Trajenta®
(linagliptin) 5mg tablets

Have you seen a patient like Carol*?

*Hypothetical patient profile

Boehringer Ingelheim

Lilly

Carol*:

70 years old
Retired schoolteacher

*Hypothetical patient profile

CAROL*:
T2D patient with moderate renal impairment

Medical History

- T2D since 2007
- Hypertension
- Dyslipidemia
- Fluctuating eGFR

Physical Characteristics

- Height: 1.62 m
- Weight: 68 kg
- BMI: 26 kg/m^2
- BP: 146/92 mmHg

Notable Laboratory Results

- Fasting blood glucose: 165 mg/dL
- HbA_{1c}: 7.7%
- Total cholesterol: 250 mg/dL
- eGFR: 52 mL/min/1.73m^2

Clinic notes from today's visit

- Carol* visits her primary care physician twice a year to follow her hypertension and T2D
- Since retirement, Carol has a sedentary lifestyle. She does not feel very motivated to exercise
- She always remembers to take her medication
- Her lab tests show an increase in HbA_{1c} and diminishing renal function (CKD3a)
- eGFR values tend to fluctuate from one visit to another
- Physical exam revealed elevated blood pressure (despite her medication); stable weight

Current Medications

- Metformin (1,000 mg BD)
- Lisinopril (20 mg OD)
- Atorvastatin (20 mg OD)

What benefits does **TRAJENTA®** *offer a patient like Carol*?*

Because **TRAJENTA®** does not require dose reduction based on renal function, it provides a simple way to keep Carol* on a licensed dose (always 5 mg once daily), despite possible changes in the stage of renal impairment.[1,8-10]

*Hypothetical patient profile

BD: Bi-daily; BMI: Body mass index; BP: Blood pressure; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; OD: Once daily; T2D: Type 2 diabetes

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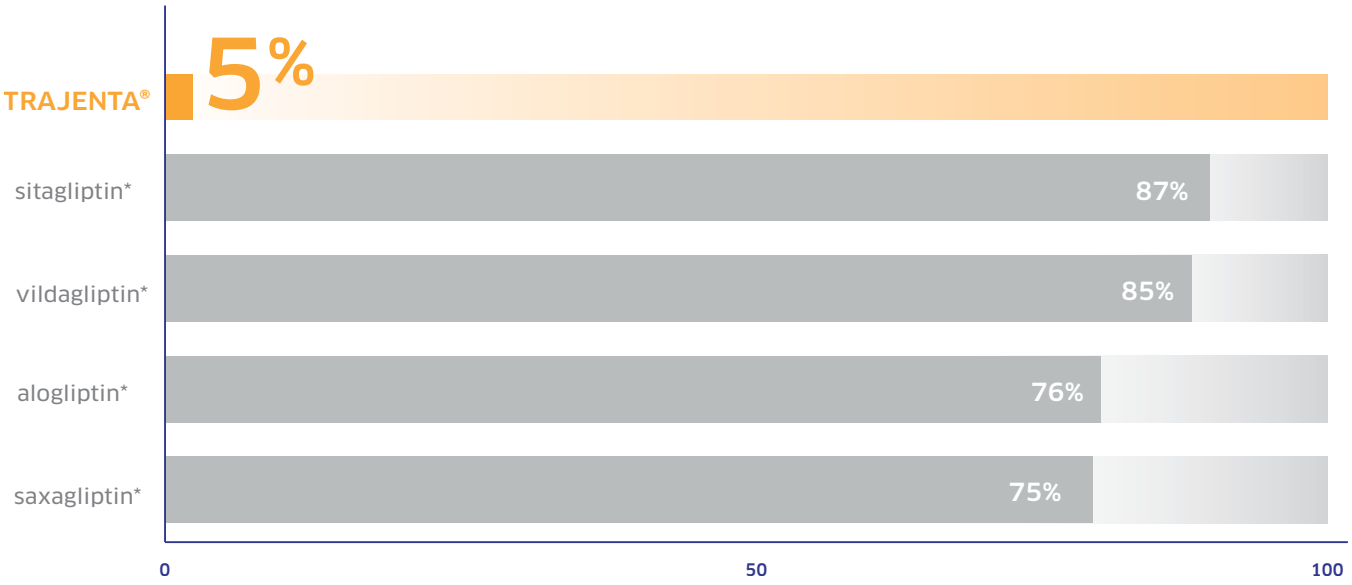
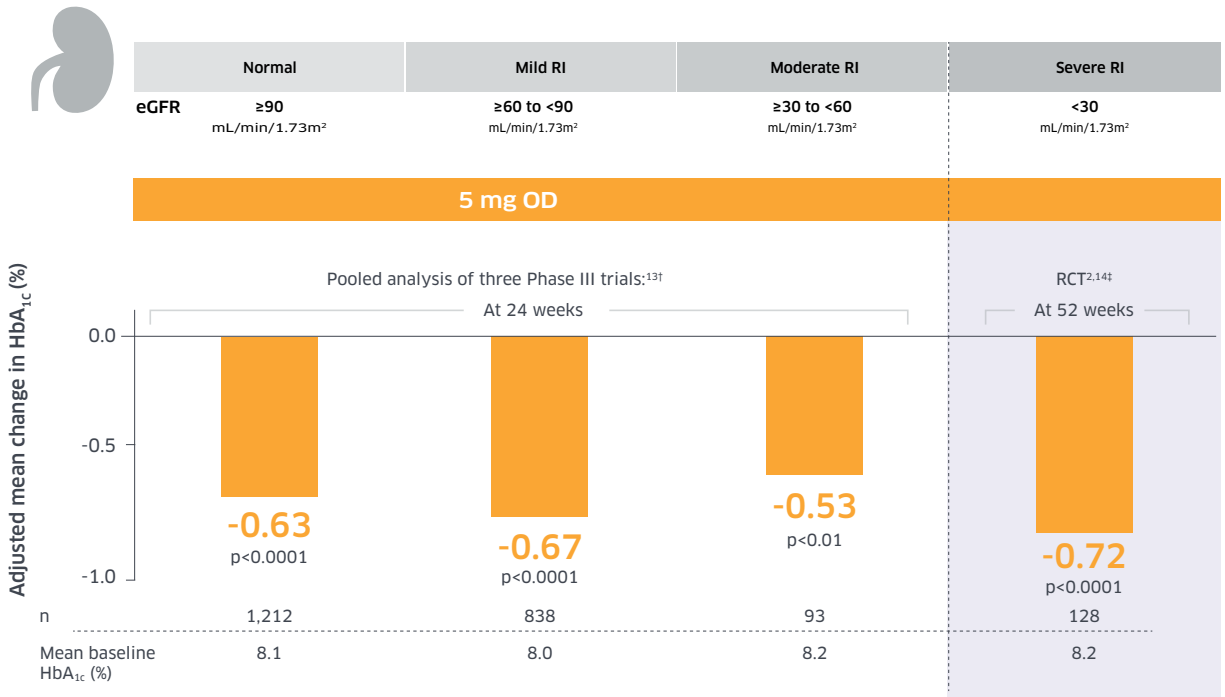
TRAJENTA®: *The DPP4i with the lowest renal excretion rate*[1-5]

