 2 CV risk factors (smoking, hypertension, T2D duration ≥ 10 years, dyslipidemia).

† When added to standard of care.

‡ The CARMELINA primary endpoint was time to first occurrence of any of the following components: CV death, non-fatal MI, non-fatal stroke. The primary endpoint occurred in 434/3,494 (12.4%) and 420/3,485 (12.1%) patients in the linagliptin and placebo groups, respectively (HR 1.02; 95% CI 0.89, 1.17). HR for time to 3P-MACE based on Cox regression analyses in patients treated with at least 1 dose of study drug (for < 65 years, HR: 1.11 (95% CI, 0.89, 1.40), for 65 to 74 years, HR: 1.09 (95% CI, 0.89, 1.33), for ≥ 75 years, HR: 0.76 (95% CI, 0.57, 1.02)). P value for treatment by age interaction = 0.0937. Median observation time was 2.2 (IQR, 1.5-2.9) years for Trajenta® and 2.2 (IQR, 1.5-2.8) years for placebo.

\# The CARMELINA key secondary endpoint was time to first occurrence of any of the following components: Death due to kidney disease, sustained ESRD or a sustained decrease of ≥40% in eGFR from baseline. HR for time to secondary kidney endpoint based on Cox regression analyses in patients treated with at least one dose of study drug (for < 65 years, HR: 1.05 (95% CI, 0.85, 1.29), for 65 to 74 years, HR: 1.06 (95% CI, 0.81, 1.38), for ≥ 75 years, HR: 1.06 (95% CI, 0.64, 1.75)). P value for treatment by age interaction = 0.9968. Median observation time was 1.9 (IQR, 1.2-2.6) years for Trajenta® and 1.7 (IQR, 1.2-2.5) years for placebo.

§ HHF was an exploratory endpoint. HHF occurred in 209/3,494 (6.0%) vs 226/3,485 (6.5%) patients in the linagliptin and placebo groups, respectively (HR: 0.90 (95% CI, 0.74, 1.08) p=0.26). HR based on Cox regression analyses in patients treated with at least one dose of study drug (for < 65 years, HR: 0.87 (95% CI, 0.63, 1.21), for 65 to 74 years, HR: 0.89 (95% CI, 0.67, 1.18), for ≥ 75 years, HR: 0.92 (95% CI, 0.63, 1.35)). P value for treatment by age interaction = 0.9788.

** Trajenta® is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy, when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy, in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control.

†† The CAROLINA primary endpoint was defined as non-inferiority of Trajenta® vs glimepiride in time to first occurrence of CV death, non-fatal MI, or non-fatal stroke. The primary endpoint occurred in 356/3,023 (11.8%) and 362/3,010 (12.0%) patients in the linagliptin and glimepiride groups, respectively (HR 0.98; 95% CI 0.84, 1.14). The HRs for 3P-MACE for linagliptin compared with glimepiride were 1.11 [95% CI 0.88,1.41] for patients aged <65 years, 0.88 [0.69,1.12] for those aged 65 to 74 years, and 0.99 [0.74,1.31] for those aged ≥ 75 years. P value for treatment by age interaction = 0.3949. Overall median observation time and treatment duration were 6.3 and 5.9 years, respectively, in the linagliptin and glimepiride groups. Median observation times across age groups were very similar, while median treatment time declined slightly with age (6.1, 5.8, and 5.5 years in participants aged <65, 65 to 74 and ≥ 75 years, respectively).

‡‡ The CAROLINA key secondary endpoint was a composite endpoint of treatment sustainability: the proportion of participants with HbA1c 7.0% at the final visit without glycaemic rescue medication, without any episodes of moderate or severe hypoglycaemia and without >2% weight gain between the end of titration and final visit. The key secondary endpoint occurred in 16.0% and 10.2% of patients in the linagliptin and glimepiride groups, respectively (OR 1.68; 95% CI, 1.43, 1.96). For patients < 65 years, the key secondary endpoint occurred in 14.0% and 8.6% of patients in the linagliptin and glimepiride groups, respectively (OR 1.73; 95% CI, 1.37, 2.18); for patients 65 to 74 years, the key secondary endpoint occurred in 18.5% and 11.7% of patients in the linagliptin and glimepiride groups, respectively (OR 1.71; 95% CI, 1.34, 2.18); for patients ≥ 75 years, the key secondary endpoint occurred in 17.1% and 11.9% of patients in the linagliptin and glimepiride groups, respectively (OR 1.52; 95% CI, 1.03, 2.24); P value for treatment by age interaction = 0.8446.

\#\# The risk for moderate or severe hypoglycaemia in the overall study cohort was substantially lower with linagliptin than glimepiride (HR=0.18 [95% CI 0.15,0.21]) with no evidence of heterogeneity across age groups (P=0.23 for treatment-by-age-group interaction); Moderate: Investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL; Severe: Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Kaplan-Meier estimate; HR and 95% CI derived from Cox regression with factor treatment; 2-sided p-value.

