10 YEARS OF SIMPLICITY.

Trajenta® (linagliptin 5mg tablets)

Jentadueto® (linagliptin/metformin HCl)

Start your journey and explore the key milestones for Trajenta® from registration to present.

2011

Trajenta® becomes registered in more than 30 countries around the world, as a once-daily, always one-dose, DPP4i for the treatment of type 2 diabetes[1]. In subsequent years, Trajenta® would become available in many more countries around the world.

Trajenta® (linagliptin 5mg tablets)

2012

The linagliptin family of products continues to grow. **Jentadueto® becomes available** to healthcare professionals around the world[2] as a fixed-dose combination of linagliptin + metformin for the treatment of type 2 diabetes[2].

Jentadueto® (linagliptin/metformin HCl)

0.5% incremental reduction in HbA_{1c} with linagliptin plus metformin compared to metformin alone[3]

(95% CI, -0.7%, -0.3%; p<0.0001)

2013

With CAROLINA underway, the CARMELINA trial begins. This second CVOT for Trajenta® ends up enrolling **nearly 7,000 T2D patients with established CV and/or kidney disease**. CARMELINA monitors the long term CV and kidney safety profile of Trajenta® vs. placebo. With CARMELINA, linagliptin becomes the only DPP4i to perform more than one CVOT[7].

CARMELINA®

2014

A meta-analysis of 83 randomized controlled trials encompassing about 50,000 subjects shows that linagliptin has **similar efficacy to other DPP4 inhibitors** in the study[4].

A key publication by Groop et al. shows that Trajenta® has **consistent efficacy regardless of kidney function**[5], with similar reduction in HbA_{1c} at eGFR levels of ≥90, 60 to 90, or 30 to 60.

2015

The linagliptin family of products continues to grow. **Glyxambi® becomes registered in the US** as a fixed-dose combination of linagliptin + empagliflozin for the treatment of T2D. The following year, Glyxambi® becomes registered in the EU[6].

Glyxambi® (empagliflozin/linagliptin tablets) Boehringer Ingelheim

2016

A key publication by Inagaki et al. shows that Trajenta® has consistent efficacy **regardless of hepatic function**[8].

A key publication by Ross et al. shows that Trajenta® has consistent efficacy **regardless of BMI**, in a prespecified subgroup analysis[9].

2018

The Trajenta® cardiovascular outcome trial (CVOT) program wraps up after tracking patients for several years. Two CVOTs (CARMELINA and CAROLINA) demonstrate the CV and kidney safety profile of Trajenta® in a broad range of **more than 13,000 T2D patients**[7-10].

Over **13,000** T2D patients in 2 CVOTs[7-10]

CARMELINA®

CAROLINA®

Results from CARMELINA, a 2+ year study in T2D patients with **established CV and/or kidney disease**, are released in October 2018[11]. CARMELINA demonstrated that Trajenta® did not increase the risk of CV events, adverse kidney outcomes, or hospitalisation for heart failure, compared to placebo[11].

The data continues to impress. Following the first release of CARMELINA results, **additional subgroup analyses** are published, shedding light on the safety profile of linagliptin for a variety of patient situations.

In October, a subgroup analysis by Inagaki et al. confirmed the results of CARMELINA **in Asian T2D patients**[12].

2019

Results from CAROLINA, a 6+ year study in relatively **early T2D patients** at increased CV risk, are released in June 2019[10]. CAROLINA demonstrated that Trajenta® did not increase the risk of CV events vs. glimepiride (primary endpoint)[10]. Also, significantly more patients taking Trajenta® vs. glimepiride achieved target HbA_{1c} without hypoglycaemia, weight gain and increased rescue medication (key secondary endpoint)[10].

Note that Trajenta® is not indicated for the prevention of hypoglycaemic events nor for the prevention of weight gain.

2020

In February, a subgroup analysis by Cooper et al. confirmed the results of CARMELINA **in Elderly T2D patients**[13].

In May, a subgroup analysis by Perkovic et al. demonstrated that Trajenta® compared to placebo did not increase the risk of CV and kidney events, **regardless of baseline kidney function**[14]. Furthermore, there was a significant reduction in risk for albuminuria progression for patients taking Trajenta® compared to placebo, in CARMELINA.

Note that Trajenta® is not indicated for the reduction of albuminuria.

In June, a subgroup analysis by Kadowaki et al. confirmed the results of CAROLINA **in Asian T2D patients**[15].

In December, a subgroup analysis by Espeland et al. confirmed the results of CAROLINA **in Elderly T2D patients**[16].

2021

Happy 10 Year Anniversary Trajenta®

After 10 years, Trajenta® and the linagliptin family of products continue to remain important therapeutics for the treatments of a broad range of T2D patients.

10 YEARS OF SIMPLICITY

In the past 10 years, linagliptin has had **more than 20 million patient-years of exposure**[18], and it continues to be an important tool for healthcare professionals worldwide[19].