Proportions of medication excreted via the kidney



TRAJENTA®: *Proven efficacy with the same dose regardless of renal function*[1,6,7]

*Adjusted mean HbA_{1c} change vs placebo from baseline by degree of renal impairment (RI)**



* A small proportion of patients in these studies were receiving treatment combinations that fall outside of the licensed indications for Trajenta® (linagliptin).
† 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. P values for between-group difference (versus placebo). Model includes continuous baseline HbA_{1c}, baseline body mass index (category), washout period, treatment, study, age group, gender, time since diagnosis of diabetes, race, renal function (MDRD) and treatment × renal function (MDRD).
‡ 1-year, randomised, double-blind, placebo-controlled study: treatment added to existing background therapy. Data based on analysis using LOCF(last observation carried forward).
eGFR (mL/min/1.73m²) = 175 × (Scr)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if Black); Scr: Serum creatinine; RCT: Randomised controlled trial; OD: Once daily.

TRAJENTA®: *The only approved DPP4i that does not require dose reduction based on renal function*[*1-5]*

Required DPP4i dose with declining renal function, as defined by SmPC[1-5]

Normal	Mild RI	Moderate RI	Severe RI	End-stage renal disease
TRAJENTA®[1]				
5 mg OD				
Sitagliptin[2]				
100 mg OD	100 mg OD	100 mg OD	50 mg OD	25 mg OD	25 mg OD
	GFR ≥60 to 90 mL/min	GFR ≥45 to 60 mL/min	GFR ≥30 to 45 mL/min	GFR ≥15 to 30 mL/min	GFR <15 mL/min
Saxagliptin[3]				
5 mg OD	5 mg OD	2.5 mg OD	2.5 mg OD	Not recommended
	CrCl >50 to ≤80 mL/min	CrCl ≥30 to ≤50 mL/min	CrCl > 15 to <30mL/min	CrCl < 15 mL/min
Vildagliptin[4]				
50 mg BD	50 mg BD	50 mg OD	50 mg OD	50 mg OD
	CrCl ≥50mL/min	CrCl ≥30 to <50 mL/min	CrCl > 15 to <30 mL/min	ESRD on haemodialysis: use with caution
Alogliptin[5]				
25 mg OD	25 mg OD	12.5 mg OD	6.25 mg OD	6.25 mg OD
	CrCl >50 to ≤80 mL/min	CrCl ≥30 to ≤50 mL/min	CrCl > 15 to <30 mL/min	Limited experience in renal dialysis. Not studied in peritoneal dialysis