Abbreviations

CI: Confidence intervals; **CV:** Cardiovascular; **DPP-4:** Dipeptidyl-peptidase 4; **eGFR:** Estimated glomerular filtration rate; **ESRD:** End stage renal disease; **HHF:** Hospitalisation for heart failure; **HR:** Hazard ratio; **IQR:** interquartile range; **MI**: myocardial infarction; **OR:** Odds ratio

References

1. Rosenstock J, et al. JAMA 2019; 321: 69-79. **2.** Rosenstock J, et al. Cardiovasc Diabetol 2018; 17:39. **3.** Cooper M, et al. Diabetes Obes Metab. 2020; 1–12.**4.** Marx N, et al. Diab Vasc Res. 2015; 12: 164-74. **5.** Rosenstock J, et al. JAMA. 2019;322(12):1155–1166. **6.** Espeland MA, et al. Diab Obes Met 2020. doi: 10.1111/dom.14254.**7.** Del Prato S, et al. J Diab Compl. 2013; 27:274-9. **8.** TRAJENTA® (linagliptin) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/4762/smpc.

Prescribing Information (UK) TRAJENTA® (Linagliptin)

Film-coated tablets containing 5 mg linagliptin. **Indication:** Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Dose and Administration:** 5 mg once daily. If added to metformin, the dose of metformin should be maintained and linagliptin administered concomitantly. When 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. **Renal impairment:** no dose adjustment required. **Hepatic impairment:** pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. **Elderly:** no dose adjustment is necessary based on age. **Paediatric population:** the safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. Take the tablets with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as possible but a double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin; a dose reduction of the sulphonylurea or insulin may be considered. Acute pancreatitis has been observed in patients taking linagliptin. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Bullous pemphigoid has been observed in patients taking Linagliptin. If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interactions:** 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. Based on these results and in vivo interaction studies, linagliptin is considered unlikely to cause interactions with other P-glycoprotein substrates. The risk for clinically meaningful interactions by other medicinal products on linagliptin is low and in clinical studies linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, warfarin, digoxin or oral contraceptives (please refer to Summary of Product Characteristics for information on clinical data). **Fertility, pregnancy and lactation:** Avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for linagliptin. **Undesirable effects:** Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies in clinical trials and from post-marketing experience. 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). ***Adverse reactions with linagliptin 5 mg daily as monotherapy:*** Common: lipase increased. Uncommon: nasopharyngitis; hypersensitivity; cough; rash; amylase increased. Rare: pancreatitis; angioedema; urticaria; bullous pemphigoid. ***Adverse reaction with linagliptin in combination with metformin plus sulphonylurea:*** Very common: hypoglycaemia. ***Adverse reaction with linagliptin in combination with insulin:*** Uncommon: constipation. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 28 tablets £33.26. **Legal category:** POM. **MA number:** EU/1/11/707/003. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. Prepared in December 2019.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone).

Prescribing Information (Ireland) TRAJENTA® (Linagliptin)

Film-coated tablets containing 5 mg linagliptin. **Indication:** Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment; combination therapy in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Dose and Administration:** 5 mg once daily. If added to metformin, the dose of metformin should be maintained and linagliptin administered concomitantly. When 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. **Renal impairment:** no dose adjustment required. **Hepatic impairment:** pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. **Elderly:** no dose adjustment is necessary based on age. **Paediatric population:** the safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. Take the tablets with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as possible but a double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin; a dose reduction of the sulphonylurea or insulin may be considered. Acute pancreatitis has been observed in patients taking linagliptin. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis. Bullous pemphigoid has been observed in patients taking Linagliptin. If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interactions:** 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. Based on these results and in vivo interaction studies, linagliptin is considered unlikely to cause interactions with other P-glycoprotein substrates. The risk for clinically meaningful interactions by other medicinal products on linagliptin is low and in clinical studies linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, warfarin, digoxin or oral contraceptives (please refer to Summary of Product Characteristics for information on clinical data). **Fertility, pregnancy and lactation:** Avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No studies on the effect on human fertility have been conducted for linagliptin. **Undesirable effects:** Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies in clinical trials and from post-marketing experience. 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). ***Adverse reactions with linagliptin 5 mg daily as monotherapy:*** Common: lipase increased. Uncommon: nasopharyngitis; hypersensitivity; cough; rash; amylase increased. Rare: pancreatitis; angioedema; urticaria; bullous pemphigoid. ***Adverse reaction with linagliptin in combination with metformin plus sulphonylurea:*** Very common: hypoglycaemia. ***Adverse reaction with linagliptin in combination with insulin:*** Uncommon: constipation. Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes:** 28 tablets. **Legal category:** POM. **MA number:** EU/1/11/707/003. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. Additional information is available on request from Boehringer Ingelheim Ireland Ltd, The Crescent Building, Northwood, Santry, Dublin 9. Prepared in December 2019.

Adverse events should be reported. Reporting forms and information can be found https://www.hpra.ie/homepage/about-us/report-an-issue.
Adverse events should also be reported to Boehringer-Ingelheim Drug Safety on 01 2913960, Fax: +44 1344 742661, or by e-mail: PV_local_UK_Ireland@boehringer-ingelheim.com