2022

Footnotes

* 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). CAROLINA assessed the CV safety profile of linagliptin vs. glimepiride. † Tradjenta® was approved by the US Food and Drug Administration (FDA) on May 2nd, 2011; Trazenta® was approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) on July 1st, 2011; Trajenta® was approved by the European Medicines Agency (EMA) on August 23rd, 2011; Trajenta® was approved by Health Canada on October 3rd, 2011; Trajenta® was approved by the Australian Therapeutic Goods Administration (TGA) on October 21st, 2011. ‡ Jentadueto® was approved by the US Food and Drug Administration (FDA) on January 30th, 2012; Jentadueto® was approved by the European Medicines Agency (EMA) on July 20th, 2012. § 24-week, double-blind, placebo-controlled, Phase III trial. Two arms received linagliptin 2.5 mg twice daily (BID) + either low (500 mg) or high (1,000 mg) dose metformin BID. Four arms received linagliptin 5 mg once daily, metformin 500 mg or 1,000 mg BID or placebo. Patients with HbA1C ≥ 11.0% were not eligible for randomization and received open-label linagliptin + high-dose metformin. High baseline defined as HbA_{1c} > 8.5% to < 11.0%. # CARMELINA included 6,979 patients with albuminuria & previous macrovascular disease, and/or impaired kidney function with or without CV comorbidities. CARMELINA assessed the CV and kidney safety profile of linagliptin vs. placebo. ** A systematic review of RCTs, health economic evaluation studies, systematic reviews, and meta-analyses, followed by primary Bayesian mixed treatment comparison meta-analyses and secondary frequentist direct comparison meta-analyses using a random effects model to compare the safety and efficacy of DPP4i in patients with T2D and inadequate glycaemic control. The weighted mean HbA_{1c} change from baseline (95% CrI) for each DPP4i as monotherapy was: for linagliptin, -0.74 (-0.96 to -0.51); for alogliptin, -0.74 (-0.99 to -0.49); for saxagliptin, -0.61 (-0.91 to -0.31); for sitagliptin, -0.75 (-0.90 to -0.60); and for vildagliptin, -0.67 (-0.87 to -0.47). †† Prespecified subgroup analysis on pooled data from three pivotal Phase III, randomised, placebo-controlled trials; treatment in monotherapy, add-on to metformin, and add-on to metformin plus sulphonylurea. Adjusted mean HbA_{1c} change from baseline with linagliptin was -0.63% (p<0.0001) in patients with a baseline eGFR ≥ 90 mL/min/1.73m², -0.67% (p<0.0001) in patients with a baseline eGFR ≥ 60 and < 90 mL/min/1.73m², and -0.53% (p<0.01) in patients with a baseline eGFR ≥ 30 and < 60 mL/min/1.73m². ‡‡ Glyxambi® was approved by the US Food and Drug Administration (FDA) on January 30th, 2015; Glyxambi® was approved by the European Medicines Agency (EMA) on November 11th, 2016. §§ Pooled analysis of 17 trials with study duration ≥ 24 weeks; FAS (LOCF), all participants who had a baseline and at least one on-treatment HbA_{1c} measurement. Adjusted mean HbA_{1c} change from baseline with linagliptin was -0.54% (95% CI -0.72, -0.36; p<0.0001) in patients with hepatobiliary disorders (including hepatic steatosis, cholelithiasis, liver disorder, hepatomegaly, gallbladder polyp and chronic hepatitis), and -0.62% (95% CI -0.67, -0.57; p<0.0001) in patients without hepatobiliary disorders. ## Mean HbA_{1c} change (unadjusted) from baseline, at 24 weeks, with linagliptin was -2.0% in patients with BMI < 25 mg/m², -1.9% in patients with BMI ≥ 25 to < 30 mg/m², -2.0% in patients with BMI ≥ 30 to < 35 mg/m², and -2.2% in patients with BMI ≥ 35 mg/m². *** The CARMELINA primary endpoint was time to first occurrence of any of the following components: CV death, death, non-fatal MI, non-fatal stroke; 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; hospitalisation for heart failure was an exploratory outcome. ††† The CAROLINA primary endpoint was time to first occurrence of any of the following components: CV death, non-fatal MI, non-fatal stroke; the CAROLINA key secondary endpoint was a composite endpoint of treatment sustainability: the proportion of participants with HbA_{1c} ≤ 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; because the confirmatory test for superiority of the primary outcome, 3P-MACE, in the overall population was not significant, all subsequent analyses are considered exploratory.

Abbreviations

BMI: body mass index; **CI**: confidence interval; **CrI**: credible interval; **CV**: cardiovascular; **CVOT**: cardiovascular outcome trial; **DPP4i**: dipeptidyl peptidase-4 inhibitor; **eGFR**: estimated glomerular filtration rate; **ESRD**: end stage renal disease; **FAS**: full analysis set; **HR**: Hazard Ratio; **LOCF**: last outcome carried forward; **OR**: Odds Ratio; **RCT**: randomized controlled trial; **T2D**: type 2 diabetes.