TRAJENTA®: *One dose, once daily for your type 2 diabetes patients*[†1]

5 mg once daily

Independent of:

- Renal function
- Hepatic function[§]
- Background T2D therapy[**]
- Age[‡]
- Disease duration
- Ethnicity
- BMI

[*] Information is derived from the Summary of Product Characteristics (SMPC) for TRAJENTA®/JENTADUETO® in the EU. It is not country-specific and may vary from the approved label in the country where you are located. Please refer to your local Prescribing Information for full details.

[†] Indicated for use in adult patients. TRAJENTA® is contraindicated in those with hypersensitivity to any of the active substances or excipients, is not licensed for paediatric use and should not be used in pregnant women. TRAJENTA® is indicated • 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 (see sections 4.4, 4.5 and 5.1 for available data on different combinations). BD: Bi-daily; CKD: Chronic kidney disease; CrCl: Creatinine clearance; GFR: Glomerular filtration rate; OD: Once daily; RI: Renal impairment.

[§] Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking.

[**] Combination therapies studied with linagliptin were: Linagliptin as add-on to metformin therapy; Linagliptin as add-on to a combination of metformin and sulphonylurea therapy; Linagliptin as add-on to a combination of metformin and empagliflozin; Linagliptin as add-on to insulin therapy.

[‡] No dose adjustment is necessary based on age. However, clinical experience in patients >80 years of age is limited and caution should be exercised when treating this population.

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SHORT VERSION OF THE 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. However, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population. 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. In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. 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: There have been post-marketing reports of bullous pemphigoid in patients taking linagliptin. 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 monotherapy: common (≥ 1/100 to <1/10) - Lipase increased; uncommon (≥ 1/1,000 to < 1/100) – Nasopharyngitis, Hypersensitivity (e.g. bronchial hyperreactivity), Cough, Rash; rare (≥ 1/10,000 to < 1/1,000) – Angioedema, Urticaria, Amylase increased; not known (cannot be estimated from the available data) – Pancreatitis, Bullous pemphigoid.
Linagliptin + Metformin: common - Lipase increased; uncommon - Nasopharyngitis, Hypersensitivity (e.g. bronchial hyperreactivity), Cough, Rash, Amylase increased; rare - Angioedema, Urticaria; not known – Pancreatitis; Bullous pemphigoid.
Linagliptin + Metformin + Sulphonylurea: very common (≥ 1/10) – Hypoglycaemia; common - Lipase increased; uncommon - Hypersensitivity (e.g. bronchial hyperreactivity), Rash, Amylase increased; rare - Angioedema, Urticaria; not known – Nasopharyngitis; Cough; Pancreatitis; Bullous pemphigoid.
Linagliptin +Insulin: common - Lipase increased; uncommon - Nasopharyngitis, Hypersensitivity (e.g. bronchial hyperreactivity), Cough, Pancreatitis, Constipation; Rash; rare - Angioedema, Urticaria; not known – Amylase increased; Bullous pemphigoid.
Linagliptin + Metformin + Empagliflozin: common - Lipase increased; uncommon - Amylase increased; not known – Nasopharyngitis, Hypersensitivity (e.g. bronchial hyperreactivity), Cough, Pancreatitis.
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: July 2017

References: 1) TRAJENTA® Summary of Product Characteristics. June 2017. **2)** Januvia® Summary of Product Characteristics. December 2017. **3)** Onglyza® Summary of Product Characteristics. August 2017. **4)** Galvus® Summary of Product Characteristics. April 2017. **5)** Vipidia® Summary of Product Characteristics. January 2015. **6)** Groop PH, et al. Diabetes Obes Metab 2014;16(6):560-568. **7)** McGill JB, et al. Diabetes Care 2013;36:237-244. **8)** Spanopoulos D et al. Clin Ther. 2018;40(1):152-154. **9)** Lang K, et al. 76th Scientific Sessions of the American Diabetes Association, 10-14 June 2016, New Orleans, USA; Poster 1523-P. **10)** Meyers JL, et al. J Postgrad Med 2011:123(3):133-143.