Trajenta®
(linagliptin) 5mg tablets

How and when to switch or add in medications in adult type 2 diabetes

Although DPP-4 inhibitors play an increasingly important role as a treatment option in adult T2D, SUs remain the most commonly prescribed second-line agent[1]

However, in a retrospective cohort study of over 119,000 adults with T2D, newly issued with at least two prescriptions for SUs within the last 90 days, approximately 70% discontinued the SU but did not switch to another hypoglycaemic agent[2]

Reasons for lack of persistence with SUs include occurrence of hypoglycaemia, weight gain, and not achieving treatment targets[3,4]

Switching or adding in medications in adult T2D: What do the NICE guidelines say?

NICE NG28[5,6]

- When reviewing or considering changing treatments for adults with T2D, think about and discuss with the person whether switching rather than adding drugs could be effective
- Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated)

Examples of factors influencing diabetes therapy choice[7]

Medication factors
e.g. efficacy, contraindications, pleiotropic effects, risk of hypoglycaemia, cost

Patient factors
e.g. patient wishes, occupation, age, diabetes duration, gender, ethnicity, genetics, presence of comorbidities

To switch or not to switch: Practical considerations

Adding in or switching T2D medications: General

- Think logically about medication burden
- Patients need to understand why they need to take their medication to be concordant
- Continue medications with evidence for hard outcome measures (e.g. micro and macrovascular complications) and impact on glucose levels[8]

Adding in an insulin

- Insulin in combination with an SU should always be questioned[9]
- SUs are usually stopped when a mixed or rapid-acting insulin is added to avoid compounding the risk of hypoglycaemia[10]
- Insulin dosing should be reviewed when adding in a DPP-4 inhibitor[11]

HbA1c

- If HbA1c <53 mmol/mol, the use of an SU alone or in combination is not recommended[12]
- If HbA1c is tighter <58 mmol/mol, switching rather than adding in a medication may be advised[5]
- If HbA1c >75 mmol/mol, then adding in a medication can be helpful[5]

Adding in or switching to Trajenta (linagliptin)

- The combination of an SGLT2 inhibitor and linagliptin may be a suitable treatment option in adults with type 2 diabetes due to their complementary modes of action[13]
- In older adults, avoid use of SUs due to hypoglycaemia risk.[14] Linagliptin is suitable for use in older adults as it is associated with low risk of hypoglycaemia when not used in combination with an SU or insulin, and has a simple dosing regimen irrespective of renal function[11]
- Advantages of adding in linagliptin in older adults with T2D rather than an SU or insulin:[15]
  - Linagliptin has fewer side effects and minimal risk of hypoglycaemia compared with SUs/insulin
  - Linagliptin does not increase major adverse cardiovascular outcomes
  - The recommended dose of linagliptin for adults with type 2 diabetes is 5 mg once daily, independent of renal and hepatic function, body mass index, age, ethnicity, background type 2 diabetes therapy, and disease duration[11,16]

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose co-transporter-2; SU: sulphonylurea; T2D: type 2 diabetes.

1. Boehringer Ingelheim Data on File; 2. Tan X et al. Diab Obes Metab 2021;23:2251–60; 3. Laires PA et al. Expert Rev Pharmacoecon Outcomes Res 2017; 17: 213–20; 4. Laires P et al. Expert Rev Pharmacoecon Outcomes Res 2019; 19: 71–9; 5. NICE. Type 2 diabetes in adults: Management. Available at: www.nice.org.uk/guidance/ng28 (accessed March 2023); 6. NICE. Type 2 diabetes in adults: choosing medicines. June 2022. Available at: https://www.nice.org.uk/guidance/ng28/resources/visual-summary-pdf-10956472093 (accessed March 2023); 7. Davies MJ et al. Diabetes Care 2022;45:2753–86; 8. Taylor SI et al. J Clin Invest 2021;13:e142243; 9. American Diabetes Association. Diabetes Care 2022;45(Suppl. 1):S125–43; 10. Home P et al. Diabetes Care 2014;37:1499–508; 11. Trajenta (linagliptin) Summary of Product Characteristics; 12. Malawana M et al JRSM Open 2018;9:2054270418773669; 13. Scheen A. Expert Opin Drug Metab Toxicol 2016;12:1407–17; 14. Strain WD et al. Diabetes Ther 2021;12:1227–47; 15. American Diabetes Association. Diabetes Care 2020;43(Suppl 1):S152–62; 16. Lajara R, et al. Clin Ther. 2014;36:1595–605.

Please refer to your local prescribing guidelines and NICE guidance.

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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.

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 (Northern 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:* 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. 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. 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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. 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Adverse events should be reported. Reporting forms and information can be found at 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