References

1. Jentadueto® EMA Summary of Product Characteristics, October 2019. **2.** Haak T, et al. Diabetes Obes Metab. 2012;14:565–74. **3.** Craddy P, et al. Diabetes Ther 2014;5:1-41. **4.** Groop P, et al. Diabetes Obes Metab. 2014; 16:560-8. **5.** Inagaki N, et al. J Diabetes Complications. 2016; 30(8):1622-1630. **6.** Ross S et al. Postgrad Med. 2016; 128(8):747-754. **7.** Rosenstock J, et al. JAMA 2019; 321: 69-79. **8.** Rosenstock J, et al. Cardiovasc Diabetol 2018; 17:39. **9.** Marx N, et al. Diab Vasc Res. 2015; 12: 164-74. **10.** Rosenstock J, et al. JAMA. 2019; doi:10.1001/jama.2019.13772. **11.** Rosenstock J, et al. Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA®). Oral presentation at the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD), Thursday, 4 October 2018, 17:15 - 18:15, Langerhans Hall, Berlin Germany. **12.** Rosenstock J, et al. CAROLINA®: Cardiovascular safety and renal microvascular outcome with linagliptin in patients with T2D at high vascular risk. Oral presentation at the 79th Scientific Sessions of the American Diabetes Association (ADA), Monday, 10 June 2019, 16:30-18:30, San Francisco, CA, USA. **13.** Inagaki N, et al. Diabetol Int. 2019 Oct 22;11(2):129-141. **14.** Cooper M, et al. Diabetes Obes Metab. 2020; 1–12. **15.** Perkovic V, et al. Diabetes Care 2020 May; dc200279. https://doi.org/10.2337/dc20-0279. **16.** Kadowaki, T, et al. Diabetol Int. 2020. doi.org/10.1007/s13340-020-00447-5. **17.** Espeland MA, et al. Diab Obes Met 2020. doi: 10.1111/dom.14254. **18.** Boehringer Ingelheim. Data on file. **19.** American Diabetes Association. Diabetes Care 2021 Jan; 44(Supplement 1): S111-S124. https://doi.org/10.2337/dc21-S009. **20.** Trajenta® EMA Summary of Product Characteristics. October 2019.

Short version of the EU Summary of Product Characteristics (SPC) Medicinal Product: Trajenta® 5 mg film-coated tablets.

Each tablet contains 5 mg of linagliptin. For the full list of excipients, consult section 6.1. of the full SPC.
Therapeutic indications: Trajenta is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control as: a) monotherapy: when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. b) combination therapy: in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control. **Posology and method of administration: Posology:** The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained, and linagliptin administered concomitantly. When linagliptin 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. **Renal impairment:** For patients with renal impairment, no dose adjustment for linagliptin is 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. **Method of administration:** The tablets can be taken with or without a meal at any time of the day. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions for use:** Linagliptin should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. **Hypoglycaemia:** Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo. In clinical trials of linagliptin as part of combination therapy with medicinal products not known to cause hypoglycaemia (metformin), rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo. When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo. Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, 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:** Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Acute pancreatitis has been observed in patients taking linagliptin. In a cardiovascular and renal safety study (CARMELINA) with median observation period of 2.2 years, adjudicated acute pancreatitis was reported in 0.3% of patients treated with linagliptin and in 0.1% of patients treated with placebo. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, 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:** Bullous pemphigoid has been observed in patients taking linagliptin. In the CARMELINA study, bullous pemphigoid was reported h 0.2% of patients on treatment with linagliptin and in no patient on placebo. If bullous pemphigoid is suspected, Trajenta should be discontinued. **Interaction with other medicinal products and other forms of interaction:** Linagliptin is considered unlikely to cause interactions with other P-gp substrates. Clinical data suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low. For more detailed information on interactions with linagliptin, please consult the full version of the SPC. **Pregnancy and lactation: Pregnancy:** The use of linagliptin has not been studied in pregnant women. As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy. **Breast-feeding:** 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. **Effects on ability to drive and use machines:** Linagliptin has no or negligible influence on the ability to drive and use machines. However patients should be alerted to the risk of hypoglycaemia especially when combined with sulphonylurea and/or insulin. **Undesirable effects: Linagliptin 5 mg daily as monotherapy or as add-on therapy** (in clinical studies, post-marketing experience, or cardiovascular outcome trials): very common (a 1/10) -hypoglycaemia (observed in combination with metformin plus sulphonylurea); common (a 1/100 to <1/10) - lipase increased; uncommon (a 1/1,000 to < 1/100) - nasopharyngitis, hypersensitivity (e.g. bronchial hyperreactivity), cough, constipation (observed in combination with insulin), rash, amylase increased; rare (a 1/10,000 to < 1/1,000) - pancreatitis, angioedema, urticaria, bullous pemphigoid. **Reporting of suspected adverse reactions:** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting systems.

Revision date: October 2019