# What are the renal considerations in type 2 diabetes prescribing?

Trajenta® (linagliptin) 5mg tablets

## Definition of CKD[1]

**Criteria for CKD (either of the following present for ≥3 months)**

*Markers of kidney damage*

- Albuminuria (AER >30 mg/24 hours; ACR >30 mg/g [>3 mg/mmol])

*Decreased Glomerular Filtration Rate (GFR)*

- GFR <60 ml/min/1.73 m² (GFR categories G3a-G5)

*ACR (albumin/creatinine ratio) is more sensitive test in diabetes than PCR (protein/creatinine ratio)

## CKD: Staging and prognosis[1]

Low risk* · Moderately increased risk · High risk · Very high risk

| Prognosis of CKD by GFR and albuminuria categories | | | Albuminuria stage, description and range (mg/g) | | |
|---|---|---|---|---|---|
| | | | A1 | A2 | A3 |
| | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | <30 mg/g | 30–300 mg/g | >300 mg/g |
| eGFR category range (ml/min/1.73 m²) | G1 | ≥90 | ≤1 | 1 | 2 |
| | G2 | 60-89 | ≤1 | 1 | 2 |
| | G3a | 45-59 | 1 | 2 | 3 |
| | G3b | 30-44 | 2 | 3 | 3 |
| | G4 | 15-29 | 3 | 3 | ≥4 |
| | G5 | <15 | ≥4 | ≥4 | ≥4 |

Increasing risk

The KDIGO Heat Map is a useful tool in assessing the cardiovascular risk of patients with kidney disease

[The numbers in the boxes are a guide to the frequency of monitoring (number of times per year)]

## Screening for CKD in people living with T2D[2,3]

### Who & when to screen?

T2 DM — Yearly, starting at diagnosis

### What defines CKD diagnosis?

- Persistent* urine ACR≥30 mg/g
- Persistent* eGFR <60 mL/min/1.73 m²
- Other evidence of kidney damage

### How to screen?

- Spot urine albumin-creatinine ratio (UACR) **and**
- Estimated glomerular filtration rate (eGFR)

### Repeat and confirm

- Evaluate possible temporary or spurious causes
- Only persistent* abnormalities define CKD
- Initiate evidence-based treatments

*Persistent: present for longer than 90 days *(two tests performed over 90 days).*

## Managing glycaemia in people with T2D and renal impairment: Treatment of CKD and T2D with metformin and further medicines*[4]

| | Stages G1 and G2 eGFR ≥60 | Stage G3a eGFR 45-59 | Stage G3b eGFR 30-44 | Stage G4 eGFR 15-30 | Stage G5 eGFR <15 |
|---|---|---|---|---|---|
| Metformin | 3 g total maximun daily dose (in 2-3 daily doses) | 2 g total maximun daily dose (in 2-3 daily doses) | 1 g total maximun daily dose (in 2-3 daily doses) | | |
| Sulfonylureas | | Increased risk of hypoglycaemia if eGFR <60. Consider reducing dose. Gliclazide and glipizide preferred as metabolised in the liver | | | |
| Pioglitazone | | | | | Avoid in those on dialysis |
| Alogliptin | | | Reduce to 12.5 mg od if CrCl ≤50 ml/min | Reduce to 6.25 mg od if CrCl <30 ml/min or dialysis required | |
| Linagliptin | No dose adjustment across CKD stages - allows for initiation even if renal profile not immediately available[5] | | | | |
| Saxagliptin | | Reduce to 2.5 mg od | | | Avoid in those on dialysis |
| Sitagliptin | | | Reduce to 50 mg od | Reduce to 25 mg od | |
| Vildagliptin | | | Reduce to 50 mg od if CrCl <50 ml/min | | |

No dose adjustment needed · Dose adjustment or further action recommended · Not recommended

**Resources:**

* Please refer to NICE NG28 for the full treatment algorithm for initial and further medicines.
•KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.
•Type 2 diabetes in adults: management NICE guideline (2015). Available at www.nice.org.uk/guidance/ng28
•Chronic kidney disease: assessment and management. NICE guideline (2021). Available at www.nice.org.uk/guidance/ng203
**Abbreviations:** CKD, chronic kidney disease; GFR, glomerular filtration rate; AER, albumin excretion rate; ACR, albumin-to-creatinine ratio; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; od: once daily.

**References:**
**1.** KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD (v0.1) - Criteria for CKD (p.18) Criteria for CKD (either of the following present for 43 months) Markers of kidney damage (one or more ) Albuminuria (AER Z30 mg /24 hour). **2.** KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney International. 2022; 102 (Suppl 5S): S1–S127. **3.** National Diabetes Audit data 2021-2022. Available at https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-diabetes-audit/dashboards Accessed 11th April 2023. **4.** Fernando K. Primary Care Hacks: The Pharmacological Management of Hyperglycaemia in People Living with Type 2 Diabetes and Chronic Kidney Disease. Available at https://www.medscape.co.uk/viewarticle/primary-care-hacks-pharmacologicalmanagement-hyperglycaemia-2022a10024hx Accessed Feb 28th 2023. **5.** TRAJENTA® SmPC

Adverse events should be reported. Reporting forms and information can be found at https://www.mhra.gov.uk/yellowcard (UK) or https://www.hpra.ie/homepage/about-us/report-an-issue (IRE). Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1627 (freephone) (UK) or 01 2913960, Fax: +44 1344 742661, or by email: PV_local_UK_Ireland@boehringer-ingelheim.com (IRE).

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## Prescribing Information (Great Britain) 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. 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 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. *Hypoglycaemia:* 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:* 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:* 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. *Effects of other medicinal products on linagliptin:* The risk for clinically meaningful interactions by other medicinal products on linagliptin is low. Rifampicin: Multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, decreased linagliptin steady state AUC and Cmax. Thus, full efficacy of linagliptin in combination with strong P-glycoprotein inducers might not be achieved, particularly if administered long term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied. *Effects of linagliptin on other medicinal products:* 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 a full list of interactions and clinical data). **Fertility, pregnancy and lactation:** The use of linagliptin has not been studied in pregnant women. As a precautionary measure, 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:** PLGB 14598/0225. **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** September 2021.

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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:* a clinical trial did not establish efficacy in paediatric patients 10 to 17 years of age. Therefore, treatment of children and adolescents with linagliptin is not recommended. Linagliptin has not been studied in paediatric patients under 10 years of age. 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 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. *Hypoglycaemia:* 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:* 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:* 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. *Effects of other medicinal products on linagliptin:* The risk for clinically meaningful interactions by other medicinal products on linagliptin is low. Rifampicin: Multiple co-administration of 5 mg linagliptin with rifampicin, a potent inductor of P-glycoprotein and CYP3A4, decreased linagliptin steady state AUC and Cmax. Thus, full efficacy of linagliptin in combination with strong P-glycoprotein inducers might not be achieved, particularly if administered long term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied. *Effects of linagliptin on other medicinal products:* 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 a full list of interactions and clinical data). **Fertility, pregnancy and lactation:** The use of linagliptin has not been studied in pregnant women. As a precautionary measure, avoid use during pregnancy. A risk to the breast-fed child cannot be excluded. 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